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RESEARCH IN THE FIELD OF 1,2,3,4-TETRAHYDROQUINOLINE DERIVATIVE TOTAL SYNTHESIS OF SUMANIROLE SYNTHETIC APPROACH TO VIRANTMYCIN AND MARTINELLIC ACID

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Présentée et soutenue publiquement par

Anh Ngoc NGO

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Nantes, 16 April 2013

Anh Ngoc NGO

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ABBREVIATIONS

Ac	Acetyl
Acac	Acetylacetone
AIDS	Acquired immunodeficiency syndrome
Alloc	(Allyloxy)carbonyl
Ar	Aryl
aq	Aqueous
Boc	*tert*-Butyloxycarbonyl
Bn	Benzyl
Bu	Butyl
CDI	Carbonyldiimidazole
m-CPBA	*meta*-Chloroperoxybenzoic acid
CSA	Camphorsulfonic acid
DIBAL-H	Diisobutylalumium hydride
DCC	*N,N′*-Dicyclohexylcarbodiimide
DEAD	Diethyl azodicarboxylate
DHQ	Dihydroquinoline
DMAP	Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DNA	Deoxyribonucleic acid
DPPA	Diphenylphosphoryl azide
EDC	Ethylcarbodiimide
Et	Ethyl
eq	Equivalent

h	Hours
HMPA	Hexamethylphosphoramide
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
Hz	Hertz
IR	Infrared
KHMDS	Potassium bis(trimethylsilyl)amide
LAH	Lithium aluminium hydride
LDA	Lithium diisopropylamine
Me	Methyl
Ms	Methanesulfonyl chloride
MS	Mass spectrometry
NBA	*N*-Bromoacetamide
NBS	*N*-Bromosuccinimide
NMM	*N*-Methylmorpholine
NMR	Nuclear magnetic resonance
Ns	Nosyl
PE	Petroleum ether
Ph	Phenyl
PPh	Triphenylphosphine
ppm	Parts per million
PTSA	*Para*-Toluenesulfonic acid
RNA	Ribonucleic acid
rt	Room temperature
t	Time

TBAI	Tetrabutylammonium iodide
TBAF	Tetra-n-butylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THQ	Tetrahydroquinoline
TLC	Thin layer chromatography
TMS	Trimethylsilyl
Ts	Tosyl
TS	Transition state
wt	Weight

GENERAL INTRODUCTION

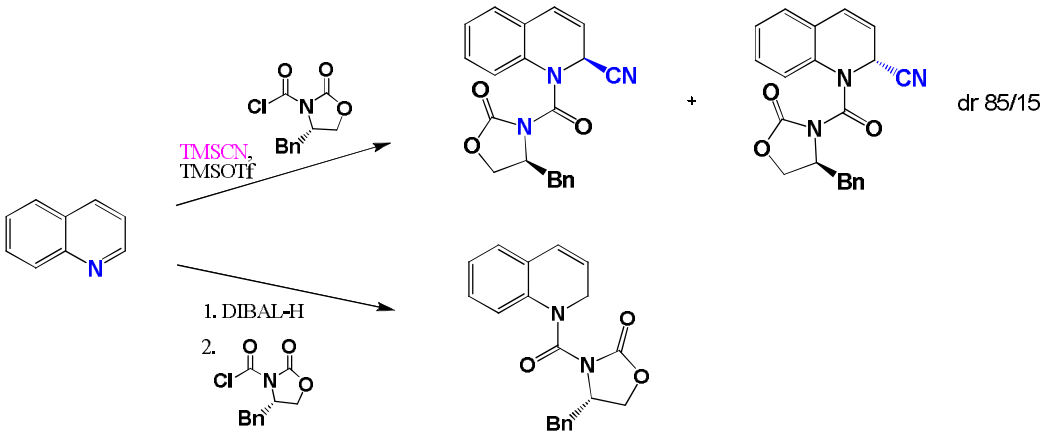
GENERAL INTRODUCTION

Heterocyclic compounds, especially nitrogen heterocycles, are the most important class of compounds in the pharmaceutical and agrochemical industries. For example, heterocycles are included in about 60% of all drug substances. Among these compounds, the 1,2,3,4-tetrahydroquinolines (1,2,3,4-THQs) have been subject to continuous investigations over the years.[1] This is primarily due to the fact that free 1,2,3,4-THQs (i.e. not fused to another ring) exhibit a broad range of biological activities. Additionally, the 1,2,3,4-THQ scaffold can be found within the framework of important pharmacological drugs as well as in some natural products of biological relevance.

We have been interested in developping a new asymmetric approach to diversely substituted 1,2,3,4-THQs with the future hope to apply our methodology to the total synthesis of several natural (or unnatural) compounds of pharmaceutical interest.

Some years ago, we reported that quinoline (also isoquinoline)-derived Reissert adducts could be accessed with fair diastereoselectivities (up to 70%) by submission of quinoline (isoquinoline) to the action of a chiral oxazolidin-derived carbamoyl chloride in the presence of TMSCN. We next observed (unpublished results) that a chiral 1,2-dihydroquinoline could be prepared by a similar reaction featuring preliminary DIBAL-H reduction of quinoline followed by addition onto the same chiral carbamoyl chloride (Scheme 1).

[1] (a) A. R. Katritzky, S. Rachwal, B. Rachwal, *Tetrahedron*, **1996**, *52*, 15031. (b) V. Sridharan, P. A. Suryavanshi, J. C. Menéndez, *Chem. Rev*. **2011**, *111*, 7157.



Scheme 1

These results led us to ask ourselves the question of whether it is possible to selectively add various electrophiles onto the 3,4-double bond of each 1,2-dihydroquinoline. If so, we would be able to easily reach new chiral 1,2,3,4-THQs and next used them to carry out some other useful transformations. If we were confident as far as the first operation on 2-cyano-1,2-dihydroquinoline is concerned - because of the probable directional effect of the CN substituent, we were more hesitating regarding the second operation, mainly because the chiral auxiliary attached at N1 is remote from the reactive double bond.

In the first part of this thesis, we present the results of a methodological study showing that electrophilic addition reactions to Reissert adduct can be done with excellent selectivities. More surprisingly, we will show that the same addition reactions to 1,2-dihydroquinoline without CN group at C2 can be achieved with relatively high diastereoselectivities. Some transformations of the primary adducts will be also reported.

The second part of the manuscript is concerned with application of the above study in the field of total synthesis. We will first report a new and original synthesis of Sumanirole, an unnatural compound exhibiting anti-parkinsonian activities. A preliminary work directed towards the synthesis of two natural alkaloids, that is Virantmycine and Martinellic acid, will be also reported.

CHAPTER 1: REMOTE CONTROL OF THE C3-C4 DOUBLE BOND ELECTROPHILIC ADDITION OF A CHIRAL 1,2-DIHYDROQUINOLINE

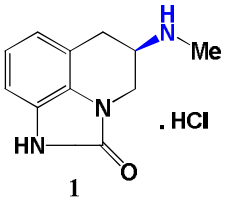
CHAPTER 1: REMOTE CONTROL OF THE C3-C4 DOUBLE BOND ELECTROPHILIC ADDITION OF A CHIRAL 1,2-DIHYDROQUINOLINE

In the course of total syntheses we have been interested in 1,2,3,4-THQs bearing a NHR or a NR1R2 substituent at C3 or C4. We will give a rapid overview of methods reported to date to reach some of these compounds.

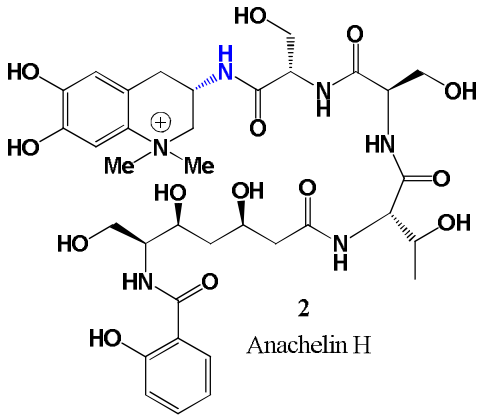
1.1. Literature review

1.1.1. Tetrahydroquinolines bearing a NHR or a NR1R2 substituent at C3

Sumanirole (PNU-95666E) **1** and Anachelin-H **2** are examples of this type of compounds (Figure 1). Sumanirole is a highly selective D2 receptor full agonist, which was developed for the treatment of Parkinson's disease and restless leg syndrome.[2] Anachelin H[3] is an iron chelator isolated from the cyanobacterium *Anabaena cylindrical*. The *N,N*-dimethylquinolinium chromophore is believed to serve as a tyrosinase activator. Anachelin H also exhibits moderate antibiotic activity against *Moraxella catarrhalis*.



1
Sumanirole



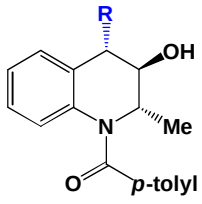
2
Anachelin H

Figure 1: 1,2,3,4-THQs bearing a NHR substituent at C3

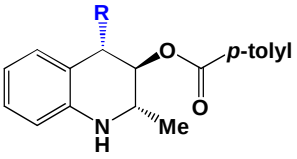
[2] (a) R. F. Heier, L. A. Dolak, J. N. Duncan, D. K. Hyslop, M. F. Lipton, I. J. Martin, M. A. Mauragis, M. F. Piercey, N. F. Nichols, P. J. K. D. Schreur, M. W. Smith, M. W. Moon, *J. Med. Chem.* **1997**, *40*, 639. (b) R. B. McCall, K. L. Lookingland, P. J. Bédard, R. M. Huff, *J. Pharmacol. Exp. Ther*. **2005**, *314*, 1248.
[3] (a) Y. Ito, K. Ishida, S. Okada, M. Murakami, *Tetrahedron*, **2004**, *60*, 9075. (b) K. Gademann, Y. Bethuel, *Org. Lett*. **2004**, *6*, 4707. (c) K. Gademann, Y. Bethuel, *Angew. Chem. Int. Ed.* **2004**, *43*, 3327. (d) Y. Bethuel, K. Gademann, *J. Org. Chem.* **2005**, *70*, 6258.

1.1.2. Tetrahydroquinolines bearing a NHR or a NR1R2 substituent at C4

Some selected examples of this type of compounds are displayed in Figure 2. The 2-methyltetrahydroquinoline derivatives **3** and **4** displayed moderate to high inhibitory activity in multidrug resistance (MDR),[4] which is considered as one of the main obstacles in successful cancer and antimicrobial therapy. The *trans*-2-carboxy-4-amidotetrahydroquinolines **5** were identified as antagonists of the glycine site at the NMDA receptor,[5] whose excitotoxicity is implicated in neurodegenerative diseases of the central nervous system (CNS) such as Alzheimer's disease and AIDS-related dementia.[6] Torcetrapib (CP 529,414) **6**[7] was developed to treat hypercholesterolemia and prevent cardiovascular disease by inhibiting cholesterylester transfer protein (CETP), which results in higher HDL level (the "good" cholesterol-containing particles) and reduces LDL levels (the "bad" cholesterol).[8]

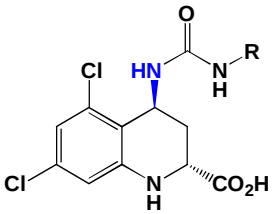


3



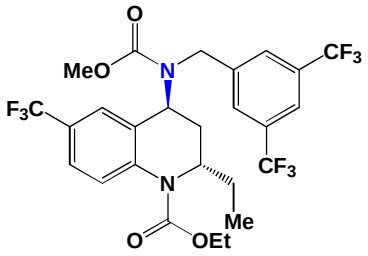
4

R = NHBn, *p*-benzylpiperazinyl, pyrrolidyl, 5-diethylamino-2-pentylamino



5

R = phenyl, *p*-tolyl, *o*-tolyl etc



6

Torcetrapid

Figure 2: 1,2,3,4-THQs bearing a NHR substituent at C4

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[4] R. Hiessböck, C. Wolf, E. Richter, M. Hitzler, P. Chiba, M. Kratzel, G. Ecker. *J. Med. Chem.* **1999**, *42*, 1921.
[5] P. D. Leeson, R. W. Carling, K. W. Moore, A. M. Moseley, J. D. Smith, G. Stevenson, T. Chan, R. Baker, A. C. Foster, S. Grimwood, J. A. Kemp, G. R. Marshall, K. Hoogsteen, *J. Med. Chem.* **1992**, *35*, 1954.
[6] B. Meldrum, J. Garthwaite, Excitatory Amino Acid Neurotoxicity and Neurodegenerative Disease. *Trends Pharmacol. Sci.* **1990**, *11*, 379.
[7] (a) M. Guinó, P. H. Phua, J-C. Caille, K. K. Hii, *J. Org. Chem.* **2007**, *72*, 6290. (b) H. Liu, G. Dagousset, G. Masson, P. Retailleau, J. Zhu, *J. Am. Chem. Soc.* **2009**, *131*, 4598.
[8] M. E. Brousseau, E. J. Schaefer, M. L. Wolfe, L. T. Bloedon, A. G. Digenio, R. W. Clark, J. P. Mancuso, D. J. Rader. *New Engl. J. Med.* **2004**, *350*, 1505.

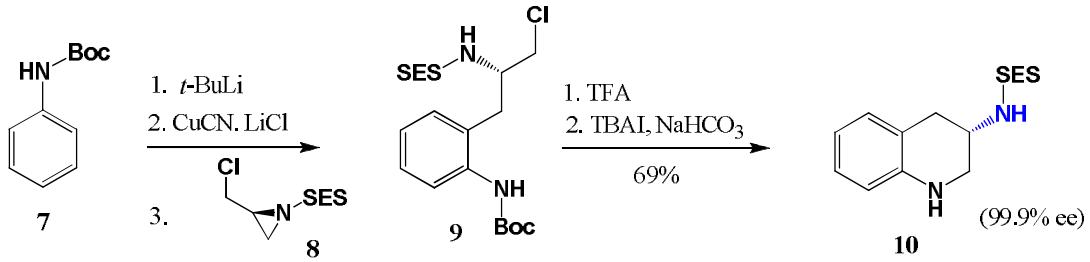
Due to the relative paucity of 3- and 4-amino-substituted 1,2,3,4-THQs, it is by no means surprising that only few methods for the asymmetric preparation of this class of compounds have been reported so far.

1.1.3. Enantioselective installation of a NHR group at C3

This installation could be achieved by intramolecular nucleophilic substitution reaction or reduction-intramolecular cyclization sequences.

- <u>The intramolecular nucleophilic substitution</u>

This sequence was employed to synthesize, with excellent enantioselectivity (99.9% ee), the 3-amino-1,2,3,4-tetrahydroquinoline **10**, which constitutes the core structure of Sumanirole **1**.[9] The sequence begins with the double deprotonation of **7**. After the addition of CuCN.LiCl, the generated cuprate undergoes reaction with the chiral aziridine **8**, previously prepared by the authors from *tert*-butyl (trimethylsilyl)ethylsulfonylcarbamate[10], to afford the chloroamino derivative **9**. Deprotection of the latter followed by cyclization, in the presence of added iodide, affords (creation of the N-C2 bond) the 3-amino-1,2,3,4-THQ **10**.

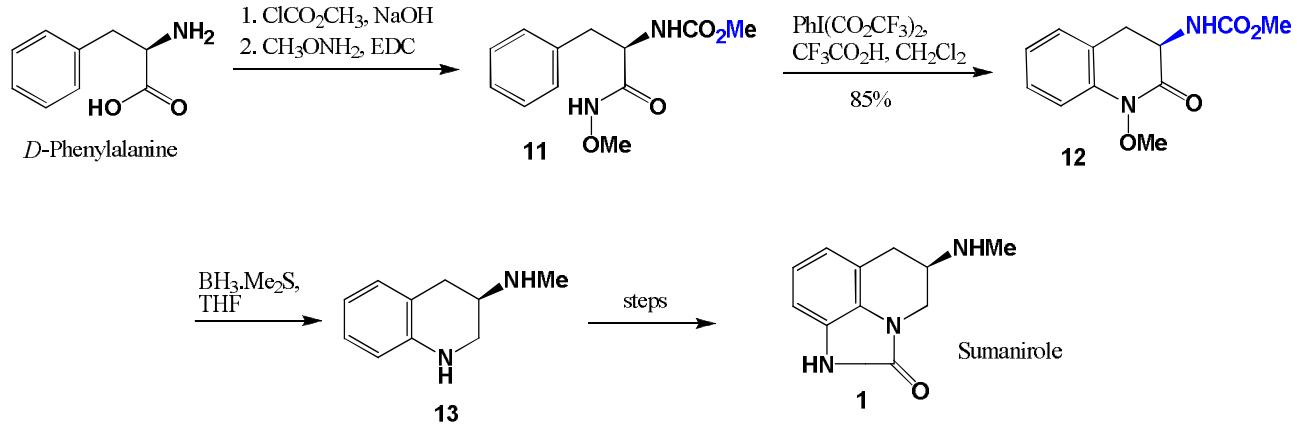


Scheme 2

The intramolecular nucleophilic substitution may come from the formation of the N-C8a bond. Thus, the cyclization of *N*-methoxyamide **11**, prepared from D-phenylalanine in 2 steps, using $PhI(CO_2CF_3)_2$ leads to the dihydroquinolone **12**[11]. Excess trifluoroacetic acid is used to increase the electrophilicity of the *N*-methoxy-*N*-acylnitrenium ion or also possibly to increase the reactivity of the bis(trifluoroacetoxy)iodobenzene reagent itself. Reduction of **12** with BH_3

[9] S. K. Kim, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2004**, *43*, 3952.
[10] J. A. Campbell, D. J. Hart, *J. Org. Chem.* **1993**, *58*, 2900.
[11] A. G. Romero, W. H. Darlington, M. W. McMillan, *J. Org. Chem.***1997**, *62*, 6582.

affords 3-(*N*-methylamino)-1,2,3,4-tetrahydroquinoline derivative **13**, an intermediate for the synthesis of Sumanirole **1**.[12]



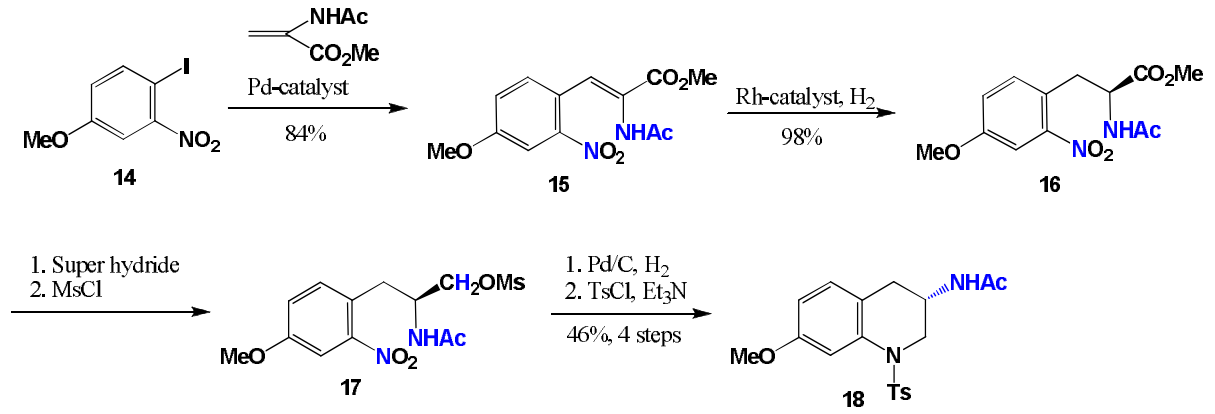
Scheme 3: Synthesis of chiral 3-methylamino-1,2,3,4-tetrahydroquinoline

- Reduction-Intramolecular Cyclization Sequences

These sequences were achieved in almost cases by rhodium-catalyzed asymmetric hydrogenation or Sharpless dihydroxylation of a cinnamyl substrate, followed by further manipulations to elaborate the 1,2,3,4-THQ skeleton.

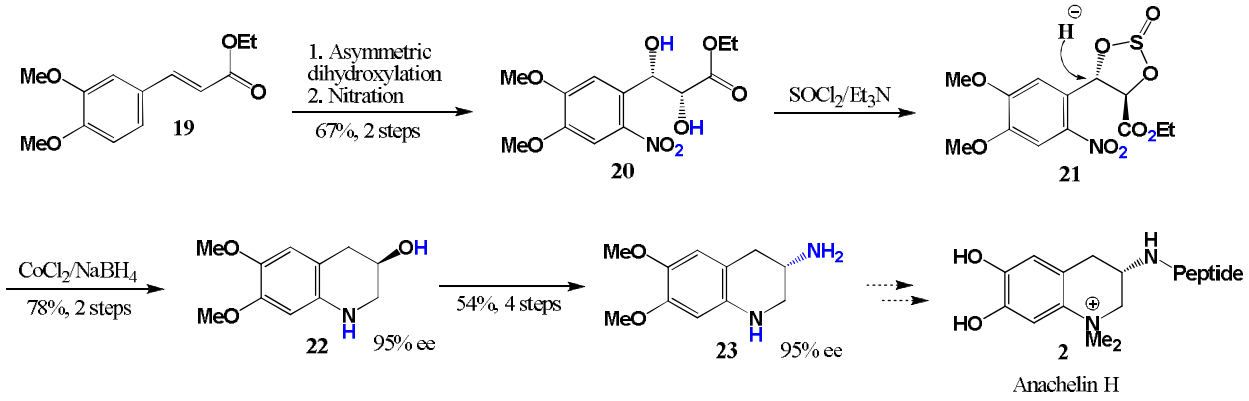
Aminoester **15** is obtained with excellent enantioselectivity (>98% ee) from 4-methoxy-2-nitroiodobenzene **14** through a Pd-catalyzed Heck reaction, followed by Rh-catalyzed asymmetric hydrogenation. After the reduction with Super hydride, the resulting alcohol is mesylated to afford the mesylate **17**. This compound, under the hydrogenation conditions catalysed by Pd/C, and *in situ* cyclization with formation of the N-C2 bond led to an unstable 3-acetamido-1,2,3,4-tetrahydroquinoline, which is transformed into the stable tosyl derivative **18**, an advanced intermediate for the synthesis of Sumanirole **1**.[13]

[12] P. G. M. Wuts, *Curr. Opin. Drug Discovery Dev.* **1999**, *2*, 557.
[13] I. Gallou-Dagommer, P. Gastaud, T. V. RajanBabu. *Org. Lett.* **2001**, *3*, 2053.



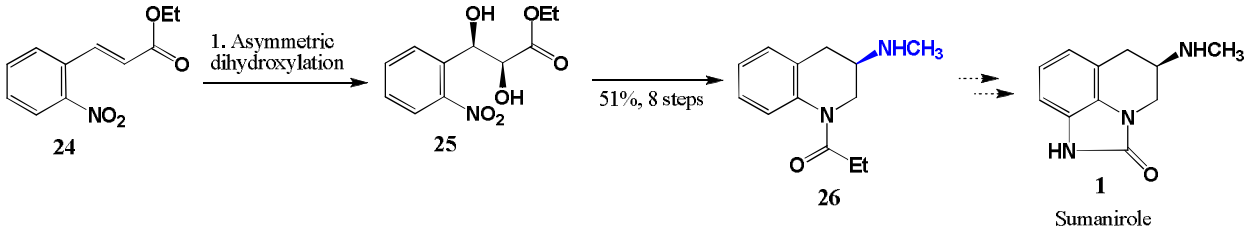
Scheme 4

The following scheme presents a synthesis of Anachelin H **2** with formation of the N-C2 bond of the 1,2,3,4-THQ core. Nitro diol **20**, prepared by the asymmetric dihydroxylation (AD-mix-α using $(DHQ)_2$-PHAL ligand) of cinnamate **19**, followed by nitration with HNO_3, is reacted with thionyl chloride to afford the sulphite **21**, which, in turn, under the multifunctional reduction, catalysed by cobalt, led to the 3-hydroxy-1,2,3,4-tetrahydroquinoline derivative **22** with excellent enantioselectivity (95%). This latter is then transformed into the (*S*)-6,7-dimethoxy-1,2,3,4-tetrahydroquinolin-3-amine **23**, an intermediate in the synthesis of Anachelin H **2**, in four additional steps.



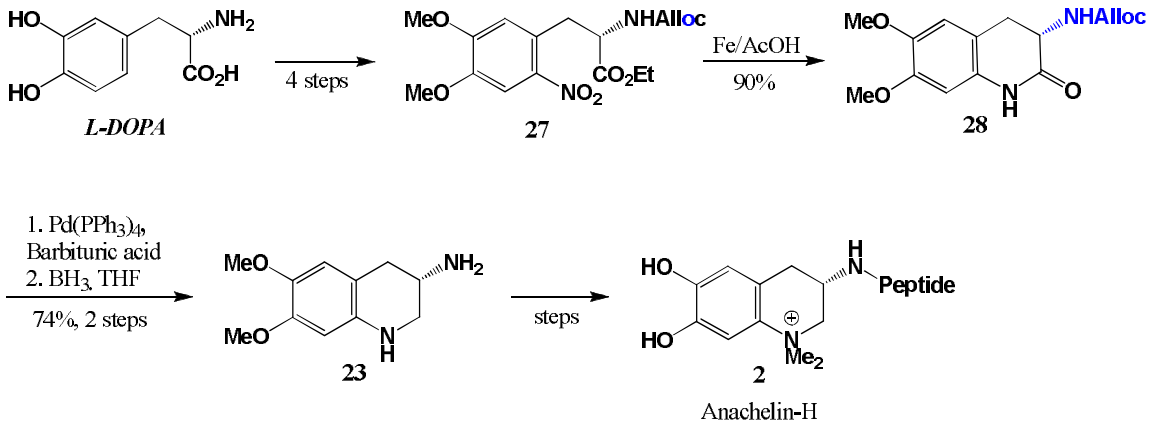
Scheme 5

A similar sequence can be applied to nitro cinnamate **24** to reach the (*R*)-1-(3-(methylamino)-3,4-dihydroquinolin-1(2*H*)-yl)propan-1-one **26**, an advanced intermediate for the synthesis of Sumanirole **1**.[14]



Scheme 6

An alternative procedure to synthesize the advanced intermediate **23** for the synthesis of Anachelin H **2** starts from L-DOPA. Nitro derivative **27**, prepared from L-DOPA in four steps,[15] is submitted to the reductive cyclization with Fe/AcOH to afford the tetrahydroquinoline derivative **28** in high yield (90%). This compound, then, is the subject of the deprotection on the allyl group in the presence of Pd(0) and the reduction on the lactam group with borane to lead to the key intermediate **23**.[3d]



Scheme 7

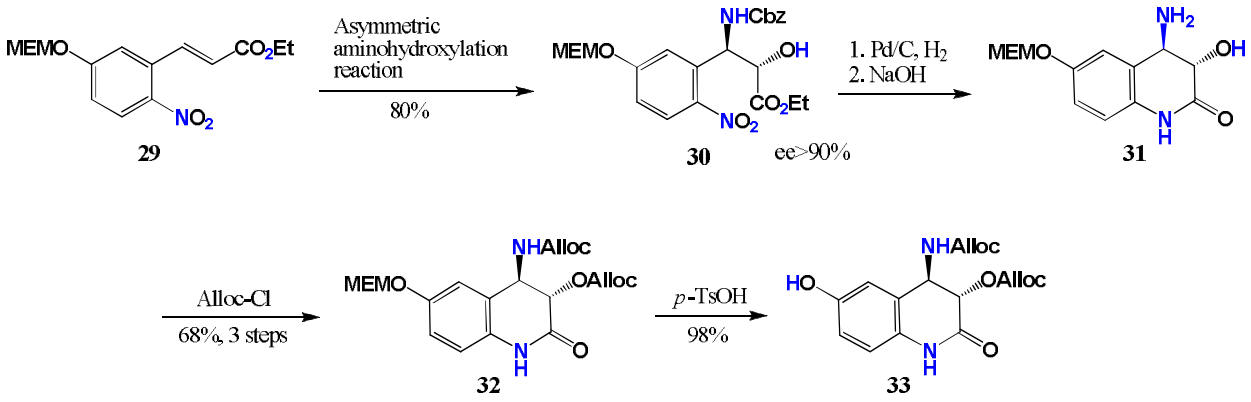
[14] (a) A. R. Jagdale, R. S. Reddy, A. Sudalai, *Tetrahedron: Asymmetry*. **2009**, *20*, 335. (b) A. R. Jagdale, R. S. Reddy, A. Sudalai, *Org. Lett.* **2009**, *11*, 803.
[15] T. Kolasa, M. J. Miller. *J. Org. Chem.* **1990**, *55*, 4246.

1.1.4. Asymmetric introduction of a NHR group at C4

Introduction of a NHR group at C4 may be achieved either by one bond formation at N-C2 or C2-C3 or C3-C4 or C4-C4a or by the simultaneous generation of three bonds.

- Formation of the N-C2 bond

A reduction-intramolecular cyclization sequence is applied to synthesize the dihydroquinolinone **31,** an enantiopure scaffold for combinatorial chemistry, which, in turn, is used in the preparation of tetrahydroquinolin-derived-natural-product-like small molecules. 1,2-aminoalcohol **30**, prepared from nitrocinnamate **29** by asymmetric aminohydroxylation in high enantiomeric excess (>90% ee), is submitted to Pd/C-Catalysed hydrogenation of the NO_2 group and subsequent deprotection of amino group to give aminoalcohol **30**, followed by cyclization utilizing NaOH to afford the tetrahydroquinoline derivative **31**. This compound, then, is subjected to the protection of the amino and alcohol functional groups as *N*-Alloc and *O*-Alloc protecting groups and subsequent removal of the OMEM group to provide the dihydroquinolone **33**.[16]



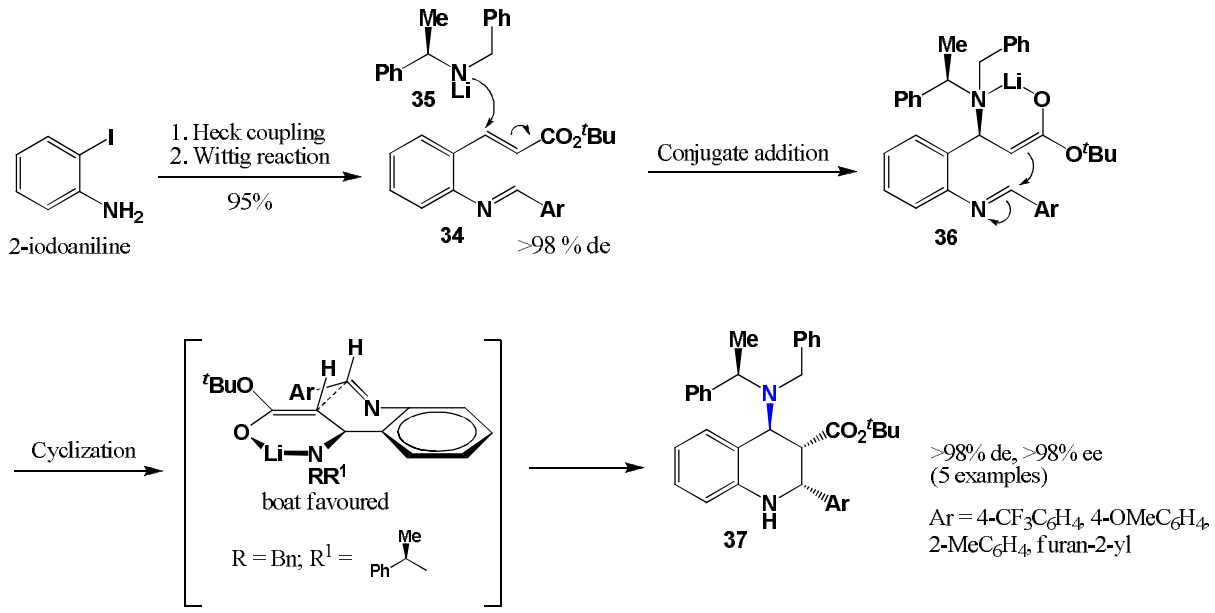
Scheme 8

- Formation of the C2-C3 bond

As a model system for the synthesis of martinelline-derived alkaloids, the addition of homochiral lithium amide to α,β-unsaturated esters has been studied.[17] 2-iodoaniline is engaged in a two-step sequence with a Heck coupling and a Wittig reaction to give α,β-unsaturated esters **34** in high yield and excellent diastereoselectivities (>98% de). These compounds, then, in turn, are the subject of the addition with homochiral lithium amides **35** that promotes the tandem conjugate

[16] S. Couve-Bonnaire, D. T. H. Chou, Z. Gan, P. Arya, *J. Comb. Chem.* **2004**, *6*, 73.
[17] S. G. Davies, N. Mujtaba, P. M. Roberts, A. D. Smith, J. E. Thomson, *Org. Lett.* **2009**, *9*, 1959.

addition-cyclization of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **36** to afford 4-amino 1,2,3,4-tetrahydroquinoline derivatives **37**.

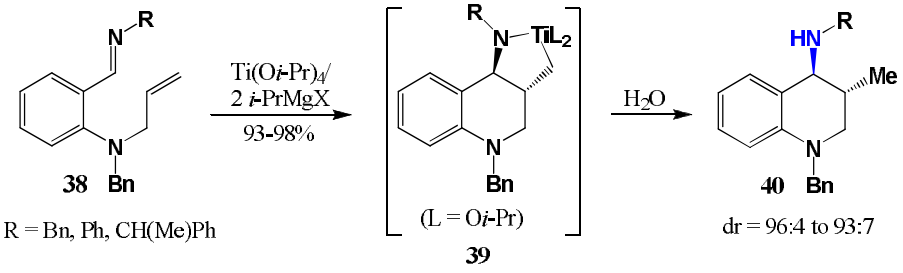


Scheme 9: Tandem Conjugate Addition – Cyclization Sequence

- <u>Formation of the C3-C4 bond</u>

Synthesis of 3-methyl-4-amino-tetrahydroquinoline derivatives **40** can be achieved through an intramolecular organometallic reaction with concomitant formation of the C3-C4 bond. Displacement of propene of (η^2-propene)Ti(O*i*Pr)$_2$, prepared from Ti(O*i*Pr)$_4$ and *i*PrMgCl, with the olefinic bond of *ω*-vinylimines **38**, followed by insertion of imine bond to the carbon-titanium bond, gives the azatitanacyclopentane intermediate **39**. This compound, in turn, is subjected to the addition of water to afford compounds **40** in high yields (93-98%) and good diastereoselectivities (96:4 to 93:7 de).[18]

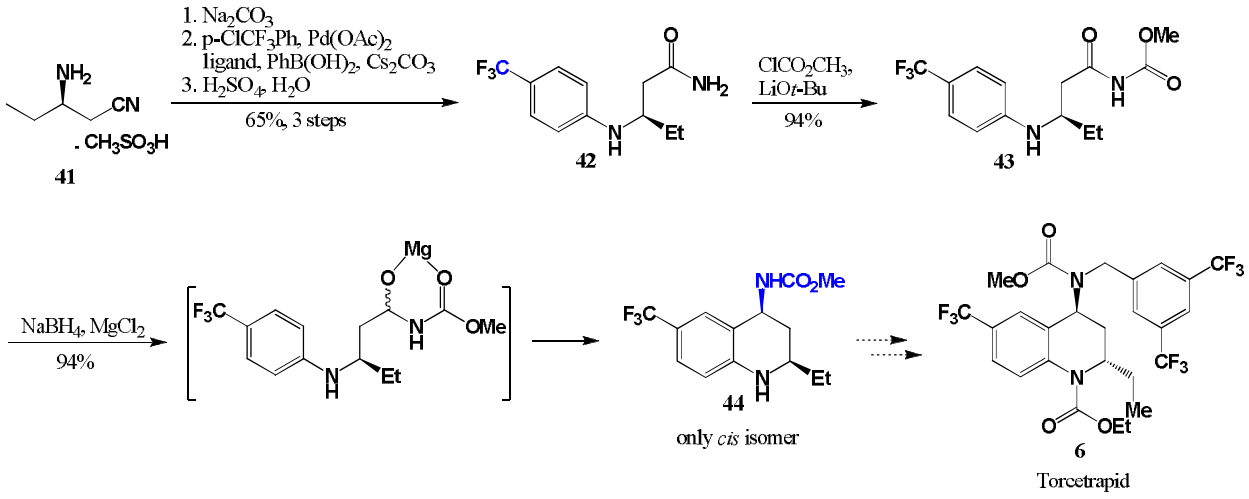
[18] W. Uchikawa, C. Matsuno, S. Okamoto, *Tetrahedron Lett.* **2004**, *45*, 9037.



Scheme 10: Cyclization of ω-Vinylimines with Ti(O-*i*-Pr)$_4$/*i*-PrMgX

- Formation of the C4-C4a bond

Synthesis of the 1,2,3,4-tetrahydroquinoline derivative **44**, an intermediate in the synthesis of Torcetrapid **6**, may be achieved through an acyl iminium cyclization as the key step with formation of the C4-C4a bond. Amide **42**, prepared from chiral nitrile **41** through a three-step sequence, is acylated with methylchloroformate to afford imide **43,** which is then subjected to a reduction/cyclization sequence with $NaBH_4/MgCl_2$ to give the torcetrapid intermediate **44** with excellent stereoselectivity (*cis* isomer only).[19]

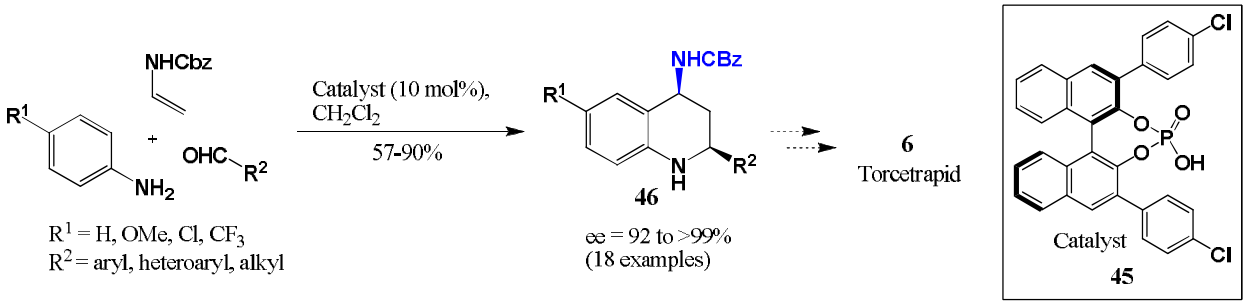


Scheme 11

- Simultaneous formation of N-C2, C2-C3, and C4-C4a bonds

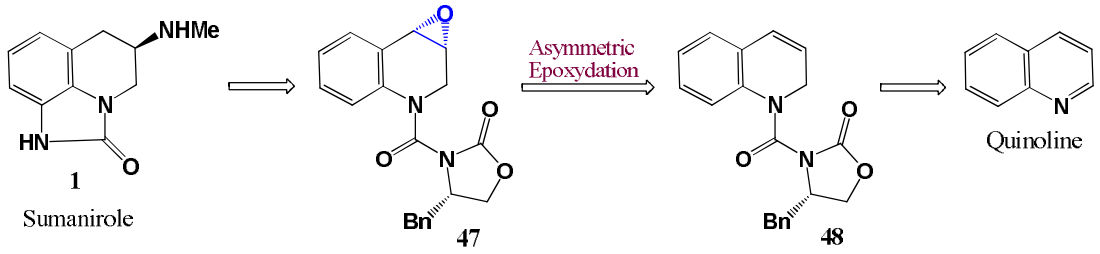
[19] D. B. Damon, R. W. Dugger, S. E. Hubbs, J. M. Scott, R. W. Scott, *Org. Process Res. Dev.* **2006**, *10*, 472.

The Povarov reaction with one-pot formation of three bonds e.i. N-C2, C2-C3, and C4-C4a, is also an efficient way to introduce a NHR group at C4 of a 1,2,3,4-THQ. This reaction is a three-component reaction involving an arylamine, an aldehyde and an enecarbamate to give, using a BINOL-derived phosphoric acid catalyst **45**, a *cis*-2,4-disubstituted tetrahydroquinoline **46** in high yields and excellent enantioselectivities (92 to >99% ee). The procedure was successfully applied to an enantioselective synthesis of Torcetrapid **6**.[7b]



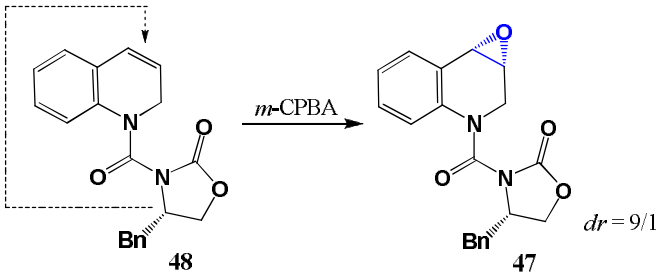
Scheme 12

In the process of total synthesis of Sumanirole **1**, after a lot of assays, we became interested in a novel retrosynthetic approach, in which epoxidation of the chiral 1,2-dihydroquinoline could be achieved with a reasonable diastereoselectivity, as displayed in Scheme 13.



Scheme 13

Actually, attachment of a chiral 4-benzyloxazolidin-2-one-3-carbonyl moiety at *N*-1 of 1,2-dihydroquinoline may control the selectivity of the C3-C4 double bond epoxidation. The observed selectivity is remarkable (*dr* = 9/1) as the chiral inducer is located far away from the reacting double bond.



Scheme 14

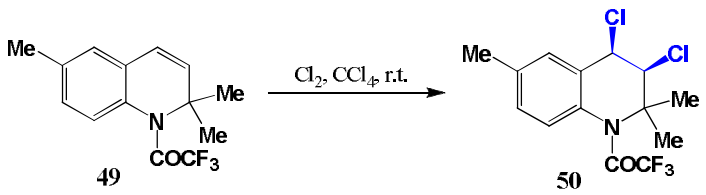
1.2. Electrophilic Addition of Br-X entities on chiral 1,2-dihydroquinoline 48

In order to find a coherent explanation of the efficiency of the chiral auxiliary in orienting the sense of epoxidation, we became curious to know whether other functionalisations of the C3-C4 double bond could be selectively accomplished. We thus studied the addition of some other electrophilic reagents on chiral 1,2-dihydroquinoline such as bromine, NBS with H_2O, MeOH or $TMSN_3$.

1.2.1. Dibromination

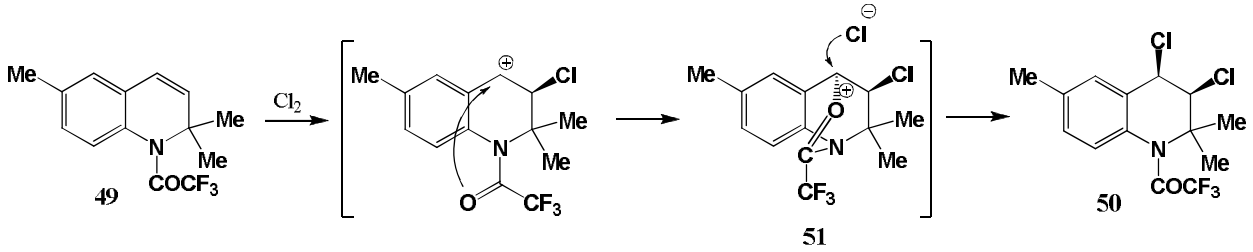
To the best of our knowledge, there are only four publications about dibromination of 1,2-dihydroquinolines.[20] At the exception of the work, reported by Willamson and Ward,[20d] the stereochemistries of the dibromation adducts were not determined as the latter were subsequently aromatised. The Australian researchers reported the dichlorination (one example of dibromation) of a series of *N*-trifluoroacetyl-2,2-dimethyl-1,2-dihydrodihydroquinolines **49** variously substituted at C6. The reactions proceeded smoothly to give stereoselectively the relatively unstable 3,4-dichloro (3,4-dibromo) adducts **50** in high yields (one example given in Scheme 15 below).

[20] (a) Y. Hamada, M. Sigiura. *Yakugaku Zasshi*. **1978**, *98*, 1. (b) J. Urbanski, L. Wrobel. *Polish Journal of Chemistry*. **1986**, *59*, 1099. (c) A. V. Aksenov, N. V. Demidova. *Chemistry of Heterocyclic Compounds.* **2002**, *38*, 913. (d) N. M. Williamson, A. D. Ward. *Tetrahedron,* **2004**, *61*, 155.



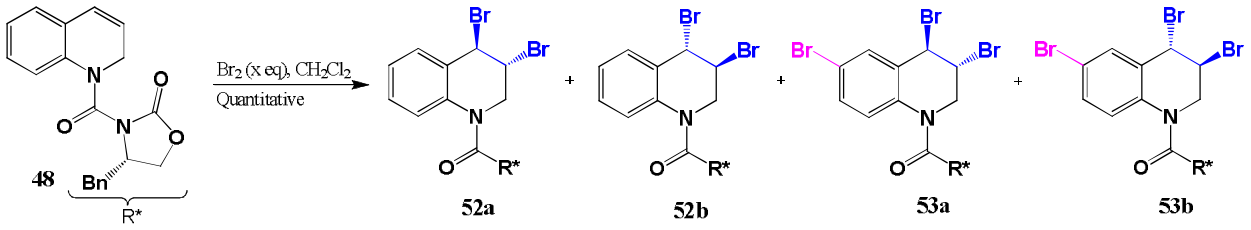
Scheme 15

Two doublets at 4.5 and 5.2 ppm were observed in the NMR spectra, corresponding to the protons at the foot of the chlorine atoms. The coupling constants for these protons were in the range of 4-6 Hz and these values were interpreted by the authors as the consequence of a relative *cis* disposition of the chlorine substituants. It is worthy of note that chlorination in acidic solution of the unprotected 1,2-DHQ led to an adduct displaying a coupling constant $J_{3,4}$ of 9.2 Hz representative of a *trans* stereochemistry. The *cis* selectivity of the chlorination of *N*-trifluoro-acetyl-1,2-DHQs **49** was interpreted as the result of the anchimeric assistance of the *N*-protecting group to give a transient intermediate **51**, which is next attacked at its benzylic position by chloride anion to give the *cis* (double inversion process) adduct **50**.



Scheme 16

With these results in mind, we first considered the dibromation of the chiral *N*-acyl-1,2-DHQ **48**. The synthesis of this starting material will be described later. In our first experiment one equivalent of undiluted bromine was added to a solution of 1,2-dihydroquinoline **48** in CH_2Cl_2 at room temperature (entry 1 in Table 1). We observed the formation of three compounds **52a**, **53a** and **53b** in a ratio of 3:6:1, respectively (Scheme 17).



Scheme 17

Spectroscopic data clearly indicated that **52a** was a dibromo compound resulting from the saturation of the C3-C4 bond whereas **53a** and **53b** were the result of an extensive bromination at C3, C4 and C6 positions. Compounds **53a** and **53b** are diastereomers; compounds **52a** and **53a** displayed the same relative and absolute configurations at C3 and C4. Given these results, it was not surprising to observe that treatment of 1,2-dihydroquinoline **48** with a large excess of bromine afforded exclusively products of tribromation **53a** and **53b** in a ratio of c.a 9:1 (entries 2 and 3). An assay using a solid form of bromide did not change significantly the ratio of products **53a** and **53b** (entry 4). To slow down the reaction rate of the reaction and also to avoid an increase in the temperature of the reaction medium that could influence both the product distribution, we next conducted the bromination of 1,2-dihydroquinoline **48** using a 1 M solution of bromine in CH_2Cl_2 at 0-20 °C or at -78 °C. Comparison between entries 1 and 5 clearly shows that slow addition of a diluted solution of Br_2 has a marked effect on product distribution. In these conditions, the formation of the tribrominated compounds **53a,b** are almost suppressed, thereby showing that bromine addition to the C3-C4 double bond bromination precedes bromination at C6. Without surprise, addition of a diluted solution of bromine in excess led again to the formation of the tribrominated compounds **53a,b** (entries 6 and 7), these products being only detected when 3 equivalents of Br_2 was used (ratio **53a**:**53b** = 9:1). The effect of both dilution and temperature is impressively demonstrated when comparing entries 8 and 9. Although decreasing temperature has a little effect on product composition (compared entries 1 and 8), use of a dilute solution of Br_2 at -78 °C resulted in the sole formation of adducts **52a** and **52b**. Moreover, the selectivity was significantly increased (ratio **52a**:**52b** = c.a. 95:5).

Table 1: Bromination of dihydro-1,2-quinoline **48**

Entry	***Reactive***	***Eq***	***Conditions***	***52a (%)***	***52b (%)***	***53a (%)***	***53b (%)***
1	Br_2	1.0	0 °C → r.t., 2 h	30.1	-	59.2	10.7
2	Br_2	3.0	0 °C → r.t., 2 h	-	-	89.3	10.7
3	Br_2	10.0	0 °C → r.t., 2 h	-	-	89.7	10.3
4	$(CH_3)_4NBr_3$	3.0	0 °C → r.t., 2 h	-	-	85	15
5*	Br_2	1.0	0 °C → r.t., 2 h	84.0	13,0	0	3.0
6*	Br_2	2.0	0 °C → r.t., 2 h	40.4	0.8	47.4	12.2
7*	Br_2	3.0	0 °C → r.t., 2 h	-	-	90.1	9.9
8	Br_2	1.0	-78 °C, 3 h	28.6	-	67.7	4.76
9*	Br_2	1.0	-78 °C, 3 h	94.6	5.4	-	-

Ratio determined from ^{1}H NMR spectrum of the crude reaction mixture.

(*): Br_2 was diluted in CH_2Cl_2 (1M solution) and dropwise added to a 0.2 M solution of **48** in CH_2Cl_2.

At least two conclusions can be drawn from these experiments:

- Substitution of nitrogen N1 with a *π-electron acceptor group (acyloxazolidinone) is not sufficient to suppress bromination at C6. However, this problem could be overcome when a dilute solution of bromine (1M in CH_2Cl_2, 1 equivalent) was employed.*
- *Relatively high diastereoselectivies in favor of compound **52a** over **52b** (or **53a** over **53b**) were observed. Decreasing the reaction temperature, in conjunction with the use of a dilute solution of Br_2, resulted in an increase in selectivity (up to 95:5).*

If, as already reported, spectral data indicated that **52a** and **52b** on one hand, and **53a** and **53b** on the other hand, are diastereomeric pairs and that **52a** and **53a** (also **52b** and **53b**) displayed the same configurations at C3 and C4, it was not self-evident to determine these configurations. NMR spectra indicated than the ^3J H3-H4 is close to 0 Hz in both **52a** and **53a**. At this juncture, we can already mention that this value is in stark contrast to that observed by Williamson and Ward (vide supra, Scheme 15) who noted a *J* H3-H4 value of 4-6 Hz for their bromine addition

products. Referring to the Karplus equation would suggest that the H3-C3-C4-H4 dihedral angle would be close to 90°, inspection of molecular models showed that such a value can be reached only if the two bromine atoms are *trans* disposed. This conclusion could be ascertained after X-Ray structures were obtained for tribrominated products **53a** and **53b** (Figure 3).

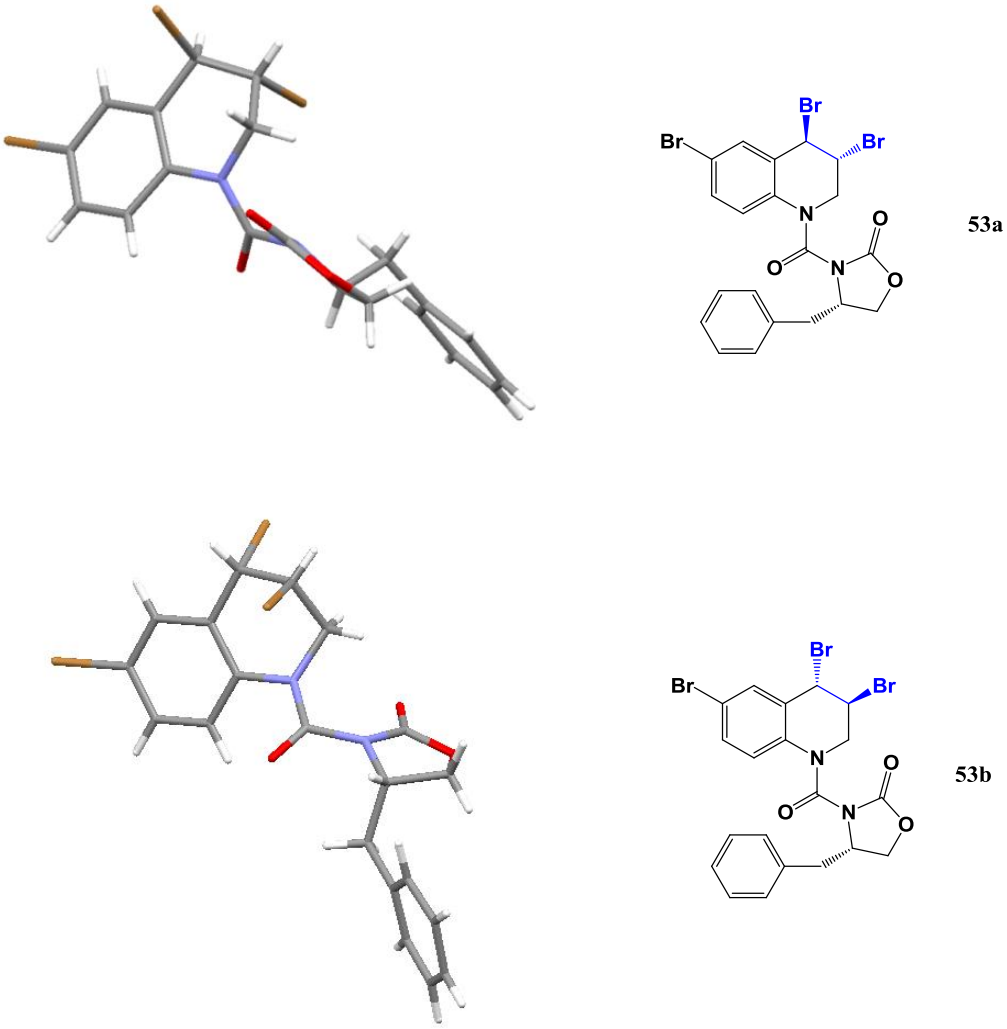
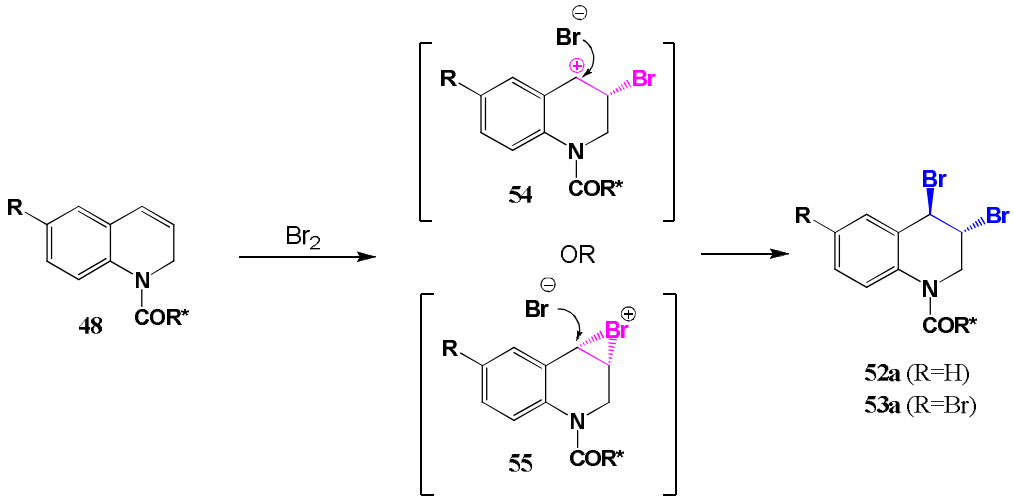


Figure 3

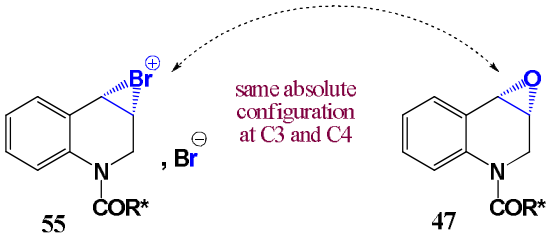
In these structures the bromine atoms at C3 and C4 have an almost *trans*-diaxial orientation, the related Br3-C3-C4-Br4 dihedral angle having a value of 163.9° in both cases. In the solid state, the H3-C3-C4-H4 dihedral angle has a value of 72.5° for compound **53a** whereas this value is of -63.2° for compound **53b**. These values are in relatively good agreement with the observed ^{3}J H3-H4 value (c.a. 0 Hz) in the NMR spectra of both **52a** and **53a**.

In conclusion, the configurations at carbons C3 and C4 for compounds **52a**, **52b**, **53a** and **53b** are those pictured above in Scheme 17. The steric course of the reaction is quite different from that reported by Williamson and Ward who obtained *cis*-products via the transient formation of a charged intermediate **51** (vide supra, Scheme 16). In our case, the acyloxazolidinone moiety branched at C1 *does not participate* in the bromination reaction. The absolute configurations at C3 and C4 for **52a** (and **53a**) could be the result of the initial formation of a bromonium intermediate **55** which was next regio- and stereoselectively open at C4 to afford **52a** (**53a**). Another possibility for formation of **52a** (**53a**) could be the selective formation of a carbocation **54** (possibly via opening of the bromonium ion) which was next selectively neutralized by attack of a bromide anion (Scheme 18).



Scheme 18

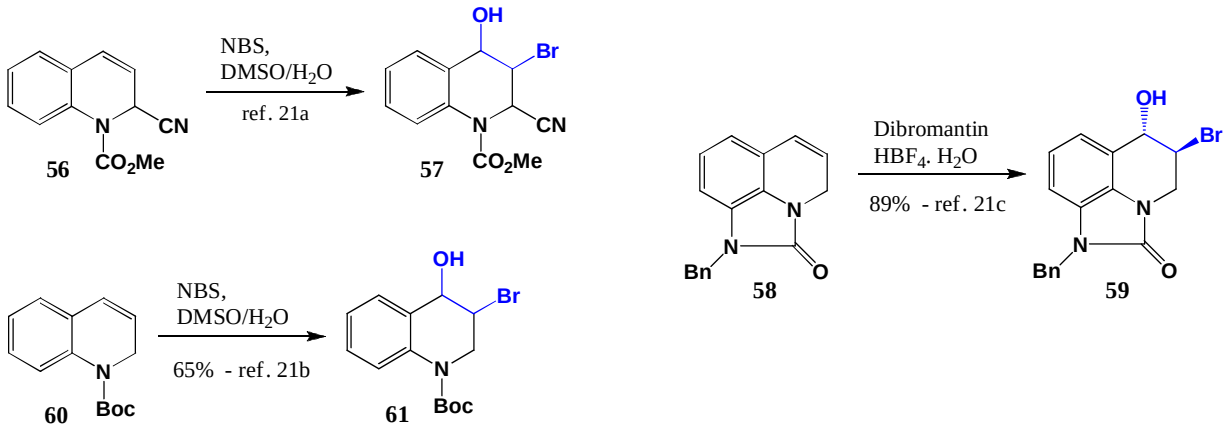
We will discussed these points into more depth later but we can already note that the stereochemistry of bromonium **55** is similar to that of the major epoxide formed (**47**) when 1,2-dihydroquinoline **48** is submitted to the action of *m*-CPBA.



Scheme 19

1.2.2. Bromohydroxylation

After having studied the dibromation of chiral 1,2-dihydroquinoline **48**, we next considered its 1,2-bromohydroxylation. So far, only very few examples of 1,2-bromohydroxylation of 1,2-dihydroquinolines have been reported. In one example in the field of sumanirole synthesis,[21c] the stereochemical relationship of 1,2-adduct was determined and shown to be *trans* (Scheme 20). However, it must be mentioned that none of the reported examples allowed for the asymmetric formation of 1,2-adducts.[21]

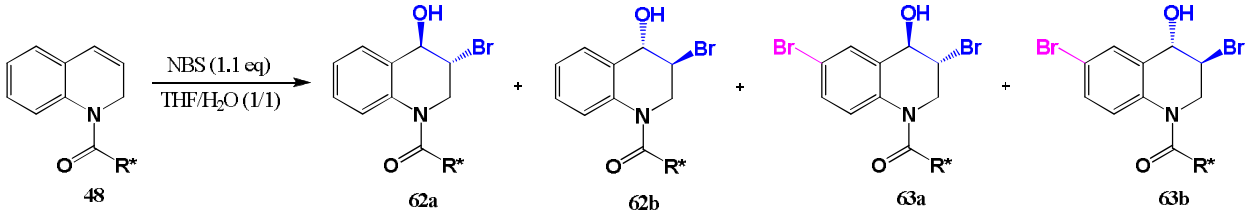


Scheme 20

1,2-Bromohydroxylation of 1,2-dihydroquinoline **48** was first considered under the action of 1.1 equivalent of NBS. The bromination agent was added to a 1:1 THF:H_2O solution of **48** precooled at 0 °C, the reaction medium being next immediately warmed up to room temperature to give the

[21] (a) Y. S. Tsizin, E. P. Prokof'ev, N. L. Sergovskaya. *Khimiya Geterotsiklicheskikh Soedinenii*. **1985**, *4*, 544. (b) R. F. Heier, L. A. Dolak, J. N. Duncan, D. K. Hyslop, M. F. Lipton, I. J. Martin, M. A. Mauragis, M. F. Piercey, N. F. Nichols, P. J. K. D. Schreur, M. W. Smith, M. W. Moon. *J. Med. Chem.***1997**, *40*, 639. (c) P. G. M. Wuts, R. L. Gu, J. M. Northuis, T. A. Kwan, D. M. Beck, M. White. *J. Pure App. Chem.* **2002**, *74*, 1359.

mixture of compounds as reported in Table 2 (entry 1) and Scheme 20. The formation of four compounds distributed in two pairs of diastereomers was formed, the minor pair arising from an overbromination process at carbon C6. Distribution of diastereomers in both pair could not been determined due to the complexity of the crude NMR spectrum.



Scheme 21

Table 2

Entry	***Equi. of NBS***	***Conditions***	***62a (%)***	***62b (%)***	***63a (%)***	***63b (%)***	***Yield[b] (%)***
1[a]	1.1	0 °C, 5 min → r.t., 2 h	73		27		70.6
2	1.1	0 °C, 1 h → r.t., 1 h	80.6	19.4			77.9

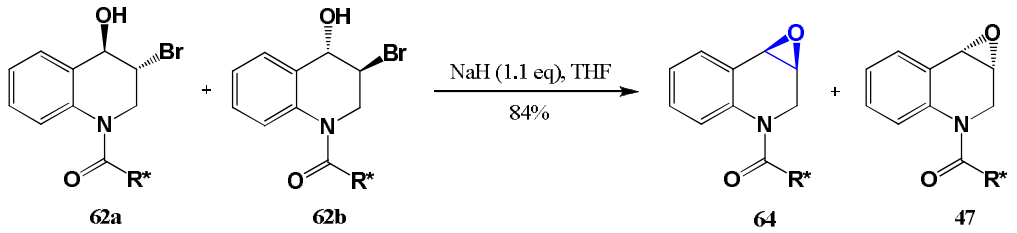
Ratio determined from ^{1}H NMR spectrum of the crude reaction mixture.

[(a)] Ratio determined after column chromatography; [(b)] Combined isolated yield of diastereomers.

In order to avoid the unwanted overbromination, the reaction medium was kept at 0 °C for 1h after the NBS agent was added to dihydroquinoline **48**. As can be seen in Table 2 (entry 2), these conditions totally suppressed the formation of the diastereomeric pair **63a**, **63b** thereby leading to a mixture of diastereomeric **62a**, **62b** formed in a ratio of c.a. 4:1 as it could be now determined from the ^{1}H NMR spectrum of the crude reaction mixture. The major diastereomer displayed a ^{3}J H3-H4 coupling constant close to 0 Hz, which suggests (vide supra, dibromation) a *trans* arrangement for the Br and OH substituents.

Although this diastereomer could be isolated as a solid, crystals suitable for X-ray analysis could not be formed. We were thus led to devise a chemical bias to determine with certainty the configurations at C3 and C4 of both bromohydroxylation adducts. To this purpose, the idea was

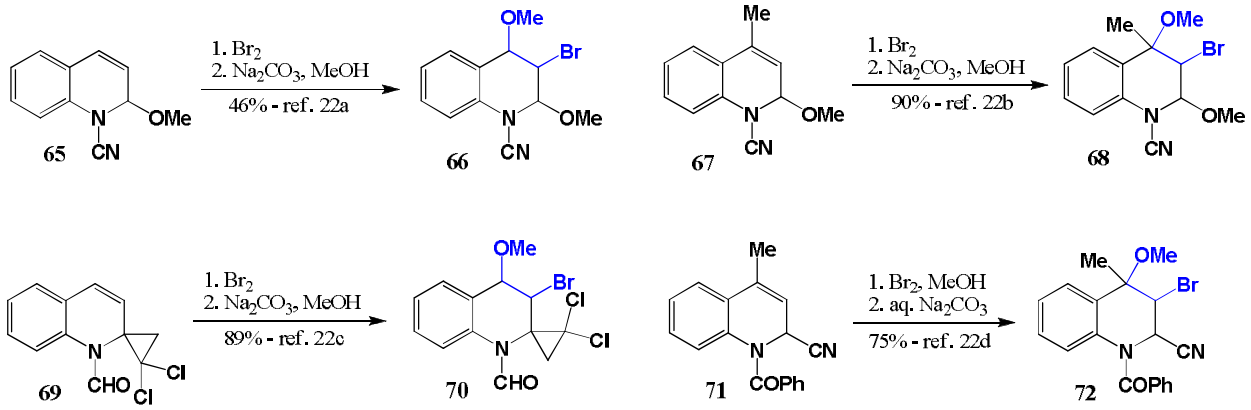
to transform the mixture of diasteromers towards their corresponding epoxides in order to finally establish a comparison with the known epoxide **47**. To this end, the 4:1 mixture of epoxides **62a** and **62b** was treated with a slight excess of NaH in THF. As shown in Scheme 22 the formation of a 4:1 mixture of diastereomeric epoxides **64** and **47** resulted in which, epoxide **64** was the major component. Of course, pure bromhydrin **62a** was epoxided to give pure epoxide **64**. It thus resulted that the major bromhydrin formed by addition of BrOH onto 1,2-dihydroquinoline **48** was **62a.**



Scheme 22

1.2.3. Bromomethoxylation

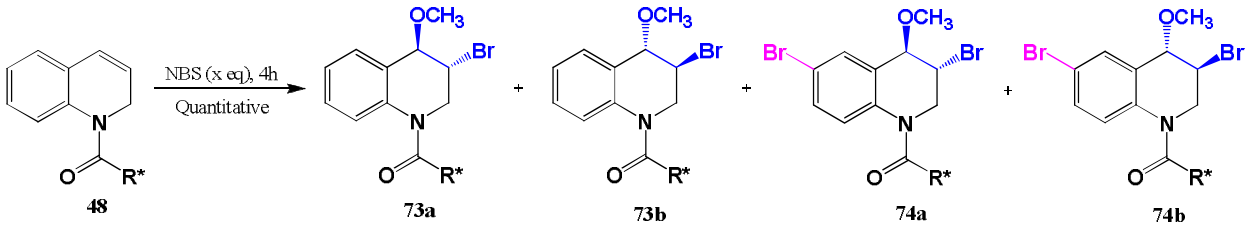
As for bromohydroxylation, only few publications about bromomethylation from 1,2-dihydroquinoline appeared in the literature and all of them are racemic approaches.[20a,21c,22] The stereochemical relationship of 1,2-adducts was never mentioned. Examples are given in Scheme 23.



Scheme 23

[22] (a) Y. Hamada, M. Sugiura. *Chem. Pharm. Bull*. **1978**, *26*, 3682. (b) Y. Hamada, M. Sugiura. *Yakugaku Zasshi*. **1979**, *99*, 445. (c) Y. Hamada, M. Sugiura. *Tetrahedron Lett*. **1981**, *22*, 2893. (d) M. Sugiura, Y. Hamada. *Heterocycles* **1992**, *34*, 561.

Bromomethoxylation of 1,2-dihydroquinoline **48** was carried out in methanol by treatment with a slight excess of NBS. In order to avoid possible overbromation, the reaction medium was maintained at 0 °C before temperature was raised to ambiant. As depicted in Table 3 (entry 1), these conditions led to the formation of a mixture of diastereomeric bromomethoxylated adducts **73a** and **73b** (Scheme 24) formed in a ratio of 85:15.



Scheme 24

Table 3

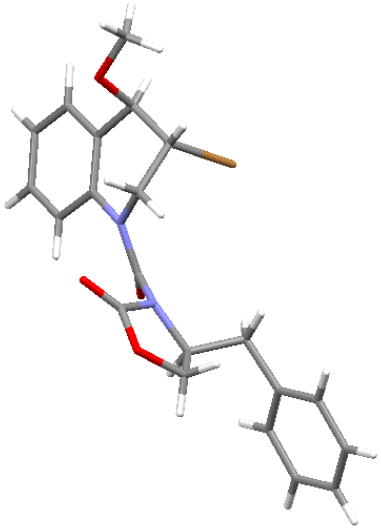
Entry	***Equiv. of NBS***	***Conditions***	***73a (%)***	***73b (%)***	***74a (%)***	***74b (%)***
1	1.1	0 °C, 1 h → r.t., 4 h	85	15	-	-
2	1.1	r.t., 4 h	86	14	-	-
3	3.0	r.t., 4 h	-	-	85	15

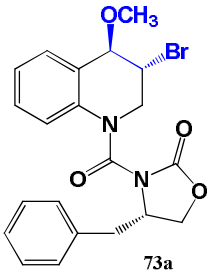
Ratio determined from ^{1}H NMR spectrum of the crude reaction mixture.

The major diastereomers **73a** and **74a** *were obtained in pure form after recrystallization.*

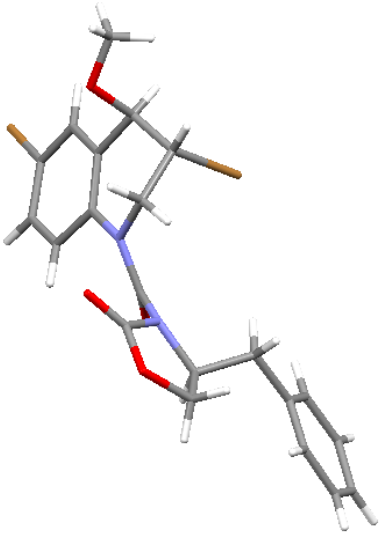
A similar result was obtained when NBS was added at r.t. instead of 0 °C (entry 2 of Table 3). As opposed to hydroxybromination, products of overbromination were not formed in these conditions. This is a reflection of the lower reactivity of NBS in methanol (vs water) towards 1,2-dihydroquinoline **48**. This was experimentally observed by comparing the reaction times of both reactions for complete conversion (1 h at r.t. for bromohydroxylation vs 4 h for bromomethoxylation). However, admixture of **48** with an excess of NBS at r.t. resulted in the sole formation of a mixture of overbrominated bromomethoxylated adducts in a ratio of 85:15 (entry 3). Observation of NMR spectra of the major adducts showed that these latter, as it was

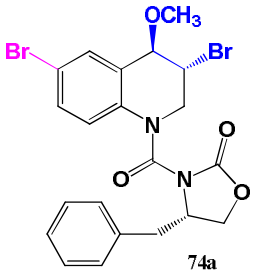
the case for the *trans*-arranged products of bromination and bromohydroxylation, displayed a small ^{3}J H3-H4 coupling constant (2.4 Hz). This observation once again suggests a similar *trans* stereochemical disposition for the Br and OMe substituents (**73a** and **74a** in Scheme 24). This was fully confirmed after a X-ray analysis of both compounds could be effected (Figure 4).





73a





74a

Figure 4

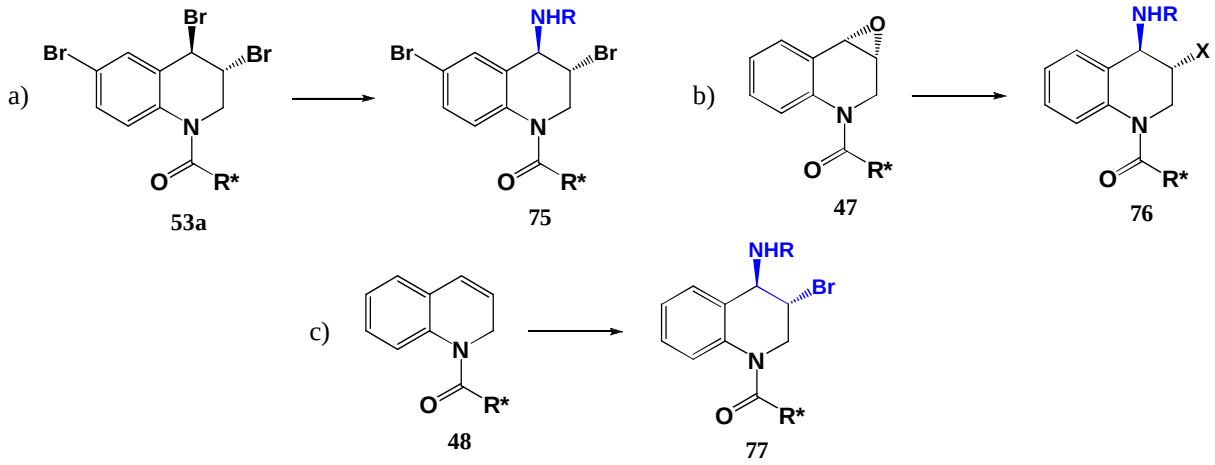
1.2.4. Bromoazidation

Several asymmetric methods to prepare 1,2,3,4-dihydroquinolines embodying a NHR substituent at C4 have been already reported and an overview of them has been given in the introduction to this chapter. In continuation of our work we thought to reach this class of compounds starting from the 1,2-dihydroquinoline **48**. To this purpose the following approaches could be envisaged (Scheme 25)

a) Amino substitution of the 3,4,6-tribromo adduct **53a** at C4

b) Opening of epoxide **47** with an amino group

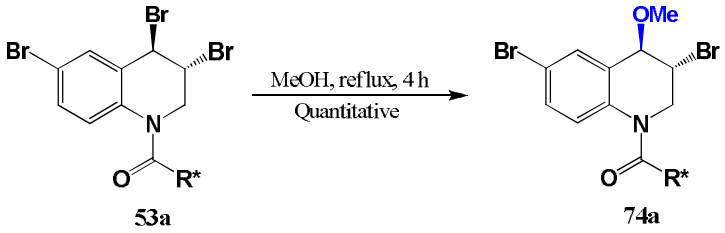
c) Bromoamidation and bromoazidation of 1,2-dihydroquinoline **48**



Scheme 25

*a) Amino substitution of the 3,4,6-tribromo adduct **53a** at C4*

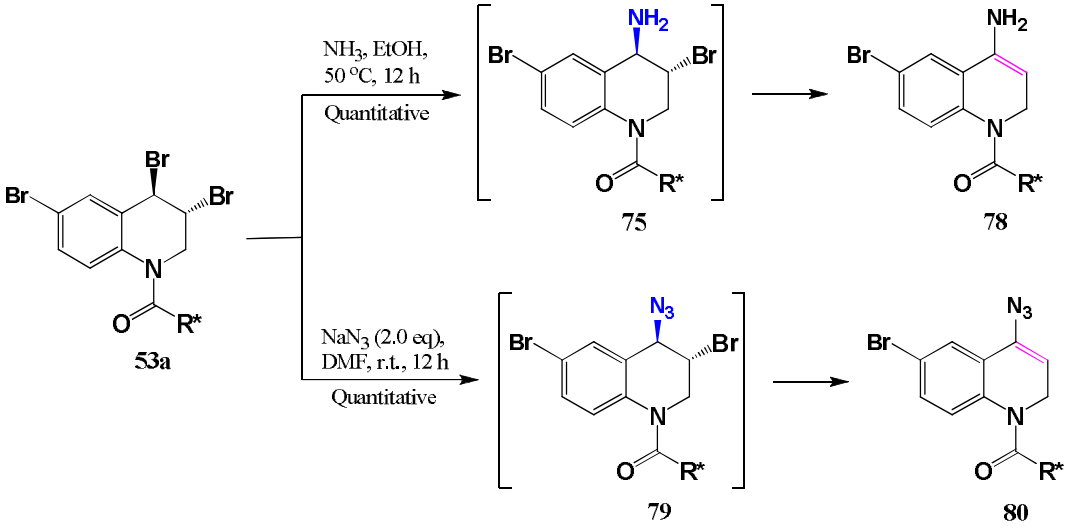
We have shown earlier that bromination of 1,2-dihydroquinoline **48** led stereoselectively to the 3,4,6-tribromo adduct **53a** (Scheme 16). It could be anticipated that the benzylic bromo substituent would be a more leaving group that the vicinal bromo substituent at C3. Indeed, when we treated the 3,4,6-tribromo adduct **53a** at reflux of MeOH, the *trans*-bromomethoxy derivative **74a** was isolated in quantitative yield (Scheme 26).



53a 74a

Scheme 26

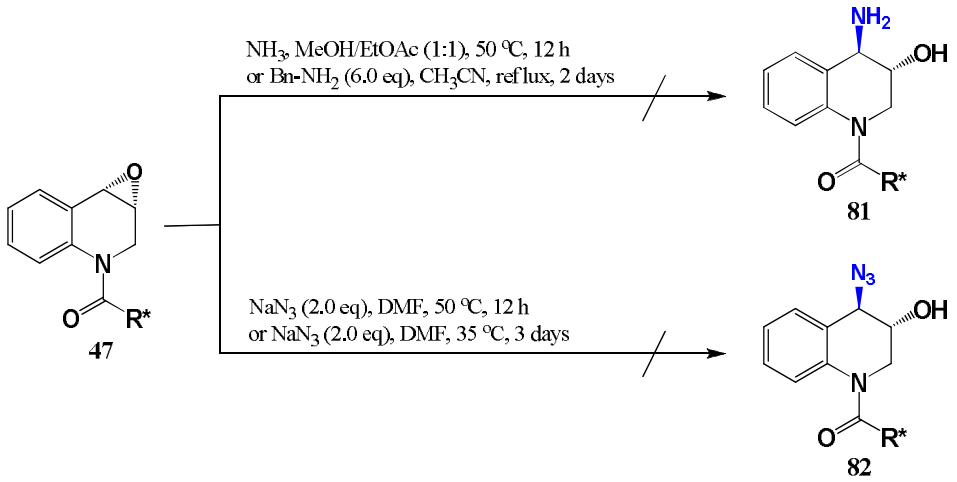
Based on this result, we thus thought to prepare the *trans*-bromoamino adduct **75** from 1,2-dihydroquinoline **48**. Treatment of **53a** with a solution of ammonia in EtOH at room temperature was unfruitful. Heating the reaction medium led to the isolation of the 4-amino-1,2-dihydroquinoline **78**, which resulted of a facile dehydrobromation of the primary adduct **75** (Scheme 27). Using sodium azide instead of ammonia also led to a similar result. The facile dehydrobromination from the primary adduct under basic condition (NH_3, N_3^-) led us to abandon this route.



Scheme 27

*b) Opening of epoxide **47** with an amino group or a precursor*

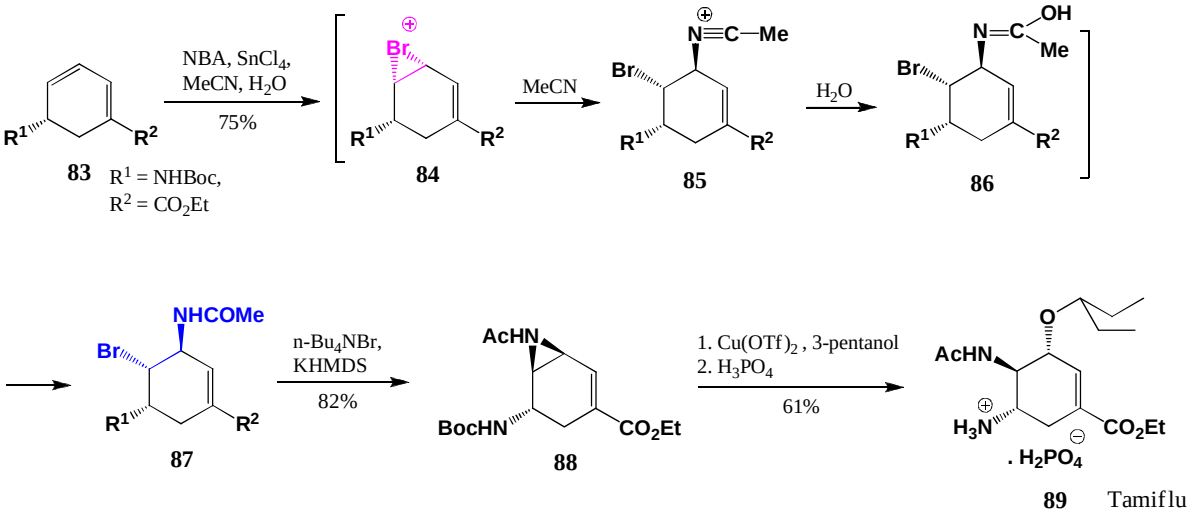
Attempts at opening epoxide **47** with ammonia or benzylamine led only to degradation products. Unsuccessful results were also obtained when epoxide **47** was treated with NaN_3 in DMF. In that case, it is to note that NaN_3 induced the deconnection of the chiral auxiliary from the dihydroquinoline moiety leading to a mixture of quinoline and oxazolidinone derivative.



Scheme 28

*c) Bromoamidation and bromoazidation of 1,2-dihydroquinoline **48***

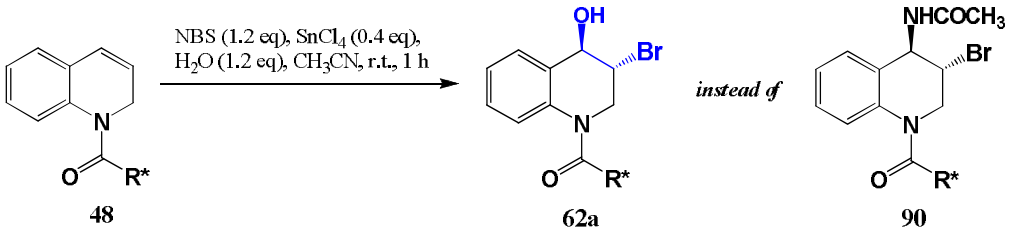
Recently, Corey et al. reported a new selective bromoamidation of alkenes which was subsequently employed as the key step of a synthesis of the anti-influenza neuramidase inhibitor Oseltamivir (Tamiflu).[23]



Scheme 29

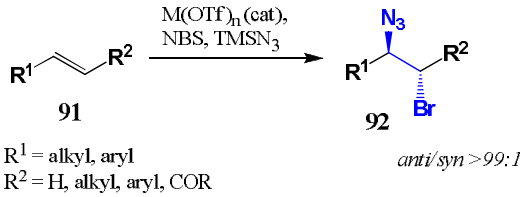
[23] (a) Y. –Y. Yeung, S. Hong, E. J. Corey. *J. Am. Chem. Soc.* **2006**, *128*, 6310. (b) Y. –Y. Yeung, S. Hong, E. J. Corey. *J. Am. Chem. Soc.* **2006**, *128*, 9644.

When we applied the Corey's conditions to the 1,2-dihydroquinoline **48** we obtained the bromhydrin **62a** instead of the desired bromoamido compound **90**. Replacement of $SnCl_4$ by $BF_3.Et_2O$ or replacement of NBA (*N*-bromoacetamide) by NBS did not change this result.



Scheme 30

This failure led us to next envisage the bromoazidation of **48**. Vicinal haloazide compounds are versatile precursors of vinyl azide,[24] amines,[25] heterocycles[26] and particularly aziridines.[27] In recent examples, this transformation was accomplished by exposure of an alkene **91** under the action of NBS and $TMSN_3$ in the presence of a metal triflate (Scheme 30). This latter was believed to activate the NBS and, thereby, facilitate the formation of a bromonium ion from the alkene.[28] Among the metal triflates screened, $Zn(OTf)_2$ and, to a less extent, $Sm(OTf)_3$ were proved to be the best catalysts.[29]

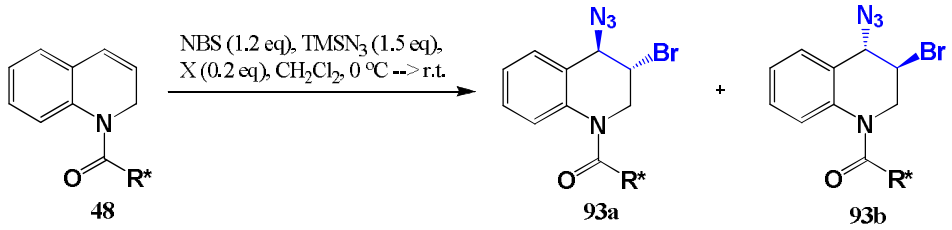


Scheme 31

Following the best reported conditions, 1,2-dihydroquinoline **48** was thus submitted to the action of NBS and $TMSN_3$ in the presence of $Zn(OTf)_2$ (Table 4, entry 1) and $Sm(OTf)_3$ (Table 4, entry

[24] A. Hassner, F. W. Fowler. *J. Org. Chem.* **1968**, *33*, 2686.
[25] H. H. Wasserman, R. P. Robinson. *J. Am. Chem. Soc*. **1985**, *107*, 519.
[26] For the synthesis of tetrazoles via Hassner-Ritter reaction: (a) S. Ranganathan, D. Ranganathan, A. K. Mehrotra. *Tetrahedron Lett.* **1973**, *14*, 2265. (b) S. N. Moorthy, D. Devaprabakara. *Tetrahedron Lett.* **1975**, *16*, 257.
[27] a) D. Van Ende, A. Krief. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 279. (b) J. N. Denis, A. Krief. *Tetrahedron.* **1979**, *35*, 2901.
[28] a) S. Hajra, M. Bhowmick, A. Karmakar. *Tetrahedron Lett.* **2005**, *46*, 3073. (b) S. Hajra, B. Maji, A. Karmakar. *Tetrahedron Lett.* **2005**, *46*, 8599. (c) S. Hajra, D. Sinha, M. Bhowmick. *J. Org. Chem.* **2006**, *71*, 9237.
[29] S. Hajra, D. Sinha, M. Bhowmick. *Tetrahedron Lett*. **2006**, *47*, 7017.

2) (Scheme 32). As can be seen, both catalyst afforded bromoazidation adducts in similar selectivity. Samarium catalyst proved to be slighty more efficient in term of yield, however. It is to mention that, in the absence of any catalysts, the reaction was less selective and needed prolonged reaction time to be complete (Table 4, entry 3). The major diastereomer **93a** could be isolated in pure form by crystallization. Its NMR spectrum (as that of the minor diastereomer **93b**) displays a small ^{3}J H3-H4 coupling constant (1.7 Hz) strongly suggesting a *trans* spatial disposition for the bromo and azido substituents branched at C3 and C4, respectively. A X-ray analysis of **93a** fully confirmed this stereochemical attribution (Figure 5).



Scheme 32

Table 4

Entry	***Conditions***	***9a (%)***	***9b (%)***	***Yield (%)***
1	$Zn(OTf)_2$, 12 h	82	18	89
2	$Sm(OTf)_3$, 12 h	83	17	99
3	48 h	72	28	80

Ratio determined from ^{1}H NMR spectrum of the crude reaction mixture.

The major diastereomer **9a** *was obtained in pure form after recrystallization.*

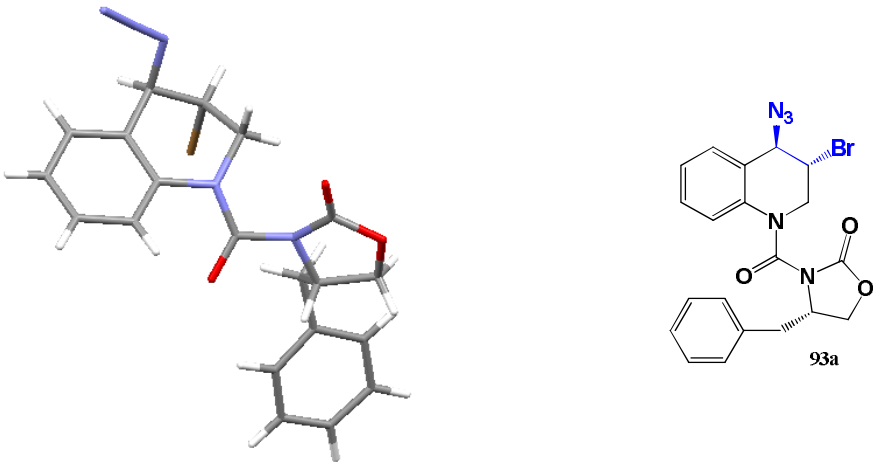
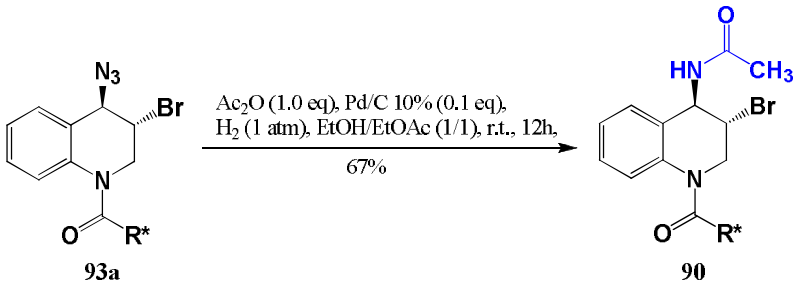


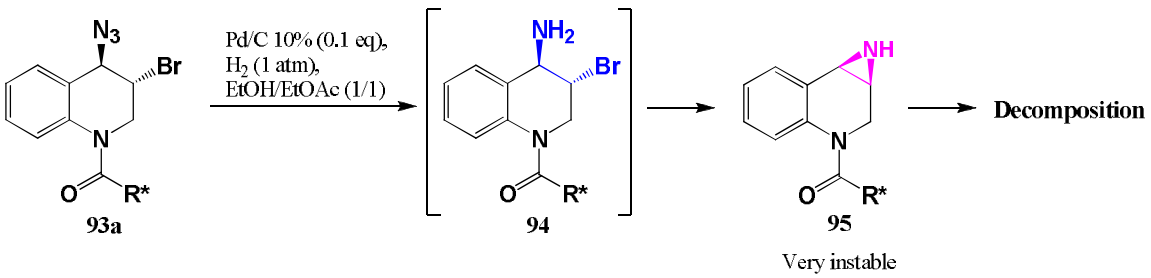
Figure 5

To achieve the introduction of an amino group at C4 it was next necessary to reduce the azido group of **93a**. This was best accomplished when **93a** was hydrogenated in the presence of AcOAc to quench the primary amino group as soon as it is generated. In these conditions, bromoamido compound **90** could be isolated in a good yield (Scheme 33). The overall transformation (bromoazidation and azide reduction) is equivalent to a bromoamidation reaction.



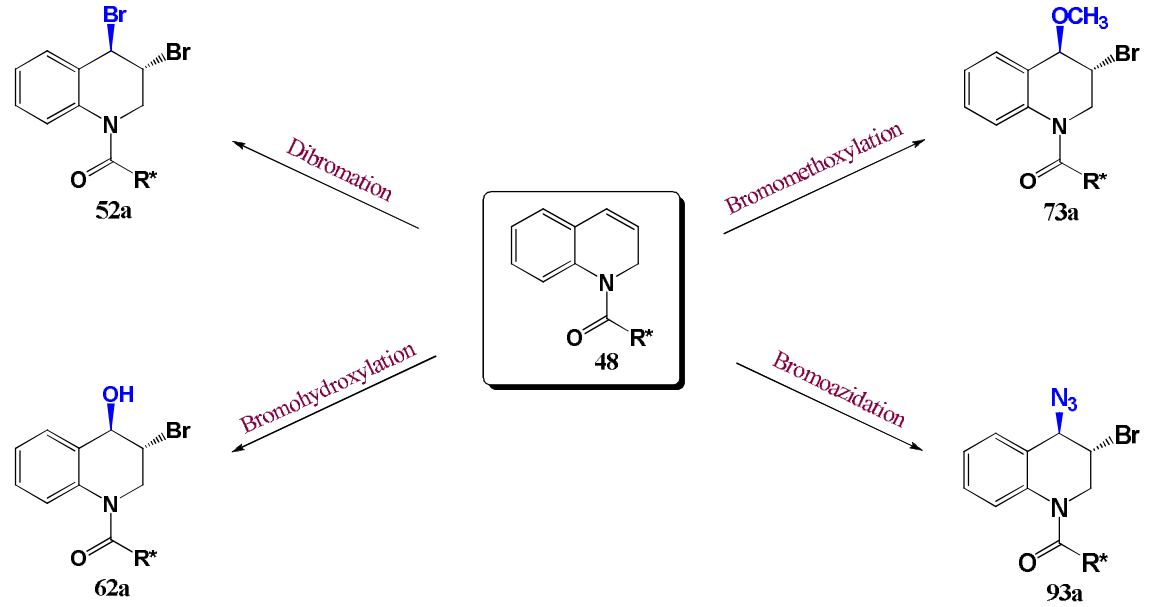
Scheme 33

Performing hydrogenation step without AcOAc led to a lower yield (30%). In these conditions the free amine probably moves to the unstable aziridine **95** characterized as traces by mass spectroscopy in the crude reaction mixture.



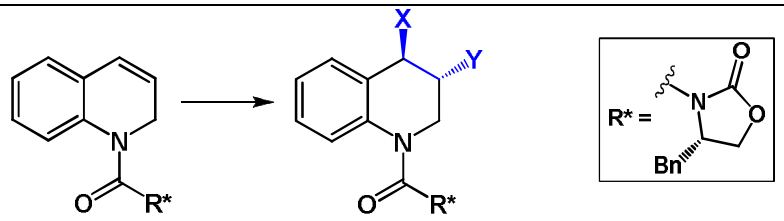
Scheme 34

In summary, we have shown that, in addition to epoxidation, 1,2-dihydroquinoline **48** may be submitted to bromination, bromohydroxylation, bromomethoxylation and bromoazidation to afford diastereoselectively (80:20 to 95:5 selectivities) the corresponding *trans*-3,4-adducts (Scheme 35). The best experimental conditions are summarized in Table 5. It is to note (we will come back to this point later) that all major diastereomers formally proceed from the opening of a same bromonium ion.



Scheme 35

Table 5



Entry	***Reagents***	***Conditions***	***X***	***Y***	***Yield (%)***	***Ratio***
1	Br_2	Br_2 (1.0 eq), CH_2Cl_2, -78 °C, 3 h,	Br	Br	99	95/5
2	Id.	$(CH_3)_4NBr_3$ (3.0 eq), CH_2Cl_2, 0 °C → r.t., 2 h	Br	Br	99	85/15
3	Aq. NBS	NBS (1.1 eq), THF/H_2O (1/1), 0 °C, 1 h → r.t., 1 h	OH	Br	78	81/19
4	NBS/MeOH	NBS (1.1 eq), MeOH, r.t., 4 h	OCH_3	Br	99	86/14
5	NBS/$TMSN_3$	NBS (1.2 eq), $TMSN_3$ (1.5 eq), $Sm(OTf)_3$ (0.2 eq), CH_2Cl_2, 0 °C → r.t., 12 h	N_3	Br	97	83/17

Before we discuss in more depth the reaction mechanism we need to gain additional information regarding the chiral auxiliary. In particular, we thought it would be useful to determine the positioning of the chiral auxiliary towards quinoline ring and which structural elements of the *N*-acyloxazolidine moiety are necessary to induce a good diastereoselectivity.

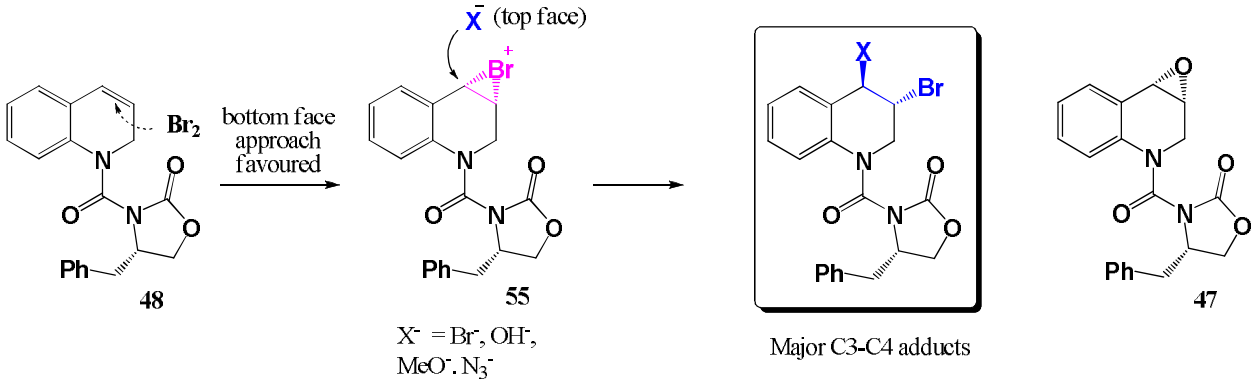
1.3. Mechanistic insights into the electrophilic addition reactions to 1,2-dihydroquinoline 48

We have shown that the 1,2-dihydroquinoline **48** reacted with a variety of Br-X reagents to give diastereoselectively C3-C4 adducts (*dr* ranging from 80:20 to 95:5). Two main characteristics of this reaction may be highlighted:

- Adducts (both major and minor) are *trans* adducts.
- The absolute configurations at the newly created stereogenic centers of major adducts can be understood through the formation of a bromonium intermediate **55** which results from approach of bromine (Br_2) from the bottom face of the C3-C4 double bond (Scheme 35). We also recall that:

  + Epoxidation of **48** with *m*-CPBA leads diastereoselectively to epoxide **47** (*dr* = 85:15) whose stereochemistry is the same as the one of displayed by the bromonium intermediate **55**.

  + Formation of *trans* adducts rules out the transient opening of the bromonium ion by the N1-CO carbonyle group. (cf Scheme 16)

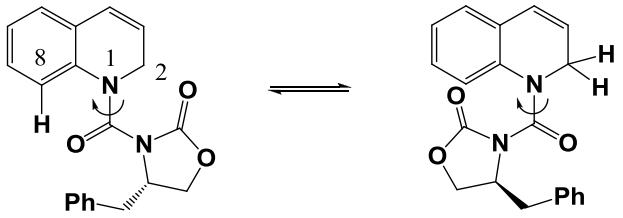


Scheme 36

In order to understand the origin of the diastereoselectivity of these reactions, the most important *question we need to answer* is: *why bromine is selectively directed towards the bottom face of the C3-C4 double bond?*

Before exploring more in-depth this question, we can already remark that the 1,2-dihydroquinoline **48** is conformationally mobile. In particular, rotations are possible around the N1-CO and the CO-N (oxazolidinone) bonds. Because no Lewis acid participates in the reaction,

the *N*-acyloxazolidinone moiety should exist in a conformation close to that shown above in Scheme 36. In other words, the inside N-CO-O oxazolidinone carbonyl group and the outside N1-CO-N carbonyl group are remotely disposed in order to minimize their electronic interactions. Consequently, only rotation around the N1-CO bond should be taken under consideration, which leads to two conformations, **48** Cf1 and **48** Cf2, as depicted in Scheme 37. Moreover, and to avoid steric interactions with protons at C2 and C8, the two ring moieties should be placed in different planes.



48 Cf1 **48** Cf2

Scheme 37

This being established, the point remains however that in both Cf1 and Cf2 conformations the chiral center is spatially remote from the reactive double bond and no clear evidence emerges to account for the diastereoselectivities observed in addition of BrX reagents to **48**. In the hope of gaining more structural information for the 1,2-dihydroquinoline **48** we decided to obtain an X-ray structure.

1.3.1. X-Ray structure of 48

The X-ray structure of 1,2-dihydroquinoline **48** is represented in Figure 6.

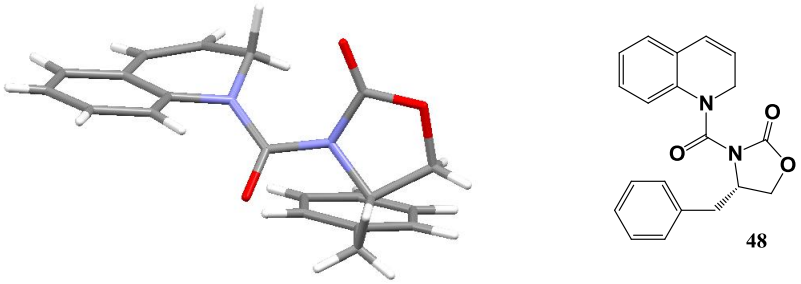
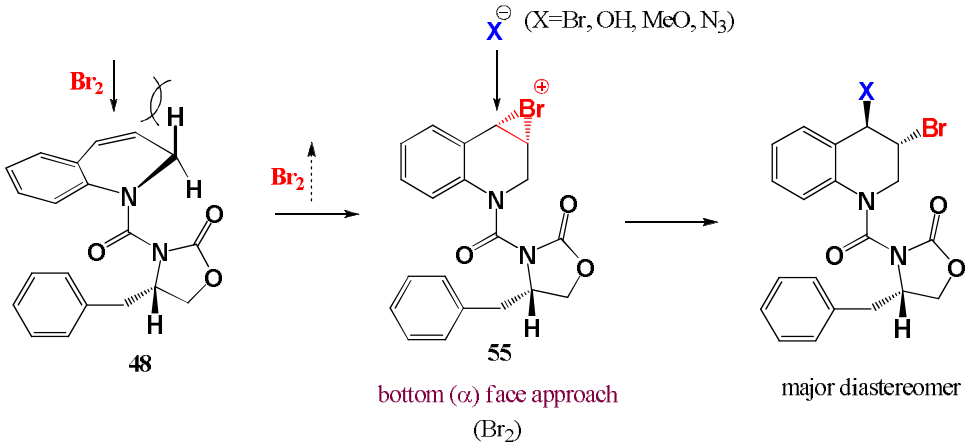


Figure 6

Several observations can be drawn from this structure:

- First of all, it can be seen that **48** crystallizes in a **Cf1** conformation. We can hypothesize that this conformation is also the most stable one in a liquid state. As expected, the two carbonyl groups are remotely disposed.
- Nitrogen at N1 is slightly pyramidalized as shown by the value of 172.99° for the C8a-N-CO-C2 dihedral angle. The free nitrogen doublet is directed towards the top face.
- The most important observation is that the conformation adopted by the 1,2-dihydro-quinoline ring places one of the C2 proton in a quasi axial position. We may thus assume that *this proton partially blocks the top face of the C3-C4 double bond and, thereby, favours approach of bromine on the bottom face* (Scheme 38). In other words, the stereochemical information borne by the chiral auxiliary is relayed to the C3-C4 bond through a conformational effect.



Scheme 38

1.3.2. Theoretical calculations

Quantum mechanical simulations

To perform our calculations, we have selected the latest version of the Gaussian program.[30] The *ab initio* simulations consisted in geometry optimization of several conformations for both the reactant and products, in transition states search and in vibrational analysis to ascertain the nature of all stationary points. We have selected the M06-2X functional to perform our calculations.[31]

[30] M. J. Frisch *et al.* Gaussian 09 Revision A. 02, **2009**, Gaussian Inc. Wallingford CT.
[31] Y. Zhao, D. G. Truhlar, *J. Phys. Chem. A.* **2006**, *110*, 13126.

This global hybrid exchange-correlation functional includes 56% of exact exchange and is known to be adequate for studying transition states.[32] A diffuse containing atomic basis set, namely 6-311++G(d,p) has been used. The bulk solvent effects (here dichloromethane) have been systematically included through the well-known PCM (Polarizable Continuum Model) model of Tomasi and coworkers.[33] Default algorithms, parameters and thresholds have been applied, except for:

- The SCF (Self-Consistent Field) convergence threshold, tightened to 10^{-10} a.u.
- The force threshold, improved to 10^{-5} a.u. during all geometry optimization.
- An ultra-fine integration grid [pruned (99,590) grid] has been systematically applied, as it is known that the M06 functional series of functional is rather sensitive to the selected DFT (Density Functional Theory) integration mesh.[34]

- Conformational analysis for the reactants

We have first performed a conformational search for the reactant that can obviously present different relative orientations of its rings. Several starting points have been used, and four different minima presenting relative free energies (G in kcal.mol^{-1}) of 0.00 (A), 0.47 (B), 0.90 (C) and 2.69 (D), respectively, have been identified (Figure 7).

[32] Y. Zhao, D. G. Truhlar, *Theor. Chem. Acc*. **2008**, *120*, 215.
[33] J. Tomasi, B. Mennucci, R. Cammi, *Chem. Rev.* **2005**, *105*, 2999.
[34] S. E. Wheeler, K. N. Houk, *J. Chem. Theory Comput.* **2010**, *6*, 395.

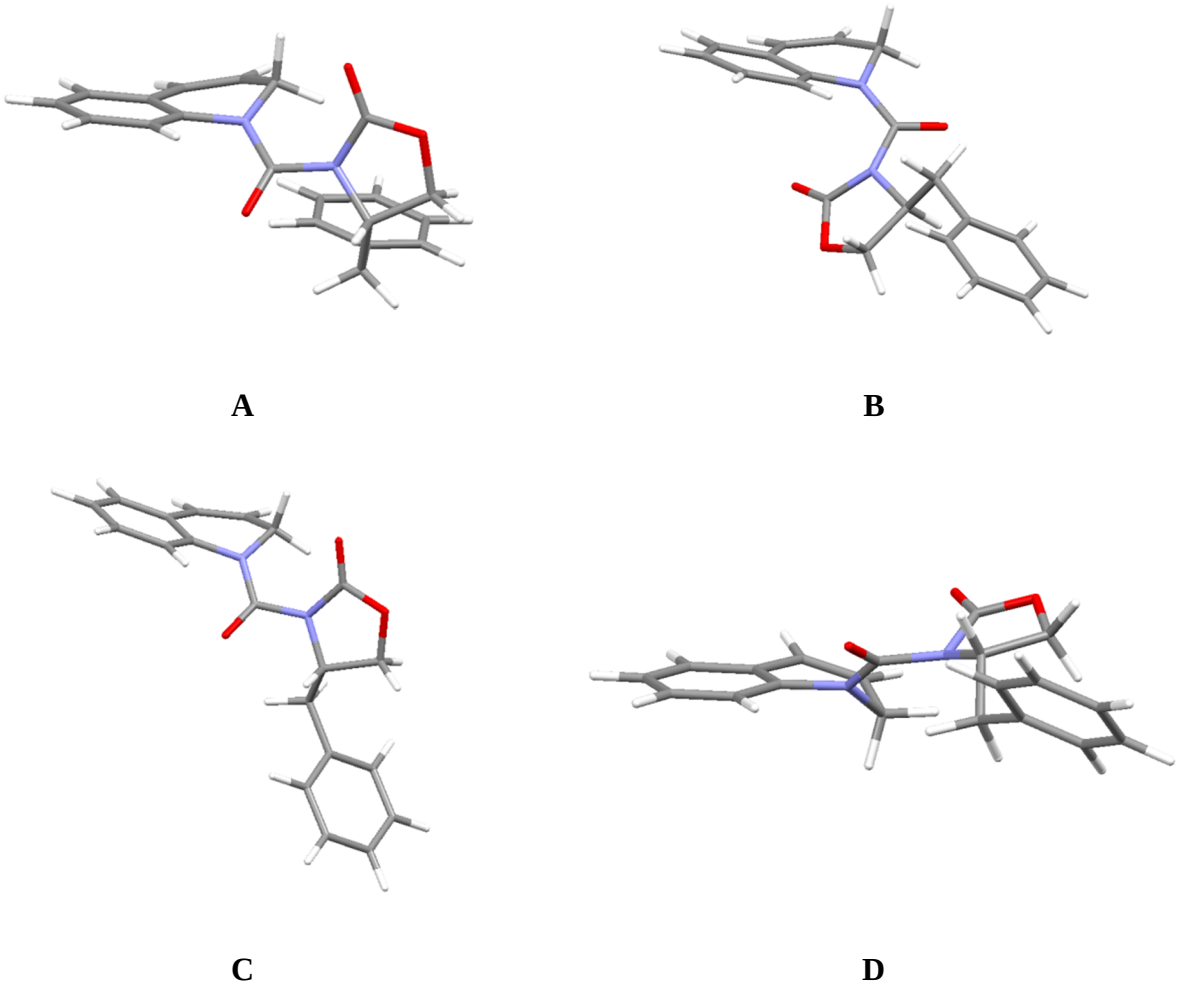


Figure 7

Therefore, the A conformer, that is *similar to the X-ray crystal structure*, should dominate significantly in the solution, confirming the above-mentioned hypothesis. Indeed, a Boltzmann averaging procedure yields 60%, 27% and 13% for the relative ratio of **A**, **B** and **C**, respectively. Figure 7 displays the four conformations **A-D**. It can be seen that **B** adopts a **Cf2**-type conformation (cf Scheme 37) whereas **A**, **C** and **D** are in a **Cf1**-type conformation. **C** differs from **A** mainly by the spatial orientation of the benzyl group at the chiral center. It is important to note that in the three most stable conformers **A**, **B** and **C** *there is a proton at C2 in a quasi axial orientation*. The N1 nitrogen is slightly pyramidalized (free doublet directed towards the upper face) in conformers **A** (C8a-N-CO-C2 dihedral angle = 169.72°) and **C** (C8a-N-CO-C2 dihedral angle = 170.38°) but almost planar in conformers **B** and **D** (C8a-N-CO-C2 dihedral angles = 179.52° and – 178.06°, respectively). Conformation **D,** which represents the least stable

conformation, is the most extended one. A striking difference with the three others is the fact that *a proton at C2 is axially directed towards the lower face.*

- Transition state identification

For the three conformers **A**, **B**, **C**, we have searched for the two transition states corresponding to a Br_2 attack through the superior and inferior faces. Firstly, for the dominant **A** conformer, we have initially identified the products corresponding to this reaction. Although one would expect the formation of a bromonium ion bridging the two carbon atoms of the double bond, we clearly found that the Br^+ ion is added on a specific carbon atom, namely C3. Tentative calculations constraining a *textbook* bromonium ion and subsequently relaxing the geometries also yielded directly the structures represented on Figure 8, implying that the three-member bromonium ring is not a stable intermediate in the present case. **A-1** is clearly the most stable of the two products, **A-2** being 2.65 kcal.mol^{-1} more energetic on the G scale.

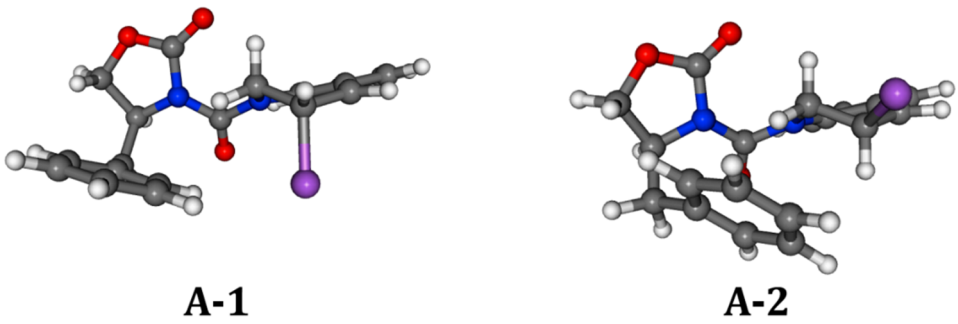


Figure 8: Products obtained for bromonium ion attacks from the inferior (A-1) and superior (**A-2**) faces.

Next, we have analyzed the transition states that well correspond to the simultaneous breaking of the Br-Br bond and the formation of a C-Br link. In the present case, **A-TS-1** is more stable than **A-TS-2** by 4.40 kcal.mol^{-1}. This implies that the reaction is clearly in favour of an attack from below, which is consistent with experiment. For the **B** and **C** conformers, the relative energies of the two transition states are 3.28 kcal.mol^{-1} (**B-TS-1** more stable than **B-TS-2**) and 6.13 kcal.mol^{-1} (**C-TS-1** more stable than **C-TS-2**), respectively. Therefore, one can conclude that the axial proton at C2 guides the reaction by repulsing a Br^+ attack from the upper side of the C3-C4

double bond as it was hypothesized from inspection of the X-ray structure of 1,2-dihydroquinoline **48**.

1.4. Determination of the structural elements of the chiral auxiliary necessary to obtain good diastereoselectivity

In order to reveal the structural elements of the chiral auxiliary necessary for obtaining a good diastereoselectivity, we have studied the electrophilic addition of NBS in MeOH onto 1,2-dihydroquinolines similar to **48** but bearing a modified oxazolidinone moiety. At the onset we aimed at evaluating:

- The steric and stereoelectronic influence of the benzyl group.
- The importance of having a cyclic five-membered ring.
- The possible remote electronic influence (at the N-CO-N level) of an electron-donating group or electron-attracting group branched at C-6 on the 1,2-tetrahydroquinoline ring.

For these different purposes (Figure 9), the benzylic substituent on the oxazolidinone was replaced by two other non-aromatic substituents (→ chiral auxiliaries **48a** and **48b**, respectively); the *carbonyl* group in the *oxazolidinone ring* was excised (→ chiral auxiliary **48c)**; the oxazolidinone ring was opened (→ chiral auxiliaries **48d** and **48e)**; Br and OMe substituents were introduced at C6 while the chiral auxiliary of **48** remained unchanged (→ 1,2-dihydroquinoline rings **48f** and **48g,** respectively).

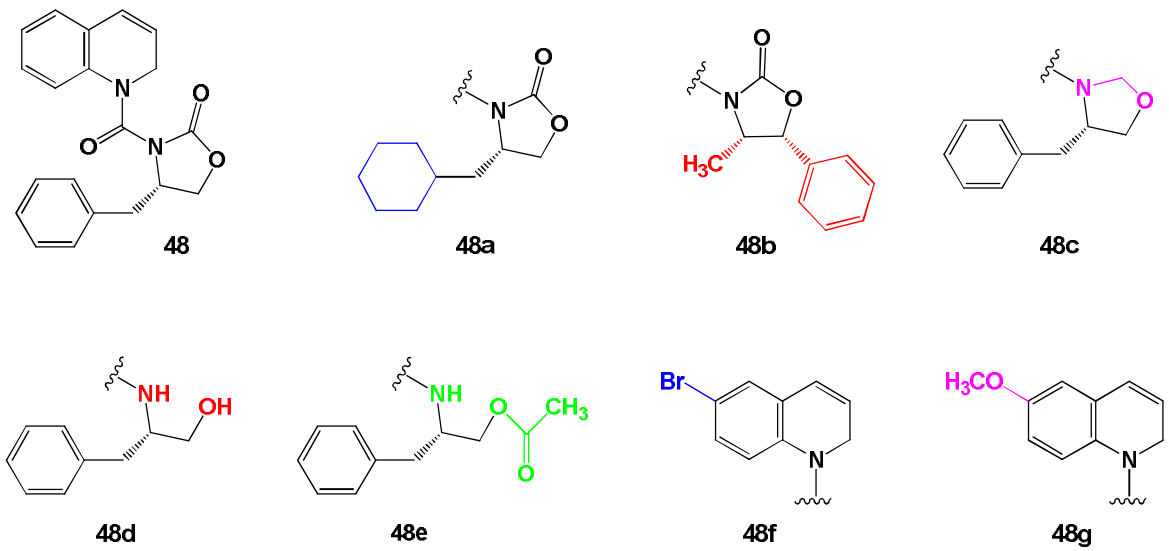
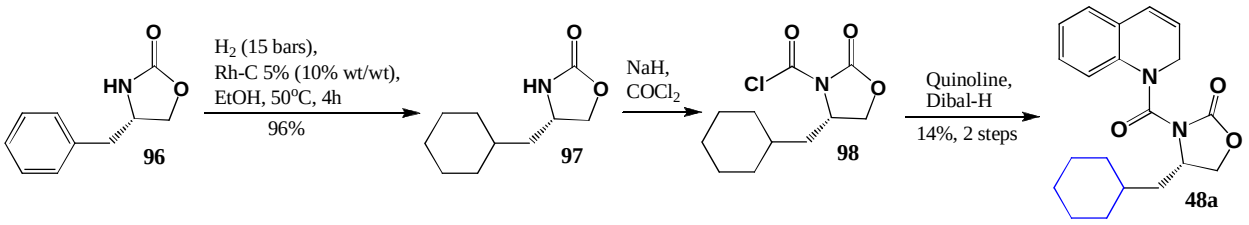


Figure 9

1.4.1. Preparation of modified structures of 1,2-dihydroquinoline 48

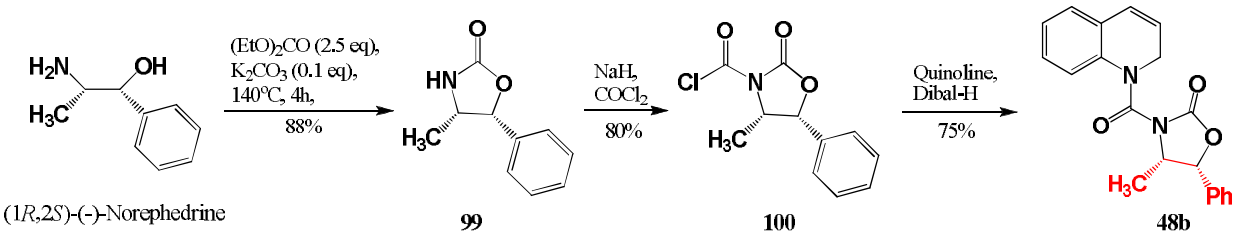
- (4*S*)-4-(Cyclohexylmethyl)-3-(quinolin-1(2*H*)-ylcarbonyl)-1,3-oxazolidin-2-one **48a**



Scheme 39: Synthesis of **48a**

Transformation of the aromatic nucleus of the (*S*)-4-benzyl-oxazolidin-2-one **96** to the corresponding cyclohexyl derivative **97** was carried out by mild hydrogenation in the presence of active Rh nanoparticles.[35] Then, the deprotonation of (*S*)-4-(cyclohexylmethyl)oxazolidin-2-one **97** by addition of NaH conducted to a nitranion which was trapped by phosgene[36] to yield the chloride acid **98**. Finally, the desired 1,2-dihydroquinoline **48a** was obtained via a reduction-acylation sequence using DIBAL-H.[37]

- (4S,5R) 4-methyl-5-phenyl-3-(quinolin-1(2H)-ylcarbonyl)-1,3-oxazolidin-2-one **48b**

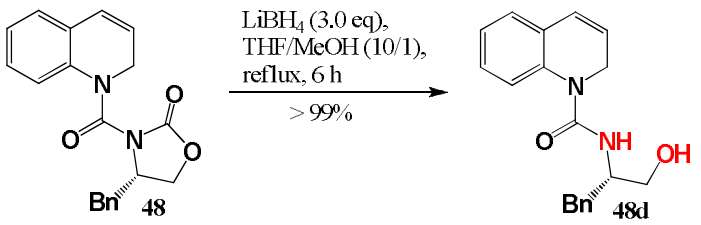


Scheme 40: Synthesis of **48b**

(*4S,5R*)-4-methyl-5-phenyloxazolidin-2-one **99** was synthetized by cyclization reaction of (*1R, 2S*)-(-)-norephedrine with diethylcarbonate at elevated temperature (Dean-Stark apparatus). The desired 1,2-tetrahydroquinoline **48b** was prepared following the procedure reported above to prepare **48a.**

[35] T. Storz, P. Dittmar. *Org. Process Res. Dev*. **2003**, *7*, 559.
[36] R.S. Garigipati, M. E. Sorenson, K. F. Erhard, J. L. Adams. *Tetrahedron Lett.* **1993**, *34*, 5537.
[37] D. E. Minter, P. L. Stotter. *J. Org. Chem.* **1981**, *46*, 3965.

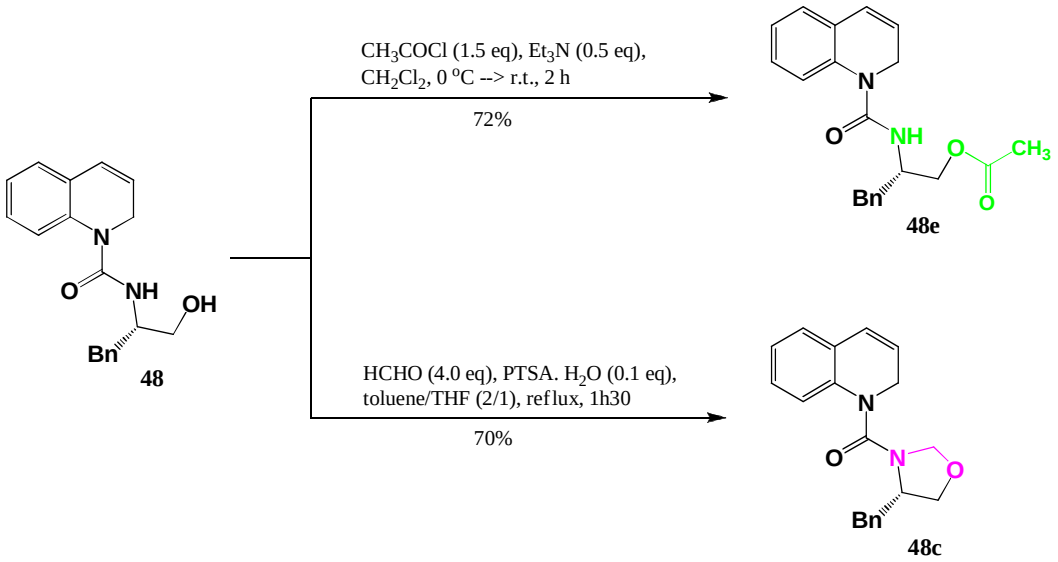
- *N*-[(2*S*)-1-hydroxy-3-phenylpropan-2-yl]quinoline-1(2*H*)-carboxamide **48d**



Scheme 41: Opening of oxazolidinone ring

Inspired by the work of T. Naito and collaborators in the reductive ring opening reaction of *N*-arylpyrrolidinones with $LiBH_4$ – MeOH – THF at 66 °C,[38] we applied the same experimental conditions to open the oxazolidinone ring of **48**. The desired 1,2-dihydroquinoline **48d** was thus isolated in excellent yield.

- (2*S*)-3-Phenyl-2-[(quinolin-1(2*H*)-ylcarbonyl)amino]propyl acetate **48e** and [(4*S*)-4-benzyl-1,3-oxazolidin-3-yl](quinolin-1(2*H*)-yl)methanone **48c**



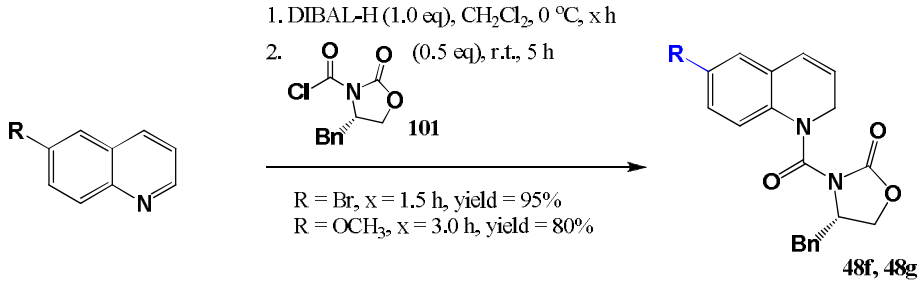
Scheme 42: Synthesis of **48c** and **48e**

From the opened 1,2-dihydroquinoline **48d**, we synthetized its acetyl derivative **48e** by one simple reaction using acetyl chloride in the presence of triethylamine. 1,2-Dihydroquinoline **48d**

[38] A. Shirai, O. Miyata, N. Tohnai, M. Miyata, D. J. Procter, D. Sucunza, A. Naito. *J. Org. Chem.* **2008**, *73*, 4464.

was cyclized by treatment with formaldehyde under acidic conditions to afford the 1,2-dihydroquinoline **48c.**

- (4*S*)-4-Benzyl-3-[(6-bromoquinolin-1(2*H*)-yl)carbonyl]-1,3-oxazolidin-2-one **48f** and (4*S*)-4-Benzyl-3-[(6-methoxyquinolin-1(2*H*)-yl)carbonyl]-1,3-oxazolidin-2-one **48g**



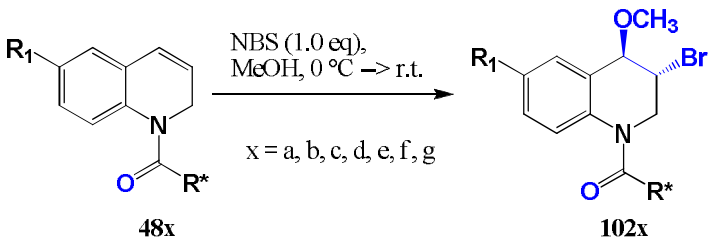
Scheme 43: Synthesis of **48f** and **48g**

Using 6-bromo-quinoline and 6-methoxy-quinoline instead of quinoline, the reduction-acylation sequence was successfully achieved to give the 6-bromo- and 6-methoxy-1,2-dihydroquinolines **48f** and **48g**, respectively.

1.4.2. Electrophilic addition of NBS in MeOH onto 1,2-dihydroquinolines bearing a modified oxazolidinone moiety

With all modified 1,2-dihydroquinolines in hand, we performed the electrophilic addition of NBS in MeOH (Table 6).

Table 6: Electrophilic addition of NBS in MeOH onto 1,2-dihydroquinolines **48x**



48x **102x**

Entry	*Substrate*	*Product*	*R_1*	*t (h)*	*Yield (%)*	*dr*
1	**48**	**73a**	H	4	93	86/14
2	**48a**	**102a**	H	4	79	92/08
3	**48b**	**102b**	H	4	90	75/25
4	**48c**	**102c**	H	2	72	82/18
5	**48d**	**102d**	H	48	59	55/45
6	**48e**	**102e**	H	6	92	63/37
7	**48f**	**102f**	Br	3	71	86/14
8	**48g**	**102g**	OCH_3	2	80	84/16

From the collected results listed in Table 6 some conclusions can be drawn:

- Exchange of the oxazolidinone C4'-benzyl substituent for a C4'-CH_2-Cy (entry 2 vs entry 1) slightly enhances the reaction diastereoselectivity. It may be concluded that the reaction diastereoselectivity is closely related to the steric hindrance of the substituent at C4' and that the benzyl substituent is not implied in electronic effects (π-stacking for example).
- The importance of the steric hindrance at C4' is also highlighted by exchange of the benzyl for a methyl substituent, which resulted in a significant decrease in the reaction diastereoselectivity (entry 3 vs entry 1).
- Excision of the carbonyl group of the oxazolidinone ring results in no significant

modification on diastereoselectivity (entry 4 vs entry 1). This is possibly because no Lewis acid is implied in the reaction. Indeed, it is well-known that the conformation of acyloxazolidinones is strongly influenced by the presence (or the absence) of a Lewis acid. In our case, it may be supposed that the conformation of the chiral auxiliary, and its spatial disposition relatively to the 1,2-dihydroquinoline ring, are not affected by the presence or the absence of a carbonyle on the chiral five-membered ring.

- Opening of the oxazolidinone ring has a deleterious effect on diastereoselectivities (entries 5 and 6 vs entry 1). This result demonstrates that the presence of a cyclic ring attached to the N1-CO moiety is *essential* for *obtaining* good *diastereoselectivity*.
- Finally, an electron-withdrawing or an electron-donating group attached at C6 has no effect on the reaction diastereoselectivity (entries 7 and 8 vs entry 1) showing that there is no electronic influence of the 1,2-tetrahydroquinoline ring on the oxazolidinone ring through the N1-CO linkage.

To sum up, the most important conclusion that can be drawn from this brief study is that the presence of a chiral five-membered ring (oxazolidine or oxazolidinone) joined to the 1,2-dihydroquinoline ring through a carbonyle linkage is of paramount importance to achieve good diastereoselectivity in a variety of addition reactions to the C3-C4 double bond of 1,2-dihydroquinoline **48**. The size of the C4'-substituent has also an important influence on the diastereoselection.

1.4.3. Determination of the absolute configuration of adducts 102x

The absolute configurations at C3 and C4 of all major *trans* adducts listed in Table 6 have been determined. Since the minor adducts are also *trans* adducts, their absolute configurations can be deduced from those of the corresponding major adducts.

- Absolute configurations at C3 and C4 of major *trans* products **102b** and **102g** (entry 3, 8) as well as those of the minor *trans* product **103d** (entry 5, structure not shown) *were assigned* on the basis of their *X-ray crystallographic* data (Figure 10).
- The major adduct **102f** (entry 7) is the same that the compound formed in bromomethoxylation of 1,2-dihydroquinoline **48** using an excess of NBS, the configuration of which has been already determined.

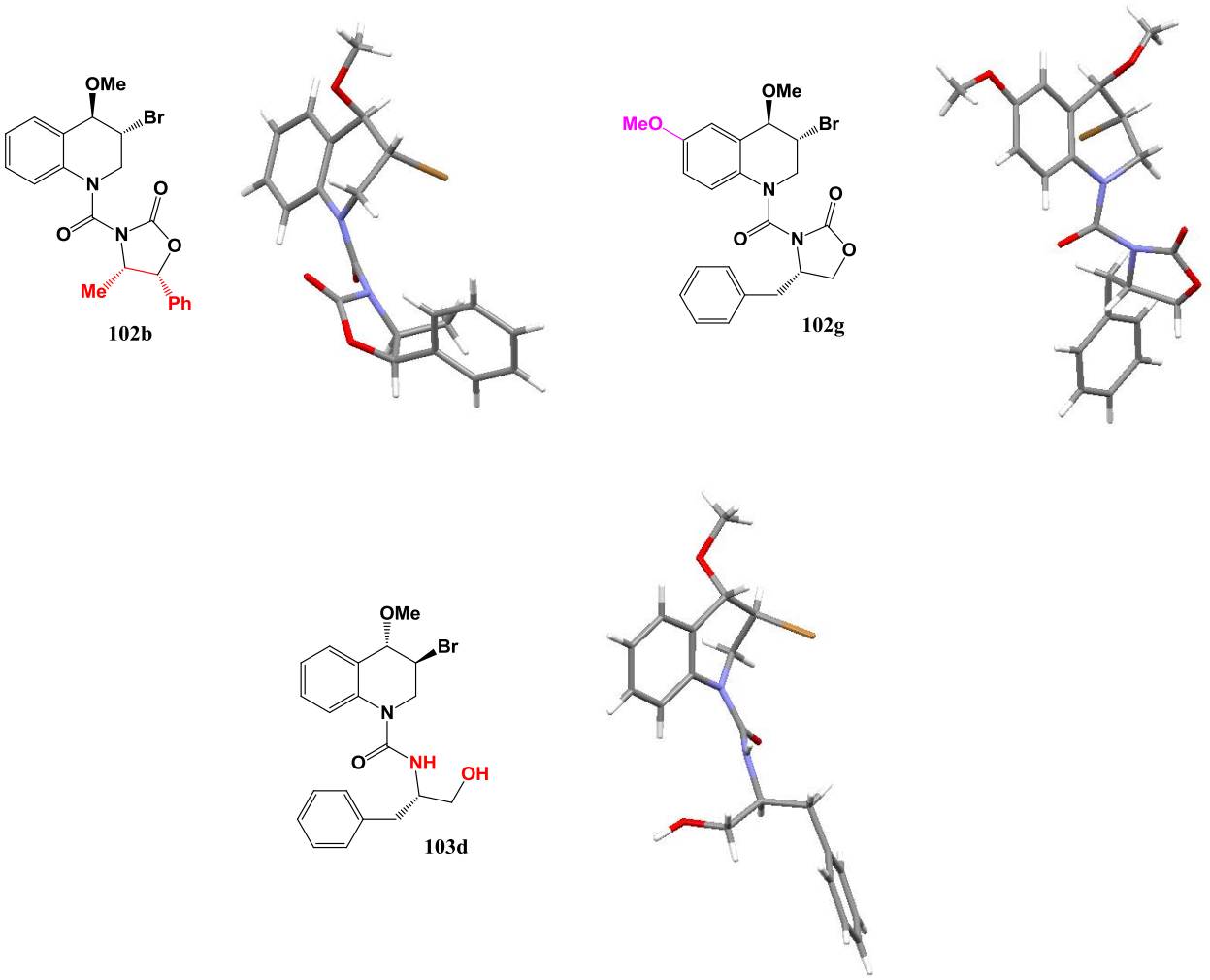
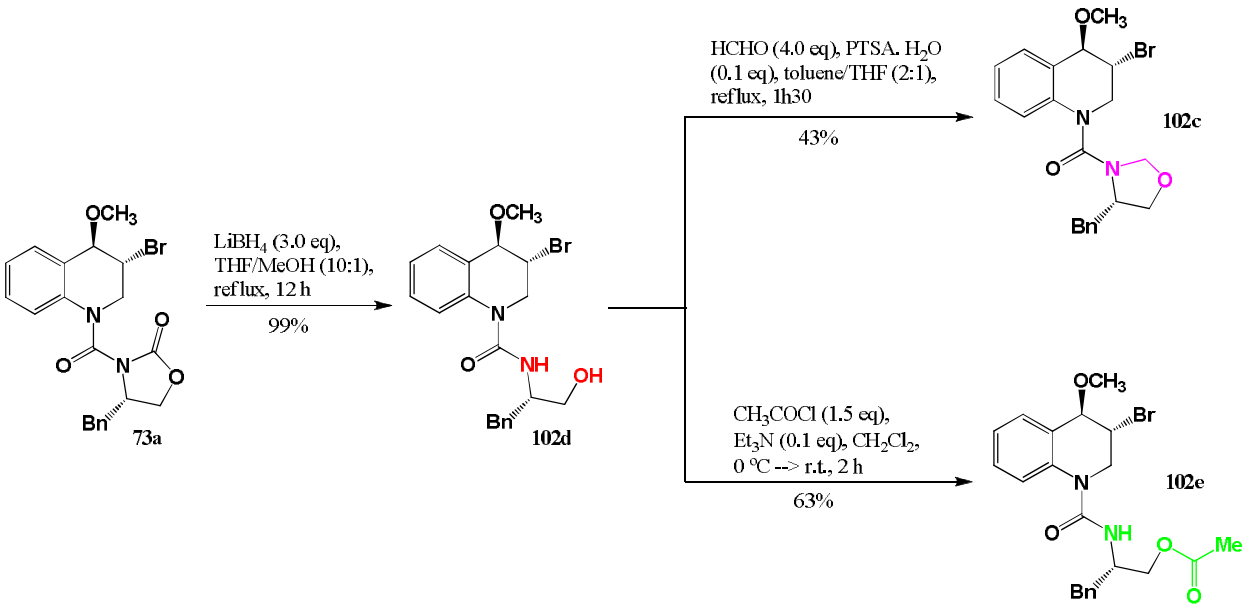


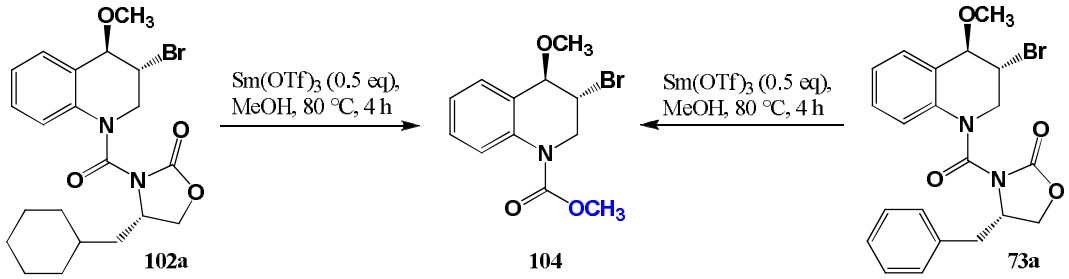
Figure 10

- Assignment of absolute configurations at C3 and C4 of major *trans* adducts **102c** and **102e** (entries 4 and 6) was made on the basis of chemical correlation with adduct **73a** (Scheme 44). Thus the oxazolidinone ring of **73a**, whose configuration was determined, was reductively opened to afford **102d** which in turn was acetylated, or cyclized with formaldehyde, to give **102e** and **102c** respectively. These compounds proved to be identical with those formed by electrophilic addition of NBS in MeOH onto the 1,2-dihydroquinolines **48e** and **48c**, respectively, thus establishing their configurations.



Scheme 44

- Finally, configurations at C3 and C4 for adduct **102a** (entry 2) was established as follows: the chiral auxiliary of major products **73a** and **102a** (entries 1 and 2) was removed under the action of samarium triflate to afford the *N*-protected 1,2,3,4-tetrahydroquinoline **104**. Specific rotations for each sample were almost identical (-45.8 vs -46.2 – c = 1.4; $CHCl_3$) thus establishing the configurations of adduct **102a** (entry 2).



Scheme 45

1.5. Electrophilic addition of BrX reagents to chiral Reissert compounds 105a and 105b

As concluded in the preceding paragraph, the influence of the chiral oxazolidinone on the 1,2-dihydroquinoline ring of **48** resulted in the orientation of one of the C2 protons in a quasi axial disposition, thereby disfavouring the bromine approach from the upper face of the C3-C4 double bond. Let us assume now that this proton is exchanged for a bulkier substituent Z (Figure 11). Provided that this exchange do not change the 1,2-dihydroquinoline ring conformation, addition of bromine, or more generally of BrX molecules, would be more diastereoselective than the addition of BrX on 1,2-dihydroquinoline **48**.

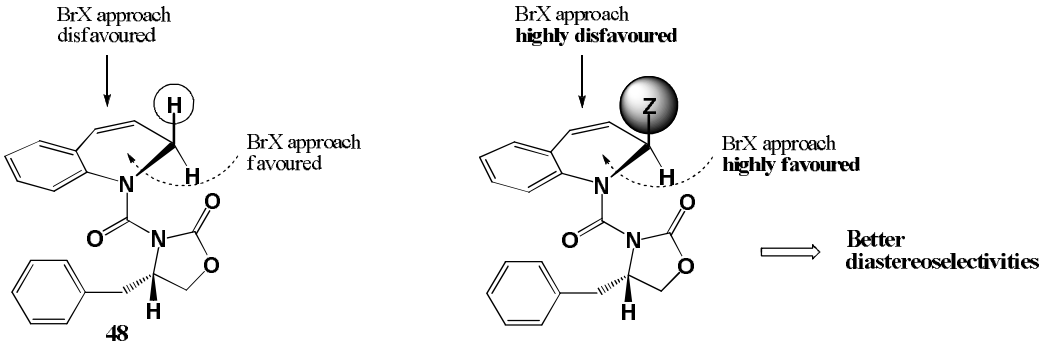
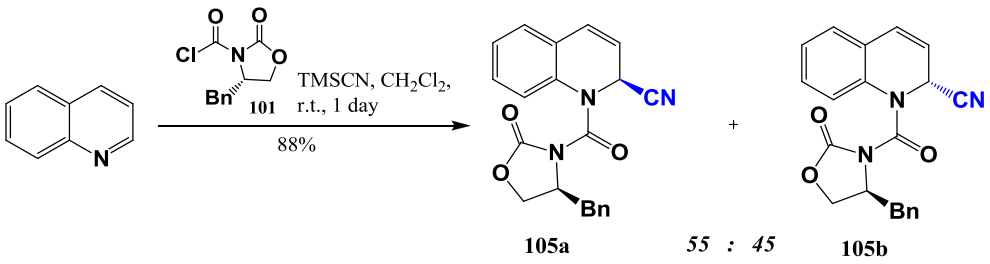


Figure 11

In order to evaluate this prediction, we choose Z = CN and thus studied addition of BrX reagents to the Reissert compounds **105a** and **105b** (Scheme 46).

Acccording to a method previously reported in our laboratory, the chiral Reissert compounds were prepared by the reaction of chiral acid chloride **101** on quinoline in the presence of trimethylsilyl cyanide.[39] In these conditions, the reaction is unselective yielding an almost equal mixture of diastereomeric adducts **105a** and **105b**. These adducts were next easily separated through column chromatography.

[39] M. Pauvert, S. Collet, M-J. Bertrand, A. Guingant, M. Evain, *Tetrahedron Lett*. **2005**, *46*, 2983.



Scheme 46

Their stereochemistries at the newly created stereogenic center C2 could be fully established after a X-ray structure was performed for each diastereomer.

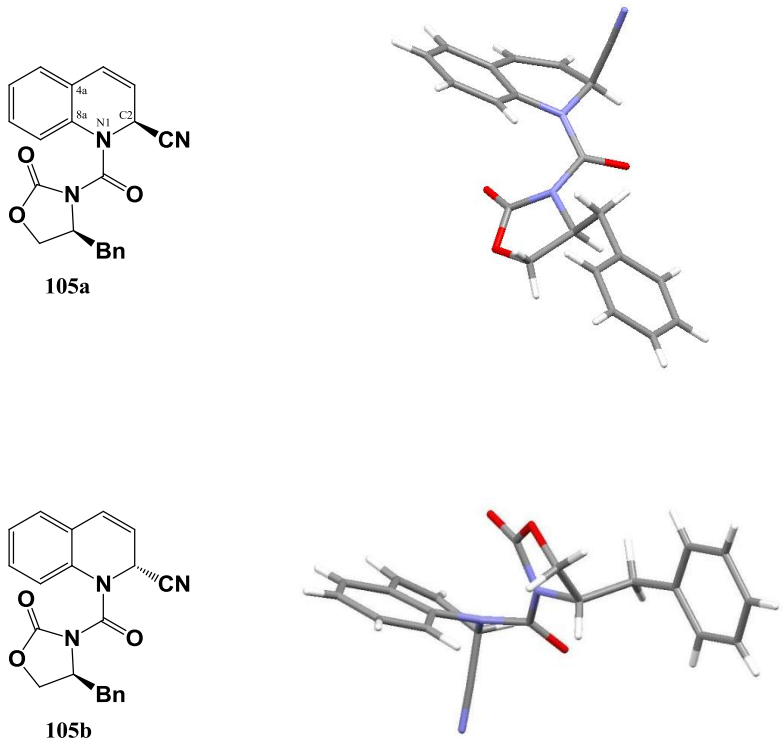


Figure 12

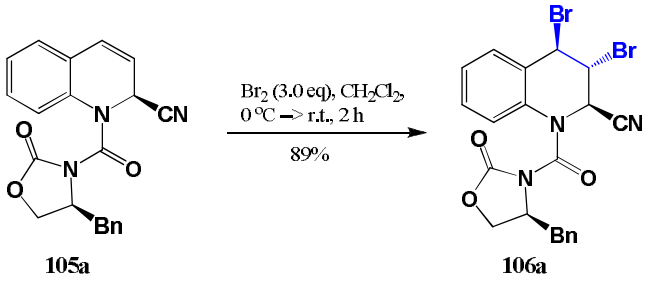
As can be seen (Figure 12), and in contrast to dihydroquinoline **48** and its adducts, each Reissert adduct adopts a **Cf2**-type conformation. Compared to **48**, the conformation of the 1,2-dihydroquinoline ring is not altered for adduct **105a**. Indeed, this latter displays the CN substituent on the top face in a quasi axial orientation. Although we could have expected for

adduct **105b** a similar conformation for the 1,2-dihydroquinoline ring with the CN substituent occupying an equatorial position, the X-ray displays a different conformation in which the CN substituent is directed towards the bottom face in a quasi axial orientation. The reason for this change of conformation is certainly due to a release of constraint between the CN group and the N1-C(O)-N moiety. The C4a-C8a-N1-C2 dihedral angle is representative of the conformational change of the dihydroquinoline ring when inversion of configuration at C2 occurs (+35.38° for adduct **105a** and -30.26° for its diasteromer **105b**).

Electrophilic addition of bromine on each of the diastereomeric Reissert adducts **105a** and **105b** as well as addition of NBS in MeOH and $TMSN_3$ on **105a** have been performed.

1.5.1. Dibromination

To date, dibromination of Reissert adducts of N-protected 1,2-dihydroquinolines has not been reported. Our initial experiments were realized on Reissert compound **105a** using one equivalent of a CH_2Cl_2 solution of bromine at 0 °C. The reaction was highly diastereoselective *affording only one diastereomer* **106a**. Stereochemistry of this adduct could not be established through X-Ray analysis; however, the small ^3J H3-H4 coupling constant (J = 2.4 Hz) strongly suggested a *trans* arrangement for the newly introduced Br substituents.

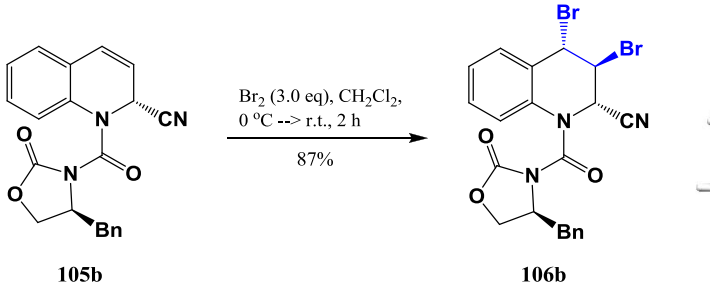


Scheme 47

It is noteworthy that, in contrast to the behaviour of **48**, excess bromine did not lead to a tribromo derivative (over-bromination at C6), a direct consequence of the *π-electron acceptor* character of the CN group at C2.

In the same conditions (excess of bromine) the diasteromeric Reissert adduct **105b** also led to a single *trans* dibromo adduct **106b,** the structure of which was firmly established through an X-Ray analysis (Figure 13). Its stereostructure is a consequence of the fact that the CN group in

105b is axially directed towards the bottom face of the reacting C3-C4 double bond. This result also brings confirmation of the stereochemistry previously attributed to the diastereomeric adduct **106a** (vide supra, Scheme **46**). Note that the **Cf2**-type conformation of Reissert adduct **105a** is maintained in its dibromo adduct.



Scheme 48

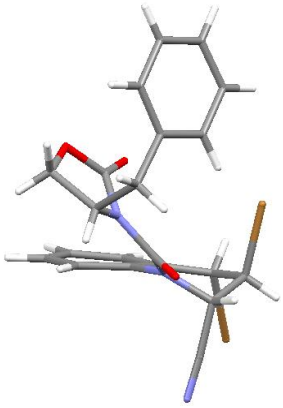
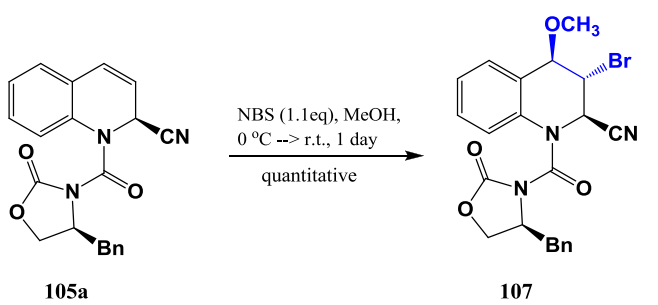


Figure 13

In conclusion, it appears that the steric course of the dibromation of Reissert adducts **105a** and **105b** is governed by the spatial orientation of the CN group at C2, which relay the information of the chiral auxiliary branched at C1. The CN group being bulkier than a proton, diastereoselectivity of the dibromination of **105a** and **105b** is significantly increased (dr = 100:0) as compared with dibromation of 1,2-dihydroquinoline **48**.

1.5.2. Bromomethoxylation

Bromomethoxylation of Reissert adduct **105a** was carried out in the presence of one equivalent of bromine in MeOH. As for the preceding reaction, addition to the C3-C4 double bond was completely diastereoselective, leading to the *trans* addition product **107** whose stereochemistry was unambigously established through X-ray analysis. In striking contrast to bromine adduct **106b**, adduct **107** adopt a **Cf1**-type conformation as can be seen in Figure 14 below. This latter observation suggest that the conformation of the Br_2 and BrX addition products, at least in the solid state, is a direct consequence of the orientation of the CN group at C2 in Reissert compounds **105a** and **105b** (which, as previously noted, exist both in a Cf2-type conformation).



Scheme 49

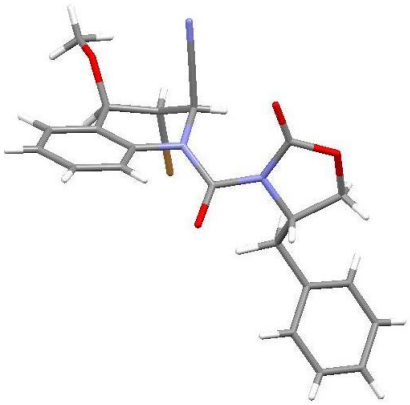
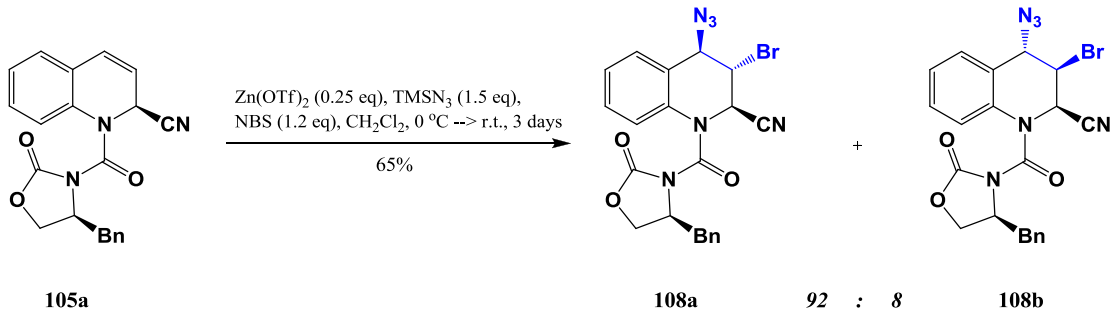


Figure 14

1.5.3. Bromoazidation

Reissert adduct **105a** was thus submitted to the action of NBS and $TMSN_3$ in the presence of $Zn(OTf)_2$ (Scheme 50). In this case, a mixture of diastereoisomers **108a** and **108b** was obtained (dr = 92:8). This lower diastereoselectivity might be explained by the presence of Lewis acid which could interact with both carbonyle groups and nitrile one changing reactive conformation of dihydroquinoline **105a**. Unfortunately, we did not have enough time to check the influence of such Lewis acid on diastereoselectivities for dibromination on bromomethoxylation reactions.



Scheme 50

The major diastereoisomer – *trans* product **108a** was also well confirmed through X-ray analysis (Figure 15).

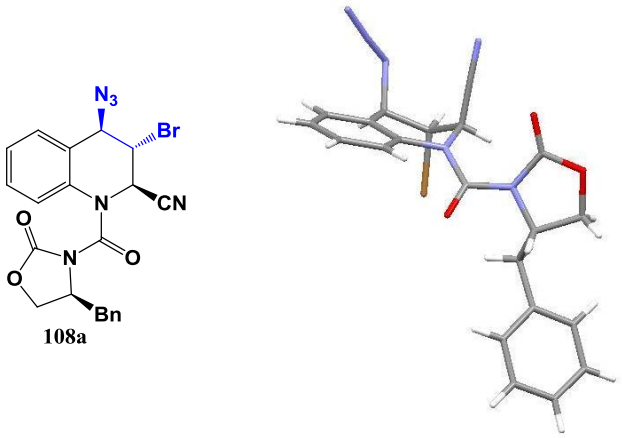


Figure 15

In conclusion, the preceding results confirm the prediction that an axial substituent bulkier than a proton at C2 of 1,2-dihydroquinoline **48** should increase diastereoselectivity of the *trans* addition of BrX reagent on the C3-C4 double bond of the corresponding compound. They also confirm that a conformational bias, fixing a substituent at C2 in a quasi axial orientation, relays the chiral information borne by the chiral auxiliary to the reacting double bond. In the following chapter we will make use of these results in the field of natural products synthesis.

EXPERIMENTAL PART

1.6. Experimental Part

1.6.1. General Information

Chromatography

Reaction progress was monitored by thin layer chromatography (TLC) performed using Merck, Kieselgel 60 plates.

Column chromatography was performed using Merck Kieselgel 60 silica gel (40-63 µm).

Nuclear Magnetic Resonance (NMR)

NMR spectra were recorded on a BRUKER AC 300 at 300 MHz for ^{1}H and 75 MHz for ^{13}C at rt from samples in solution of suitable solvents. The reference used is tetramethylsilane (TMS). The chemical shift values (δ) are expressed in parts per million (ppm) and coupling constants (J) in Hertz (Hz). Spectral coupling patterns are designated as follows: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet signal.

Polarimetry

Optical rotations were obtained with a digital polarimeter Perkin Elmer 341 at 20 °C and at a wavelength of 589 nm (c = g/100 mL).

Mass Spectroscopy

The mass spectra were performed by electron impact (EI, 70 eV) or chemical ionization (CI, 500eV) with NH_3 on a Hewlett Packard 5989A

HRMS were carried out either in Maldi, CI or EI mode (70ev).

Infrared Spectroscopy

IR spectra were recorded films for oily products and KBr platelets for solids on a *Bruker Vector-22 Fourier transform spectrometer*.

Chiral HPLC

Enantiomeric excess was determined by HPLC using a Daicel Chiralcel OD-H column (0.46 cm i.d. × 25 cm) with UV detection at 219 and 254 nm. 2-Propanol and hexanes were used as solvents, and the flow rate was set at 1.0 mL/min.

Melting points: were determined without correction.

Solvents

THF, CH_2Cl_2, toluene, DMF were of reagent grade and were dried through a solvent purification system. Acetonitrile were dried by distillation from calcium hydride. All other reagents were purified by distillation, the pressure being reduced if the boiling point of the compound was greater than 110 °C at atmospheric pressure.

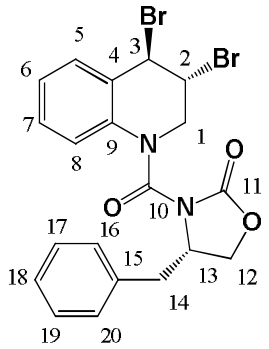
Room temperature (r.t.) refers to 20-25 °C.

Reactions carried out under an inert atmosphere refer to the use of argon or nitrogen.

1.6.2. Synthesis and Physical Properties

General procedure 1: Bromination.

(4*S*)-4-Benzyl-3-{[(3*R*,4*R*)-3,4-dibromo-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}-1,3-oxazolidin-2-one **52a**



$C_{20}H_{18}Br_2N_2O_3$

M = 494.18 g/mol

MP = 167 °C

To a solution of dihydroquinoline **48** (0.334 g, 1 mmol) in dry CH_2Cl_2 (5 mL) at -78 °C was added dropwise slowly a solution of bromine (51.5 µL, 1.0 mmol) in CH_2Cl_2 (1.0 mL). The reaction was then stirred for 3 h at -78 °C. The resulting mixture was quenched by addition of saturated aqueous $Na_2S_2O_3$ solution (20 mL). After phase separation, the aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give product **52** as a white solid (0.489 g, 0.99 mmol, 99%, *dr* = 95/5). R_f = 0.41 (PE/EtOAc, 4:1). Additional purification could be achieved by recrystallisation from PE/EtOAc to afford the major product **52a** as colourless crystals.

$[\alpha]_D^{20}$**:** -56.3 (c = 0.96, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.63 and 3.52 (AB part of ABX system,2 H, *J* = 12.9, 10.7, 3.5 Hz, H_{14}), 4.16 and 4.30(AB part of ABX system, 2 H, *J* = 9.5, 9.0, 8.5 Hz, H_{12}), 4.21 (ddd, 1 H, *J* = 14.0,3.2, 1.2 Hz, H_1), 4.60 (dd, 1 H, *J* = 14.0, 1.0 Hz, H_1), 4.80-4.91 (m, 1 H, H_{13}), 4.88 (br. s, 1 H, H_2), 5.65 (br. s, 1 H, H_3), 7.15-7.21 (m, 3 H, Ar-H), 7.26-7.42 (m, 4 H, Ar-H), 7.40 (d, 1 H, *J* = 7.8 Hz, H_5), 7.60 (d, 1 H, *J* = 9.0 Hz, H_8).

^{13}C NMR (75 MHz in $CDCl_3$, δ ppm): 38.9 (C_{14}), 47.9 (C_3), 48.6 (C_1), 49.1 (C_2), 56.7 (C_{13}), 68.2 (C_{12}), 124.2 (C_8), 124.7 (Cq), 125.7 (C_6), 127.5 (C_{18}), 129.0 (2$\underline{C}H_{Ar}$), 129.2 (2$\underline{C}H_{Ar}$), 129.4 (C_7), 132.1 (C_5), 135.1 (Cq), 135.2 (Cq), 153.5 (C_{10}), 153.8 (C_{11}).

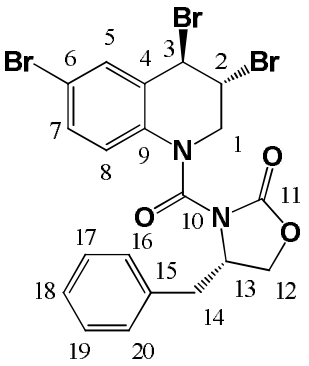
IR: (ν cm^{-1}) 3080, 3026 ($\nu_{C\text{-}Haro}$), 2971, 2929 ($\nu_{C\text{-}Hsat}$), 1773 ($\nu_{C=O\ carbamate}$), 1693 ($\nu_{C=O\ urea}$), 1604, 1582, 1491, 1453 ($\nu_{C=Caro}$).

MS (CI): m/z = 514, 512, 510 $[M+NH_4]^+$, 497, 495, 493 $[M+H]^+$, 415, 413, 335.

HRMS (ESI):

Calculated for $C_{20}H_{19}Br_2N_2O_3$ $[M+H]^+$ = 492.9757; Found $[M+H]^+$ = 492.9767.

(4*S*)-4-Benzyl-3-{[(3*R*,4*R*)-3,4,6-tribromo-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}-1,3-oxazolidin-2-one **53a**



$C_{20}H_{17}Br_3N_2O_3$

M = 573.07 g/mol

MP: 185.1 °C

According to the general procedure 1, reaction of the dihydroquinoline **48** (0.334 g, 1 mmol) with three equivalents of bromine (0.155 mL, 3.0 mmol) or tetramethylammoniumbromide ($(CH_3)_4NBr_3$) (0.942 g, 3.0 mmol) gave product **53** as a white solid (0.568 g, 0.99 mmol, 99%, *dr* = 95/5). R_f = 0.28 (PE/EtOAc, 4:1). Additional purification could be achieved by recrystallisation from PE/EtOAc to afford the major product **53a** as colourless crystals.

$[\alpha]_D^{20}$**:** -30.1 (c = 1.0, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.62 and 3.49 (AB part of ABX system, 2 H, *J* = 13.1, 10.6, 3.6 Hz, H_{14}), 3.49 (dd, 1 H, *J* = 13.1, 3.6 Hz, H_{14}), 4.16 and 4.31 (AB part of ABX system, 2 H, *J* = 9.3, 9.0, 8.7 Hz, H_{12}), 4.17 (ddd, 1 H, *J* = 14.6, 3.3, 1.3 Hz, H_1), 4.56 (dd, 1 H, *J* = 14.6, 1.2 Hz, H_1), 4.79-4.89 (m, 1 H, H_{13}), 4.82 (dd, 1 H, *J* = 3.3, 1.2 Hz, H_2), 5.54 (br. s, 1 H, H_3), 7.18-7.21 (m, 2 H, Ar-H), 7.28-7.35 (m, 3 H, Ar-H), 7.43 (dd, 1 H, *J* = 9.0, 2.2 Hz, H_7), 7.50 (d, 1 H, *J* = 9.0 Hz, H_8), 7.53 (d, 1 H, *J* = 2.2 Hz, H_5).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 38.8 (C_{14}), 46.4 (C_3), 48.3 (C_2), 48.5 (C_1), 56.7 (C_{13}), 68.2 (C_{12}), 118.2 (C_6), 125.9 (C_8), 126.7 (Cq), 127.6 (C_{18}), 129.0 (2$\underline{C}H_{Ar}$), 129.2 (2$\underline{C}H_{Ar}$), 132.5 (C_7), 134.2 (Cq), 134.3 (C_5), 135.1 (Cq), 152.5 (C_{10}), 153.2 (C_{11}).

IR: (ν cm^{-1}) 3088, 3024 ($\nu_{C\text{-}Haro}$), 2974, 2934 ($\nu_{C\text{-}Hsat}$), 1774 ($\nu_{C=O\ carbamate}$), 1670 ($\nu_{C=O\ urea}$), 1596, 1485, 1454 ($\nu_{C=Caro}$), 1224 ($\nu_{C\text{-}Oester}$), 1071 ($\nu_{C\text{-}O}$).

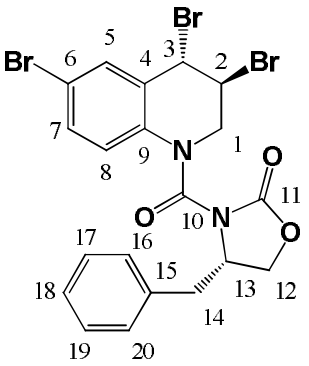
MS (CI): m/z = 592, 590 $[M+NH_4]^+$, 575,573 $[M+H]^+$, 495, 493, 415, 413.

Elemental analysis: for $C_{20}H_{17}Br_3N_2O_3$

Calculated: %C = 41.92 %H = 2.99 %N = 4.89.

Found: %C = 41.98 %H = 3.07 %N = 4.95.

(4*S*)-4-Benzyl-3-{[(3*S*,4*S*)-3,4,6-tribromo-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}-1,3-oxazolidin-2-one **53b**



$C_{20}H_{17}Br_3N_2O_3$

M = 573.07 g/mol

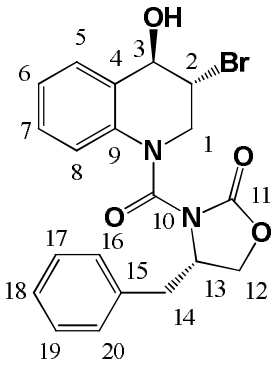
The minor product can be isolated from the solution after separation of the major product by recrystallization followed by silica gel chromatography (PE/CH_2Cl_2, 1:1). Additional purification could be achieved by recrystallisation from PE/EtOAc to afford the minor product **53b** as colourless crystals.

^{1}HNMR (300 MHz, $CDCl_3$, δ ppm): 2.98 and 3.63 (AB part of ABX system, 2 H, *J* = 13.3, 9.6, 3.6 Hz, H_{14}), 3.96 and 4.50 (AB part of ABX system, 2 H, *J* = 13.7, 4.7, 2.8 Hz, H_1), 4.21-4.33 (m, 2 H,H_{12}), 4.48-4.58 (m, 1 H, H_{13}), 4.72 (ddd, 1 H, *J* = 4.7, 3.3, 2.8 Hz, H_2), 5,45 (d, 1 H, *J* = 3.3 Hz, H_3), 7.23-7.44 (m, 6 H, Ar-H), 7.42 (dd, 1 H, *J* = 8.9, 2.2 Hz, H_7), 7.55 (d, 1H, *J* = 2.2Hz, H_5).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 37.9 (C_{14}), 47.2 (C_3), 48.3 (C_2), 50.2 (C_1), 57.9 (C_{13}), 67.4 (C_{12}), 118.2 (C_6), 125.7 (C_8), 127.6 (C_{18}), 129.2 (2$\underline{C}H_{Ar}$), 129.6 (2$\underline{C}H_{Ar}$), 132.6 (C_7), 133.9 (C_5), 135.0 (Cq), 135.4 (Cq), 152.6 (C_{10}), 153.6 (C_{11}).

MS (EI): m/z (rel. int.) = 574 ($[M]^+$, 17), 572 ($[M]^+$, 18), 493 (70), 413 (100), 288 (37).

(4*S*)-4-Benzyl-3-{[(3*R*,4*R*)-3-bromo-4-hydroxy-3,4-dihydroquinolin-1(2*H*)-yl-]carbonyl}-1,3-oxazolidin-2-one **62a**



$C_{20}H_{19}BrN_2O_4$

M = 431.28 g/mol

MP: 119.1 °C

To a solution of dihydroquinoline **48** (0.334 g, 1.0 mmol) in a 1:1 mixture of THF and H_2O (10mL) at 0 °C was added NBS (0.196 g, 1.1mmol). After 1 h stirring at 0 °C, the solution was warmed up to room temperature and stirred for 1 h. The resulting mixture was diluted by addition of H_2O (30 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel chromatography (PE/EtOAc, 7:3, R_f = 0.22) to yield the product **62a** as a light yellow solid (0.337 g, 0.78 mmol, 78%, *dr* = 81/19).

$[\alpha]_D^{20}$**:** +16.4 (c = 0.961, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.68 and 3.51 (AB part of ABX system, 2 H, *J* = 13.2, 10.6, 3.6 Hz, H_{14}), 3.16 (s, 1 H, O-H), 4.08-4.21 (m, 3 H, $2H_1$ + $1H_{12}$), 4.26 (dd, 1 H, *J* = 8.7, 8.5 Hz, H_{12}), 4.36 (dd, 1 H, *J* = 6.6, 3.3 Hz, H_2), 4.75-4.85 (m, 1 H, H_{13}), 4.82 (s, 1 H, H_3), 7.17-7.22 (m, 3 H, Ar-H), 7.28-7.36 (m, 4 H,Ar-H), 7.44 (dd, 1 H, *J* = 7.7, 1.2 Hz, H_5), 7.57 (d, 1 H, *J* = 8.3 Hz, H_8).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 38.8 (C_{14}), 48.7 (C_1), 49.4 (C_2), 56.8 (C_{13}), 68.1 (C_{12}), 70.1 (C_3), 123.4 (C_8), 125.6 (C_6), 127.2 (Cq), 127.5 (C_{18}), 129.1 (C_7 + 4$\underline{C}H_{Ar}$), 130.1 (C_5), 135.2 (Cq_{Ar}), 136.0 (Cq), 153.3 (C_{10}), 153.5 (C_{11}).

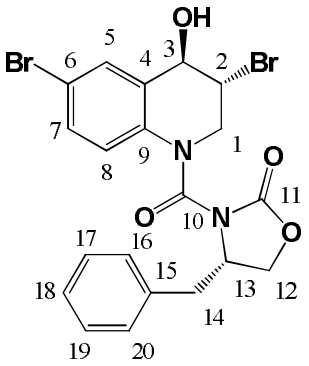
IR: (ν cm^{-1}) 3458 (ν_{OH}), 3062, 3029 ($\nu_{C\text{-}Haro}$), 2931 ($\nu_{C\text{-}Hsat}$), 1775 ($\nu_{C=Ocarbamate}$), 1672 ($\nu_{C=Ourea}$), 1605, 1584, 1492, 1454 ($\nu_{C=Caro}$), 1222 ($\nu_{C\text{-}Oester}$), 1018 ($\nu_{C\text{-}O}$), 768, 710 ($\nu_{C\text{-}Oaro}$).

MS (EI): m/z (rel. int.) = 432 ($[M]^+$, 60), 430 ($[M]^+$, 61), 415 (90), 413 (100).

HRMS (EI):

Calculated for $C_{20}H_{19}BrN_2O_4$ $[M]^+$ = 430.0523; Found $[M]^+$ = 430.0521.

(4*S*)-4-Benzyl-3-{[(3*R*,4*R*)-3,6-dibromo-4-hydroxy-3,4-dihydroquinolin-1(2*H*)-yl-]carbonyl}-1,3-oxazolidin-2-one **63a**



$C_{20}H_{18}Br_2N_2O_4$

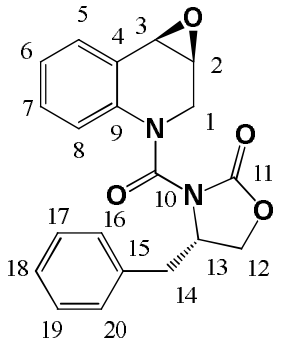
M = 510.18 g/mol

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.68 and 3.40 (AB part of ABX system, 2 H, *J* = 13.2, 10.6, 3.6 Hz, H_{14}), 3.55 (s, 1 H, O-H), 3.89-3.95 (m, 1 H, $1H_1$), 4.15 (t, 1 H, *J* = 8.7 Hz, $1H_{12}$), 4.29-4.55 (m, 3 H, $1H_1$, H_3, $1H_{12}$), 4.78 (m, 1 H, H_{13}), 4.89 (t, 1 H, *J* = 6.3 Hz, H_2), 7.09 (d, 1 H, *J* = 8.7 Hz, H_8), 7.20-7.23 (m, 2 H, Ar-H), 7.31-7.39 (m, 4 H, Ar-H), 7.63 (d, 1 H, *J* =2.2 Hz, H_5).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 37.7 (C_{14}), 49.8 (C_2), 51.6 (C_1), 56.6 (C_{13}), 67.7 (C_{12}), 73.1 (C_3), 118.8 (C_6), 123.7 ($\underline{C}H_{Ar}$), 127.8 ($\underline{C}H_{Ar}$), 129.3 ($3\underline{C}H_{Ar}$), 129.4 ($2\underline{C}H_{Ar}$), 131.3 (Cq), 132.0 ($\underline{C}H_{Ar}$), 134.7 (Cq), 136.0 (Cq), 152.3 (C_{10}), 153.2 (C_{11}).

MS (EI): m/z (rel. int.) = 512 ($[M]^+$, 14), 510 ($[M]^+$, 27), 508 ($[M]^+$, 14), 493 (12), 413 (40), 411 (40), 117 (56), 91 (100).

(4*S*)-4-Benzyl-3-[(1a*S*,7b*R*)-1a,7b-dihydrooxireno[*c*]quinolin-3(2*H*)-ylcarbonyl]-1,3-oxazolidin-2-one **64**



$C_{20}H_{18}N_2O_4$

M = 350.37 g/mol

MP: 65 °C

To a cooled suspension of sodium hydride (60% in mineral oil, 60.0 mg, 0.51 mmol) in THF (10 mL) was added bromhydrin **62a** (0.587 g, 1.36 mmol) and the reaction was stirred for 1 h at 0 °C and for 30 min at room temperature. The resulting mixture was quenched by addition of H_2O (100 mL) and extracted with EtOAc (3 x 50 mL). The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash chromatography (PE/EtOAc, 6:4, R_f = 0.22) to give product **64** as a brown solid (0.400 g, 1.14 mmol, 84%).

$[\alpha]_D^{20}$**:** +95.9 (c = 1.09, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.75 and 3.70(AB part of ABX system, 2 H, *J* = 13.4, 10.2, 2.7 Hz, H_{14}), 3.52 (d, 1 H, *J* = 14.4 Hz, H_1), 3.91 (dd, 1 H, *J* = 4.2, 2.1 Hz, H_2), 3.95 (d, 1 H, *J* = 4.2 Hz, H_3), 4.11-4.23 (m, 2H, H_{12}), 4.39-4.45 (m, 2 H, $1H_1$ + H_{13}), 7.19-7.35 (m, 8 H, Ar-H), 7.47 (dd, 1 H, *J* = 7.5, 0.7 Hz, Ar-H).

^{13}C NMR (300 MHz, $CDCl_3$, δ ppm): 38.0 (C_{14}), 44.2 (C_1), 50.9 (C_{13}), 57.5 (C_2), 58.6 (C_3), 67.3 (C_{12}), 124.0 ($\underline{C}H_{Ar}$), 125.9 ($\underline{C}H_{Ar}$), 126.4 (Cq), 127.3 ($\underline{C}H_{Ar}$), 129.0 ($2\underline{C}H_{Ar}$), 129.4 ($\underline{C}H_{Ar}$), 129.6 ($2\underline{C}H_{Ar}$), 130.0 ($\underline{C}H_{Ar}$), 135.9 (Cq), 137.0 (Cq), 153.1 (C_{10}), 154.3 (C_{11}).

IR: (ν cm^{-1}) 2924, 2854 ($\nu_{C\text{-}Hsat}$), 1773 ($\nu_{C=Ocarbamate}$), 1676 ($\nu_{C=Ourea}$), 1606, 1585, 1496, 1454 ($\nu_{C=Caro}$).

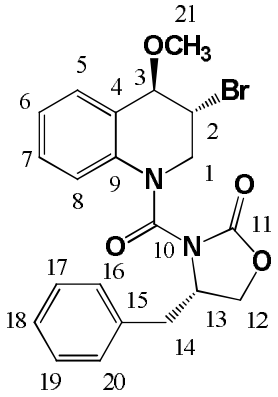
MS (EI): m/z (rel. int.) =350 $[M]^+$ (24), 333 (15), 174 (13), 91 (100).

HRMS (Maldi-PEG 400):

Calculated for $C_{20}H_{19}N_2O_4$ $[M+H]^+$ = 351.13; Found $[M+H]^+$ = 351.1330.

General procedure 2: NBS/MeOH.

(4*S*)-4-Benzyl-3-{[(3*R*,4*R*)-3-bromo-4-methoxy-3,4-dihydroquinolin-1(2*H*)-yl-]carbonyl}-1,3-oxazolidin-2-one **73a**



$C_{21}H_{21}BrN_2O_4$

M = 445.31 g/mol

MP: 151.1 °C

To a solution of dihydroquinoline **48** (0.334 g, 1.0 mmol) in dry MeOH (5 mL) at 0 °C was added NBS (0.196 g, 1.1 mmol) and the reaction was stirred at room temp for 4 h. The solvent was evaporated and the crude residue was treated by addition of H_2O (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel chromatography (PE/EtOAc, 7:3, R_f = 0.38) to give product **73** as a white solid (0.414 g, 0.93 mmol, 93%, *dr* = 86/14). Additional purification could be achieved by recrystallisation from PE/EtOAc to afford the major isomer as colourless crystals.

$[\alpha]_D^{20}$**:** -12.0 (c = 0.496, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.66 and 3.52 (AB part of ABX system, 2 H, *J* = 13.1, 10.5, 3.6 Hz, H_{14}), 3.58 (s, 3 H,H_{21}), 4.11-4.18 (m, 3 H,2H_1 +1H_{12}), 4.29 (dd, 1 H, *J* = 8.8, 8.4 Hz, H_{12}), 4.41 (d, 1 H, *J* = 2.4 Hz, H_3), 4.51 (dd, 1 H, *J* = 5.0, 2.4 Hz, H_2), 4.79-4.90 (m, 1 H,H_{13}), 7.17-7.22 (m, 3 H, Ar-H), 7.26-7.40 (m, 5 H, Ar-H), 7.64 (d, 1 H, *J* = 8.4Hz, H_8).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 38.9 (C_{14}), 46.3 (C_2), 49.1 (C_1), 56.7 (C_{13}), 57.8 (C_{21}), 68.1 (C_{12}), 78.9 (C_3), 123.6 (C_8), 124.9 (Cq), 125.3 (C_6), 127.5 (C_{18}), 128.9 (C_7), 129.1 (4$\underline{C}H_{Ar}$), 131.0 (C_5), 135.4 (Cq), 136.1 (Cq), 153.3 (C_{10} +C_{11}).

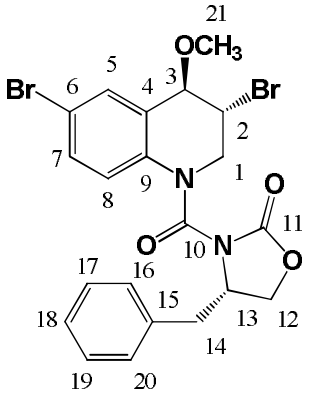
IR: (ν cm^{-1}) 3059, 3028 ($\nu_{C\text{-}Haro}$), 2930 ($\nu_{C\text{-}Hsat}$), 2826 (ν_{OCH3}), 1775 ($\nu_{C=Ocarbamate}$), 1670 ($\nu_{C=Ourea}$), 1601, 1483, 1457 ($\nu_{C=Caro}$), 1217 ($\nu_{C\text{-}Oester}$), 1073 ($\nu_{C\text{-}O}$), 762, 707 ($\nu_{C\text{-}Oaro}$).

MS (EI): m/z (rel. int.) = 446 ($[M]^+$, 96), 444 ($[M]^+$, 100), 413 (89).

Elemental analysis: for $C_{21}H_{21}BrN_2O_4$

Calculated: %C = 56.64, %H = 4.75 %, N = 6.29 ; Found: %C = 56.61, %H = 4.74, %N = 6.43.

(4*S*)-4-Benzyl-3-{[(3*R*,4*R*)-3,6-dibromo-4-methoxy-3,4-dihydroquinolin-1(2*H*)-yl-]carbonyl}-1,3-oxazolidin-2-one **74a**



$C_{21}H_{20}Br_2N_2O_4$

M = 524.20 g/mol

MP: 174.9 °C

According to the general procedure 2, reaction of the dihydroquinoline **48** (0.334 g, 1.0mmol) with three equivalents of NBS (0.535 g, 3.0mmol) gave a mixture of isomers as a white solid (0.435 g, 0.83mmol, 83%, *dr* = 85/15). R_f = 0.43 (PE/EtOAc, 7:3). Additional purification could be achieved by recrystallisation from PE/EtOAc to afford the major isomer **8a** as colourless crystals.

$[\alpha]_D^{20}$**:** -56.2 (c = 0.514, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.65 and 3.50 (AB part of ABX system, 2 H,, *J* = 13.1, 10.5, 3.7 Hz, H_{14}),3.58 (s, 3 H,H_{21}), 4.08-4.20 (m, 3 H,2H_1 + 1H_{12}), 4.29 (dd, 1 H, *J* = 8.7, 8.5 Hz, H_{12}),4.35 (d, 1 H, *J* = 2.3 Hz, H_3), 4.48 (dd, 1 H, *J* = 4.9, 2.3 Hz, H_2),4.78-4.86 (m, 1 H,H_{13}), 7.19-7.22 (m, 2 H, Ar-H), 7.28-7.36 (m, 3 H, Ar-H), 7.44 (dd, 1 H, *J* = 8.9, 2.3 Hz, H_7), 7.51 (d, 1 H, *J* = 2.3Hz, H_5), 7.52 (d, 1 H, *J*= 8.9Hz, H_8).

^{13}CNMR (75 MHz, $CDCl_3$, δ ppm): 38.9 (C_{14}), 45.6 (C_2), 48.9 (C_1), 56.7 (C_{13}), 58.0 (C_{21}), 68.1 (C_6), 78.5 (C_3), 118.0 (C_6), 125.3 (C_8), 126.9 (Cq), 127.5 (C_{18}), 129.1 (2$\underline{C}H_{Ar}$), 129.2 (2$\underline{C}H_{Ar}$), 132.0 (C_7), 133.6 (C_5), 135.2 (2Cq_{Ar}), 153.4 (C_{10} + C_{11}).

IR : (ν cm^{-1}) 3060, 3028 ($\nu_{C\text{-}Haro}$), 2986 ($\nu_{C\text{-}Hsat}$), 2826 (ν_{OCH3}), 1775 ($\nu_{C\text{-}Ocarbamate}$), 1670 ($\nu_{C=Ourea}$), 1602, 1483, 1457 ($\nu_{C=Caro}$), 1217 ($\nu_{C\text{-}Oester}$), 1073 ($\nu_{C\text{-}O}$), 762, 707 ($\nu_{C\text{-}Haro}$).

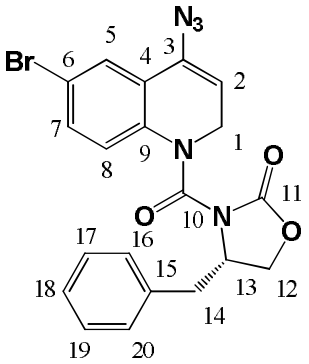
MS (CI): m/z = 544, 542, 540 $[M+NH_4]^+$, 527, 525, 523 $[M+H]^+$, 493.

Elemental analysis: for $C_{21}H_{20}Br_2N_2O_4$

Calculated: %C = 48.12 %H = 3.85 %N = 5.34.

Found: %C = 48.28 %H = 3.90 %N = 5.38.

(4*S*)-3-[(4-azido-6-bromoquinolin-1(2*H*)-yl)carbonyl]-4-benzyl-1,3-oxazolidin-2-one **80**



$C_{20}H_{16}BrN_5O_3$

M = 454.28 g/mol

To a solution of tribromo **53a** (0.287 g, 0.5 mmol) in DMF (5 mL) was added sodium azide (65 mg, 1 mmol). The reaction solution was stirred at r.t. for 12 h and then quenched with water (50 mL). After phase separation, the aqueous phase was extracted with Et_2O (2 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel (PE then PE/Et_2O, 3:2) to give the product **80** as an orange oil (quantitative).

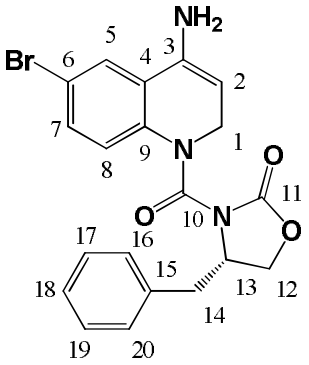
^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.92 and 3.27 (AB part of ABX system, 2 H, *J* = 13.7, 8.7, , 3.6 Hz, H_{14}), 4.16 and 4.35 (AB part of ABX system, 2 H, *J* = 9.4, 9.0, 8.2 Hz, H_{12}), 4.30 and 4.49 (AB part of ABX system, 2 H, *J* = 16.6, 6.1, 2.9 Hz, H_1), 4.80 (m, 1 H, H_{13}), 5.64 (dd, 1 H, *J* = 6.1, 2.9 Hz, H_2), 7.15-7.17 (m, 2 H, Ar-H), 7.21-7.36 (m, 4 H, Ar-H), 7.38 (dd, 1 H, *J* = 8.7, 2.3 Hz, H_7), 7.58 (d, 1 H, *J* = 2.3 Hz, H_5).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 37.4 (C_{14}), 45.7 (C_1), 56.5 (C_{13}), 67.2 (C_{12}), 108.9 (C_3), 118.8 (C_6), 124.6 ($\underline{C}H_{Ar}$), 126.2 (C_5), 126.4 (Cq), 127.7 ($\underline{C}H_{Ar}$), 129.1 (3$\underline{C}H_{Ar}$), 129.6 (2$\underline{C}H_{Ar}$), 131.8 ($\underline{C}H_{Ar}$), 134.7 (Cq), 135.5 (Cq), 152.3 (C_{10}), 153.2 (C_{11}).

IR (ν cm^{-1}): 3027 ($\nu_{C\text{-}Haro}$), 2918 ($\nu_{C\text{-}Hsat}$), 2120 (ν_{N3}), 1779 ($\nu_{C\text{-}Ocarbamate}$), 1682 ($\nu_{C=Ourea}$).

MS (CI): m/z = 471, 473 $[M+NH_4]^+$, 454, 456 $[M+H]^+$.

(4*S*)-3-[(4-amino-6-bromoquinolin-1(2*H*)-yl)carbonyl]-4-benzyl-1,3-oxazolidin-2-one **78**



$C_{20}H_{18}BrN_3O_3$

M = 428.28 g/mol

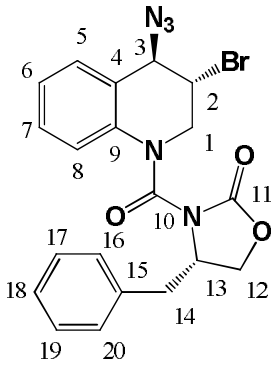
A solution of tribromo **53a** (0.297 g, 0.52 mmol) in a mixture of EtOH-EtOAc (20 mL, 1:1) was saturated with gaseous NH_3. The reaction solution was stirred under nitrogen at 50 °C for 12 h. After evaporation of solvents *in vacuo*, 30 mL of 10% NaOH aqueous solution was added and the aqueous phase was extracted with EtOAc. The combined organic layers were washed with water, dried over $MgSO_4$ and then concentrated under reduced pressure. Purification by chromatography on silica gel (EP/EtOAc 4:1, R_f = 0.24) gave the product **78** as a brown oil (quantitative).

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.95 and 3.19 (AB part of ABX system, 2 H, *J* = 13.7, 8.3, 3.2 Hz, H_{14}), 4.08-4.20 (m, 2 H, $1H_1$, $1H_{12}$), 4.27-4.40 (m, 2 H, $1H_1$, $1H_{12}$), 4.80 (m, 1 H, H_{13}), 6.35 (dd, 1 H, *J* = 5.9, 2.9 Hz, H_2), 7.13-7.15 (m, 2 H, Ar-H), 7.20-7.36 (m, 4 H, Ar-H), 7.39 (dd, 1 H, *J* = 8.6, 2.2 Hz, H_7), 7.74 (d, 1 H, *J* = 2.2 Hz, H_5).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 37.1 (C_{14}), 47.6 (C_1), 56.5 (C_{13}), 67.1 (C_{12}), 117.8 (C_3), 119.1 (C_6), 124.8 ($\underline{C}H_{Ar}$), 127.6 ($\underline{C}H_{Ar}$), 128.3 (C_2), 129.2 ($2\underline{C}H_{Ar}$), 129.3 (Cq), 129.7 ($2\underline{C}H_{Ar}$), 130.1 (C_5), 131.9 (C_7), 134.6 (Cq), 135.3 (Cq), 152.4 (C_{10}), 153.3 (C_{11}).

MS (EI): m/z (rel. int.) = 429 ($[M]^+$, 3), 427 ($[M]^+$, 3), 288 (100).

(4*S*)-4-Benzyl-3-{[(3*R*,4*R*)-4-azido-3-bromo-3,4-dihydroquinolin-1(2*H*)-yl-]carbonyl}-1,3-oxazolidin-2-one **93a**



$C_{20}H_{18}BrN_5O_3$

M = 456.29 g/mol

MP: 155.6 °C

To a solution of dihydroquinoline **48** (0.334 g, 1.0 mmol) in dry CH_2Cl_2 (10 mL) was added $Sm(OTf)_3$ (0.120 g, 0.20 mmol). The reaction was cooled to 0 °C and $TMSN_3$ (0.20 mL, 1.5 mmol) and NBS (0.214 g, 1.20 mmol) were successively added while stirring. The solution was warmed up to r.t. and stirred for 12 h. The resulting mixture was quenched by addition of a saturated aqueous $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (3 × 60 mL). The combined extracts were washed with water and then brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (PE/EtOAc, 4:1, R_f = 0.37) to give product **93a** as a white solid (0.452 g, 0.99 mmol, 99%, *dr* = 83/17). Additional purification could be achieved by recrystallisation from PE/EtOAc to afford the major isomer as colourless crystals.

$[\alpha]_D^{20}$**:** -62.2 (c = 1.062, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.65 and 3.51 (AB part of ABX system, 2 H, *J* = 13.0, 10.6, 3.6 Hz, H_{14}), 4.09-4.24 (m, 3 H, $2H_1$ + $1H_{12}$), 4.30 (t, 1 H, *J* = 8.6 Hz, $1H_{12}$), 4.39 (dd, 1 H, *J* = 5.4, 2.3 Hz, H_2), 4,79 (d, 1 H, *J* =2.3 Hz, H_3), 4.79-4.91 (m, 1 H, H_{13}), 7.19-7.44 (m, 8 H, Ar-H), 7.68 (d, 1 H, *J* = 8.3 Hz, H_8).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 38.8 (C_{14}), 46.6 (C_2), 49.2 (C_1), 56.7 (C_{13}), 61.8 (C_3), 68.1 (C_{12}), 122.0 (Cq), 124.3 (C_8), 125.6 (C_6), 127.5 (C_{18}), 129.1 ($2\underline{C}H_{Ar}$), 129.2 ($2\underline{C}H_{Ar}$), 129.5 (C_7), 130.2 (C_5), 135.2 (Cq), 136.2 (Cq), 153.4 (C_{10}), 153.5 (C_{11}).

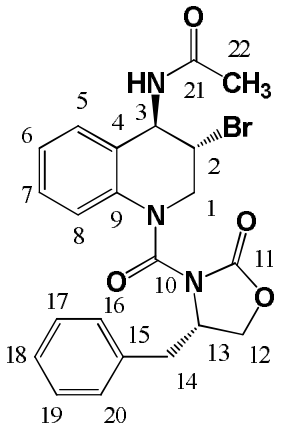
IR (ν cm^{-1}): 2928 ($\nu_{C\text{-}Hsat}$), 2109 (ν_{N3}), 1769 ($\nu_{C=Ocarbamate}$), 1693 ($\nu_{C=Ourea}$), 1604, 1584, 1494, 1454 ($\nu_{C=Caro}$), 1225 ($\nu_{C\text{-}Oester}$), 760, 709 ($\nu_{C\text{-}Haro}$).

MS (CI): m/z = 475, 473 $[M+NH_4]^+$, 458, 456 $[M+H]^+$, 430 , 415, 413, 352, 333.

HRMS (Maldi-PEG400):

Calculated for $C_{20}H_{18}BrN_5O_3Na$ $[M+Na]^+$ = 478.0485; Found: $[M+Na]^+$ = 478.0485

N-[(3*R*,4*R*)-3-bromo-1-{[(4*S*)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]carbonyl}-1,2,3,4-tetrahydroquinolin-4-yl]acetamide **90**



$C_{22}H_{22}BrN_3O_4$

M = 472.33 g/mol

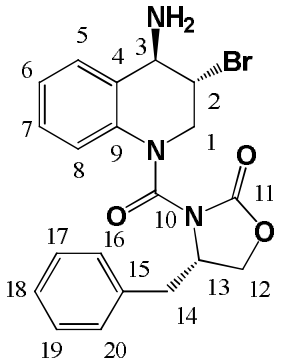
Tetrahydroquinoline **93a** (0.456 g, 1.0 mmol), acetic anhydride (94 µl, 1.0 mmol) and a substoichiometric amount of 10% Pd/C (0.106 g, 0.1 mmol) were added to a mixture of EtOH-EtOAc (40 ml, 1:1) under hydrogen atmosphere and stirred at r.t. for 12 h. After filtration and evaporation of solvents *in vacuo*, the residue was purified by flash column chromatography on silica gel (PE/EtOAc 7:3, R_f = 0.27) to yield amide **90** as a yellow oil (0.316g, 0.67 mmol, 67%).

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 1.96 (s, 3 H, H_{22}), 2.71 and 3.52 (AB part of ABX system, 2 H, *J* = 13.2, 10.4, 3.6 Hz, H_{14}), 4.01-4.17 (m, 3 H, $2H_1$, $1H_{12}$), 4.24 (dd, 1 H, *J* = 8.8, 8.2 Hz, $1H_{12}$), 4.53 (dd, 1 H, *J* = 5.7, 2.8 Hz, H_2), 4.70-4.81 (m, 1 H, H_{13}), 5.22 (dd, 1 H, *J* = 6.6, 2.2 Hz, H_3), 6.73 (d, 1 H, *J* = 6.6 Hz, NH), 7.14-7.21 (m, 3 H, Ar-H), 7.25-7.34 (m, 5 H, Ar-H), 7.56 (d, 1H, *J* = 8.3 Hz, H_8).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 23.3 (C_{22}), 38.7 (C_{14}), 46.9 (C_2), 49.6 (C_1), 52.5 (C_3), 57.1 (C_{13}), 68.0 (C_{12}), 123.2 (C_8), 124.9 (C_4), 125.8 (C_6), 127.5 ($\underline{C}H_{Ar}$), 129.0 ($\underline{C}H_{Ar}$), 129.2 ($4\underline{C}H_{Ar}$), 130.6 (C_5), 135.3 (Cq), 136.8 (Cq), 153.3 (C_{10}), 153.6 (C_{11}), 169.5 (C_{21}).

MS (CI): m/z = 472, 474 $[M+H]^+$.

(4*S*)-3-{[3*R*,4*R*)-4-amino-3-bromo-3,4-dihyroquinolin-1(2*H*)-yl]carbonyl}-4-benzyl-1,3-oxazolidin-2-one **94**



$C_{20}H_{20}BrN_3O_3$

M = 430.30 g/mol

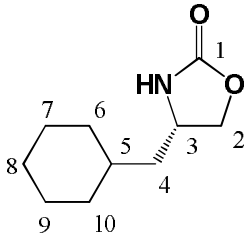
10% Pd/C (27 mg, 0.025 mmol) was added to a solution of azide **93a** (0.114 g, 0.25 mmol) in EtOH (5 mL). The reaction solution was stirred under hydrogen atmosphere at r.t. for 4 h. After filtration through a pad of Celite and concentration *in vacuo*, the residue was purified by chromatography on silica gel (PE/AcOEt 1:1, R_f = 0.39) to give amine **94** as a yellow oil (32 mg, 0.075 mmol, 30%).

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.68 and 3.52 (AB part of ABX system, 2 H, *J* = 13.1, 10.6, 3.6 Hz, H_{14}), 3.00 (bs, 2 H, NH_2), 4.07-4.22 (m, 3 H, $2H_1$, $1H_{12}$), 4.27 (dd, 1 H, *J* = 8.7, 8.5 Hz, $1H_{12}$), 4.38 (dd, 1 H, *J* = 5.8, 2.8 Hz, H_2), 4.75-4.84 (m, 2 H, H_3, H_{13}), 7.19-7.37 (m, 7 H, Ar-H), 7.44 (dd, 1 H, *J* = 7.7, 1.1 Hz, Ar-H), 7.58 (d, 1 H, *J* = 8.3 Hz, Ar-H).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 38.8 (C_{14}), 48.8 (C_1), 49.3 (C_2), 56.8 (C_{13}), 68.1 (C_{12}), 70.2 (C_3), 123.5 ($\underline{C}H_{Ar}$), 125.8 ($\underline{C}H_{Ar}$), 127.5 ($\underline{C}H_{Ar}$), 129.1 ($4\underline{C}H_{Ar}$), 129.5 (Cq), 130.1 ($\underline{C}H_{Ar}$), 135.3 (Cq), 136.1 (Cq), 15.3 (C_{10}), 153.5 (C_{11}).

MS (CI): m/z = 448, 450 $[M+NH^4]^+$, 430, 432 $[M+H]^+$.

(4*S*)-4-(Cyclohexylmethyl)-1,3-oxazolidin-2-one **97**



$C_{10}H_{17}NO_2$

M = 183.25 g/mol

MP = 84.8 °C

To a solution of oxazolidinone **96** (0.250 g, 1.41 mmol) in EtOH (5 mL) was added 5% Rh-C (25 mg, 10% wt/wt). Under vigorous stirring, the suspension was hydrogenated in a stainless steel glass-coated autoclave at 50 °C under an atmosphere of hydrogen (15 bars) for 4 h. The suspension was filtered through Celite and washed with EtOH. The clear filtrate was evaporated *in vacuo* without further purification to obtain **97** as colourless crystals (0.248 g, 1.35 mmol, 96%). R_f = 0.47 (PE/EtOAc, 7:3).

$[\alpha]_D^{20}$**:** -13.9 (c = 1.018, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 0.83-1.00 (m, 2 H, *c*-Hexyl-H), 1.10-1.32 (m, 3 H,H_5 + 2H_8), 1.35-1.44 (m, 1 H,H_4), 1.50-1.59 (m, 1 H, H_4), 1.67-1.70 (m, 6 H, *C*-Hexyl-H), 3.91-4.00 (m, 2 H,H_2), 4.44-4.51 (m, 1 H,H_3), 6.27 (s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 26.1 (C_7, C_9), 26.4 (C_8), 33.0 ($C_{C\text{-}Hex}$), 33.7 ($C_{C\text{-}Hex}$), 34.5 (C_5), 43.2 (C_4), 50.6 (C_3), 70.9 (C_2), 160.2 (C_1).

IR: (ν cm^{-1}) 3259 ($\nu_{N\text{-}H}$), 2980, 2926, 2845 ($\nu_{C\text{-}Hsat}$), 1745, 1712 ($\nu_{C=O}$).

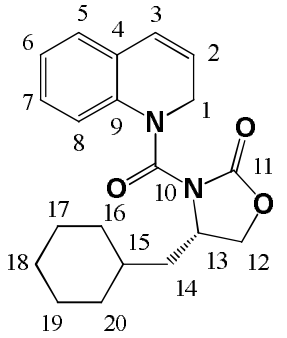
MS (CI): m/z = 201$[M+NH_4]^+$.

Elemental analysis: for $C_{10}H_{17}NO_2$

Calculated:	%C = 65.54	%H = 9.35	%N = 7.64
Found:	%C = 65.23	%H = 9.29	%N = 7.71

General procedure 3: Preparation of dihydroquinoline derivatives

(4*S*)-4-(Cyclohexylmethyl)-3-(quinolin-1(2*H*)-ylcarbonyl)-1,3-oxazolidin-2-one **48a**



$C_{20}H_{24}N_2O_3$

M = 340.42 g/mol

A solution of oxazolidinone **97** (2.68 g, 10.9 mmol) in dry toluene (67 mL) at 0 °C under nitrogen atmosphere was added NaH (60% suspension in oil) (0.67 g, 19.3 mmol). The mixture was stirred at room temperature for 3 h, and then cooled to -17 °C (ice/salt), cannulated to a 20% solution of phosgene in toluene (13 mL, 25.4 mmol) at the same temperature. The solution was allowed to warm to the room temperature and stirred at that temperature for 18 h, and then filtered, concentrated in vacuo. The resulting residue was washed with a small amount of petroleum ether to give product **98** without further purification as a white powder.

A solution of quinoline (2.58 mL, 21.8 mmol) in CH_2Cl_2 (30 mL) at 0 °C was added a solution of 1M DIBAL-H in hexane (21.8 mL, 21.8 mmol) and the reaction was stirred for 1 h at room temperature. The resulting solution was cannulated to a solution of unpurified chloride acid **98** above in CH_2Cl_2 (4 mL) at 0 °C. After stirring for 5 h with gradual return to room temperature, the mixture was poured into H_2O (250 mL). The emulsion was stirred for 30 min and then acidified to pH4 with 6N HCl solution. After phase separation, the aqueous phase was extracted with CH_2Cl_2 (3 x 100 mL). The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (Toluene/PE/Et_2O, 2:1:1) to afford product **48a** as a yellow oil (1.04 g, 3.05 mmol, 28%, 2 steps).

$[\alpha]_D^{20}$**:** -43.9 (c = 0.976, $CHCl_3$).

^{1}H NMR (300 MHz in $CDCl_3$, δ ppm): 0.94-1.02 (m, 2 H, *c*-Hexyl-H), 1.17-1.25 (m, 3 H,H_{15} + 2H_{18}), 1.43 (m, 1 H, H_{14}), 1.49-1.69 (m, 6 H, *c*-Hexyl-H), 1.91 (m, 1 H,H_{14}),3.99 (dd, 1 H, *J*= 8.3, 7.8 Hz, 1H_{12}), 4.16 (d, 1 H, *J* = 17.0 Hz, 1H_1),4,48-4,56 (m, 3 H,1H_1 +1H_{12} +H_{13}), 6.02 (ddd, 1 H, *J* = 9.6, 5.7, 2.3 Hz, H_2), 6.57 (dd, 1 H, *J* = 9.6, 2.3 Hz, H_3), 7.11-7.22 (m, 3 H, Ar-H),7,35 (d, 1 H, *J* =7.8Hz, H_8).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 26.0 (C_{18}), 26.2($C_{c\text{-}Hex}$), 26.3 ($C_{c\text{-}Hex}$), 32.7 ($C_{c\text{-}Hex}$), 34.1 ($C_{c\text{-}Hex}$), 34.5 (C_{15}), 40.6 (C_{14}), 45.6 (C_1), 54.0 (C_{13}), 68.9 (C_{12}), 122.7 (C_8), 125.4 (C_6), 125.6 (C_3), 126.5 (C_2), 126.7 (C_7), 127.6 (C_5), 128.6 (Cq), 136.2 (Cq), 152.4 (C_{10}), 153.4 (C_{11}).

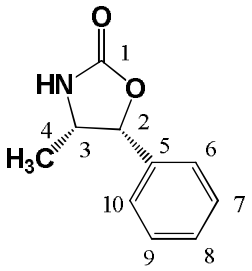
IR: (ν cm^{-1}) 3053 ($\nu_{C\text{-}Haro}$), 2924, 2851 ($\nu_{C\text{-}Hsat}$), 1778 ($\nu_{C=Ocarbamate}$), 1682 ($\nu_{C=Ourea}$), 1602, 1572, 1491, 1449 ($\nu_{C=Caro}$), 1220 ($\nu_{C\text{-}Oester}$).

MS (CI): m/z = 358 $[M+NH_4]^+$, 341 $[M+H]^+$.

HRMS (ESI):

Calculated for $C_{20}H_{25}N_2O_3$ $[M]^+$ = 341.1865; Found: $[M+H]^+$ = 341.1852.

(4*S*,5*R*)-4-Methyl-5-phenyl-1,3-oxazolidin-2-one **99**



$C_{10}H_{11}NO_2$

M = 177.20 g/mol

MP = 105 °C

To a solution of (1*R*,2*S*)-(-)-norephedrine (2.0 g, 13.2 mmol) in diethyl carbonate (4.0 mL, 33.1 mmol) was added K_2CO_3 (0.183 g, 1.32 mmol) and the reaction was stirred for 4 h at 140 °C using a Dean-Stark apparatus. After cooling to room temperature, the mixture was diluted by addition of H_2O (30 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo to afford product **99** as a white solid (2.05 g, 11.62 mmol, 88%).

$[\alpha]_D^{20}$**:** -159.0 (c = 0.57, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 0.81 (d, 3H, *J* = 6.6 Hz, H_4), 4.21 (dq, 1 H, *J* = 7.9, 6.6 Hz, H_3), 5.71 (d, 1 H, *J* = 7.9 Hz, H_2), 5.88 (s, 1 H, NH), 7.27-7.32 (m, 2 H, Ar-H), 7.34-7.41 (m, 3 H, Ar-H).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 17.7 (C_4), 52.5 (C_3), 81.1 (C_2), 126.1 (2$\underline{C}H_{Ar}$), 128.6 (3$\underline{C}H_{Ar}$), 135.0 (C_5), 159.5 (C_1).

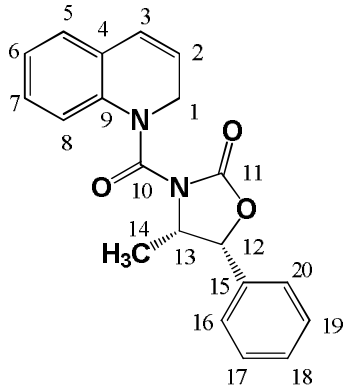
IR: (ν cm^{-1}) 3165 (ν_{N-H}), 3026 (ν_{C-Haro}), 2971, 2912, 2841 (ν_{C-Hsat}), 1749 ($\nu_{C=Ocarbamate}$), 1237 ($\nu_{C-Oester}$).

MS (CI): m/z = 195 $[M+NH_4]^+$, 178 $[M+H]^+$.

HRMS (ESI):

Calculated for $C_{10}H_{11}NO_2$ $[M]^+$ = 178.0863; Found: $[M]^+$ = 178.0898

(4*S*,5*R*) 4-methyl-5-phenyl-3-(quinolin-1(2*H*)-ylcarbonyl)-1,3-oxazolidin-2-one **48b**



$C_{20}H_{18}N_2O_3$

M = 334.37 g/mol

MP = 149 °C

According to the general procedure 3, the reaction gave product **48b** as a white solid (60%, 2 steps). R_f = 0.20 (PE/EtOAc, 4:1). Additional purification could be achieved by recrystallisation from PE/EtOAc affording the major product as colourless crystals.

$[\alpha]_D^{20}$**:** -139.0 (c = 0.95, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 1.00 (d, 3 H, *J* = 6.5 Hz, H_{14}), 4.15 and 4.63 (AB part of ABX system, *J* = 19.2, 5.4, 2.3 Hz, H_1), 4.73-4.82 (m, 1H, H_{13}), 5.59 (d, 1 H, *J* = 8.3 Hz, H_{12}), 6.03-6.09 (m, 1 H, H_2), 6.60 (dd, 1H, *J* = 9.6, 1.4 Hz, H_3), 7.14-7.22 (m, 6 H, Ar-H), 7.40-7.44 (m, 3 H, Ar-H).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm: 15.1 (C_{14}), 45.2 (C_1), 55.6 (C_{13}), 79.2 (C_{12}), 122.2 (C_8), 125.6 (C_2, C_6), 126.4 (2*C*H$_{Ar}$), 126.5 (Cq), 126.6 (C_3), 126.8 (C_7), 127.4 (C_5), 128.8 (2*C*H$_{Ar}$), 129.1 (C_{18}), 134.8 (Cq), 136.4 (Cq), 152.2 (C_{10}), 152.8 (C_{11}).

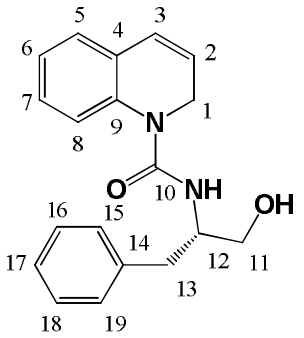
IR: (ν cm^{-1}) 3054, 3028 ($\nu_{C\text{-}Haro}$), 2973, 2932, 2866 ($\nu_{C\text{-}Hsat}$), 2828 (ν_{OCH3}), 1769 ($\nu_{C=Oester}$), 1698 ($\nu_{C=Ourea}$), 1601, 1577, 1501 ($\nu_{C=Caro}$), 1214, 1074 ($\nu_{C\text{-}Oester}$).

MS (CI): m/z = 352 $[M+NH_4]^+$, 335 $[M+H]^+$.

HRMS (Maldi-PEG400):

Calculated for $C_{20}H_{18}N_2O_3Na$ $[M+Na]^+$ = 357.1210; Found: $[M+Na]^+$ = 357.1217.

N-[(2*S)*-1-hydroxy-3-phenylpropan-2-yl]quinoline-1(2*H)*-carboxamide **48d**



$C_{19}H_{20}N_2O_2$

M = 308.37 g/mol

To a solution of dihydroquinoline **48** (0.334 g, 1.0 mmol) in a mixture of THF (20 mL) and MeOH (2 mL) was added $LiBH_4$ (65 mg, 3.0 mmol). After 6 h stirring at reflux, the reaction was cooled to 0 °C and then acidified with 1M HCl and basified with 10% NaOH. The mixture was extracted with CH_2Cl_2 (3 x 100 mL). The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (CH_2Cl_2/EtOAc, 7:3) to afford product **48d** as a colourless oil (0.305 g, 0.99 mmol, 99%).

$[\alpha]_D^{20}$**:** -132.0 (c = 0.996, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.71 and 2.92 (AB part of ABX system, 2 H, *J* = 14.1, 8.9, 6.1 Hz, H_{13}), 3.56 and 3.70 (AB part of ABX system, *J* = 10.5, 5.9, < 1.0 Hz, H_{11}), 3.76 (s, 1 H, H_{OH}), 4.11 (ddd, 1 H, *J* = 16.9, 3.5, 2.0 Hz, H_1), 4.10-4.21 (m, 1 H, H_{12}), 4.55 (ddd, 1 H, *J* = 16.9, 4.7, 1.2 Hz, H_1), 5.27 (d, 1 H, *J* = 6.0 Hz, NH), 6.02 (m, 1 H, H_2), 6.45 (d, 1 H, *J* = 9.6 Hz, H_3), 6.65 (d, 1 H, *J* = 7.8 Hz, H_8), 6.96-7.09 (m, 3 H, Ar-H), 7.16-7.19 (m, 2 H, Ar-H), 7.23-7.34 (m, 3 H, Ar-H).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 37.0 (C_{13}), 42.5 (C_1), 54.4 (C_{12}), 65.1 (C_{11}), 122.3 (C_8), 124.8 (C_6), 125.7 (C_3), 126.6 (C_{17}), 126.9 (C_5), 127.7 (C_7), 127.8 (C_2), 128.6 (2$\underline{C}H_{Ar}$), 129.2 (2$\underline{C}H_{Ar}$ + 1Cq_{Ar}), 136.5 (Cq), 137.8 (Cq_{Ar}), 156.4 (C_{10}).

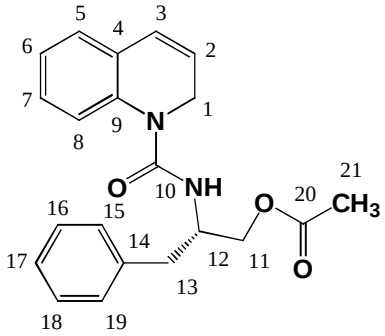
IR: (ν cm^{-1}) 3420 (ν_{N-H}), 3027 (ν_{C-Haro}), 2927, 2849 (ν_{C-Hsat}), 1643 ($\nu_{C=Ourea}$), 1601, 1487, 1456 ($\nu_{C=Caro}$), 752, 702 (ν_{C-Haro}).

MS (EI): m/z (rel. int.)= 308 ($[M]^+$, 9), 158 (6), 130 (100).

HRMS (Maldi-PEG200):

Calculated for $C_{19}H_{21}N_2O_2$ $[M+H]^+$ = 309.1538; Found: $[M+H]^+$ = 309.1607

(2*S*)-3-Phenyl-2-[(quinolin-1(2*H*)-ylcarbonyl)amino]propyl acetate **48e**



$C_{21}H_{22}N_2O_3$

M = 350.41 g/mol

To a solution of dihydroquinoline **48d** (0.463 g, 1.5 mmol) in CH_2Cl_2 (10 mL) were successively added Et_3N (0.1 mL, 0.75 mmol) and acetyl chloride (0.16 mL, 2.25 mmol). After 2 h stirring at room temperature, the mixture was quenched by addition of H_2O (30 mL). After phase separation, the aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL). The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (EP/EtOAc, 7:3, R_f = 0.33) to yield product **48e** as a yellow oil (3.78 g, 0.108 mmol, 72%).

$[\alpha]_D^{20}$**:** -143.0 (c = 1.03, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.04 (s, 3 H, H_{21}), 2.83 (d, 2 H, *J* = 7.1 Hz, H_{13}),4.04 (d, 1 H, *J* = 2.2 Hz, $1H_{11}$), 4.06 (d, 1 H, *J* = 4.8 Hz, $1H_{11}$), 4.28-4.46 (m, 3 H, $2H_1 + H_{12}$), 5.18 (d, 1 H, *J* = 8.1 Hz, NH), 6.07 (dt, 1 H, *J* = 9.5, 4.1 Hz, H_2), 6.48 (d, 1 H, *J* = 9.5 Hz, H_3), 6.90-6.93 (m, 1 H, H_6), 7.07-7.16 (m, 5 H, Ar-H), 7.22-7.32 (m, 3 H, Ar-H).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 21.0 (C_{21}), 37.8 (C_{13}), 42.5 (C_1), 51.0 (C_{12}), 65.2 (C_{11}), 122.6 (C_8), 125.0 (C_6), 125.9 ($\underline{C}H_{Ar}$), 126.9 ($\underline{C}H_{Ar}$), 127.2 ($\underline{C}H_{Ar}$), 127.6 ($\underline{C}H_{Ar}$), 128.3 ($\underline{C}H_{Ar}$), 128.8 ($2\underline{C}H_{Ar}$), 129.4 ($2\underline{C}H_{Ar}$), 129.7 (Cq), 136.9 (Cq), 137.4 (Cq), 155.3 (C_{10}), 171.0 (C_{20}).

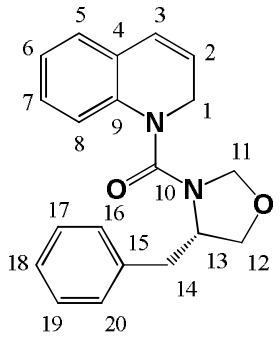
IR: (ν cm^{-1}) 3061, 3027 ($\nu_{C\text{-}Haro}$), 2968, 2922, 2857 ($\nu_{C\text{-}Hsat}$), 1732 ($\nu_{C=Oester}$), 1644 ($\nu_{C=Ourea}$), 1599, 1537, 1493 ($\nu_{C=Caro}$), 1257, 1231, 1042 ($\nu_{C\text{-}Oester}$).

MS (EI): m/z (rel. int.) = 350 ($[M]^+$, 8), 176 (8), 130 (100).

HRMS (Maldi-PEG400)**:**

Calculated for $C_{21}H_{23}N_2O_3$ $[M+H]^+$ = 351.1703; Found: $[M+H]^+$ = 351.1707

[(4*S*)-4-Benzyl-1,3-oxazolidin-3-yl](quinolin-1(2*H*)-yl)methanone **48c**



$C_{20}H_{20}N_2O_2$

M = 320.38 g/mol

A suspension of paraformaldehyde (0.480 g, 16 mmol), dihydroquinoline **48d** (1.23g, 4.0 mmol), and *p*-toluenesulfonic acid (76 mg, 0.4 mmol) in a 2:1 toluene-THF mixture (30 mL) was refluxed for 1h30. The solvent was then evaporated, and the crude residue was taken with CH_2Cl_2 (30 mL). The solid was filtered off, and the organic phase was washed with aqueous NaOH, water and brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (PE/EtOAc, 4:1, R_f = 0.26) to give product **48c** as a light yellow oil (0.359 g, 11.2 mmol, 70%).

$[\alpha]_D^{20}$**:** -291.3 (c = 0.944, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.73 and 3.20 (AB part of ABX system, 2 H,, J = 13.3, 9.4, 4.7 Hz, H_{14}), 3.62 (dd, 1 H, J= 8.7, 6.8 Hz, H_{12}), 3.90-3.97 (m, 2 H,$1H_1$ + $1H_{12}$), 4.33 (d, 1 H, J = 4.7 Hz, H_{11}), 4.44-4.61 (m, 3 H, $1H_1$ + $1H_{11}$ + H_{13}), 6.00-6.06 (ddd, 1H, J = 9.5, 6.1, 2.3 Hz, H_2), 6.48 (dd, 1 H, J = 9.5 Hz, H_3), 6.98-7.02 (m, 2 H, Ar-H), 7.06-7.12 (m, 2 H, Ar-H), 7.14-7.34 (m, 5 H, Ar-H).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 38.2 (C_{14}), 44.4 (C_1), 57.3 (C_{13}), 71.3 (C_{12}), 81.4 (C_{11}), 120.8 (C_8), 123.6 (C_6), 126.3 (C_3),126.9 (C_2, C_5, C_{18}), 127.8 (Cq), 128.0 (C_7), 128.7 (2$\underline{C}H_{Ar}$), 129.4 (2$\underline{C}H_{Ar}$), 137.6 (2Cq), 156.9 (C_{10}).

IR: (ν cm^{-1}) 3027 ($\nu_{C\text{-}Haro}$), 2927, 2862 ($\nu_{C\text{-}Hsat}$), 1651 ($\nu_{C=Ourea}$), 1600, 1487, 1454 ($\nu_{C=Caro}$), 1059 ($\nu_{C\text{-}O}$), 751, 702 ($\nu_{C\text{-}Haro}$).

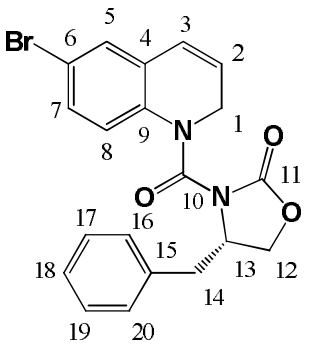
MS (EI): m/z (rel. int.)= 320 ($[M]^+$, 35), 229 (37), 130 (100).

HRMS (ESI)**:**

Calculated for $C_{20}H_{21}N_2O_2$ $[M+H]^+$ = 321.1603; Found: $[M+H]^+$ = 321.1593.

General procedure 4: Reduction - Acylation

(4*S*)-4-Benzyl-3-[(6-bromoquinolin-1(2*H*)-yl)carbonyl]-1,3-oxazolidin-2-one **48f**



$C_{20}H_{17}BrN_2O_3$

M = 413.26 g/mol

A solution of 6-bromo quinoline (1.00 mL, 7.16 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added a solution of 1M DIBAL-H in hexane (7.2 mL, 7.16 mmol) and the reaction was stirred for 1 h at room temperature. The resulting solution was cannulated to a solution of chloride acid **101** (0.88 g, 3.58 mmol) in CH_2Cl_2 (1.3 mL) at 0 °C. After stirring for 5 h with gradual return to room temperature, the mixture was poured into H_2O (80 mL). The emulsion was stirred for 30 min and then acidified to pH4 with 6N HCl solution. After phase separation, the aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL). The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (Toluene/PE/Et_2O, 2:1:1) to afford product **48f** as a colourless oil (1.41 g, 3.40 mmol, 95%).

$[\alpha]_D^{20}$**:** -10.8 (c = 0.910, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.93 and 3.23 (AB part of ABX system, 2 H, *J* = 13.6, 8.5, 3.4 Hz, H_{14}), 4.15 and 4.33 (AB part of ABX system, 2H, *J* = 9.2,8.8, 8.5 Hz, H_{12}), 4.19 and 4.39 (AB part of ABX system, 2 H, *J* = 17.1, 5.5, 2.5 Hz, H_1), 4.79 (m, 1 H, H_{13}), 6.04 (ddd, 1 H, *J* = 9.6, 5.5, 2.5 Hz, H_2), 6.52 (dd, 1 H, *J* = 9.6, 1.9 Hz, H_3), 7.14-7.19 (m, 2 H, Ar-H), 7.24-7.36 (m, 6 H, Ar-H).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 37.2 (C_{14}), 46.0 (C_1), 56.5 (C_{13}), 67.0 (C_{12}), 118.5 (C_6), 124.6 (C_7), 125.3 (C_3), 126.8 (C_2), 127.5 ($\underline{C}H_{Ar}$), 129.1 (2$\underline{C}H_{Ar}$), 129.3 ($\underline{C}H_{Ar}$), 129.6 (2$\underline{C}H_{Ar}$), 130.3 (Cq), 130.4 ($\underline{C}H_{Ar}$), 134.8 (Cq), 135.0 (Cq), 152.4 (C_{10}), 153.2 (C_{11}).

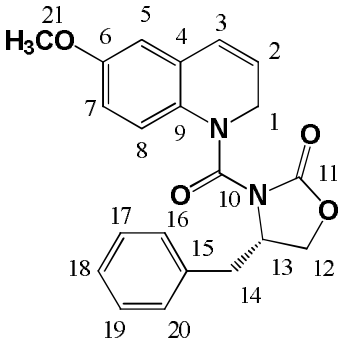
IR: (ν cm^{-1}) 3028 ($\nu_{C\text{-}Haro}$), 2916, 2856 ($\nu_{C\text{-}Hsat}$), 1771 ($\nu_{C=Ocarbamate}$), 1683 ($\nu_{C=Ourea}$), 1591, 1485, 1455 ($\nu_{C=Caro}$), 1218, 1055 ($\nu_{C\text{-}Oester}$), 755, 704 ($\nu_{C\text{-}Haro}$).

MS (CI): m/z = 432, 430 $[M+NH_4]^+$, 415, 413 $[M+H]^+$.

HRMS (Maldi-PEG400):

Calculated for $C_{20}H_{17}BrN_2O_3Na$ $[M+Na]^+$ = 435.0315; Found: $[M+Na]^+$ = 435.0318

(4*S*)-4-Benzyl-3-[(6-methoxyquinolin-1(2*H*)-yl)carbonyl]-1,3-oxazolidin-2-one **48g**



$C_{21}H_{20}N_2O_4$

M = 364.39 g/mol

According to the general procedure 4 and starting from 6-methoxyquinoline, the reaction was stirred for 3 h at room temperature before adding acid chloride **101** to give **48g** as a colourless oil (80%). R_f = 0.28 (PE/EtOAc, 7:3).

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.90 and 3.22 (AB part of ABX system, 2 H, *J* = 13.6, 8.6, 3.2 Hz, H_{14}), 3.81 (s, 3 H, H_{21}), 4.12 and 4.30 (AB part of ABX system, 2H, *J* = 9.1, 8.8, 8.5 Hz, H_{12}), 4.16 (ddd, 2H, *J* = 17.0, 2.4, 2.2 Hz, H_1), 4.40 (dd, 1 H, *J* = 17.0, 5.4 Hz, $1H_1$), 4.75(m, 1 H, H_{13}), 6.02 (ddd, 1 H, *J* = 9.6, 5.4, 2.4 Hz, H_2), 6.55 (dd, 1 H, *J* = 9.6, 2.2 Hz, H_3), 6.68 (d, 1 H, *J* = 2.9 Hz, H_5), 6.77 (dd, 1 H, *J* = 8.9, 2.9 Hz, H_7), 7.13-7.16 (m, 2 H, Ar-H), 7.24-7.35 (m, 4 H, Ar-H).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 37.4 (C_{14}), 46.1 (C_1), 55.6 (C_{21}), 56.5 (C_{13}), 67.1 (C_{12}), 111.6 (C_5), 113.2 (C_7), 124.3 (C_8), 126.2 (C_2), 126.5 (C_3), 127.5 (C_{18}), 129.1 ($2\underline{C}H_{Ar}$ + $1Cq_{Ar}$), 129.6 ($2\underline{C}H_{Ar}$), 135.0 ($2Cq_{Ar}$), 152.4 (C_{10}), 153.5 (C_{11}), 157.3 (C_6).

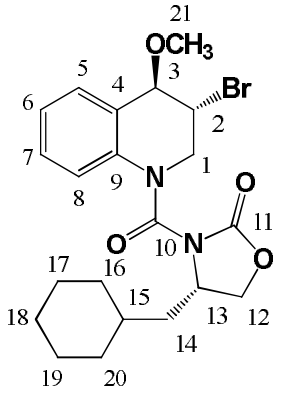
IR: (ν cm^{-1}) 3028, 3002 ($\nu_{C\text{-}Haro}$), 2915 ($\nu_{C\text{-}Hsat}$), 2836 (ν_{OCH3}), 1790 ($\nu_{C=Ocarbamate}$), 1683 ($\nu_{C=Ourea}$), 1606, 1576, 1495 ($\nu_{C=Caro}$), 1055 ($\nu_{C\text{-}Oester}$).

MS (CI) : m/z = 382 $[M+NH_4]^+$, 365 $[M+H]^+$.

HRMS (Maldi-PEG400):

Calculated for $C_{21}H_{20}N_2O_4Na$ $[M+Na]^+$ = 387.1315; Found: $[M+Na]^+$ = 387.1323

(4*S*)-4-(Cyclohexylmethyl)-3-{[(3*R*,4*R*)-3-bromo-4-methoxy-3,4-dihydroquinolin-1(2*H*)-yl-]carbonyl}-1,3-oxazolidin-2-one **102a**



$C_{21}H_{27}BrN_2O_4$

M = 451.35 g/mol

MP: 76.4 °C

According to the general procedure 2 and starting from dihydroquinoline **48a** (0.170 g, 0.5 mmol), the reaction gave a mixture of diastereoisomers (0.178 g, 0.395 mmol, 79%, *dr* = 92/08). Further purification by silica gel chromatography (PE/EtOAc, 4:1, R_f = 0.27) isolated the major product **102a** as a white solid.

$[\alpha]_D^{20}$**:** +4.5 (c = 0.73, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 0.87-0.99 (m, 2 H, *c*-Hexyl-H), 1.12-1.27 (m, 3 H,H_{15} + 2H_{18}), 1.35-1.45 (m, 1 H, H_{14}), 1.61-1.74 (m, 6 H, *c*-Hexyl-H), 1.94-2.03 (m, 1 H,H_{14}), 3.54 (s, 3 H,H_{21}), 4.02 and 4.57 (AB part of ABX system, 2H, *J*= 9.0, 8.6, 8.4 Hz, H_{12}), 4.10 (d, 2 H, *J* = 2.0 Hz, H_1), 4.37 (d, 1 H, *J* = 2.3 Hz, H_3), 4.45 (dd, 1 H, *J* = 2.3, 2.0 Hz, H_2), 4.69 (m, 1H, H_{13}), 7.16 (td, 1 H, *J* = 7.5, 1.1 Hz, H_6), 7.27-7.36 (m, 2 H, H_5, H_7), 7.61 (br. d, 1 H, *J* = 8.3 Hz, H_8).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 25.9 ($C_{c\text{-}Hex}$), 26.0 (C_{18}), 26.2 ($C_{c\text{-}Hex}$), 32.4 ($C_{c\text{-}Hex}$), 33.9 ($C_{c\text{-}Hex}$), 34.3 (C_{15}), 40.8 (C_{14}), 45.9 (C_2), 48.8 (C_1), 53.8 (C_{13}), 57.7 (C_{21}), 69.0 (C_{12}), 78.8 (C_3), 123.3 (C_8),125.0 (C_6), 128.7 (C_7), 130.7 (C_5), 133.7 (Cq),136.0 (Cq), 153.3 (C_{10}), 153.4 (C_{11}).

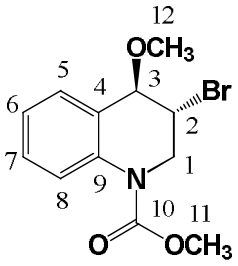
IR: (ν cm^{-1}) 2922, 2850 ($\nu_{C\text{-}Hsat}$), 1771 ($\nu_{C=O\ carbamate}$), 1694 ($\nu_{C=O\ urea}$), 1606, 1586, 1492, 1449 ($\nu_{C=Caro}$), 1219, 1073($\nu_{C\text{-}O\ ester}$).

MS (EI): m/z (rel. int.) = 452 ($[M]^+$, 8), 450 ($[M]^+$, 8), 421 (7), 419 (10), 339 (100).

HRMS (Maldi-PEG400):

Calculated for $C_{21}H_{27}BrN_2O_4Na$ $[M+Na]^+$ = 473.1046; Found: $[M+Na]^+$ = 473.1065

Methyl (3*R*,4*R*)-3-bromo-4-methoxy-3,4-dihydroquinoline-1(2*H*)-carboxylate **104**



$C_{12}H_{14}BrNO_3$

M = 300.15 g/mol

To a solution of **73a** (0.223 g, 0.50 mmol) in dry MeOH (5.0 mL) was added $Sm(OTf)_3$ (0.149 g, 0.25 mmol). The reaction mixture was refluxed for 4 h. After cooling to room temperature, the mixture was filtered through a plug of celite with subsequent washing with EtOAc. The filtrate was concentrated *in vacuo*. The crude product was purified by column chromatography (PE/Et_2O, 1:4) to give product **104** as a yellow oil (0.116g, 0.39 mmol, 77%).

According to the above procedure and starting from **102a** (0.226 g, 0.5 mmol), the reaction gave product **104** (0.111g, 0.37 mmol, 74%).

$[\alpha]_D^{20}$**:** -45.8 (c = 1.365, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 3.52 (s, 3 H, H_{12}), 3.83 (s, 3 H,H_{11}), 3.90 (dd, 1 H, *J* = 11.7, 4.8 Hz, $1H_1$), 4.41-4.47 (m, 3 H,$1H_1$, H_2, H_3), 7.12 (m, 1 H,H_6), 7.30-7.34 (m, 2 H,H_5, H_7), 7.83 (d, 1 H, *J* = 8.6Hz, H_8).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 45.4 (C_2), 46.5 (C_1), 53.4 (C_{11}), 57.4 (C_{12}), 80.0 (C_3), 123.4 (C_8), 124.1 (C_6), 124.7 (C_4), 128.9 (C_7), 130.5 (C_5), 136.8 (C_9), 155.3 (C_{10}).

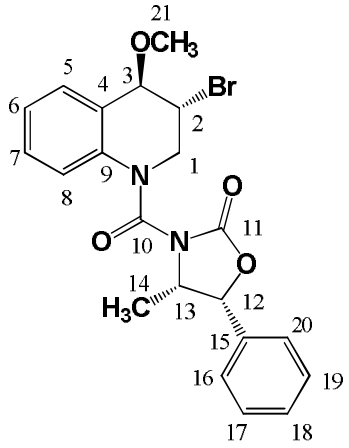
IR: (ν cm^{-1}) 2952 ($\nu_{C\text{-}Hsat}$), 2823 (ν_{OCH3}), 1713 ($\nu_{C=O}$), 1606, 1583, 1491 ($\nu_{C=Caro}$), 1219 ($\nu_{C\text{-}Oester}$), 1074 ($\nu_{C\text{-}O}$).

MS (EI): m/z (rel. int.) = 301 ($[M]^+$, 59), 299 ($[M]^+$, 63), 270 (19), 268 (18), 220 (6), 188 (100).

HRMS (Maldi-PEG1000):

Calculated for $C_{12}H_{14}BrNO_3$ $[M]^+$ = 299.0152; Found: $[M]^+$ = 299.0152

(4*S*,5*R*)-3-{[(3*R*,4*R*)-3-bromo-4-methoxy-3,4-dihydroquinolin-1(2H)-yl]carbonyl}-4-methyl-5-phenyl-1,3-oxazolidin-2-one **102b**



$C_{21}H_{21}BrN_2O_4$

M = 445.31 g/mol

MP: 152 °C

According to the general procedure 2 and starting from dihydroquinoline **48b** the reaction gave product mixture of diastereoisomers as a white solid (90%, *dr* = 75/25). R_f = 0.41 (EP/EtOAc, 7:3). Additional purification could be achieved by recrystallisation from PE/EtOAc to afford the major product **102b** as colourless crystals.

$[\alpha]_D^{20}$**:** -38.6 (c = 0.75, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 0.97 (d, 3H, *J* = 6.5 Hz, H_{14}), 3.59 (s, 3 H,H_{21}), 4.17 (d, 2 H, *J* = 2.9 Hz, H_1), 4.42 (d, 1 H, *J* = 2.9 Hz, H_3), 4.48 (t, 1 H, *J* = 2.9 Hz, H_2), 4.95 (dq, 1 H, *J* = 8.6, 6.5 Hz, H_{13}), 5.67 (d, 1 H, *J* = 8.6 Hz, H_{12}), 7.17-7.25 (m, 3 H, Ar-H), 7.30-7.47 (m, 5 H, Ar-H), 7.55 (d, 1 H, *J* = 8.3 Hz, H_8).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 15.4 (C_{14}), 46.3 (C_2), 49.4 (C_1), 55.2 (C_{13}), 58.0 (C_{21}), 79.2 (C_3), 79.4 (C_{12}), 123.3 (C_8), 125.3 ($\underline{C}H_{Ar}$), 125.6 (C_4), 126.4 ($2\underline{C}H_{Ar}$), 128.8 ($\underline{C}H_{Ar}$), 128.9 ($2\underline{C}H_{Ar}$), 129.2 ($\underline{C}H_{Ar}$), 130.4 ($\underline{C}H_{Ar}$), 134.9 (Cq), 136.4 (Cq), 152.9 (C_{10}), 153.1 (C_{11}).

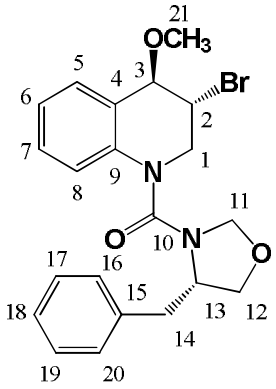
IR: (ν cm^{-1}) 2988, 2935 ($\nu_{C\text{-}Hsat}$), 2830 (ν_{OCH3}), 1771 ($\nu_{C=O\ carbamate}$), 1685 ($\nu_{C=O\ urea}$), 1606, 1587, 1493 ($\nu_{C=Caro}$), 1229, 1212 ($\nu_{C\text{-}Oester}$), 1072 ($\nu_{C\text{-}O}$).

MS (CI): m/z = 446, 444 $[M+H]^+$, 415, 413.

HRMS (Maldi-PEG400):

Calculated for $C_{21}H_{21}BrN_2O_4Na$ $[M+Na]^+$ = 467.0577; Found: $[M+Na]^+$ = 467.0582.

[(4*S*)-4-benzyl-1,3-oxazolidin-3-yl][(3*R*,4*R*)-3-bromo-4-methoxy-3,4-dihydroquinolin-1(2*H*)-yl)methanone **102c**



$C_{21}H_{23}BrN_2O_3$

M = 431.32 g/mol

According to the general procedure 2 and staring from dihydroquinoline **48c**, the reaction mixture was stirred for 2 h at room temperature and gave product mixture of diastereoisomers (72%, *dr* = 82/18). Further purification by silica gel chromatography (PE/EtOAc, 7:3, R_f = 0.45) isolated the major product **102c** as a light yellow oil.

$[\alpha]_D^{20}$**:** -140.0 (c = 0.624, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.83 and 3.27 (AB part of ABX system, 2 H, *J* = 13.4, 9.2, 4.6 Hz, H_{14}),3.57 (s, 3 H, H_{21}), 3.63-3.70 (m, 2 H, $1H_1$, $1H_{12}$),4.02 (dd, 1 H, *J* = 8.8, 6.8 Hz, H_{12}), 4.29-4.37 (m, 3 H, $1H_1$, H_3, $1H_{11}$), 4.48-4.51 (m, 1 H, H_2), 4.63-4.73 (m, 1 H, H_{13}), 4.84 (d, 1 H, *J* = 4.7 Hz, $1H_{11}$), 7.02-7.11 (m, 2 H, Ar-H), 7.20-7.37 (m, 7 H, Ar-H).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 38.1 (C_{14}), 46.3 (C_2), 46.8 (C_1), 57.6 (C_{13}), 57.7 (C_{21}), 71.2 (C_{12}), 79.6 (C_3), 81.3 (C_{11}), 120.4 (C_8), 123.0 (C_6), 123.4 (C_4), 126.9 ($\underline{C}H_{Ar}$), 128.8 ($2\underline{C}H_{Ar}$), 129.2 ($\underline{C}H_{Ar}$), 129.5 ($2\underline{C}H_{Ar}$), 131.6 (C_5), 137.6 (C_9, C_{15}), 157.3 (C_{10}).

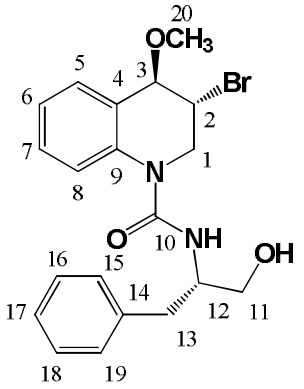
IR: (ν cm^{-1}) 3061, 3026 ($\nu_{C\text{-}Haro}$), 2987, 2928, 2863 ($\nu_{C\text{-}Hsat}$), 2822 (ν_{OCH3}), 1653 ($\nu_{C=Ourea}$), 1605, 1579, 1490, 1461 ($\nu_{C=Caro}$), 1072 ($\nu_{C\text{-}Oester}$), 754, 701 ($\nu_{C\text{-}Haro}$).

MS (EI): m/z (rel. int.) = 432 ($[M]^+$, 74), 430 ($[M]^+$, 75), 341 (85), 339 (89), 269 (50), 267 (55), 188 (60), 130 (100).

HRMS (Maldi-PEG400):

Calculated for $C_{21}H_{23}BrN_2O_3Na$ $[M+Na]^+$ = 544.9682; Found: $[M+Na]^+$ = 544.9700

(3*R*,4*R*)-3-bromo-*N*-[(2*S*)-1-hydroxy-3-phenylpropan-2-yl)-4-methoxy-3,4-dihydroquinoline-1(2*H*)-carboxamide **102d**



$C_{20}H_{23}BrN_2O_3$

M = 419.31 g/mol

MP: 129.2 °C

According to the general procedure 2 and starting from dihydroquinoline **48d**, the reaction was stirred for 2 days at room temperature and gave a mixture of diastereoisomers (59%, *dr* = 55/45). Further purification by silica gel chromatography (EP/EtOAc, 1:1) isolated the major (R_f = 0.29) and minor product (R_f = 0.24) **102d** and **103d** as a white solid and a crystalline solid respectively.

$[\alpha]_D^{20}$**:** -168.0 (c = 1.088, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.69 and 3.01 (AB part of ABX system, 2 H, *J* = 14.2, 9.9, 5.7 Hz, H_{13}), 3.52 (s, 3 H, H_{20}), 3.57-3.63 (m, 2 H, $1H_1$, $1H_{11}$), 3.78 (dd, 1 H, *J* = 11.0, 3.3 Hz, H_{11}), 4.23-4.33 (m, 1 H, H_{12}), 4.35 (d, 1 H, *J* = 2.1 Hz, H_3), 4.45-4.48 (m, 1 H, H_2), 4.59 (dd, 1 H, *J* = 14.1, 3.1 Hz, H_1), 5.30 (d, 1 H, *J* = 7.4 Hz, NH), 6.59 (dd, 1 H, *J* = 9.3, 2.0 Hz, H_8), 7.04-7.13 (m, 2 H, Ar-H), 7.21-7.39 (m, 6 H, Ar-H).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 37.1 (C_{13}), 45.7 (C_1), 47.2 (C_2), 54.7 (C_{12}), 57.7 (C_{20}), 66.3 (C_{11}), 80.0 (C_3), 122.4 (C_8), 124.6 (C_6), 126.2 (C_4), 127.0 (C_{17}), 128.9 (2$\underline{C}H_{Ar}$), 129.3 (2$\underline{C}H_{Ar}$), 129.4 (C_7), 131.7 (C_5), 137.2 (Cq), 137.8 (Cq), 157.6 (C_{10}).

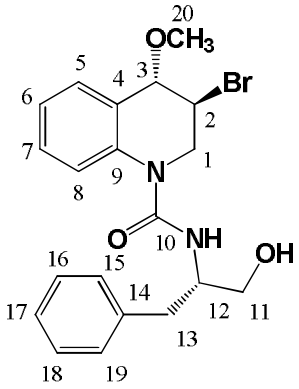
IR: (ν cm^{-1}) 3337 (ν_{N-H}), 3061, 3027 (ν_{C-Haro}), 2933, 2869 (ν_{C-Hsat}), 2820 (ν_{OCH3}), 1642 ($\nu_{C=Ourea}$), 1606, 1578, 1510, 1459 ($\nu_{C=C-Aryl}$), 1211 (ν_{C-O}).

MS (CI): m/z = 421, 419 $[M+H]^+$, 389, 387.

HRMS (Maldi-PEG400)**:**

Calculated for $C_{20}H_{24}BrN_2O_3$ $[M+H]^+$ = 419.0965; Found: $[M+H]^+$ = 419.0964

(3*S*,4*S*)-3-bromo-*N*-[(2*S*)-1-hydroxy-3-phenylpropan-2-yl)-4-methoxy-3,4-dihydroquinoline-1(2*H*)-carboxamide **103d**



$C_{20}H_{23}BrN_2O_3$

M = 419.31 g/mol

MP: 136.8 °C

$[\alpha]_D^{20}$**:** +22.5 (c = 0.636, $CHCl_3$).

^{1}HNMR (300 MHz, $CDCl_3$, δ ppm): 2.87 (d, 2 H, *J* = 7.5 Hz, H_{13}), 3.53 (s, 3 H, H_{20}), 3.64 and 3.77 (AB part of ABX system, 2 H, *J* = 11.0, 5.6, 3.4 Hz, H_{11}), 3.86 (dd, 1 H, *J* = 13.7, 2.6 Hz, $1H_1$), 4.05-4.15 (m, 1 H,H_{12}),4.33-4.39 (m, 2 H, $1H_1$, H_3), 4.44-4.47 (m, 1 H, H_2), 5.45 (d, 1 H, *J* = 7.1 Hz, NH),6.95 (dd, 1 H, *J* = 8.0, 1.5 Hz, H_8), 7.09-7.30 (m, 7 H, Ar-H), 7.36 (dd, 1 H, *J* = 7.4, 1.9 Hz, H_5).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 37.0 (C_{13}), 46.4 (C_1), 46.7 (C_2), 54.8 (C_{12}), 57.7 (C_{20}), 65.2 (C_{11}), 80.6 (C_3), 122.4 (C_8), 124.6 (C_6), 126.8 (Cq+C_{17}), 128.8 (2$\underline{C}H_{Ar}$), 129.4 (3$\underline{C}H_{Ar}$), 131.5 (C_5), 137.6 (Cq), 137.9 (Cq), 157.1 (C_{10}).

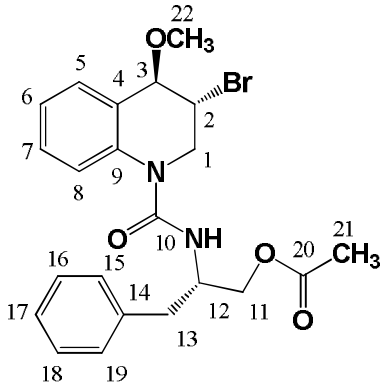
IR: (ν cm^{-1}) 3409 (ν_{N-H}), 3059, 3020 (ν_{C-Haro}), 2921 (ν_{C-Hsat}), 2821 (ν_{OCH3}), 1639 ($\nu_{C=Ourea}$), 1604, 1582, 1492, 1457 ($\nu_{C=Caro}$), 1078 (ν_{C-O}), 775, 703 (ν_{C-Haro}).

MS (CI): m/z = 421, 419 $[M+H]^+$.

Elemental analysis: for $C_{20}H_{23}BrN_2O_3$

Calculated:	%C = 57.29	%H = 5.53	%N = 6.68
Found:	%C = 57.38	%H = 5.60	%N = 6.57

(2*S*)-2-({[(3*R*,4*R*)-3-bromo-4-methoxy-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}amino)-3-phenylpropylacetate **102e**



$C_{22}H_{25}BrN_2O_4$

M = 461.35 g/mol

MP = 97 °C

According to the general procedure 2 and starting from dihydroquinoline **48e**, the reaction was stirred for 6 h at room temperature and gave a mixture of diastereoisomers (92%, *dr* = 63/37). Further purification by silica gel chromatography (EP/EtOAc, 7:3, R_f = 0.38) isolated the major product **102e** as a white solid.

$[\alpha]_D^{20}$**:** -128.6 (c = 1.0, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.03 (s, 3 H, H_{21}), 2.80 and 2.96 (AB part of ABX system, 2 H, *J* = 14.1, 8.4, 6.4 Hz, H_{13}), 3.53 (s, 3 H, H_{22}), 3.68 (dd, 1 H, *J* = 13.1, 1.3 Hz, $1H_1$), 4.10 (d, 1 H, *J* = 1.5 Hz, $1H_{11}$), 4.11 (d, 1 H, *J* = 1.2 Hz, $1H_{11}$), 4.37 (br. s, 1 H, H_3), 4.39-4.52 (m, 3 H, $1H_1$, H_2, H_{12}), 5.23 (d, 1 H, *J* = 8.2 Hz, NH), 6.83 (dd, 1 H, *J* = 7.9, 1.6 Hz, H_8), 7.09-7.39 (m, 8 H, Ar-H).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 21.0 (C_{21}), 37.6 (C_{13}), 45.8 (C_1), 46.9 (C_2), 51.2 (C_{12}), 57.7 (C_{22}), 65.2 (C_{11}), 80.2 (C_3), 122.4 (C_8), 124.4 ($\underline{C}H_{Ar}$), 126.2 (Cq), 127.0 ($\underline{C}H_{Ar}$), 128.8 ($2\underline{C}H_{Ar}$), 129.2 (C_{17}), 129.3 ($2\underline{C}H_{Ar}$), 131.6 ($\underline{C}H_{Ar}$), 137.5 (2Cq), 156.1 (C_{10}), 170.9 (C_{20}).

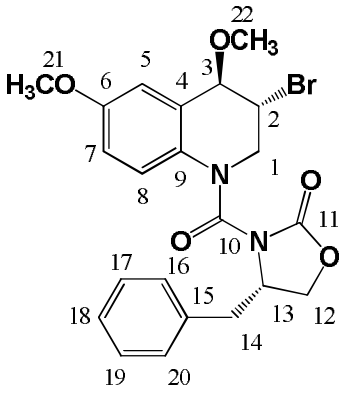
IR: (ν cm^{-1}) 3380 (ν_{N-H}), 3065, 3028 (ν_{C-Haro}), 2925 (ν_{C-Hsat}), 2817 (ν_{OCH3}), 1741 ($\nu_{C=Oester}$), 1646 ($\nu_{C=Ourea}$), 1605, 1580, 1510, 1460 ($\nu_{C=Caro}$).

MS (CI): m/z = 463, 461 $[M+H]^+$.

HRMS (Maldi-PEG400):

Calculated for $C_{22}H_{25}BrN_2O_4Na$ $[M+Na]^+$ = 483.0890; Found: $[M+Na]^+$ = 483.0885.

(4*S*)-4-Benzyl-3-{[(3*R*,4*R*)-3-bromo-4,6-dimethoxy-3,4-dihydroquinolin-1(2*H*)-yl-]carbonyl}-1,3-oxazolidin-2-one **102g**



$C_{22}H_{23}BrN_2O_5$

M = 475.33 g/mol

MP: 183.4 °C

According to the general procedure 2 and starting from dihydroquinoline **48g**, the reaction mixture was stirred for 2 h at room temperature to give a mixture of diastereoisomers as a yellow solid (80%, *dr* = 84/16). R_f = 0.32 (EP/EtOAc, 7:3). Additional purification could be achieved by recrystallisation from PE/EtOAc to afford the major product **102g** as colourless crystals.

$[\alpha]_D^{20}$**:** -40 (c = 0.17, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.65 and 3.52 (AB part of ABX system, 2 H, *J* = 13.1, 10.6, 3.7 Hz, H_{14}), 3.58 (s, 3 H, H_{22}), 3.82 (s, 3 H, H_{21}), 4.10-4.16 (m, 3 H, $2H_1$, $1H_{12}$), 4.28(dd, 1 H, *J* = 8.8, 8.5 Hz, H_{12}),4.38 (d, 1 H, *J* = 2.2 Hz, H_3), 4.49 (dd, 1 H, *J* = 2.6, 2.2 Hz, H_2), 4.78-4.89 (m, 1 H, H_{13}), 6.86 (d, 1 H, *J* = 2.9 Hz, H_5), 6.92 (dd, 1H, *J* = 9.1, 2.9 Hz, H_7), 7.19-7.22 (m, 2 H, Ar-H), 7.26-7.32 (m, 3 H, Ar-H), 7.56 (d, 1 H, *J* = 9.1 Hz, H_8).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 39.1 (C_{14}), 46.4 (C_2), 49.2 (C_1), 55.7 (C_{21}), 56.8 (C_{13}), 57.9 (C_{22}), 68.1 (C_{12}), 79.2 (C_3), 114.5 (C_5), 115.6 (C_7), 125.0 (C_8), 127.5 (C_{18}), 129.1 (4$\underline{C}H_{Ar}$), 129.2 (Cq), 135.4 (2Cq), 153.3 (C_{10}), 153.6 (C_{11}), 156.9 (C_6).

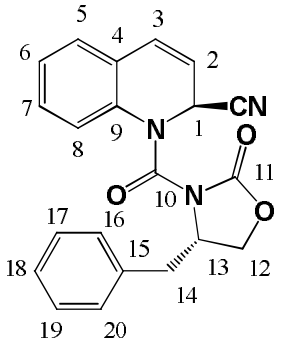
IR: (ν cm^{-1}) 3028 ($\nu_{C\text{-}Haro}$), 2932 ($\nu_{C\text{-}Hsat}$), 2828 (ν_{OCH3}), 1768 ($\nu_{C=O\ carbamate}$), 1696 ($\nu_{C=O\ urea}$).

MS (EI): m/z (rel. int.)= 476 ($[M]^+$, 18), 474 ($[M]^+$, 18), 363 (43), 160 (100).

HRMS (Maldi-PEG400):

Calculated for $C_{22}H_{23}BrN_2O_5Na$ $[M+Na]^+$ = 497.0683; Found: $[M+Na]^+$ = 497.0690.

(2*S*)-1-{[(4*S*)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]carbonyl}-1,2-dihydroquinoline-2-carbonitrile **105a**



$C_{21}H_{17}N_3O_3$

M = 359.38 g/mol

MP = 173 °C

A solution of quinoline (0.54 mL, 4.56 mmol) and acyl chloride **101** (1.20 g, 5.02 mmol) in dry CH_2Cl_2 (8 mL) under nitrogen atmosphere was stirred at r.t. for 10 minutes. Then the TMSCN (1.22 mL, 9.12 mmol) was added. The mixture was stirred for 24 h and then diluted with CH_2Cl_2. The organic phase was washed successively with water, then brine, dried over $MgSO_4$ and concentrated under reduced pressure. After purified by chromatography on silica gel (EP/EtOAc: 7/3), two isomers were separated in 88% overall yield (*dr* = 55/45).

$[\alpha]_D^{20}$**:** -321.4 (c = 0.77, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.98 and 3.42 (AB part of ABX system, 2 H, *J* = 13.3, 9.3, 3.4 Hz, H_{14}), 4.15 and 4.29 (AB part of ABX system, 2 H, *J* = 9.8, 8.8, 8.5 Hz, H_{12}), 4.74-4.84 (m, 1 H, H_{13}), 5.76 (d, 1 H, *J* = 6.3 Hz, H_1), 6.04 (dd, 1 H, *J* = 9.2, 6.3 Hz, H_2), 6.84 (d, 1 H, *J* = 9.2 Hz, H_3), 6.99-7.02 (m, 1 H, Ar-H), 7.19-7.40 (m, 8 H, Ar-H).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 36.2 (C_{14}), 43.0 (C_1), 55.6 (C_{13}), 66.3 (C_{12}), 114.6 (C_{21}), 118.8 (C_2), 120.4 (C_8), 125.3 (C_6), 126.7 ($\underline{C}H_{Ar}$), 126.8 ($\underline{C}H_{Ar}$), 128.2 (C_7), 128.3 ($2\underline{C}H_{Ar}$), 128.4 ($2\underline{C}H_{Ar}$), 129.0 (C_3), 133.1 (Cq), 133.6 (2Cq), 150.6 (C_{10}), 151.1 (C_{11}).

IR: (ν cm^{-1}) 3020 ($\nu_{C\text{-}Haro}$), 1785 ($\nu_{C=O\ carbamate}$), 1685 ($\nu_{C=O\ urea}$), 1490 ($\nu_{C=Caro}$).

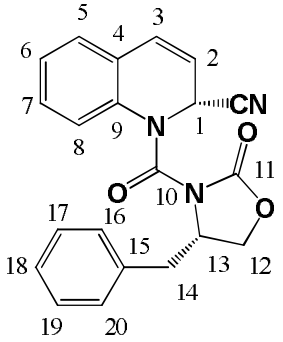
MS (EI): m/z (rel. int.) = 409 ($[M]^+$, 1), 280 (2), 254 (9), 155 (100), 141 (48), 128 (15), 86 (4).

Elemental analysis: for $C_{21}H_{17}N_3O_3$

Calculated:	%C = 70.18	%H = 4.77	%N = 11.69
Found:	%C = 70.09	%H = 4.78	%N = 11.68

(2*R*)-1-{[(4*S*)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]carbonyl}-1,2-dihydroquinoline-2-carbonitrile

105b



$C_{21}H_{17}N_3O_3$

M = 359.38 g/mol

MP = 196 °C

$[\alpha]_D^{20}$**:** +396.0 (c = 0.75, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.89 and 3.71 (AB part of ABX system, 2 H, *J* = 13.4, 10.0, 3.5 Hz, H_{14}), 4.17 and 4.25 (AB part of ABX system, 2 H, J_{AB} = 9.0, 6.7, 2.7 Hz, H_{12}), 4.53-4.61 (m, 1 H, H_{13}), 5.74 (dd, 1 H, *J* = 6.3, 0.8 Hz, H_1), 6.09 (dd, 1 H, *J* = 9.3, 6.3 Hz, H_2), 6.83 (d, 1 H, *J* = 9.3 Hz, H_3), 7.17-7.39 (m, 9 H, Ar-H).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 36.2 (C_{14}), 44.1 (C_1), 58.1 (C_{13}), 66.8 (C_{12}), 115.7 (C_{21}), 120.0 (C_2), 120.3 (C_8), 126.2 (Cq), 126.3 (C_6), 127.5 ($\underline{C}H_{Ar}$), 128.1 ($\underline{C}H_{Ar}$), 129.2 ($3\underline{C}H_{Ar}$), 129.6 ($2\underline{C}H_{Ar}$), 129.9 (C_3), 134.4 (Cq), 135.4 (Cq), 151.5 (C_{10}, C_{11}).

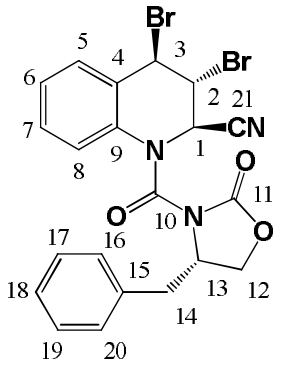
IR: (ν cm^{-1}) 1773 ($\nu_{C=O\ carbamate}$), 1692 ($\nu_{C=O\ urea}$), 1371, 1098.

MS (EI): m/z (rel. int.) = 359 ($[M]^+$, 1), 204 (7), 155 (100), 129 (5), 91 (25), 77 (6), 65 (7).

Elemental analysis: for $C_{21}H_{17}N_3O_3$

Calculated:	%C = 70.18	%H = 4.77	%N = 11.69
Found:	%C = 69.82	%H = 4.84	%N = 11.49

(2*R*,3*R*,4*R*)-1-{[(4*S*)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]carbonyl)-3,4-dibromo-1,2,3,4-tetrahydroquinoline-2-carbonitrile **106a**



$C_{21}H_{17}Br_2N_3O_3$

M = 519.19 g/mol

MP = 163 °C

To a solution of the dihydroquinoline **105a** (2.68 g, 7.47 mmol) in dry CH_2Cl_2 (50 mL) at 0 °C was added dropwise bromine (1.15 ml, 22.4 mmol) and the reaction was stirred for 10 min at 0 °C and for 2 h at room temperature. The resulting mixture was quenched by addition of saturated aqueous $Na_2S_2O_3$ solution (100 mL). After phase separation, the aqueous phase was extracted with CH_2Cl_2 (3 x 100 mL). The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo to give product **106a** as a white solid (3.45 g, 6.65mmol, 89%). R_f = 0.49 (PE/EtOAc, 7:3).

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.74 and 3.48 (AB part of ABX system, 2 H, *J* = 13.0, 12.4, 3.2 Hz, H_{14}), 4.18 and 4.31 (AB part of ABX system, 2H, *J*= 9.4, 9.1, 8.7 Hz, H_{12}), 4.80-4.90 (m, 1 H,H_{13}), 5.02 (br. s, 1 H,H_2), 5.52 (s, 1 H, H_1), 5.65 (d, 1 H, *J* = 2.4 Hz, H_3), 7.20-7.37 (m, 8 H, Ar-H), 7.62 (dd, 1 H, *J* = 6.9, 2.0 Hz, H_5).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 38.1 (C_{14}), 45.1 (C_3), 49.5 (C_2), 49.7 (C_1), 57.0 (C_{13}), 68.0 (C_{12}), 114.3 (C_{21}), 123.8 (C_8), 125.8 (C_4), 127.3 ($\underline{C}H_{Ar}$), 127.8 ($\underline{C}H_{Ar}$), 129.2 (2$\underline{C}H_{Ar}$), 129.3 (2$\underline{C}H_{Ar}$), 129.8 (C_7), 132.3 (C_5), 133.4 (Cq), 134.7 (Cq),152.5 (C_{10}), 152.8 (C_{11}).

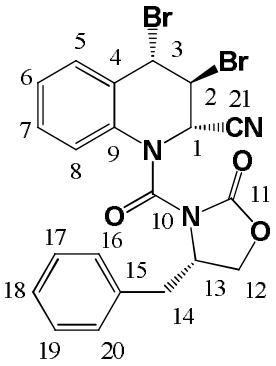
IR (ν cm^{-1}): 3062, 3029 ($\nu_{C\text{-}Haro}$), 2979 ($\nu_{C\text{-}Hsat}$), 1782 ($\nu_{C=Ocarbamate}$), 1703 ($\nu_{C=Ourea}$), 1605, 1583, 1491, 1454 ($\nu_{C=Caro}$), 1222 ($\nu_{C\text{-}Oester}$).

MS (CI): m/z = 522, 520, 518 $[M+H]^+$, 493, 440, 438,358.

Elemental analysis: for $C_{21}H_{17}Br_2N_3O_3$

Calculated:	%C = 48.58	%H = 3.30	%N = 8.09
Found:	%C = 48.32	%H = 3.37	%N = 8.05

(2*S*,3*S*,4*S*)-1-{[(4*S*)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]carbonyl)-3,4-dibromo-1,2,3,4-tetrahydroquinoline-2-carbonitrile **106b**



$C_{21}H_{17}Br_2N_3O_3$

M = 519.19 g/mol

MP = 137 °C

Similar to the above procedure and starting from dihydroquinoline **105b** gave product **106b** as a white solid (87%). Additional purification could be achieved by recrystallisation from PE/EtOAc to afford product **106b** as colourless crystals. R_f = 0.42 (PE/EtOAc, 7:3).

$[\alpha]_D^{20}$**:** +113.9 (c = 0.5, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.97 and 3.73 (AB part of ABX system, 2 H, *J* = 13.3, 10.1, 3.0 Hz, H_{14}), 4.21-4.23 (m, 2 H, H_{12}), 4.49-4.56 (m, 1 H, H_{13}), 4.90 (dd, 1 H, *J* = 4.3, 3.5 Hz, H_2), 5.54 (d, 1 H, *J* = 3.5 Hz, H_1), 5.56 (d, 1 H, *J* = 4.3 Hz, H_3), 7.19 (dd, 1 H, *J* = 8.0, 1.3 Hz, H_8), 7.18-7.37 (m, 7 H, Ar-H), 7.64 (d, 1 H, *J* = 7.5 Hz, H_5).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 37.9 (C_{14}), 46.2 (C_3), 49.3 (C_2), 50.6 (C_1), 58.4 (C_{13}), 67.1 (C_{12}), 114.9 (C_{21}), 121.6 (C_8), 126.4 (Cq), 127.0 ($\underline{C}H_{Ar}$), 127.6 ($\underline{C}H_{Ar}$), 129.2 ($2\underline{C}H_{Ar}$), 129.6 ($2\underline{C}H_{Ar}$), 130.1 (C_7), 131.8 (C_5), 134.5 (Cq), 135.2 (Cq), 151.3 (C_{10}), 152.2 (C_{11}).

IR (ν cm^{-1}): 3068 ($\nu_{C\text{-}Haro}$), 2980 ($\nu_{C\text{-}Hsat}$), 1784 ($\nu_{C=Ocarbamate}$), 1668 ($\nu_{C=Ourea}$), 1604, 1578, 1490, 1455 ($\nu_{C=Caro}$), 768, 703 ($\nu_{C\text{-}Haro}$).

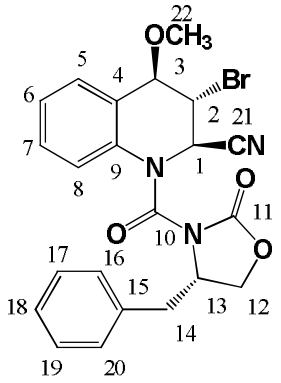
MS (CI) : m/z = 539, 537, 535 $[M+NH_4]^+$,522, 520, 518 $[M+H]^+$, 377, 358, 333.

Elemental analysis: for $C_{21}H_{17}Br_2N_3O_3$

Calculated: %C = 48.58 %H = 3.30 %N = 8.09

Found: %C = 48.28 %H = 3.34 %N = 7.99

(2*R*,3*R*,4*R*)-1-{[(4*S*)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]carbonyl}-3-bromo-4-methoxy-1,2,3,4-tetrahydroquinoline-2-carbonitrile **107**



$C_{22}H_{20}BrN_3O_4$

M = 470.32 g/mol

MP = 213.2 °C

To a solution of dihydroquinoline **105a** (0.359 g, 1 mmol) in dry MeOH (25 mL) was added NBS (0.196 g, 1.1 mmol) at 0 °C and the mixture was stirred at room temperature for 24 h. The solvent was then removed and the residue was extracted with CH_2Cl_2 after addition of water. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography (PE/EtOAc, 7:3) to afford **107** as a white solid. Additional purification could be achieved by recrystallisation from PE/EtOAc to afford product **107** as colourless crystals.

$[\alpha]_D^{20}$**:** -143.2 (c = 1.045, $CHCl_3$).

^{1}H NMR(300 MHz, $CDCl_3$, δ ppm): 2.90 and 3.51 (AB part of ABX system, 2 H, *J* = 13.1, 9.9, 3.6 Hz, H_{14}), 3.76 (s, 3H, H_{22}), 4.14 and 4.28 (AB part of ABX system, 2 H, *J* = 9.8, 8.9,8.4 Hz, H_{12}), 4.21 (dd, 1H, *J* = 7.6, 5.2 Hz, H_2),4.46 (d, 1H, *J* = 7.6 Hz, H_3), 4.83 (m, 1H,H_{13}), 5,46 (d, 1H, *J* = 5.2 Hz, H_1), 6.87 (d, 1H, *J* = 3.4 Hz, H_8), 7.24-7.40 (m, 7H, Ar-H), 7.51 (dd, 1H, *J* = 6.9, 1.5 Hz, H_5).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 37.6 (C_{14}), 49.1 (C_2), 52.0 (C_1), 56.8 (C_{13}), 60.4 (C_{22}), 67.8 (C_{12}), 79.4 (C_3), 115.5 (C_{21}), 122.3 (C_8), 126.1 (C_5), 127.2 (C_6), 127.8 ($\underline{C}H_{Ar}$), 129.0 ($\underline{C}H_{Ar}$), 129.4 (4$\underline{C}H_{Ar}$), 130.3 (Cq), 134.6 (Cq), 134.8 (Cq), 152.0 (C_{10}), 152.4 (C_{11}).

IR (ν cm^{-1}): 3063, 3030 ($\nu_{C\text{-}Haro}$), 2989, 2932, 2909 ($\nu_{C\text{-}Hsat}$), 2826 (ν_{OCH3}),1778 ($\nu_{C=Ocarbamate}$), 1707 ($\nu_{C=Ourea}$), 1604, 1586, 1493, 1457 ($\nu_{C=Caro}$), 1223 ($\nu_{C\text{-}Oester}$), 1078 ($\nu_{C\text{-}O}$).

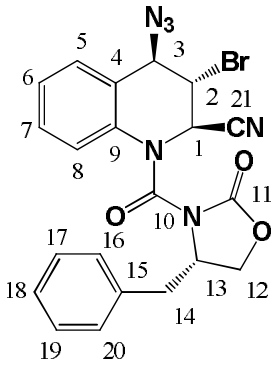
MS (CI): m/z = 489, 487 $[M+NH_4]^+$, 358.

Elemental analysis: for $C_{22}H_{20}BrN_3O_4$

Calculated: %C = 56.18 %H = 4.29 %N = 8.93

Found: %C = 56.31 %H = 4.31 %N = 9.01

(2*R*,3*R*,4*R*)-4-azido-1-{[(4*S*)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]carbonyl}-3-bromo-1,2,3,4-tetrahydroquinoline-2-carbonitrile **108a**



$C_{21}H_{17}BrN_6O_3$

M = 481.30 g/mol

MP = 177 °C

To a solutionof dihydroquinoline **105a** (0.359 g, 1.0 mmol) in dry CH_2Cl_2 (10 mL) was added $Zn(OTf)_2$ (91 mg, 0.25 mmol). The reaction mixture was cooled to 0 °C then $TMSN_3$ (0.20 mL, 1.5 mmol) and NBS (0.214 g, 1.20 mmol) were successively added while stirring. After completion of the reaction (TLC monitoring) (3 days), the reaction was quenched by addition of a saturated aqueous $NaHCO_3$ solution (50 mL) and extracted with CH_2Cl_2 (3 × 60 mL). The combined extracts were successively washed with water and brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (PE/EtOAc, 7:3, R_f = 0.37) to yield product **108** as a white solid (0.313 g, 0.65 mmol, 65%, *dr* = 92/08). Additional purification could be achieved by recrystallisation from PE/EtOAc to afford the major isomer **108a** as colourless crystals.

$[\alpha]_D^{20}$**:** -124.6 (c = 1.05; $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.93 and 3.50 (AB part of ABX system, 2 H, *J* = 13.2, 9.8, 3.3 Hz, H_{14}), 4.14 and 4.29 (AB part of ABX system, 2 H, *J* = 9.8,8.9, 8.5 Hz, H_{12}), 4.17 (dd, 1 H, *J* = 8.6, 5.6 Hz, H_2), 4.77-4.87 (m, 1 H, H_{13}), 4.83 (d, 1 H, *J* = 8.6 Hz, H_3), 5.48 (d, 1 H, *J* = 5.6 Hz, H_1), 6.81 (d, 1 H, *J* = 7.3 Hz, H_8), 7.25-7.42 (m, 7 H, Ar-H), 7.56 (dd, 1 H, *J* = 7.7, 1.1 Hz, H_5).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 37.4 (C_{14}), 50.3 (C_2), 52.5 (C_1), 56.7 (C_{13}), 62.7 (C_3), 67.8 (C_{12}), 115.4 (C_{21}), 122.4 (C_8), 126.3 (C_5), 127.5 ($\underline{C}H_{Ar}$), 127.9 ($\underline{C}H_{Ar}$), 128.5 (Cq), 129.4 (4$\underline{C}H_{Ar}$), 129.6 (C_7), 134.5 (Cq), 135.1 (Cq), 152.0 (C_{10}), 152.2 (C_{11}).

IR (ν cm^{-1}): 2984, 2914 ($\nu_{C\text{-}Hsat}$), 2110 (ν_{N3}), 1777 ($\nu_{C=Ocarbamate}$), 1701 ($\nu_{C=Ourea}$), 1605, 1585, 1493, 1456 ($\nu_{C=Caro}$), 1226 ($\nu_{C\text{-}Oester}$).

MS (CI) : m/z = 500, 498 $[M+NH_4]^+$, 483, 481 $[M+H]^+$, 455, 377, 358.

HRMS (Maldi-PEG400)**:**

Calculated for $C_{21}H_{17}BrN_6O_3Na$ $[M+Na]^+$ = 503.0438; Found: $[M+Na]^+$ = 503.0455

CHAPTER 2: SYNTHESIS OF ALKALOIDS OF TETRAHYDROQUINOLINE TYPE

CHAPTER 2: SYNTHESIS OF ALKALOIDS OF TETRAHYDROQUINOLINE TYPE

2.1. Total Synthesis of Sumanirole

2.1.1. Introduction

Parkinson disease is the second most common neurodegenerative disorder after Alzheimer's disease. Its prevalence is about 0.3% of the whole population in industrialized countries. It is more common in the elderly and prevalence rises from 1% in those over 60 years of age to 4% of the population over 80.[40] The diminution of the dopaminergic neurons, which make and use the dopamine, a neurotransmitter involved in the control of body movements, especially automatic movements (blinking, walking, certain gestures when speaking,…), is the cause of Parkinson disease. Currently, there is no cure for this disease. Existing treatments alleviate the symptoms but do not alter disease progression. The most popular method is using L-Dopa, the precursor to the neurotransmitters dopamine, norepinephrine and epinephrine (Figure 16). The disadvantage of this treatment is that effectiveness decreases after a few years of use.

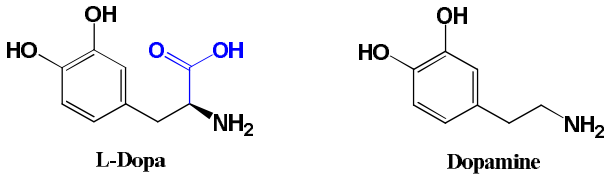


Figure 16

An alternative method of treatment is the use of dopamine agonists that ultimately become fixed at some postsynaptic D2 receptors, well-preserved during the disease. The most well-known among these agonists is apomorphine (Figure 17). These agonists are less efficient than L-Dopa but, on the long term, have less deleterious effects on mobility. Nevertheless, they generate a number of side effects such as nausea, somnolence and postural hypotension.

Research on structure-activity relationship has shown that the rigid phenylethylamine motif in apomorphine and the rigid pyrroethylamine motif in pergolide and apocriptine are mainly responsible of the dopaminergic activity of these molecules.

[40] L. M. de Lau, M. M. Breteler. *Lancet Neurol.* **2006**, *5*, 525

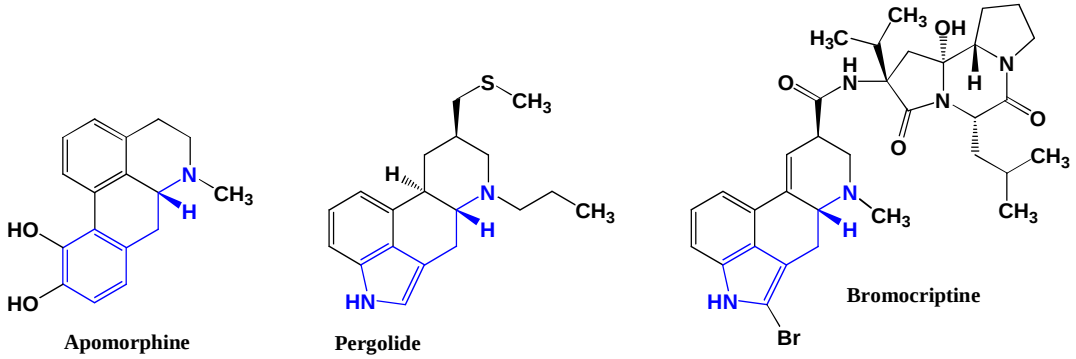
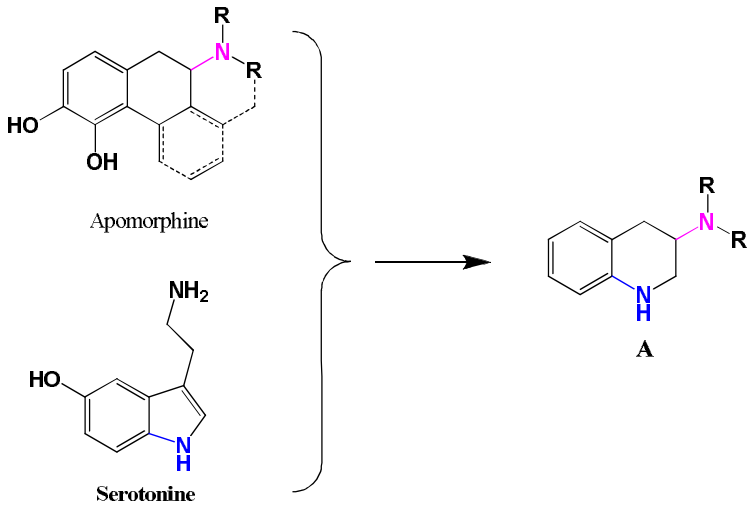


Figure 17

Based on studies on apomorphine as well as others carried out on serotonin, a major neuromodulator of the central nervous system, Moon[2a,41] and coworkers chose to synthesize non-hydroxylated analogs of tetrahydronaphthylamine containing a heteroatom on the tetralin ring (Scheme 51).



Scheme 51

In view of the results published by Kornfeld,[42] various tricyclic analogues of compound **A** have been synthesized (Figure 18).

[41] M. W. Moon, J. K. Morris, R. F. Heier, C. G. Chidester, W. E. Hoffmann, M. F. Piercey, J. S. Althaus, P. F. Von Voigtlander, D. L. Evans, L. M. Figur, R. A. Lahti. *J. Med. Chem.* **1992**, *35*, 1076

[42] N. J. Bach, E. C. Kornfeld, N. D. Jones, M. O. Chaney, D. E. Dorman, J. W. Paschal, J. A. Clemens, E. B. Smalstig. *J. Med. Chem.* **1980**, *23*, 481

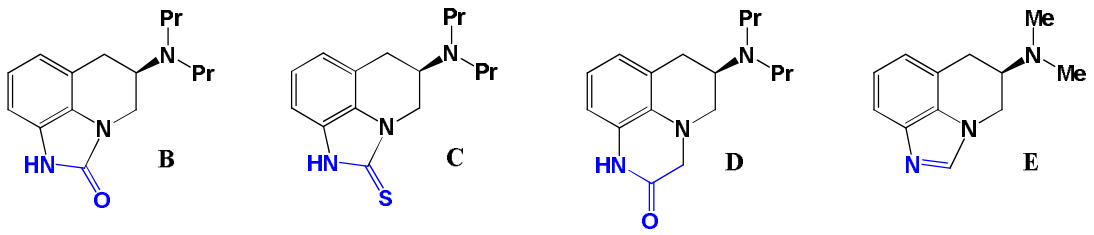
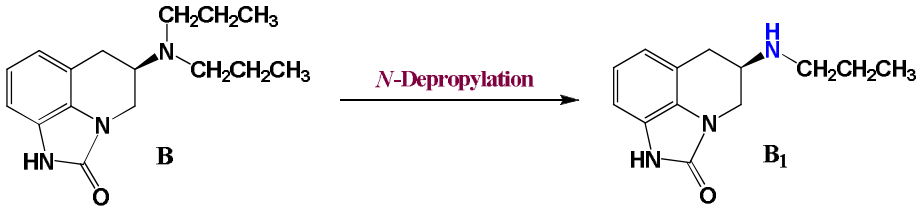


Figure 18

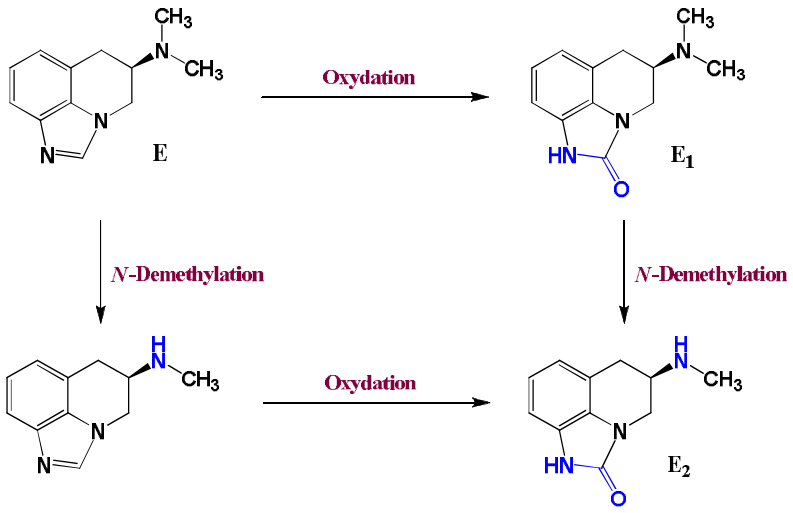
All these compounds exhibited significant *in vitro* dopaminergic activity, compounds **B** and **E** being the most promising ones. In 1993, Moon[43] showed that compound **B** was metabolized in compound **B1**, better candidate for drug development for bioavailability reasons (Scheme 52).



Scheme 52

After other investigations, it turned out that compound **E** was metabolized as shown in the following scheme to give two imidazoquinoline derivatives **E1** and **E2**, each exhibiting good dopaminergic **D2** activities (Scheme 53).

[43] M. W. Moon, J. K. Morris, R. F. Heier, R. S. P. Hsi, M. O. Manis, M. E. Royer, R. R. Walters, C. F. Lawson, M. W. Smith, R. A. Lahti, M. F. Piercey, V. H. Sethy. *Drug Des. Discovery.* **1993**, *9*, 313



Scheme 53

Among these compounds, only compound **E2** exhibits a very good activity both *in vitro* and *in vivo*. This compound, named Sumanirole, was next the subject of many biological studies as well as synthetic studies in order to prepare an optically pure molecule with a satisfactory global yield. In June 2004, Pfizer, which owns the patent application of this molecule, decided to stop clinical phase III trials. The reason "officially" invoked was that Sumanirole was not enough distinguished in comparison with available current drugs on the market.

2.1.2. Literature Review

In introduction to our own synthesis of Sumanirole we present herein a brief overview of already reported syntheses of this molecule. Our presentation is restricted to those syntheses that have led to the molecule in its biologically active non-racemic chiral form. Focusing on the mode of introduction of chirality, a synthesis can be classified into one of the following three categories:

- Mid-stage resolution with L-tartaric acid or (*R*)-naproxen
- Use of a chiral starting material (D-phenylalanine).
- Recourse to an epoxidation of Jacobsen or to a Sharpless asymmetric dihydroxylation.

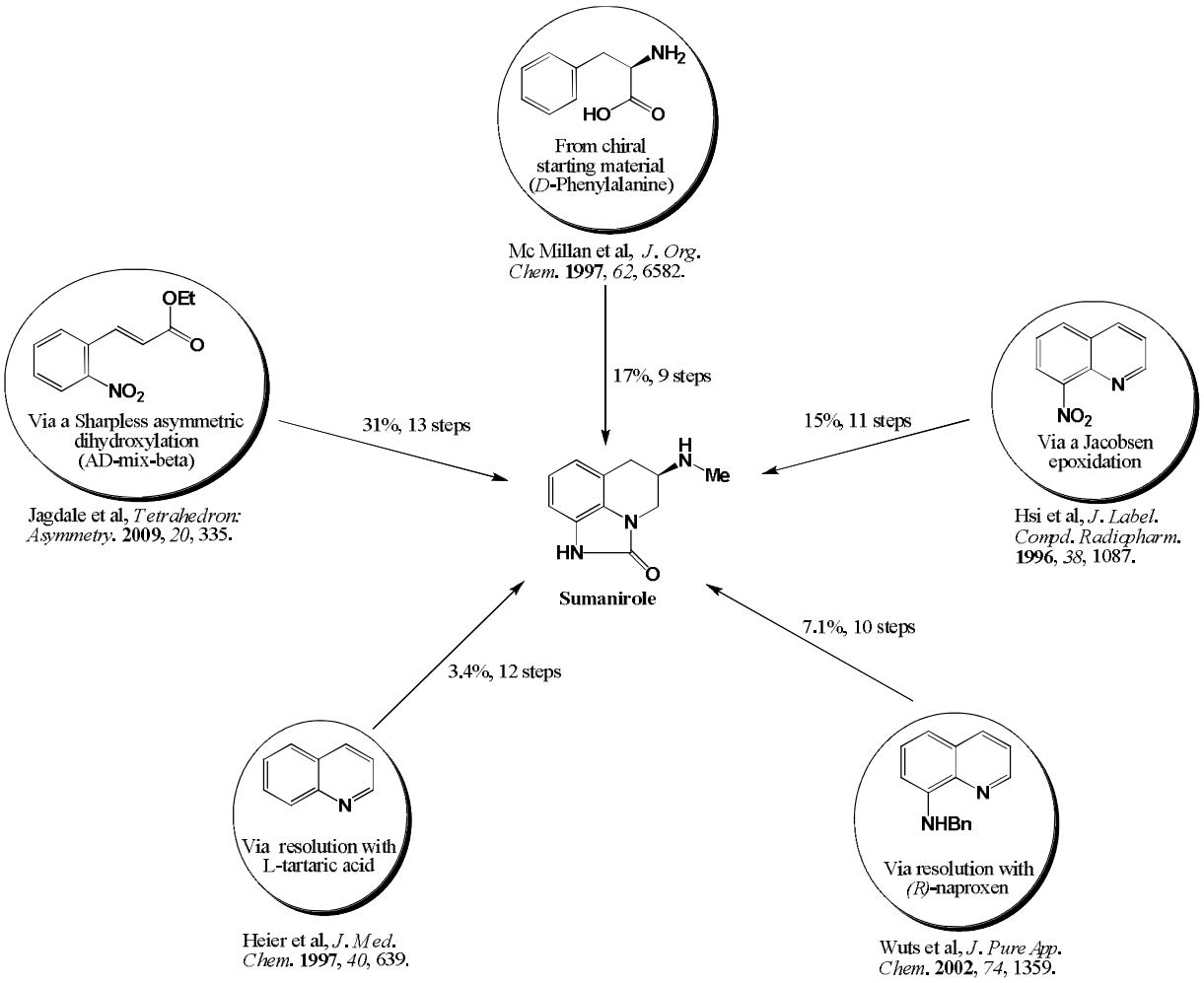


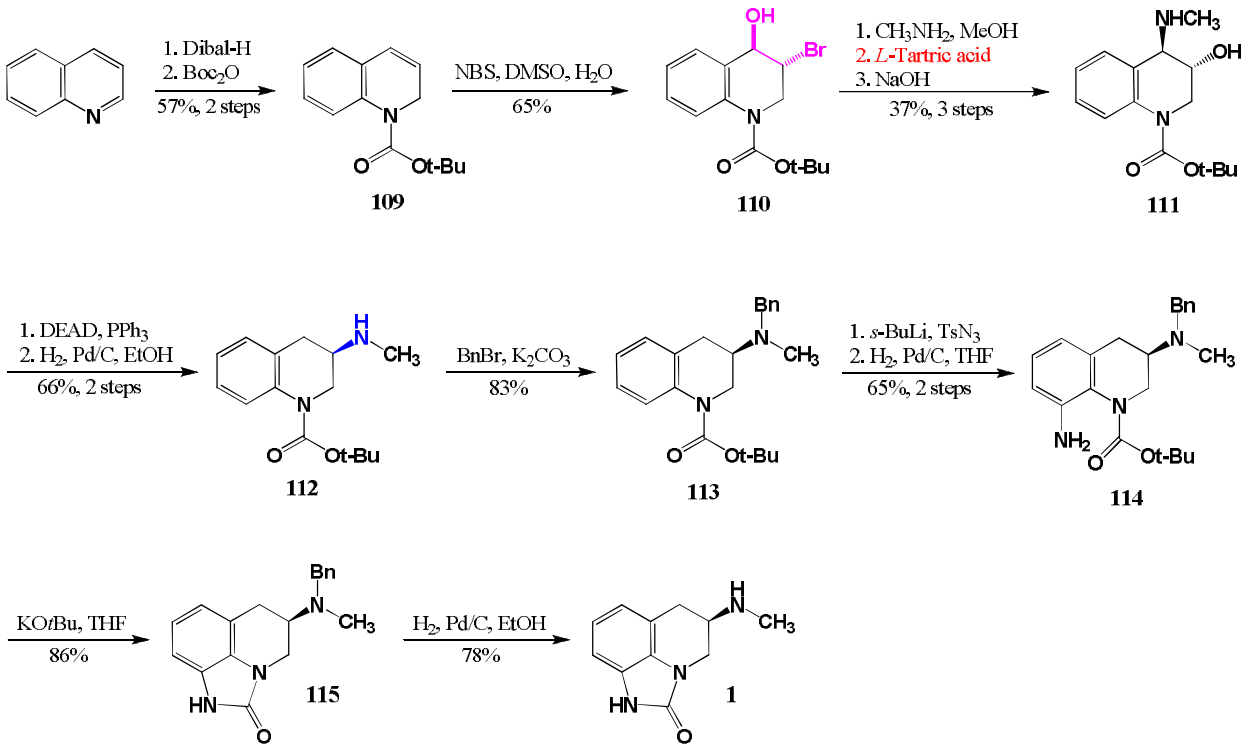
Figure 19

2.1.2.1.Syntheses via a mid-stage resolution

- With L-Tartaric acid

In 1997 Moon[2a,44] and collaborators reported a synthesis of (*R)*-(-)-Sumanirole with a L-tartaric acid-based resolution step (Scheme 54).

[44] M .W. Moon, J. K. Morris, R. F. Heier, C. G. Chidester, W. E. Hoffmann, M. F. Piercey, J. S. Althaus, P. F. Von Voigtlander, D. L. Evans, L. M. Figur, R. A. Lahti. *J. Med. Chem.* **1992**, *35*, 1076.

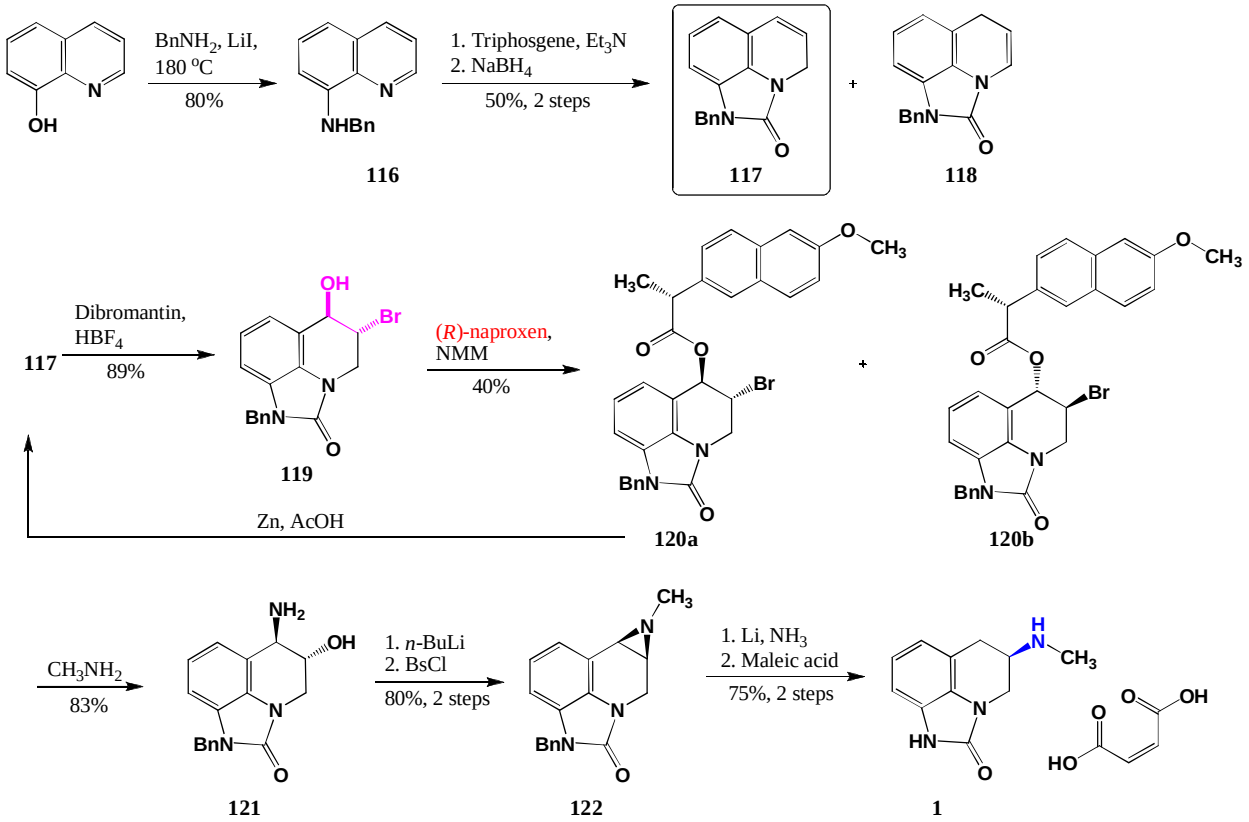


Scheme 54

1,2-Dihydroquinoline **109**, prepared by a reduction-acylation sequence from quinoline, was subjected to the action of *N*-bromosuccinimide in a mixture of DMSO and water to give the bromohydrin **110**. This compound was then treated with methylamine leading to the *in situ* formation of amino alcohol via a transient epoxide. The *trans* racemic amino alcohol was coupled with L-tartaric acid to afford a *trans* mixture of diastereomeric salts. After crystallization and basic treatment, the *trans* amino alcohol **111** was recovered as an optically pure material. This compound was then engaged in a Mitsunobu reaction to give an aziridine which, in turn, was regioselectively opened under hydrogenation conditions to give the key (*R*)-amino derivative **112.** Introduction of a primary amino group at C8 could be achieved after the secondary amino group at C3 was protected with a benzyl group to give **113**. Thus, orthometallation of **113** under the action of sec-BuLi followed by trapping with TsN_3 allowed the introduction of an azide group at C8. This latter was hydrogenated (Pd/C) to finally deliver the bis-amino compound **114**. Treatment of **114** with potassium tert-butoxide resulted in the formation of the imidazolone ring. After a final hydrogenolysis step, (*R*)-(-)-Sumanirole **1** was obtained in a global yield of 3.4% after 12 steps.

- With (*R*)-Naproxen

In 2002 Wuts[21c,45] et al. reported a different approach to (*R*)-(-)-Sumanirole in which chirality was introduced via a resolution step making use of (*R*)-naproxen (Scheme 55).



Scheme 55

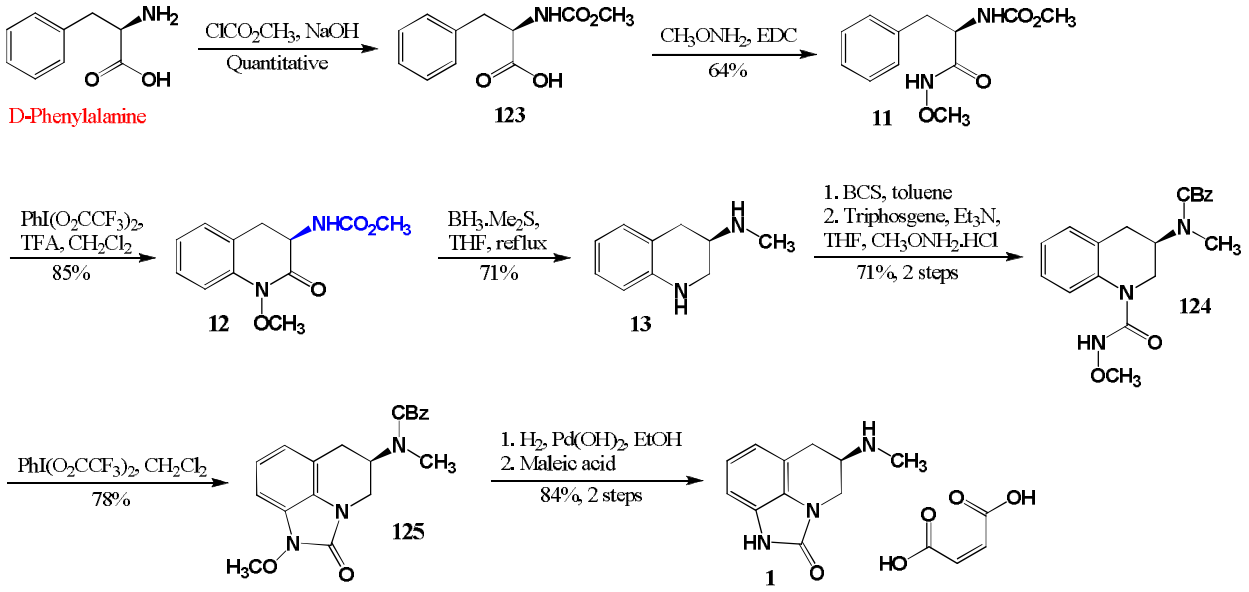
8-Aminoquinoline **116**, a relatively expensive material, was synthesized from 8-hydroxyquinoline by an improved Bucherer reaction. Installation of the imidazolone ring was then achieved under the action of triphosgene and triethylamine. Tricyclic compound **117** was accompanied, however, by 1,4-dihydroquinoline **118** formed in significant proportion (up to 30%). **117** was subsequently transformed to a racemic *trans* bromhydrine **119**, which, under the action of (*R*)-naproxen in the presence of *N*-methylmorpholine, led to the formation of two chiral diastereomeric esters **120a** and **120b** readily separated by crystallization. Treatment of ester **120b** with an aqueous methylamine solution afforded, via the regioselective opening of a

[45] P. G. M. Wuts. *Curr. Opin. Drug Discov. Devel.* **1999**, *2*, 557.

transient epoxide, amino alcohol **121** next transformed to aziridine **122** through the combined action of *n*-BuLi and benzyl sulfonyl chloride. Finally, regioselective opening of aziridine **122** through reduction with lithium in ammonia led to (*R*)-(-)-Sumanirole in an overall yield of 7.1% for 10 steps. It should be noted that this sequence allowed recycling of the undesired chiral ester **120a** through the retro-formation of racemic bromhydrine **119**.

2.1.2.2.Synthesis from D-phenylalanine as chiral starting material

This synthesis was reported by McMillan[11] et al. in 1997 (Scheme 56).



Scheme 56

D-phenylalanine was first amino-protected in the form of a methyl carbamate under Schotten-Baumann conditions to give **123**. The carboxylic acid function of **123** was then converted into its corresponding Weinreb amide **11** by using the conditions of Kikugawa[46]. This amide was next treated with bis-(trifluoroacetoxy)iodobenzene and trifluoroacetic acid to afford tetrahydroquinoline **12** which, in turn, was reduced with the Me_2S-borane complex to afford the (*R*)-3-methylamino tetrahydroquinoline **13**. After the exocyclic amine function was protected as a benzyl carbamate, treatment with triphosgene and *O*-methylhydroxylamine furnished *N*-methoxy urea compound **124**. This latter was subjected to an oxidative cyclization reaction

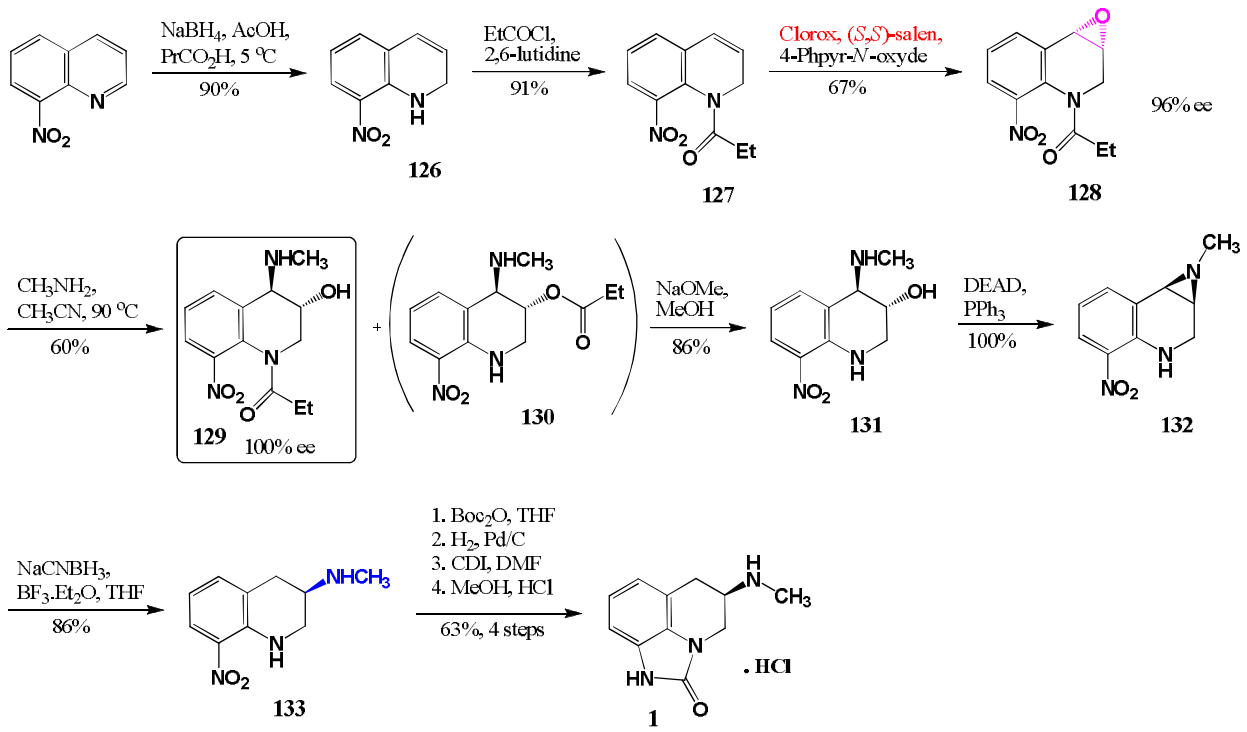
[46] M. Kawase, T. Kitamura, Y. Kikugawa *J. Org. Chem.* **1989**, *54*, 3394.

leading to the tricyclic compound **125**. Deprotection of both amino groups was effected through hydrogenation in the presence of Pearlman's catalyst to provide (*R*)-(-) Sumanirole **1** isolated under the form of its maleate in an overall yield of 17% for 9 steps.

2.1.2.3.Asymmetric syntheses

- Chirality introduction through a Jacobsen Epoxidation

The synthesis reported by Hsi[47] et al. in 1996 described the synthesis of Sumanirole starting from 8-nitroquinoline and introducing chirality via a Jacobsen epoxidation.



Scheme 57

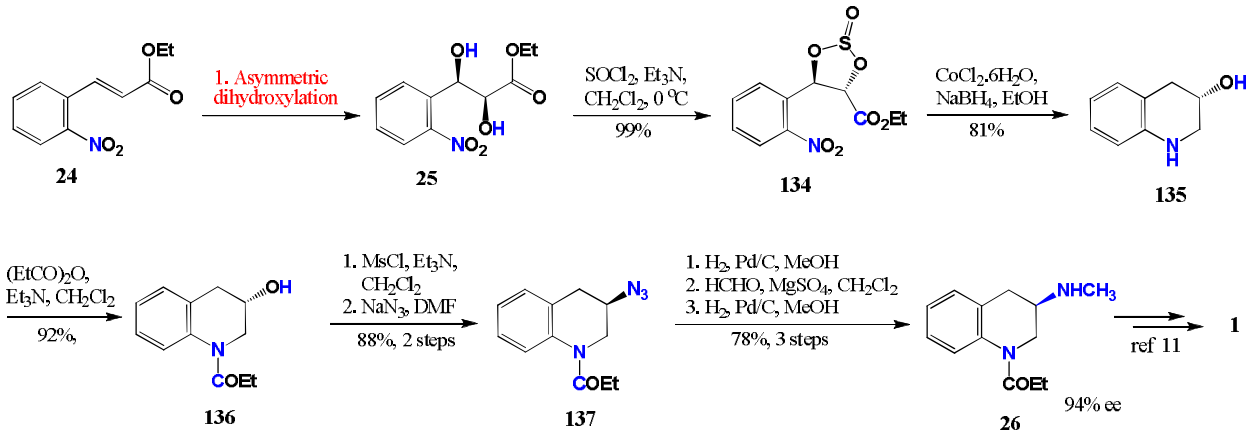
1,2-Dihydroquinoline **127**, prepared by reduction of 8-nitroquinoline and subsequent carbamate protection of N1 nitrogen, underwent Jacobsen epoxidation to afford epoxide **128** in good yield and with high selectivity (96% ee). Regioselective aminolysis of this epoxide led to the formation of amino hydroxy compound **129** accompanied by ester by-product **130** resulting from the migration of the N1-acyl protecting group towards the C3-OH group (ratio 10:1). The amide function of **129** was hydrolyzed under the action of sodium methylate to afford hydroxy amine

[47] R. F. Heier, M. W. Moon, W. T. Stolle, J. A. Easter, R. S. P. Hsi. *J. Label. Compd. Radiopharm.* **1996**, *38*, 1087.

131, which was subjected to the conditions of the intramolecular Mitsunobu reaction to deliver the aziridine **132**. Regioselective reduction of the latter with sodium cyanoborohydride afforded the (*R*)-3-methylamino-8-nitro-tetrahydroquinoline **133**, which was transformed to (*R*)-(-)-Sumanirole **1** through a sequence of four reactions (overall yield of 15% for 11 steps).

- Chirality introduction through a Sharpless asymmetric dihydroxylation

Recently, Sudalai[14] et al. successfully applied the Co-catalyzed one-pot reductive cyclization of nitrocyclic sulphites in the synthesis of (*R*)-1-(3-(methylamino)-3,4-dihydroquinolin-1(2*H*)-yl)propan-1-one **26**, an advanced intermediate for the synthesis of Sumanirole **1** (Scheme 58).

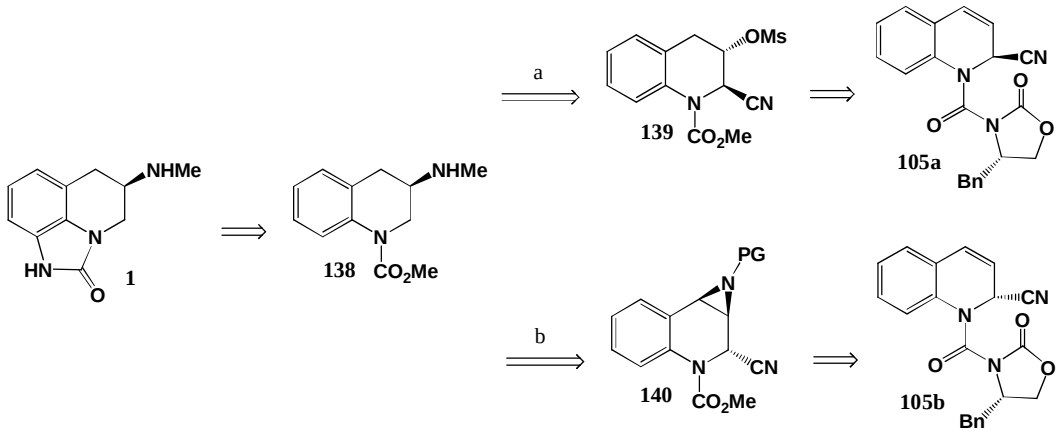


Scheme 58

The chiral nitrodiol **25**, prepared from nitro cinnamate by Sharpless asymmetric dihydroxylation (AD-mix-β) using $(DHQD)_2$-PHAL as ligand, was transformed into the corresponding cyclic sulphite **134** under the combined action of sulphonyl chloride and triethylamine. This latter compound next underwent an one-pot reductive cyclization with cobalt(II) chloride and sodium borohydride to afford the (*S*)-tetrahydroquinolin-3-ol **135**, whose N1 amino group was selectively protected with propionic anhydride to give amide **136** in high yield. The free hydroxyl group was mesylated and then treated with sodium azide to furnish azide **137**. This latter was hydrogenated in the presence of Pd/C to afford a primary amine next transform into a *N*-methyl amino compound **26** through the reduction of a formamide intermediate. Finally, (*R*)-(-)-Sumanirole **1** was derived from amino carbamate **26** following a sequence already reported (Synthesis of Mc Millan).[11]

2.1.3. Previous work in the laboratory

Early laboratory survey was performed using the chiral Reissert adduct **105a** or **105b**[39] as possible starting point (Scheme 59). It was initially believed that the cyano group could serve to control the stereochemistry of the double bond epoxidation and then be reductively excised later in the synthesis as such or under the form of a close derivative (a carboxylic acid, for example).

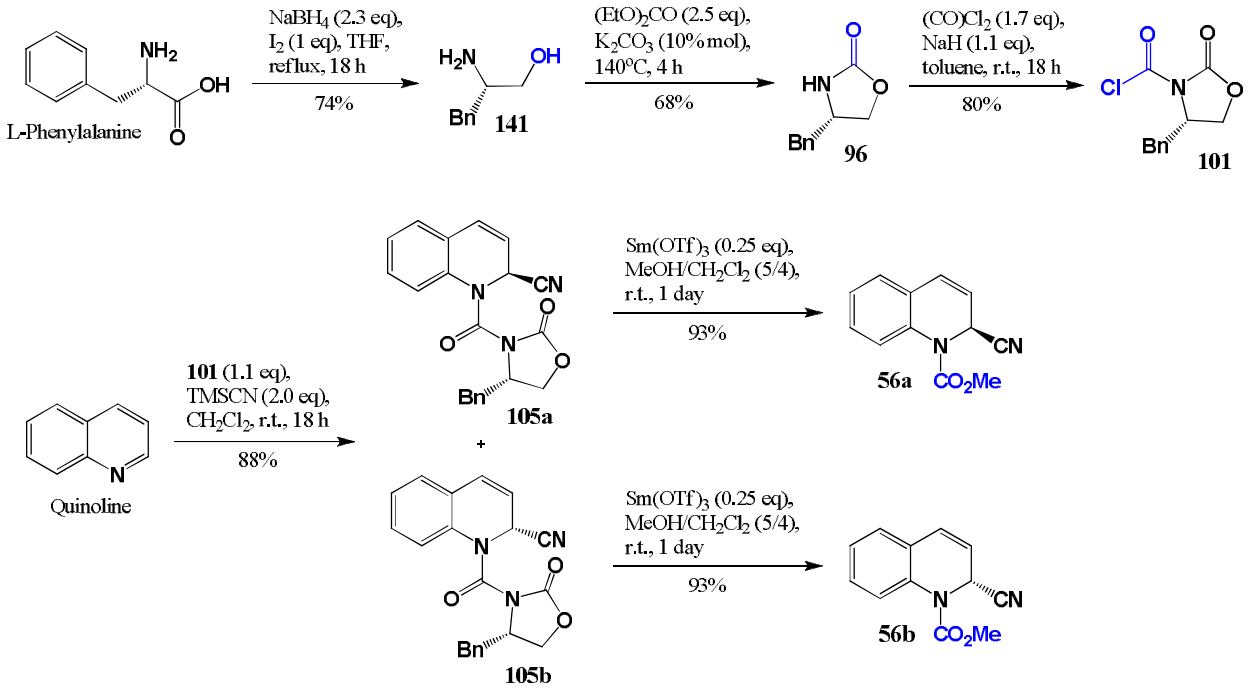


Scheme 59

2.1.3.1. Preparation of chiral Reissert adducts 105a and 105b

The chiral Reissert adducts **105a** and **105b** were synthetized by a four-step reaction sequence from L-phenylalanine, a cheap and commercially available chiral starting material (Scheme 60). Phenylalaninol **141**, prepared from L-phenylalanine by reduction with sodium borohydride in the presence of diiode,[48] was condensated with diethyl carbonate to lead to (*S*)-4-benzyloxazolidin-2-one **96** in an overall yield of 74%. Deprotonation of **96** by sodium hydride generated a nitranion, which was trapped by phosgene[49] to afford the chloride acid **101** in a 80% yield. After the salt of acyl quinoline was generated by the reaction of chloride acid **101** and quinoline, the addition of trimethylsilyl cyanide led to the formation of two diastereomers **105a** and **105b** which were separated perfectly by chromatography on silica gel. Finally, the chiral auxiliary was efficiently removed by samarium triflate in a mixture of CH_2Cl_2 and MeOH. In addition, the oxazolidin-2-one could be recovered by chromatography on silica gel.

[48] (a) J. M. Simek, T. Tuck, K. C. Bush. *J. Chem. Ed.* **1997**, *74*, 107. (b) N. J. McKennon, A. I. Meyers. *J. Org. Chem.* **1993**, *58*, 3568.
[49] R. S. Garigipati, M. E. Sorenson, K. F. Erhard, J. L. Adams. *Tetrahedron Lett.* **1993**, *34*, 5537.



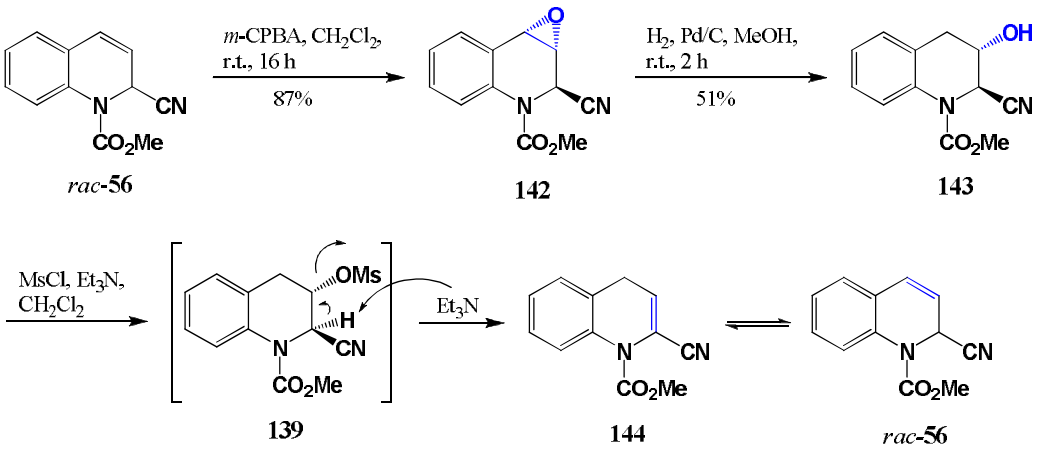
Scheme 60

2.1.3.2. Stereoselective introduction of methylamino group at C3

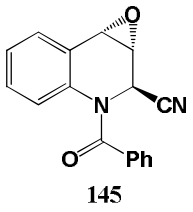
All following reactions were initially performed on a racemic mixture of **56.**

- Indirect introduction based on the use of an epoxy group

The Reissert adduct *rac*-**56** was reacted with *m*-chloroperbenzoic acid (*m*-CPBA) to yield the expected epoxide **142,** which was then reduced by hydrogenation in the presence of Pd/C to furnish the hydroxy compound **143** with a modest yield of 51% (not optimized) (Scheme 61). The *anti*- position of the epoxide relative to the cyano group at C2 was assigned by analogy with the *N*-benzoyle analogue **145** obtained in a previous study (Figure 20)



Scheme 61



145

Figure 20

Hydroxy-nitrile **143** was next treated with methanesulfonyl chloride and triethylamine to afford an unstable mesylate **139** which could not be isolated due to its rapid transformation to a mixture of unsaturated nitriles **144** and *rac*-**56**. Obviously, the acidic character of the proton, α to the cyano group, is the reason of such a rapid evolution of epoxy-nitrile **142**. This adverse result led us to abandon this route.

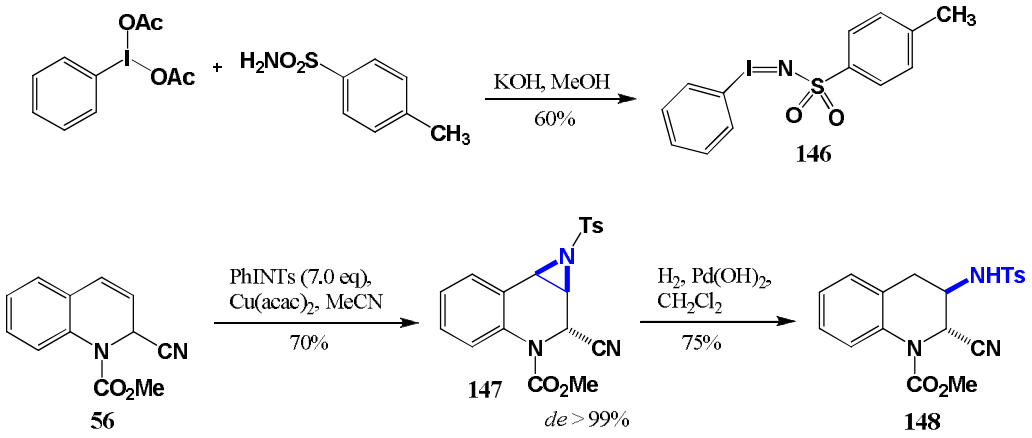
- Strategies based on the direct introduction of an aziridine group

– Introduction of an amino group at C3 through a tosylated aziridine intermediate

The Reissert adduct *rac*-**56** was reacted with copper(II) acetylacetonate ($Cu(acac)_2$) and *N*-tosyliminobenzyliodinane (PhINTs) **146**, prepared according to the procedure described by Gillepsie[50] from *para*-toluenesulfonamide and diacetoxyiodobenzene, to afford the desired aziridine **147** in a yield of 50-80% depending on the purity of the PhINTs. This reaction was very

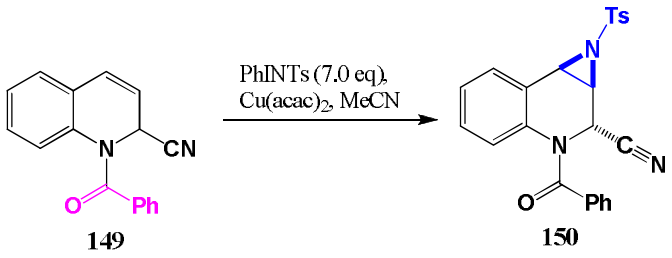
[50] K. Gillepsie. *Synthetic Page*. **2001**, 123.

capricious and required many precautions to obtain optimal results (exothermicity of the reaction is highly dependent on the purity of PhINTs). After extensive optimization trials, the best yields were recorded when 7.0 eq. of PhINTs were used. The arizidine **147** was then reduced through hydrogenation in the presence of Pearlman catalyst to give the tosylated amine **148** in 75% yield (Scheme 62).



Scheme 62

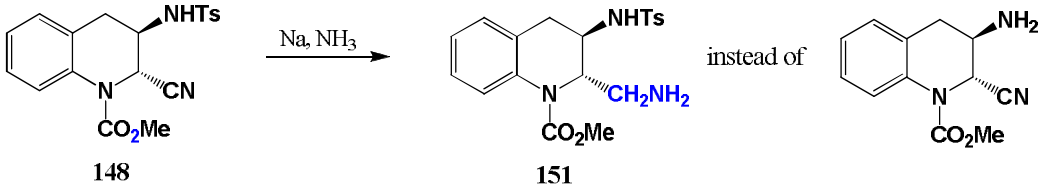
The expected relative *anti* disposition of aziridine and CN groups for compound **148** was confirmed by analogy after a X-ray crystallography analysis had been performed on **150**, obtained from Reissert adduct **149** under similar conditions (Scheme 63).



Scheme 63

Attempts to reduce the tosylated amine **148** by sodium and ammonia did not afford the expected free primary amine at C3 but mainly a mixture of products, one of which exhibiting a primary amine function which seems to be the result of the reduction of the CN group at C2 (Scheme 64).

Electrochemical analysis (cyclic voltammetry) carried out on compound **148** showed that any reduction of tosyl group should necessarily induce a concomitant reduction of the cyano group.



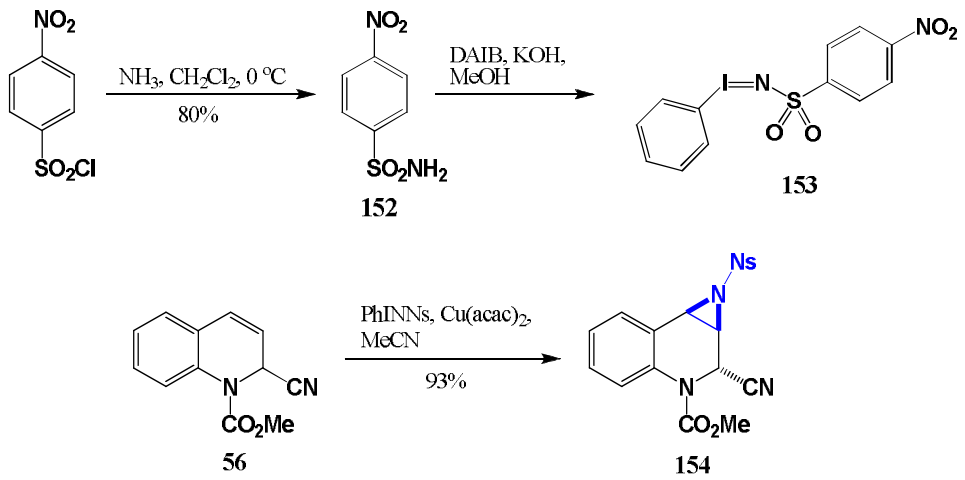
Scheme 64

In order to circumvent this problem, another synthetic route was designed. This route is based on the replacement of the tosyl group by a nosyl group (*para*-nitrobenzenesulfonyl) or a Ses (trimethylsilylethylsulfonyl) group which, based on literature data, were expected to be more easily deprotected.

– Introduction of an amino group at C3 through a nosylated aziridine intermediate

The benzenesulfonamide derivative **152**, synthesized by action of ammonia on *para*-nitrosulfonyle chloride,[51] was treated with diacetoxyiodobenzene to form the PhINNs adduct **153**. The latter was next reacted with the Reissert compound **56** to afford the nosylated aziridine **154** in excellent yield as a single diastereomer (Scheme 65) with a presumed relative *anti* disposition between aziridine and CN groups.

[51] M. S. Congreve, C. Kay, J. J. Scicinski, S. V. Ley, G. Williams, P. J. Murray, S. C. McKeown, S. P. Watson. *Tetrahedron Lett.* **2003**, *44*, 4153.



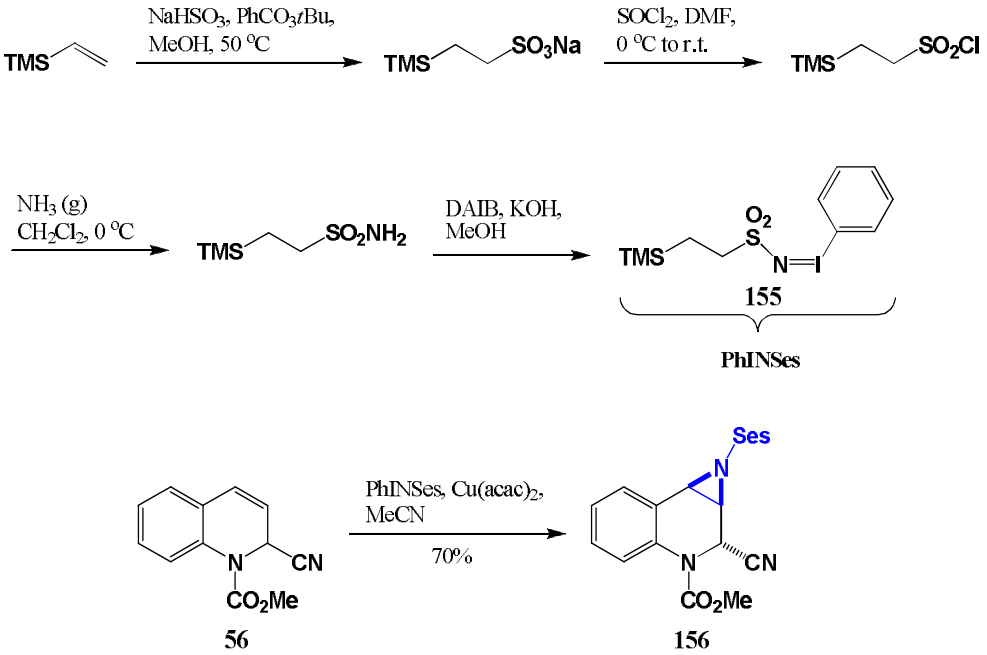
Scheme 65

Reduction of nosylated arizidine **154** in the presence of Pearlman's catalyst could not be properly effected, as already experienced with tosylated aziridine **150**. Moreover, the resulting formed products could not be identified so that it was difficult to draw from this failure a conclusion that could be of any use.

– Introduction of an amino group at C3 through a Ses aziridine intermediate

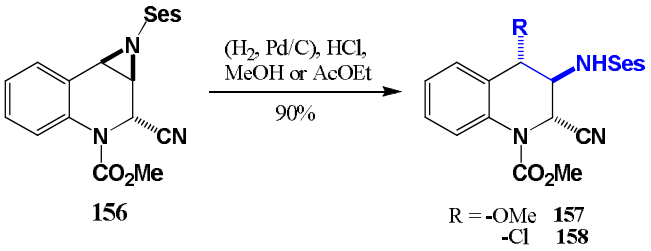
PhINSes **155**, required for the aziridination reaction, was synthesized from vinyltrimethylsilane by a four-step reaction sequence (27% overall yield) following the procedure reported by Weinreb[52] and Dodd[53]. The Reissert adduct **56** was thus reacted with PhINSes **155** in the presence of $Cu(acac)_2$ to give the Ses aziridine **156** in 70% yield as a single diastereomer (Scheme 66).

[52] S. M. Weinreb, C. E. Chase, P. Wipf, S. Venkatraman. *Organic Syntheses*. **1998**, *75*, 161
[53] P. Dauban, R. H. Dodd. *J. Org. Chem.* **1999**, *64*, 5304.



Scheme 66

As already experienced with nosylated aziridine **154**, attempts at reducing the Ses arizidine **156** under hydrogenation in the presence of Pearlman's catalyst or Pd/C did not furnish the desired amine. Reduction of **156** in an acidic medium, expected to favor the breaking of the C4-N bond, instead of the desired amine, led to compounds **157** and **158** resulting from the addition of methoxy and chloride ion respectively at the benzylic position.[54] Subsequent studies showed that reduction conditions, i.e. H_2 and Pd/C, were not necessary for the opening of aziridine **156** and formation of **157** or **158**.

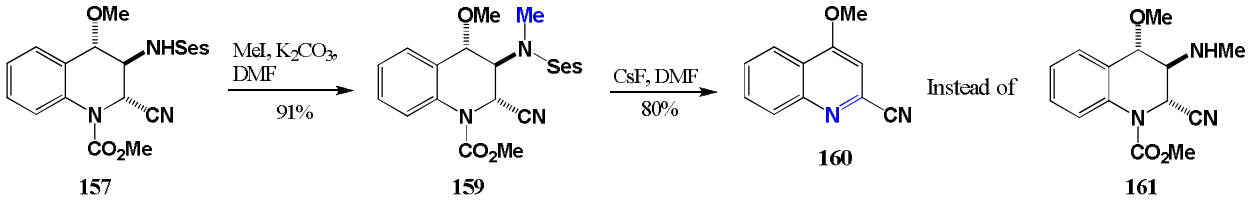


Scheme 67

[54] J. Legters, L. Thijs, B. Zwanenburg. *Recl. Trav. Chim. Pays-Bas*. **1992**, *111*, 16.

Compounds **157** and **158** could fulfill our expectations because the superfluous benzylic groups were expected to be excised by conventional reactions, i.e. hydrogenation in the presence of acetic acid to remove the methoxy group[55]; hydrogenation in the presence of Et_3N[56] or reduction by a mixture of $ZnCl_2$ and $NaBH_3CN$[20d] to remove chlorine. Therefore, they were processed further.

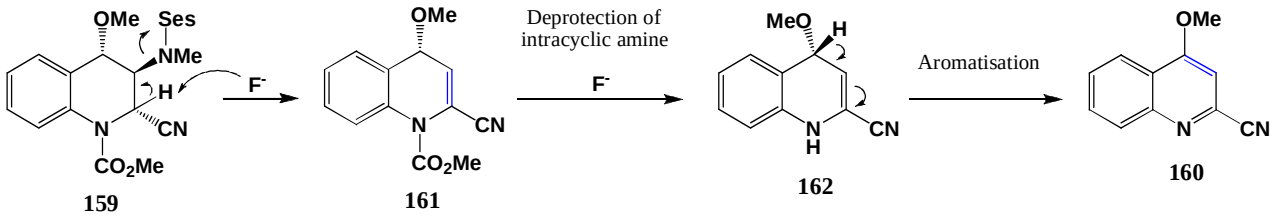
We first took advantage of the presence of the Ses group to perform the monomethylation of the exocyclic amino group. This was carried out successfully by reacting **157** with iodomethane in the presence of potassium carbonate to afford the Ses-protected monomethylamine **159** in 91% yield (Scheme 68). The loss of Ses group was then envisioned according to the protocol described by Weinreb[57], i.e. cesium fluoride in DMF. However, the expected deprotected amine **161** could not be isolated in these conditions. Instead, formation of fully aromatised compound **160** was observed.



Scheme 68

The formation of compound **160** could be explained by considering the basic character of fluoride ions. After deprotonation at α position of the cyano group, the electroattractive character of Ses group promoted the departure of the exocyclic amine to generate intermediate **161**. Deprotection of the intracyclic amine led to an unstable intermediate **162**, which was then easily transformed to the final aromatised compound **160**. The reverse order of events (that is, first N1-CO_2Me deprotection) can also be envisaged.

[55] T. Akiyama, H. Morita, K. Fuchibe. *J. Am. Chem. Soc.* **2006**, *128*, 13070.
[56] M. Kratzel, R. Hiessböck. *Heterocycles.* **2000**, *52*, 853.
[57] S. M. Weinreb, D. M. Demko, T. A. Lessen. *Tetrahedron Lett.* **1986**, *27*, 2099.



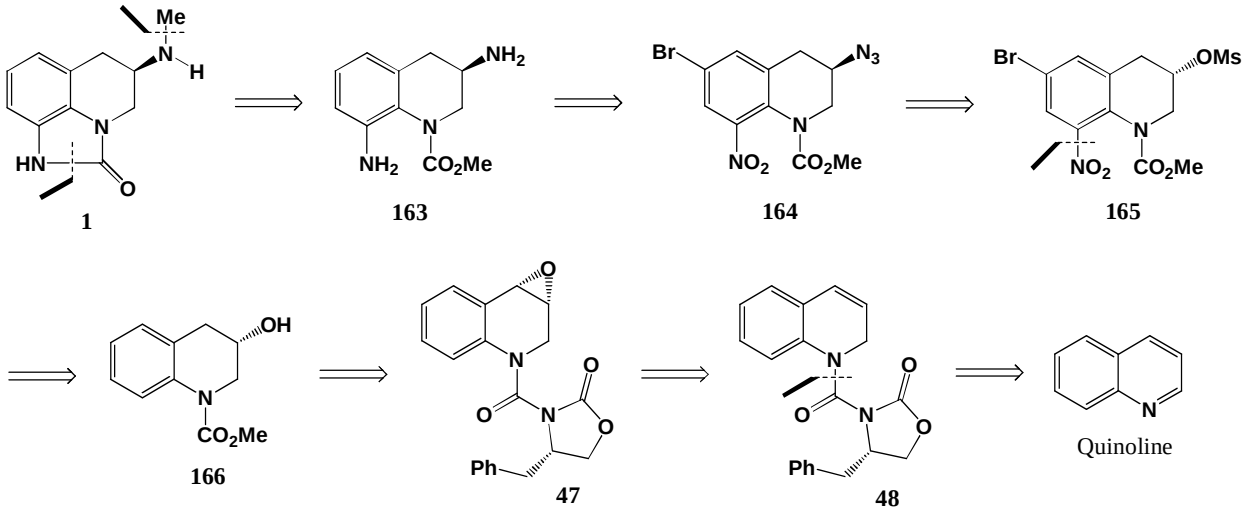
Scheme 69

The accumulation of setbacks finally led us to abandon the Reissert adduct-based strategy and to consider another route to Sumanirole **1**.

2.1.4. Total Synthesis of Sumanirole

2.1.4.1.Retrosynthesis

Taking advantage of the results already mentioned in the first part of this manuscript concerning the epoxidation of the chiral 1,2-dihydroquinoline **48**, a new strategy to reach (*R*)-**1** was then devised (Scheme 70).



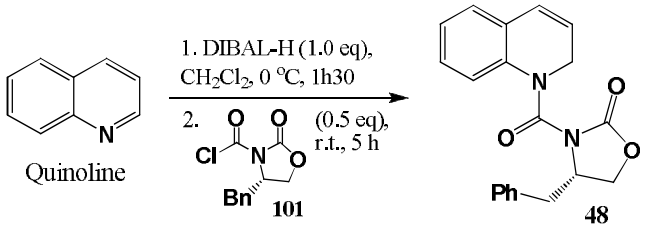
Scheme 70

Retrosynthetically, it was envisaged that (*R*)-1 could be derived from diamine **163**, which in turn could be obtained through reduction of an appropriately functionalized tetrahydroquinoline such as **164**, itself derived from mesylate **165**. Access to **165** could be devised from alcohol **166**, which could be obtained from **47** by regioselective opening of the epoxide ring and removal of the oxazolidinone moiety. Finally, the preparation of **47** could be envisaged through the

diastereoselective epoxidation of the chiral 1,2-dihydroquinoline **48** already mentioned in the first chapter, this latter prepared from quinoline.

2.1.4.2.Twelve-step synthesis of Sumanirole

Following this strategy, preparation of the 1,2-dihydroquinoline **48** was performed inspired by an earlywork of Minter and Slatter[37] who reported the 1,2-reduction of quinoline with subsequent trapping of the aminoalane intermediate with a large excess of methyl chloroformate. Quinoline was first treated with one equivalent of DIBAL-H for 1 hour, then the resulting red solution of aminoalane was syringed into a solution of chiral carbamoyl chloride **101**[58] in methylene chloride maintained at 0 °C, forming 1,2-dihydroquinoline **48** (Scheme 71).



Scheme 71: Reduction/Acylation

Excesses of quinoline and DIBAL-H were used to ensure total consumption of eletrophile **101**. The course of the reaction being impossible to monitor by TLC, we chose to optimize reaction conditions changing reaction time and number of equivalent of electrophile **101**. All assays are reported in the following table (Table 7). First assay, cannulating aminoalane on acid chloride **101**, led to a 30-40% yield of the desired dihydroquinoline **48** (entry 1). Reversing addition process led to a dramatic decrease of the yield of the reaction (entry 2). The use of a stoichiometric amount of each partner was also unsatisfactory (entry 3). Introduction of a Lewis acid such as Et_2AlCl was envisaged to improve the reactivity of chiral carbamoyl chloride **101**, but no effect on the yield was recorded (entry 4). Finally, improved and reproducible yields were recorded decreasing the reaction time of the reaction (entries 1, 5-7). The best result was obtained with 5 h of reaction (entry 6) while 2.5 h was not enough to complete the reaction (entry 5). The long reaction time led to the degradation of the product.

[58] W. H. Pirkle, K. A. Simmons. *J. Org. Chem.* **1983**, *48*, 2520.

Table 7: Optimization of the reduction/acylation reaction

Entry	***Reaction time (h)[a]***	***Additive***	***Equivalent of acid chloride 101***	***Yield (%)[b]***
1	18	-	0,5	30-40
2 [c]	18	-	0,5	6
3	18	-	1	14
4	18	Et_2AlCl[d]	0,5	29
5	2,5	-	0,5	32
6	**5**	**-**	**0,5**	**61**
7	48	-	0,5	19

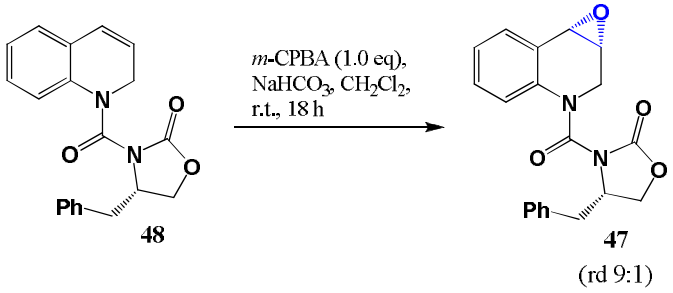
[a] Time of reaction between aminoalane (quinoline/ DIBAL-H) and acid chloride **101** with graduating rise of the temperature from 0 °C to r.t.

[b] Isolated yield after purification on silica gel

[c] Acid chloride **101** in toluene was syringed into the mixture of DIBAL-H and quinoline

[d] 1.5 eq of 1M solution of Et_2AlCl in hexane was added to acid chloride **101** before addition of the mixture of DIBAL-H and quinoline

With the 1,2-dihydroquinoline **48** in hand, the key epoxidation reaction could be performed. We were thus pleased to observe that treatment of **48** with one equivalent of *m*-CPBA led to a mixture of diastereomeric epoxides in a ratio as high as 9:1 ratio (*vide supra*) (Scheme 72). Addition of sodium bicarbonate as a buffering agent was crucial to trap the *m*-chlorobenzoic acid formed during the reaction, thereby avoiding its subsequent addition to the epoxide products. After chromatographic separation, the stereochemistry of the major epoxide **47** was fully ascertained by single-crystal X-ray diffraction (Figure 21).



Scheme 72

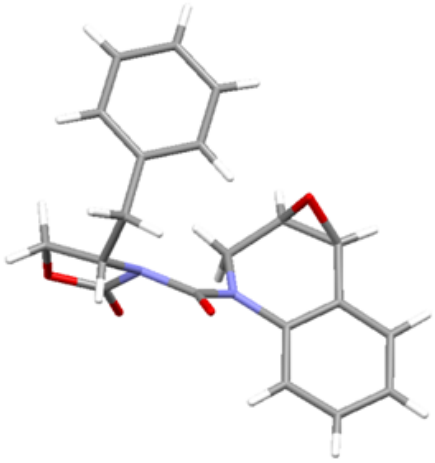
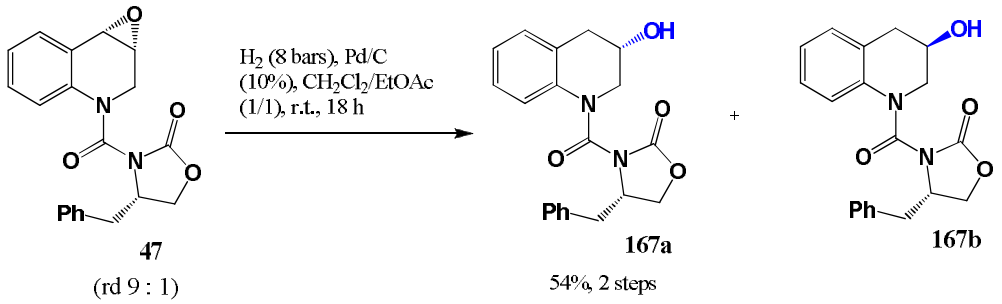


Figure 21

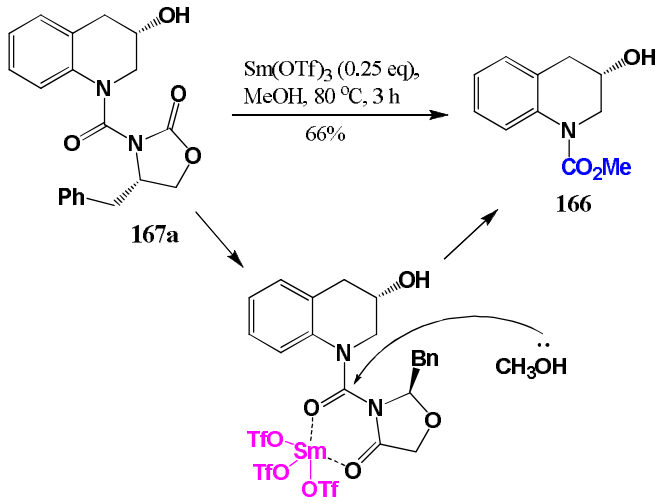
The absolute configuration at C3 will be inverted by a nucleophilic substitution at a later stage of the synthesis in order to obtain the desired configuration. Because of hydrolysis sensitivity, epoxide **47** was directly engaged in the hydrogenation step under hydrogen atmosphere (8 bars) in the presence of Pd/C, furnishing the diastereomeric mixture of alcohols **167a** and **167b**. After separation of diastereomers by chromatography on silica gel, the pure alcohol **167a** was obtained with a yield of 54% over two steps (Scheme 73).



Scheme 73

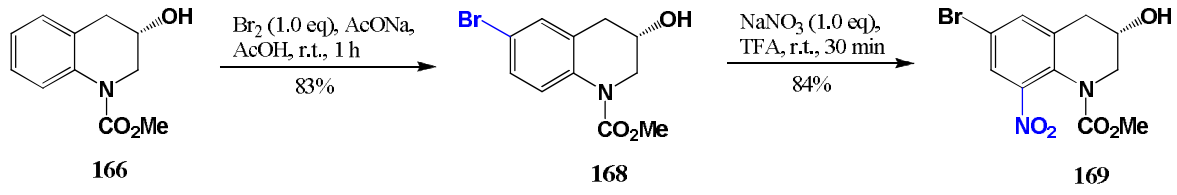
At this juncture, we made the choice to perform the OH → NHMe transformation at a later stage in the synthesis and to concentrate first on the elaboration of the imidazolone ring. Direct installation of an amino group at C8 through nitration was unrealistic because the most nucleophilic center for SEAr in **167a** would be carbon C6. It appeared thus necessary to temporary protect this carbon and a bromination/nitration sequence[41] was envisaged. Before applying this protocol, the chiral auxiliary in **167a** had to be removed. This could be easily

performed by treatment of alcohol **167a** with samarium (III) triflate in methanol at 80 °C.[39] Following this procedure, the reaction proceeded cleanly without compromising the chiral center and led to the 1,2-dihydroquinoline **166** with a yield of 66% and an enantiomeric excess of 98% (measured by HPLC on a chiral column) (Scheme 74). Samarium triflate forms a six membered rings chelate with both carbonyle groups, facilitating the attack of methanol on the urea function. The chiral auxiliary **96** could be recovered in a satisfactory yield (66%) after separation by column chromatography.



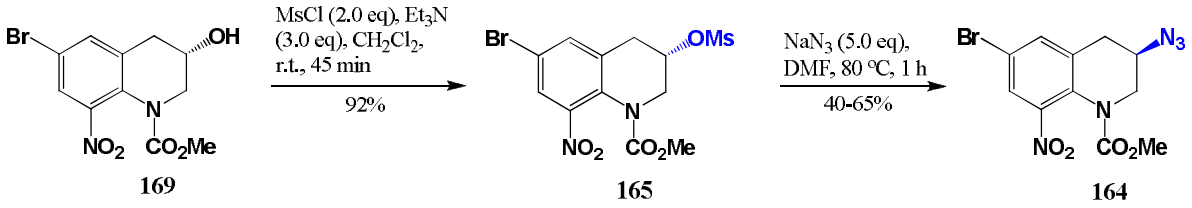
Scheme 74

The alcohol **166** was then brominated at C6 with bromine and sodium acetate in acetic acid to give the expected 6-bromo derivative **168**, which was next submitted to the action of HNO_3 in TFA to afford the 6-bromo-8-nitro-1,2-dihydroquinoline **169** in about 70% yield over two steps. Neither dehydration at C3-C4 nor *O*-nitration has been observed using these acidic conditions (Scheme 75).



Scheme 75

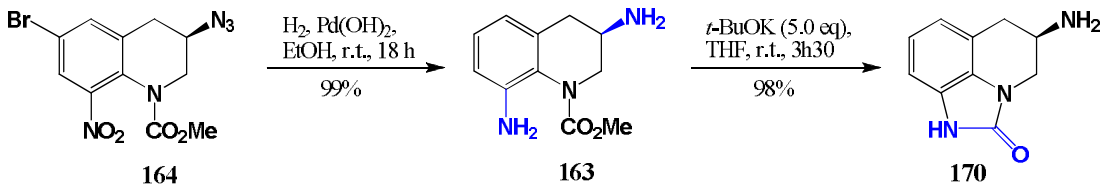
At this stage we suspended the imidazolidone ring construction and returned to the installation of the NHMe group at C3. Alcohol **169** was thus treated with mesyl chloride and triethylamine in dichloromethane to give mesylate **165**, which was next transformed to azido compound **164** through the action of sodium azide in dimethylformamide (Scheme 76). After these two steps, the configuration of stereogenic center at C3 was inverted. Data obtained by chiral HPLC seemed to confirm that no erosion of enantiomeric excess happened during the inversion. This was consistent with an S_N2 azidation. However, the yield of this reaction was decreased (40-65%) by the formation of the corresponding 1,2-dihydroquinoline due to an elimination process at C3-C4 positions. The leaving group seemed to be very sensitive to the reaction temperature. Performing the reaction at room temperature (instead of 80 °C) had no impact on the yield. The addition of a substoichiometric amount of 15-crown-5 ether (10 mol%), only increased slightly the rate of reaction without favoring substitution towards elimination. Moreover, conditions using diphenylphosphoryl azide[59] applied to mesylate **165,** led exclusively to elimination product. This last result led us to stop here our optimization investigations.



Scheme 76

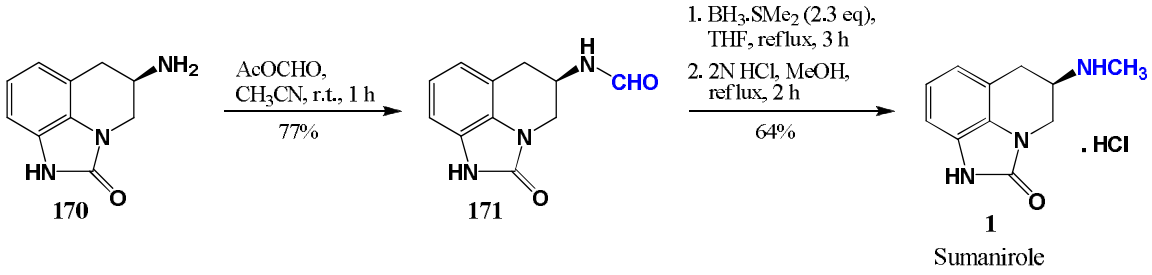
At this point our expectation was that reduction of both the azido and nitro groups as well as the hydrogenolysis of the C-Br bond would be effected in one single chemical operation. To our delight, hydrogenation of **164** in the presence of Pearlman's catalyst delivered the diamino compound **163** in almost quantitative yield (Scheme 77). Construction of the imidazolone ring was achieved by treatment of **163** with an excess of *tert*-BuOK (THF solution) in a very good yield. Regioselectivity of the reaction was attributed to the combination of two positive effects: a much greater acidity for aniline and a greater proximity of aniline moiety compared to aliphatic amine.

[59] Y. Yoshimura, K. Kitano, K. Yamada, H. Satoh, M. Watanabe, S. Miura, S. Sakata, T. Sasaki, A. Matsuda. *J. Org. Chem.* **1997**, *62*, 3140.



Scheme 77

To finish the synthesis, a monomethylation of primary amine has to be performed. Generally, the use of the obvious nucleophilic substitution on halogenoalkanes is not useful synthetic method because polycondensation cannot be avoided.[60] For the introduction of only one alkyl group, reductive alkylation, also known as reductive amination of carbonyl compounds, is an interesting alternative. Sudalai and co. recently published a *N*-monomethylation of a similar model through the use of formaldehyde in the presence of $MgSO_4$, followed by hydrogenation.[14b] These conditions applied to intermediate **170** led to a mixture of mono- and dimethylated compounds. Then, a two-step sequence described earlier by Moon and co-workers,[2a] was envisaged (Scheme 78). Compound **170** was first formylated with acetyl formate, prepared by mixing formaldehyde and acetic anhydride, to give formamide **171** in 77% yield. This latter was reduced selectively by borane-dimethyl sulfide complex to afford, after acidification, Sumanirole **1** as its hydrochloride in 64% yield. The structure of **1** and absolute configuration at C3 were confirmed by comparison of NMR spectra and optical rotation with literature values.[47]



Scheme 78

In summary, we have achieved a synthesis of Sumanirole in twelve steps from quinoline with an overall yield of 4.3%. A key feature of our synthesis is the diastereoselective epoxidation of the C3-C4 double bond in the 1,2-dihydroquinoline **48**, in spite of the fact that the chiral *N*-acyl-

[60] H. Kato, K. Ohmori, K. Suzuki. *Synlett.* **2001**, 1003 and references cited therein.

oxazolidinone auxiliary is remotely situated. Another remarkable feature is the concomitant transformation of three different groups under hydrogenation.

2.2. Synthetic studies towards Martinellic Acid

2.2.1. Introduction

Martinellic acid and martinelline (Figure 22) are two pyrroloquinoline alkaloids isolated by Witherup[61] and coworkers at Merck Laboratories in 1995 from the root bark of the tropical plant *Martinella iquitosensis.* This plant has been used for a long time as an eye medication by different ethnolinguistic groups in South America. These alkaloids are the first examples of non-peptidic compounds to be identified as bradykinin (BK) B1 and B2 receptors antagonists. In a structural point of view, these alkaloids display a pyrrolo[3,2-*c*]quinoline core, which had not been reported before. Their biological properties added to their structural originality have made these compounds attractive synthetic targets. Thus, several groups have developed new synthetic strategies for their preparation under racemic or non-racemic forms. In the first part of this chapter we will briefly review the syntheses reported up to now.

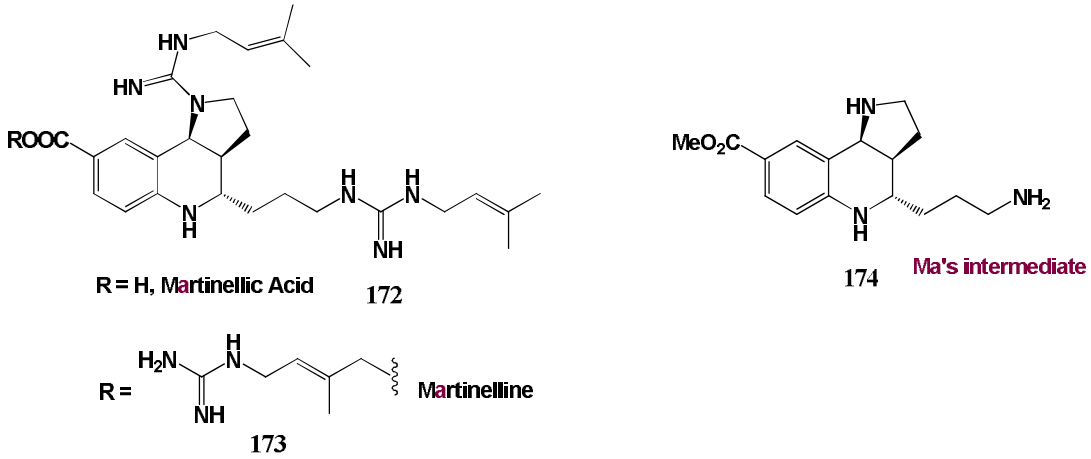


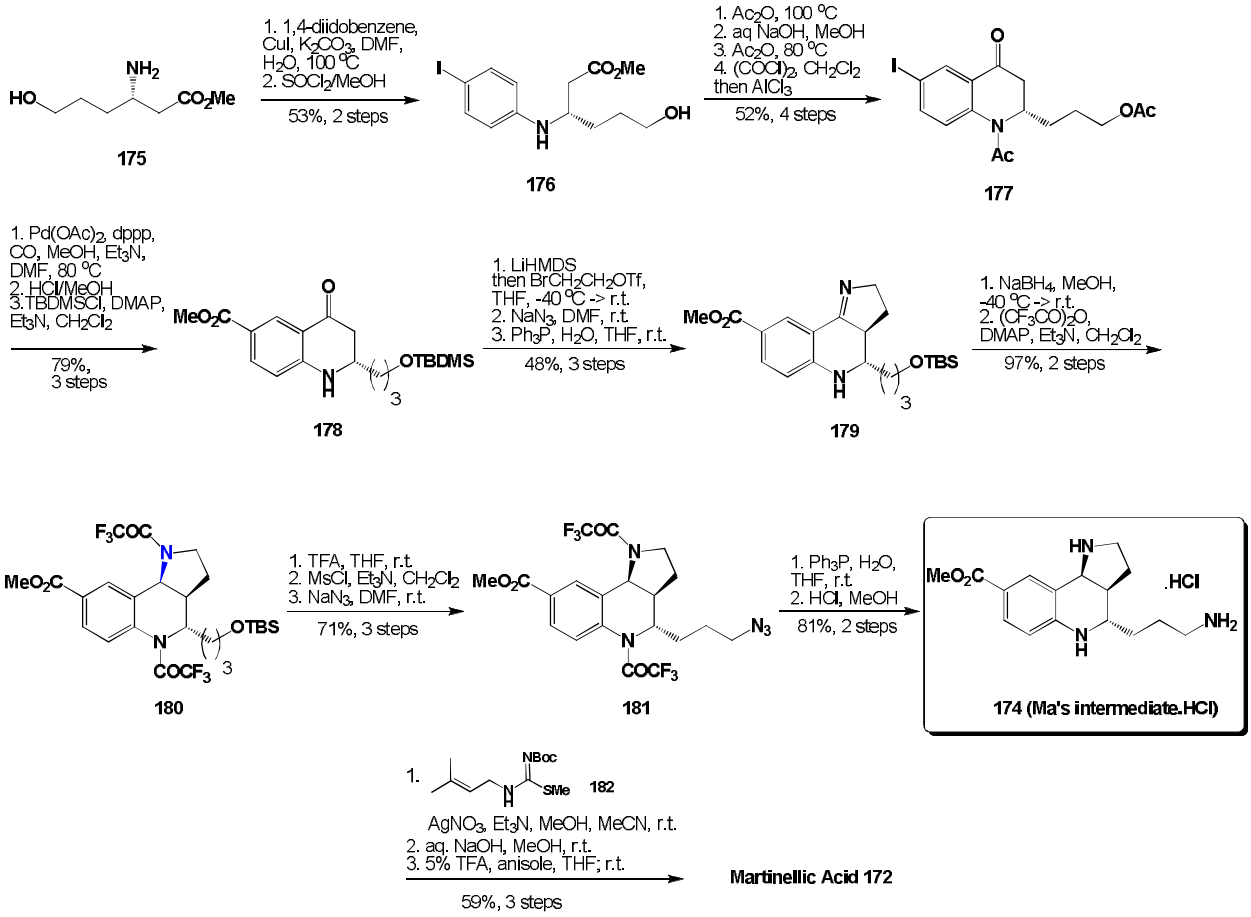
Figure 22

2.2.2. Literature review – Synthesis of Ma's intermediate

Most of syntheses have in common, as an advanced intermediate, the so-called Ma's intermediate. Our review will focus on the different preparation of this compound.

- The first synthesis was reported in a non-racemic form, by Ma[62,63] and co-workers in 2001.

[61] K. M. Witherup, R. W. Ransom, A. C. Graham, A. M. Bernad, M. J. Salvatore, W. C. Lumma, P. S. Anderson, S. M. Pitzenberger, S. L. Varga. *J. Am. Chem. Soc.* **1995**, *117*, 6682.
[62] D. Ma, C. Xia, J. Jiang, J. Zhang. *Org. Lett.* **2001**, *3*, 2189.
[63] D. Ma, C. Xia, J. Jiang, J. Zhang, W. Tang. *J. Org. Chem.* **2003**, *68*, 442.

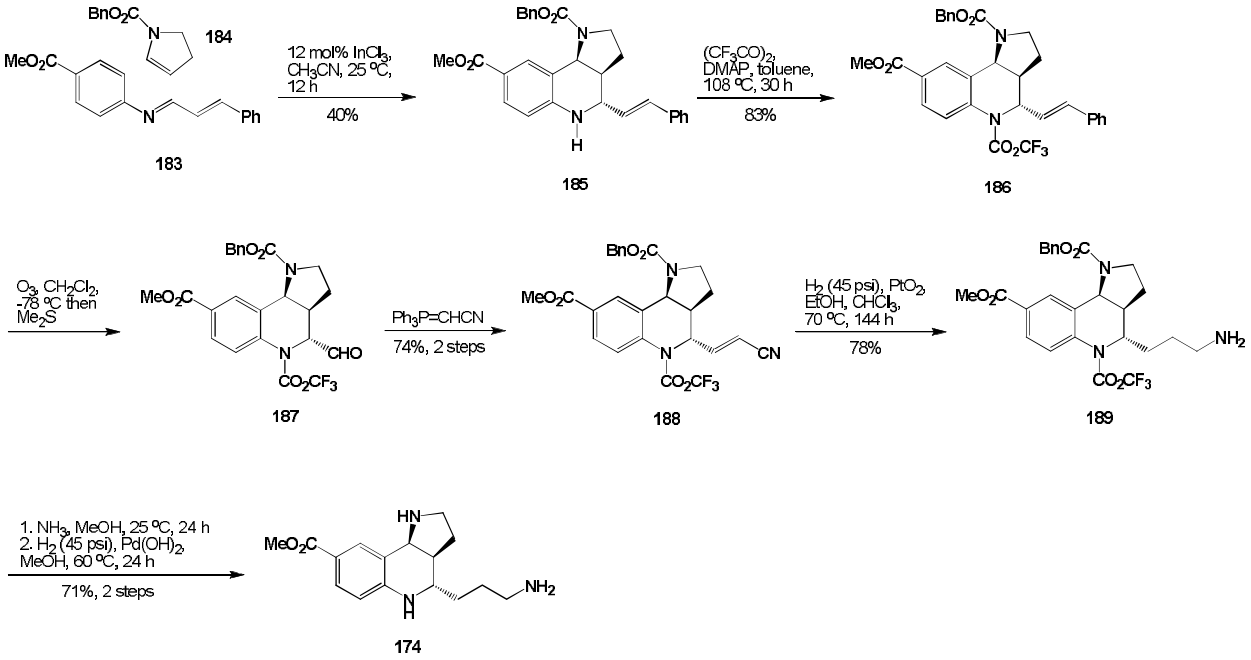


Scheme 79

Optically pure *β*-Amino ester **175**, prepared from 1,4-butandiol according to Davies procedure, was coupled with 1,4-diiodobenzene to afford *N*-aryl *β*-amino acid, which in turn was esterified to furnish **176**. After protection of the hydroxyl group and transformation of the ester group into an acid chloride, the latter underwent an intramolecular Friedel-Crafts reaction to afford the 4-oxoquinoline **177**. This compound was subjected to a Pd-catalyzed carbonylation reaction followed by an OH-protecting group switch to give **178**. After enolate formation and alkylation with $TfOCH_2CH_2Br$, the resulting product was converted into the corresponding azide derivative (OTf → N_3), which was subsequently transformed to the cyclic imine **179** through an intramolecular Staudinger reaction. Selective reduction of **179,** followed by protection of the two amino groups as trifluoroacetamides afforded **180**. This compound was then treated with TFA in THF to liberate the hydroxyl group, which was next converted into azide **181** through the formation of a mesylated intermediate. Finally, reduction of **181** with triphenylphosphine and water, followed by deprotection of the indolic nitrogen with HCl/MeOH gave the HCl salt of

Ma's intermediate **174** in 22 steps (4.2% overall yield). Martinellic acid **172** is then obtained after treatment of triamine **174** with methylisothiourea **182** followed by deprotection of ester and carbamate moieties.

- Few months later, a seven-step synthesis in racemic form was reported by Hadden[64] and co-workers.

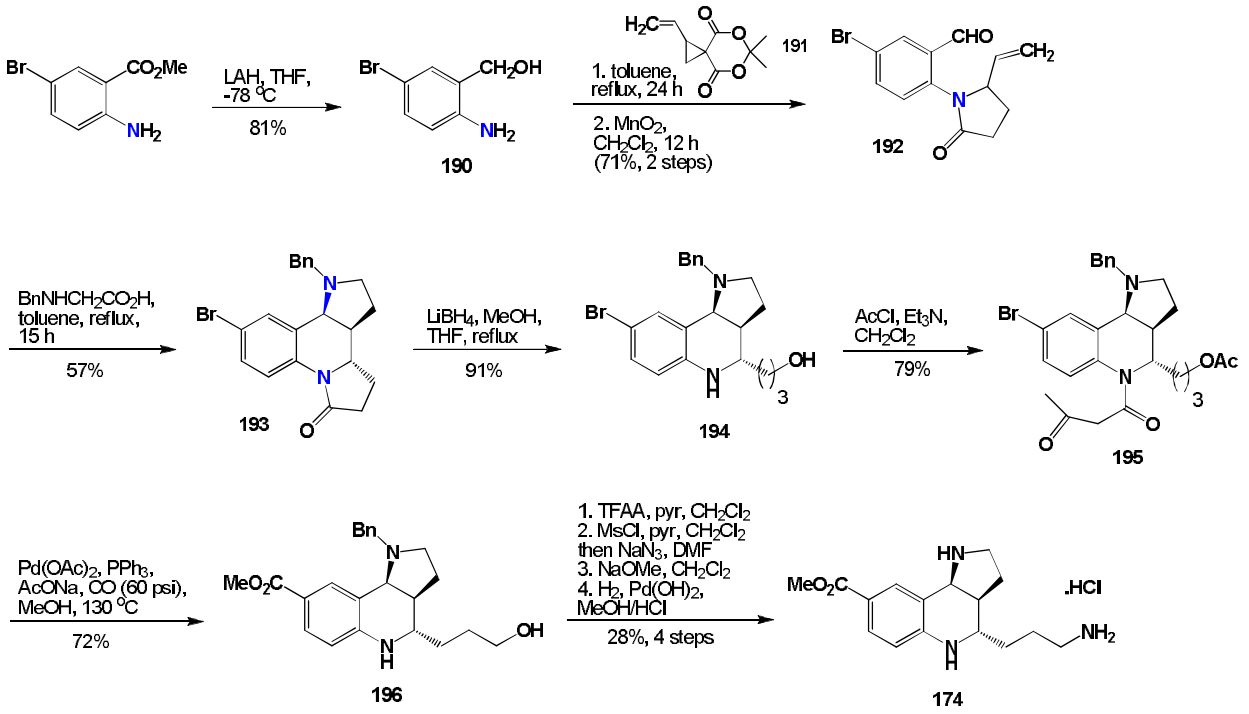


Scheme 80

An amino Diels-Alder-like reaction between the cinnamaldehyde imine **183** and the cyclic enamine **184** led to the formation of a 1.1:1 mixture of *exo-endo* stereoisomers in which the desired *exo*-isomer **185** was separated successfully by flash chromatography. After the amino group in **185** was protected as a trifluoroacetamide, the resulting product **186** was subjected to the conditions of ozonolysis to afford an unstable aldehyde **187,** which was reacted with (triphenylphosphoranylidene)acetonitrile to give a mixture of *Z* and *E* α,β-unsaturated nitriles **188**. This mixture was then hydrogenated in the presence of Adam's catalyst to furnish the primary amine **189**. Finally, after removal of protecting groups, the Ma's intermediate **174** was isolated in 13.6 % overall yield (7 steps).

[64] M. Hadden, M. Nieuwenhuyzen, D. Osborne, P. J. Stevenson, N. Thompson. *Tetrahedron Lett.* **2001**, *42*, 6417.

- Later, Snider[65] and coworkers reported a new synthesis in a racemic form *via* Ma's intermediate.

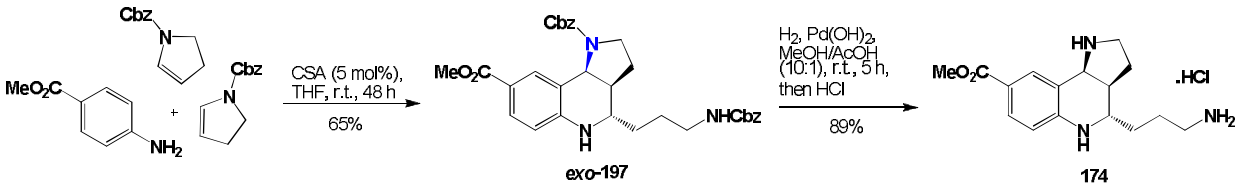


Scheme 81

The bromoanthranilic alcohol **190**, prepared from methyl 2-amino-5-bromobenzoate, was reacted with Meldrum's acid-activated vinylcyclopropane **191** followed by MnO_2 oxidation of the primary alcohol to give pyrrolidinone **192**. The aldehyde function was then condensed with *N*-benzylglycine to form a transient azomethineylide which cyclized to give the fused tetracyclic compound **193**. Selective reduction of the pyrrolidinone ring afforded amino alcohol **194**, which was tri-acetylated to give acetoxy acetoamide **195**. Pd-catalyzed methoxycarbonylation of this compound occurred with concomitant *N,O*-bis-deacylation to afford free amino alcohol **196**. Transformation of the primary hydroxyl group into an azide group was effected through the formation of a mesylate intermediate after protection of the secondary amine as a trifluoroacetamide. After deprotection of the trifluoroacetamide sodium methylate, hydrogenation of the azide group and *N*-Bn deprotection were simultaneously effected under the action of Pearlman's catalyst to give the HCl salt of Ma's intermediate **174** (90-95% pure) in 4.7% overall yield (11 steps).

[65] B. B. Snider, Y. Ahn, S. M. O'Hare. *Org. Lett.* **2001**, *3*, 4217.

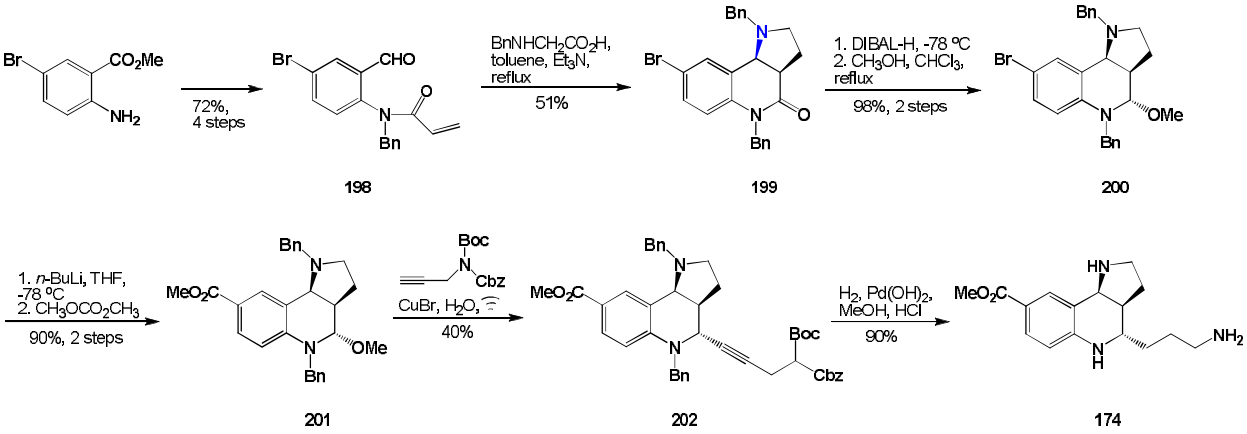
- The shortest approach (two steps) featuring a three-component reaction was reported by Powell and Batey in 2002.[66]



Scheme 82

N-Cbz-2-pyrroline and methyl 4-aminobenzoate were reacted at room temperature in the presence of a protic acid catalyst to yield the tricyclic triamine core of Martinellic acid **197** as a mixture of diastereomers. The desired *exo* product was isolated in high purity after flash chromatography separation. This product was then deprotected with Pearlman's catalyst to afford Ma's intermediate hydrochloride **174** after acidification in 58% overall yield.

- Four years later, a different approach was described by Y. He[67,68] and co-workers from methyl 4-bromoanthranilate.



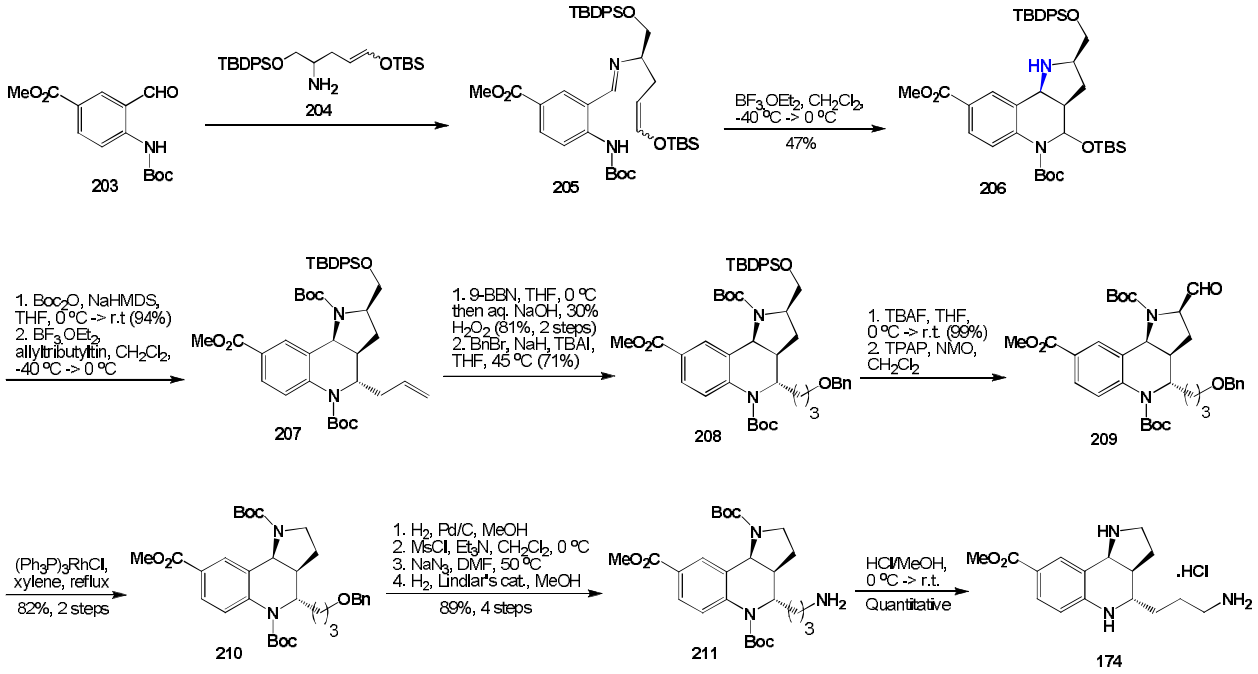
Scheme 83

Aldehyde **198**, prepared in four steps from methyl 4-bromoanthranilate, was reacted with *N*-benzylglycine following an intramolecular cycloaddition to furnish a mixture of pyrrolo-quinolinones, from which the desired *cis*-isomer **199** could be separated in 51% yield. DIBAL-H

[66] D. A. Powell, R. A. Batey. *Org. Lett.* **2002**, *4*, 2913.
[67] Y. He, R. Moningka, C. J. Lovely. *Tetrahedron Lett*. **2005**, *46*, 1251.
[68] Y. He, H. Mahmud, R. Moningka, C. J. Lovely, H. V. Rasika Dias. *Tetrahedron*. **2006**, *62*, 8755.

reduction followed by a methanolic treatment stereoselectively afforded the methoxy derivative **200**. This product was next methoxycarbonylated to give ester **201**, which was then subjected under sonication to the action of a copper acetylide to furnish a single alkylated pyrroloquinoline **202** via an iminium intermediate. Finally, hydrogenation in the presence of Pearlman's catalyst fully reduced the alkyne group and effected simultaneous removal of all protecting groups to give Ma's intermediate **174** in 10 steps and in 11.7% overall yield.

- An asymmetric synthesis with significant improvement of the overall yield, compared to the Ma's achievement, was reported by Ikeda[69] and coworkers in 2007.



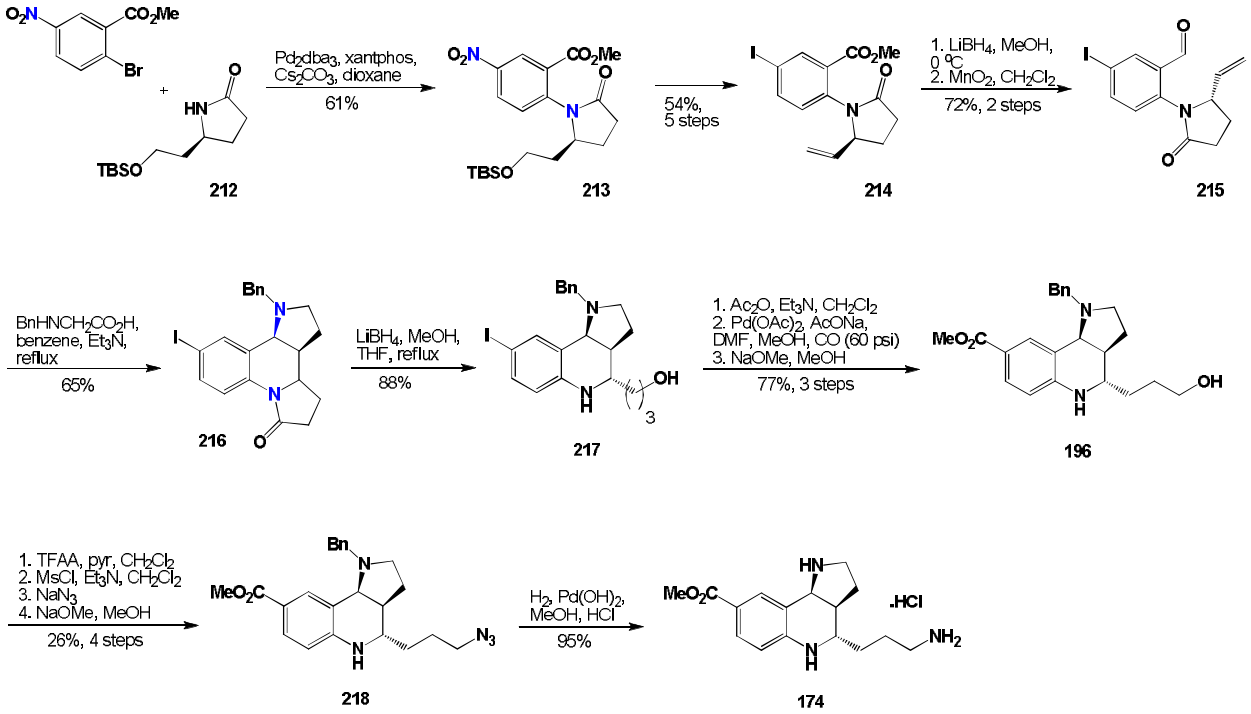
Scheme 84

Imine **205**, prepared by reaction between aldehyde **203** and chiral amine **204**, led, through the activation of $BF_3.OEt_2$ to a mixture of diastereoisomers (*dr* = 4.2:1) having the tricyclic core of Martinellic acid. The major isomer **206** could be successfully separated from this mixture. After Boc-protection of the indolic nitrogen, the resulting product was subjected to a Hosomi–Sakurai type allylation, leading diastereoselectively to **207** having an allyl chain at C2. After hydroboration–oxidation of the allylic double bond and benzyl-protection of the resulting hydroxyl group, the TBDPS-oxymethyl group was removed via the formation of aldehyde **209**

[69] S. Ikeda, M. Shibuya, Y. Iwabuchi. *Chem. Commun.* **2007**, 504.

subsequently decarbonylated using the Tsuji–Wilkinson reaction. The resulting compound **210** was successfully converted, through a five-step sequence of reactions, to Ma's intermediate **174** isolated in 18.4% overall yield (13 steps from **205)**.

- To our knowledge, the last effort towards this natural product synthesis via Ma's intermediate was reported by Badarinarayana and Lovely in 2007.[70]



Scheme 85

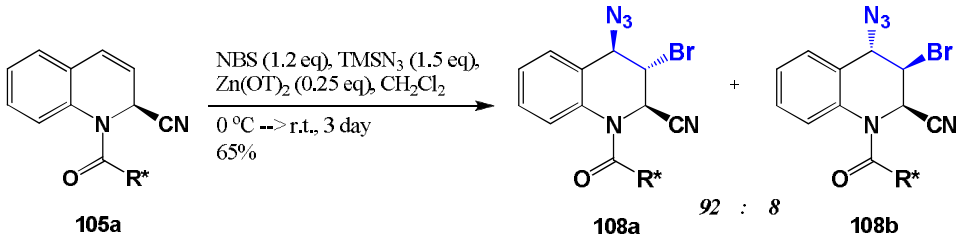
A Pd-catalyzed aryl amidation reaction between methyl 2-bromo-5-nitrobenzoate and pyroglutamate-derived lactam **212**, gave the *N*-aryl lactam **213**, next transformed to **214** through a sequence of five reactions. Reduction-oxidation of the ester group in **214** afforded aldehyde **215**. Coupling of this aldehyde with *N*-benzylglycine led to the transient formation of an azomethine ylide, which [3+2] cycloadded with the vinylic chain. This resulted in the formation of a mixture of tetracyclic compounds in which the major isomer **216** could be separated in 65% yield. Reductive ring opening of the lactam ring in **216** gave the amino alcohol **217,** which in turn was methoxycarbonylated through a three-step sequence to furnish **196**. The hydroxyl group in **196** was transformed into azide **218** in 4 steps. Both one-step reduction of azide functionality

[70] V. Badarinarayana, C. J. Lovely. *Tetrahedron Lett.* **2007**, *48*, 2607.

and cleavage of the *N*-benzyl group provided the HCl salt of Ma's intermediate **174** in 2.6% overall yield (18 steps).

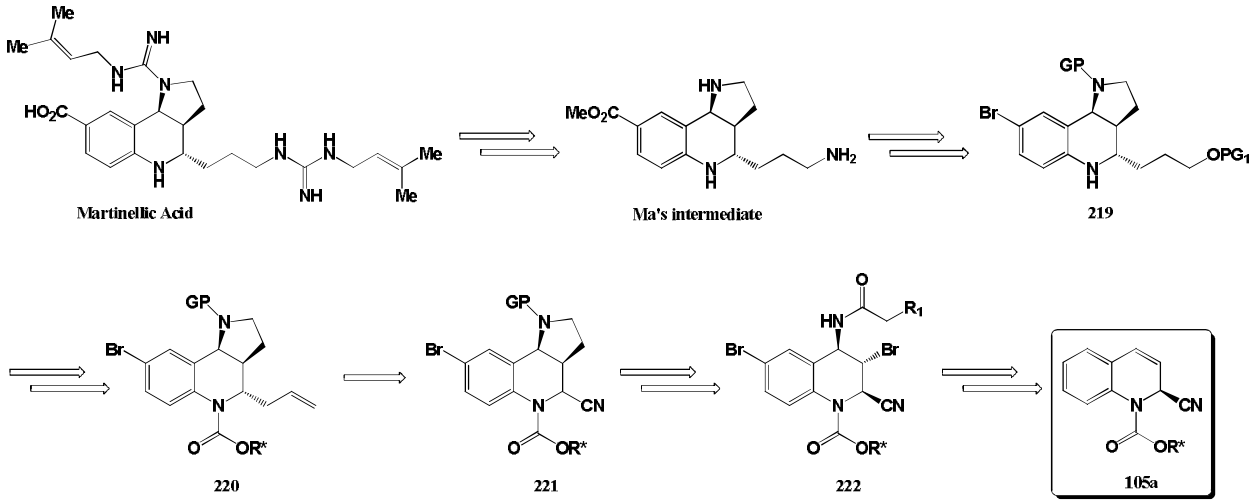
2.2.3. Our synthetic preliminaries towards the synthesis of Martinellic acid

As described in the first chapter "Remote control of the C3-C4 double bond epoxidation of a chiral 1,2-dihydroquinoline", the electrophilic addition of trimethylsilyl azide on the Reissert adduct **105a** selectively furnished a mixture of addition products (*dr* = 92/8) from which the major diastereomer **108a** could be successfully isolated.



Scheme 86

We became interested in using this product as a possible starting point for the synthesis of martinellic acid. Our envisaged strategy is depicted in the following Scheme 87.

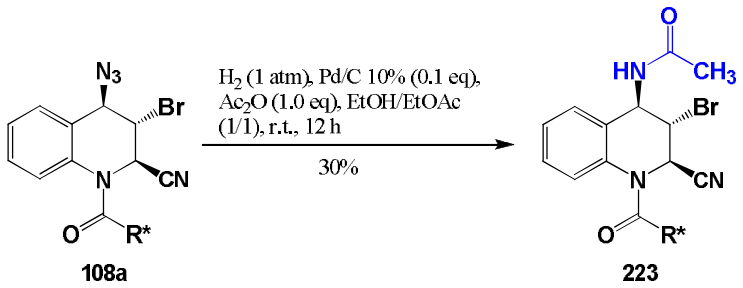


Scheme 87

Basically, martinellic acid would be derived from Ma's intermediate, which in turn would be obtained from bromo alcohol derivative **219** through manipulation of functional groups. Access to key compound **219** could be envisaged from allyl derivative **220** via standard manipulations. Access to intermediate **220** could be envisaged from the amino nitrile **221** through the transient

formation of an iminium derivative. At this point, and based on the pKa values of the potential sites of deprotonation, we were aware that the formation of amino nitrile **221** from the bromo-acetamido derivative **222**, would not be effected without problems. Nevertheless, we decided to explore the feasibility of this strategy. The preparation of compound **222** from the Reissert adduct **105a** was thus our first target.

To reach this compound we applied to **108a** the same conditions successfully used with the analogue compound lacking the CN substituent. We were pleased to observe that this reaction led to the bromo-acetamido derivative **223**. The yield was substantially lower, however, a fact we tentatively attributed to partial reduction of the CN group. At this point, we did not make effort to optimize the reaction delaying it in case the strategy would be feasible.

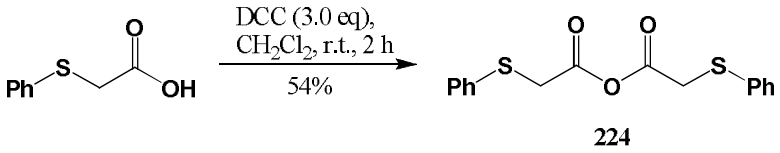


108a **223**

Scheme 88

The next and most challenging task was the transformation of compound **222** to the tricyclic key intermediate **221.** In order to increase the pKa value of the methyl substituent of the acetamido group in **223**, we thought to first substitute it with a SPh group. Compound **225** thus became a new target (Scheme 90).

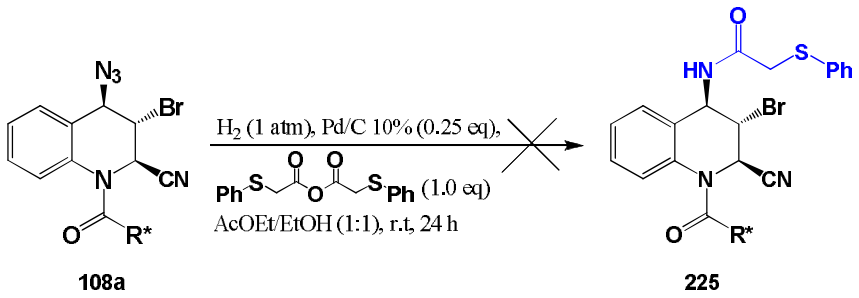
2-(Phenylthio)acetic anhydride **224** being not commercially available, we had to prepare it. This was accomplished by treatment of 2-(phenylthio)acetic acid with *N*,*N*'-dicyclohexylcarbodiimide in CH_2Cl_2 as shown in Scheme 89.



224

Scheme 89

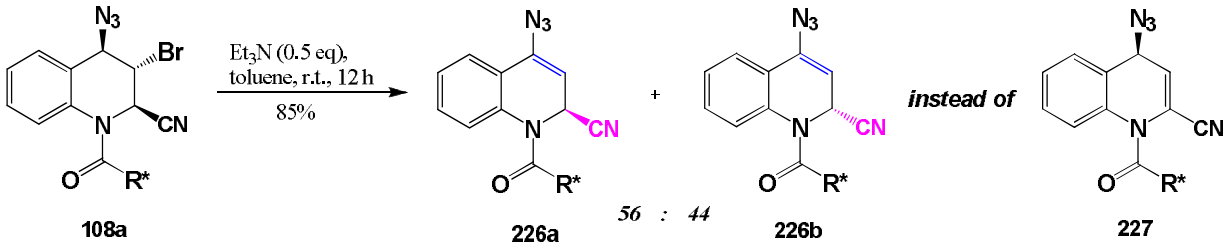
With the 2-(phenylthio)acetic anhydride in hand, the synthesis of the 2-(phenyl)acetamido derivative **225** could now be examined. Applying the same conditions as previously reported for the bromo-acetamido derivative **223** failed to give any trace of desired compound. Increasing the quantity of Pd/C catalyst used, recourse to alternative catalysts such as Pearlman's or changing the nature of solvents did not bring any positive result as well. Poisoning of the catalyst or (and) degradation of the anhydride reagent could explain this failure.



108a **225**

Scheme 90

We thus considered the bromo-acetamide derivative again and thought that, if it were possible to effect dehydrobromination of this compound, with formation of the unsaturated nitrile **228a**, the cyclisation reaction would be more easily accomplished. Of course, it may be considered that treatment of **223** with an excess of base would first generate the unsaturated nitrile **228a** rather than deprotonate the acetamido group first. Dehydrobromination reaction was first attempted on bromo-azido compound **108a** under the action of Et_3N in toluene. Contrary to our expectations, these conditions did not lead to unsaturated nitrile **227** but merely to a mixture of diastereoisomers **226a** and **226b** in which the double bond became in conjugation with both the phenyl ring and the azido group. These two diastereoisomers could be well separated on silica gel by flash chromatography.



108a **226a** *56 : 44* **226b** **227**

Scheme 91

The configurations of the major diastereoisomer was rigorously assigned after a X-ray structure could be obtained (Figure 23).

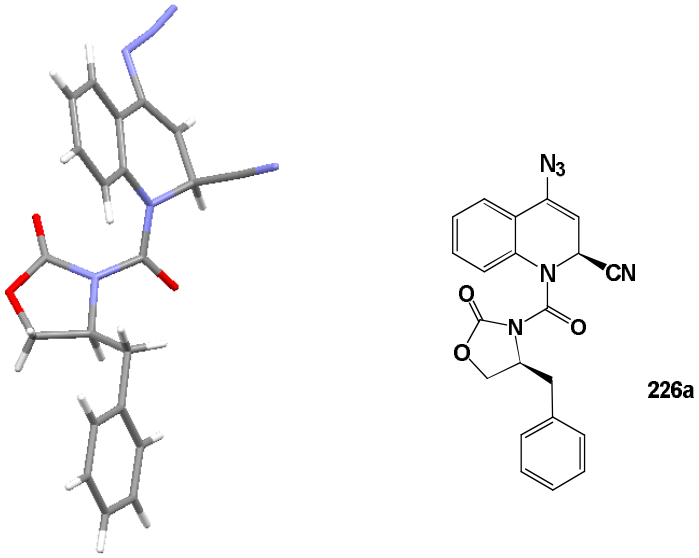
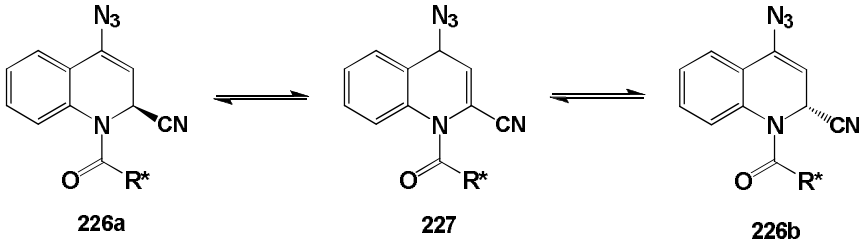


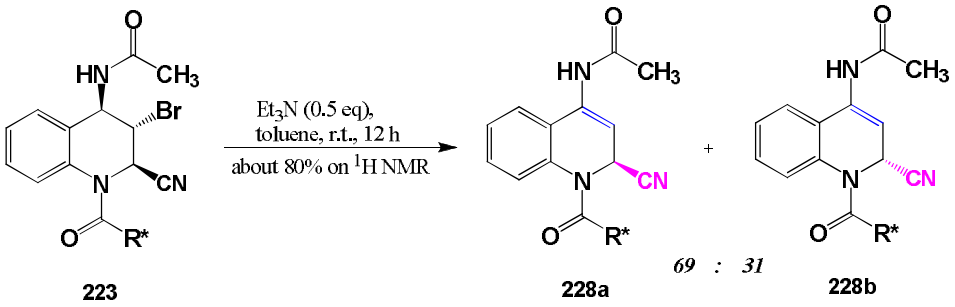
Figure 23

The formation of diastereoisomers **226a** and **226b** also indicated that epimerization at C2 occurred during the reaction. The possibility exists that unsaturated nitrile **227** is the precursor in the formation of **226a** and **226b,** but this was not demonstrated (Scheme 92).



Scheme 92

The same basic conditions applied to the bromo-acetamido derivative **223** led to a similar result (Scheme 93). A little difference can be found in the ratio of the two diastereoisomeric products.



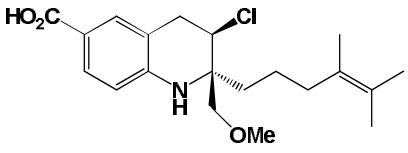
Scheme 93

In conclusion to this preliminary study, it appears that, if the formation of the bromo-acetamido derivative **223** could be accomplished from the Reissert adduct **108a**, its transformation to the key tricyclic compound **221** (annelation of the pyrrolidine ring) could not be effected through an intramolecular conjugated addition on an α,β-unsaturated nitrile as a well-defined or transient intermediate. This strategy was not processed further.

2.3. Synthetic studies towards Virantmycin

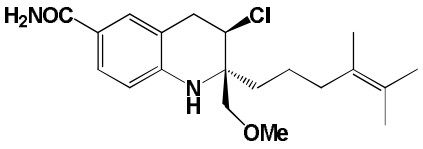
2.3.1. Introduction

(-)-Virantmycin **229**, an antiviral antibiotic, isolated from a strain *Streptomyces nitrosporeus* in 1980, is an unusually substituted tetrahydroquinoline with a chloro group at C3.[71] It was found to possess both strong inhibitory activity against RNA and DNA viruses, and antifungal activity.[72] Later, in 1996, benzastatins C and D[73], isolated from *Streptomyces sp.*, whose structures are closely related to Virantmycin demonstrated inhibitory activity against glutamate toxicity and lipid peroxidation. These three natural products are unique 2,2-disubstituted tetrahydroquinoline alkaloids with contiguous quaternary and tertiary stereocenters.

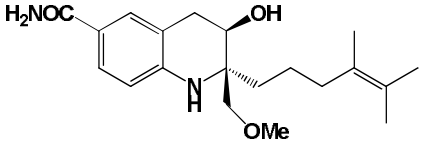


229

Virantmycin



Benzastatin C



Benzastatin D

Figure 24

2.3.2. Literature review – Total Synthesis of Virantmycin

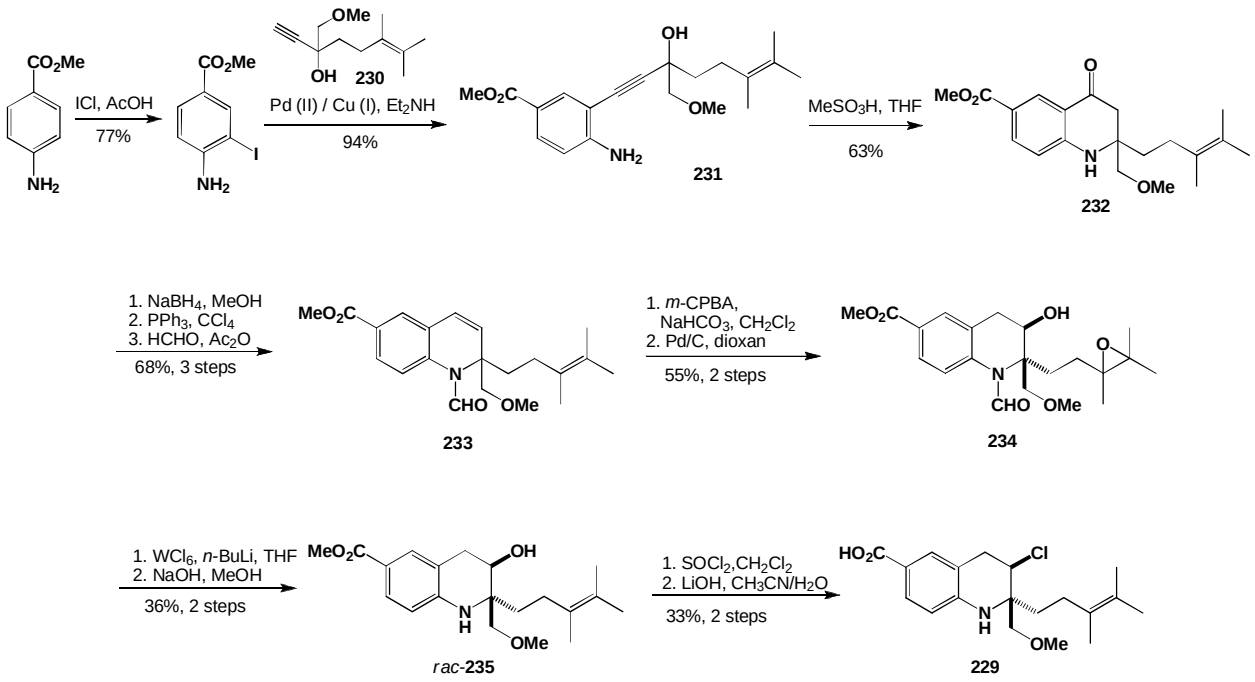
The stereoselective construction of the chiral quaternary stereocenter in virantmycin is one of its most challenging synthetic problems.[74] Moreover, the presence of one tertiary stereocenter vicinal to the quaternary carbon atom has made the total synthesis of this molecule even more

[71] S. Ōmura, A. Nakagawa, H. Hashimoto, R. Oiwa, Y. Iwai, A. Hirano, N. Shibukawa, Y. Kojima. *J. Antibiot.* **1980**, *33*, 1395.
[72] A. Nakagawa, Y. Iwai, H. Hashimoto, N. Miyazaki, R. Oiwa, Y. Takahashi, A. Hirano, N. Shibukawa, Y. Kojima, S. Ōmura. *J. Antibiot.* **1981**, 34, 1408. (b) S. Ōmura, A. Nakagawa. *Tetrahedron Lett.* **1981**, *22*, 2199.
[73] (a) W.-G. Kim, J.-P. Kim, C.-J. Kim, K.-H. Lee, I.-D. Yoo. *J. Antibiot.* **1996**, *49*, 20. (b) W.-G. Kim, J.-P. Kim, I.-D. Yoo. *J. Antibiot.* **1996**, *49*, 26.
[74] (a) K. Fuji, *Chem. Rev.* **1993**, 93, 2037. (b) E. J. Corey, A. Guzman-Perez, *Angew. Chem. Int. Ed.* **1998**, *37*, 388. (c) K. Funabashi, H. Ratni, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2001**, *123*, 10784.

challenging. The earliest work about the racemic total synthesis of Virantmycin was reported in 1986,[75] and it took nearly one decade for the first enantioselective synthesis to be reported.[76]

2.3.2.1.Racemic syntheses

- The first total synthesis of racemic Virantmycin was described by Hill and Raphael.[75]



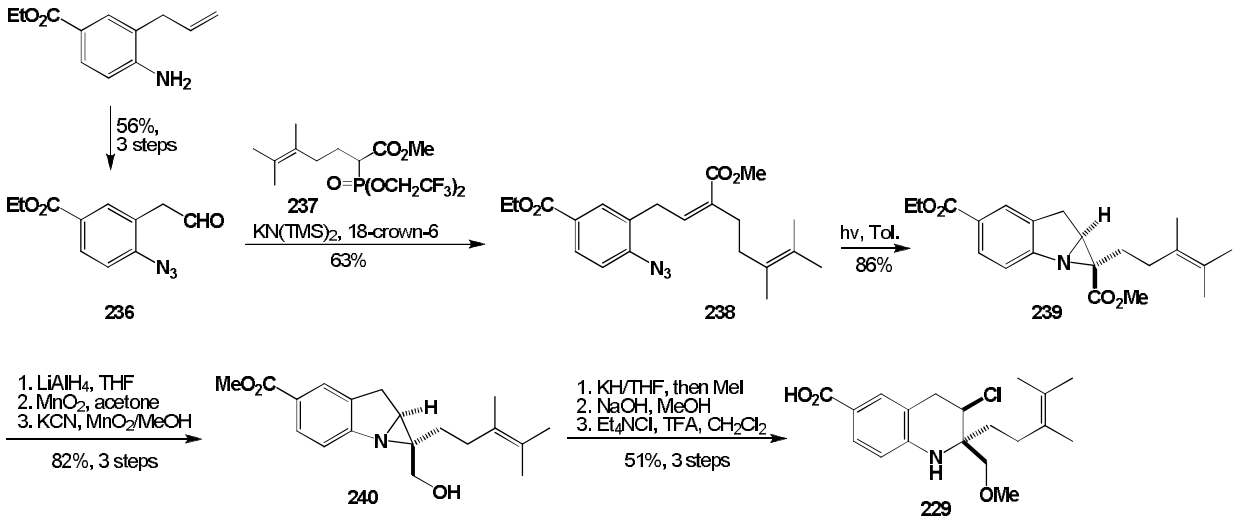
Scheme 94

Methyl 4-amino-3-iodobenzoate, prepared from methyl 4-aminobenzoate, was coupled efficiently with acetylenic alcohol **230** to give the hydroxyacetylene **231**. This product was submitted to a tandem acid-catalysed Meyer-Schuster rearrangement and an intramolecular Michael reaction to afford the bicyclic aminoketone **232**. Reduction of keto group, followed by dehydration of the resulting alcohol furnished a 1,2-dihydroquinoline, which, in turn, was converted to the stable *N*-formyl derivative **233**. **233** was then subjected to an epoxidation reaction (both double bonds were oxidized) to give a diastereoisomeric mixture of epoxides. The benzylic epoxide was selectively hydrogenolyzed to furnish a mixture of hydroxy-epoxides **234**. After regeneration of the remote double bond, the formyl group was removed to produce the

[75] (a) M. L. Hill, R. A. Raphael, *Tetrahedron Lett.* **1986**, *27*, 1293. (b) M. L. Hill, R. A. Raphael. *Tetrahedron* **1990**, *46*, 4587.
[76] M. Ori, N. Toda, K. Takami, K. Tago, H. Kogen. *Angew. Chem. Int. Ed.* **2003**, *42*, 2540.

hydroxy-amine **235**. The *cis* relationship between the hydroxyl group and the methoxymethyl group has been determined at this stage by NOE spectroscopy. Installation of the chloro group at C3 with retention of configuration was carried out following a double inversion process to give the methyl ester of (±)-Virantmycin. Finally, hydrolysis of the ester group at C6 delivered (±)-Virantmycin **229** in 2.0% overall yield (12 steps).

- In 1991, Morimoto[77] reported an efficient synthesis using an intramolecular nitrene-addition reaction as a key step.

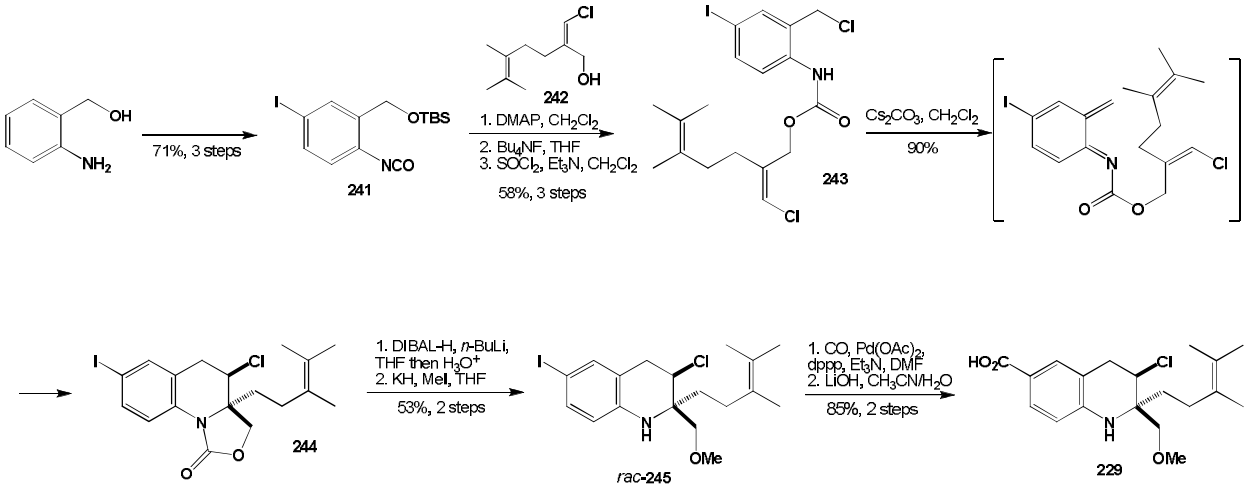


Scheme 95

Azide aldehyde **236**, prepared from ethyl 4-amino-3-(2-propenyl)benzoate, was subjected to an Horner-Emmons reaction with phosphonate **237** to give the (*Z*)-olefin **238** with high stereoselectivity (ratio > 50:1). This product was then subjected to an intramolecular nitrene-addition reaction by photolysis leading to aziridine **239** with complete stereoselection. Transformation of this latter compound to ester-alcohol **240** was accomplished in three steps. Methylation of the alcohol function, saponification of ester at C6 and then stereo- and regioselective opening of the aziridine group by a chloride ion finally afforded (±)-Virantmycin **229** in 13% overall yield (11 steps).

[77] (a) Y. Morimoto, F. Matsuda, H. Shirahama. *Synlett*. **1991**, 201. (b) Y. Morimoto, F. Matsuda, H. Shirahama. *Tetrahedron*. **1996**, *52*, 10609.

- In 1999, another approach with a slightly improved overall yield was carried out by Steinhagen and Corey.[78]

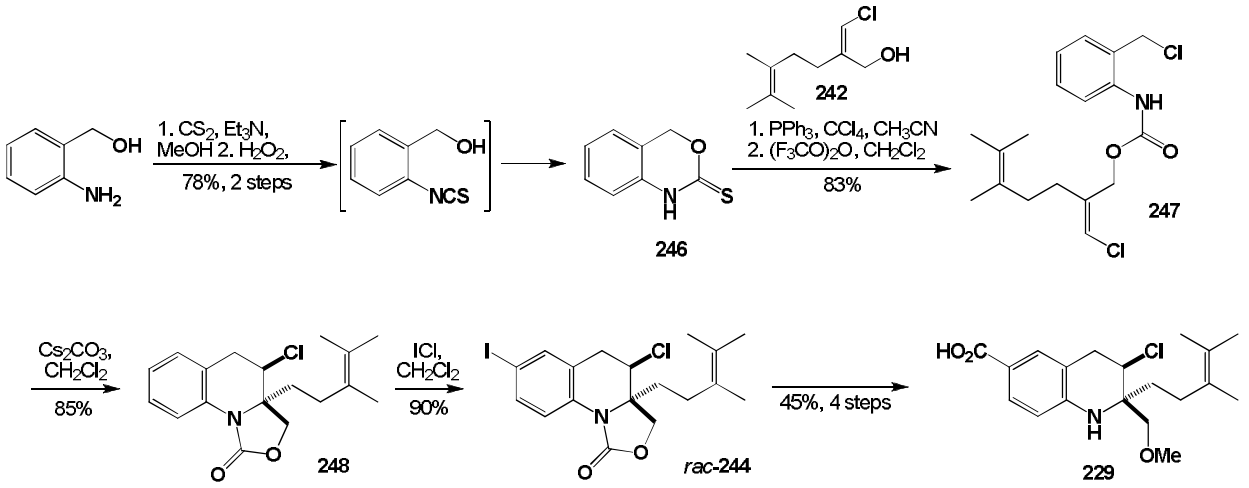


Scheme 96

Isocyanate **241**, prepared from 2-aminobenzyl alcohol, was reacted with allylic alcohol **242** to afford the corresponding carbamate, which, in turn, underwent a sequential desilylation, followed by chlorination to give the chloro carbamate **243.** This product was subjected to an internal [4 + 2] cycloaddition by generating and then trapping an *O*-azaxylylene intermediate to form the tetrahydroquinoline derivative **244** with complete stereoselection. Reductive cleavage of the cyclic urethane subunit of **244** gave an amino alcohol, which was methylated to afford the amino ether *rac*-**245**. This latter compound was then methoxycarbonylated to afford the methyl ester of (±)-Virantmycin, which was then hydrolyzed to produce (±)-Virantmycin **229** in 17% overall yield (11 steps).

- An optimization towards the Corey's precursor **244** by shortening the number of steps and increasing the overall yield was performed by Keck[79] and co.

[78] H. Steinhagen, E. J. Corey. *Org. Lett.* **1999**, *1*, 823.
[79] D. Keck, S. Vanderheiden, S. Bräse, *Eur. J. Org. Chem.* **2006**, 4916.



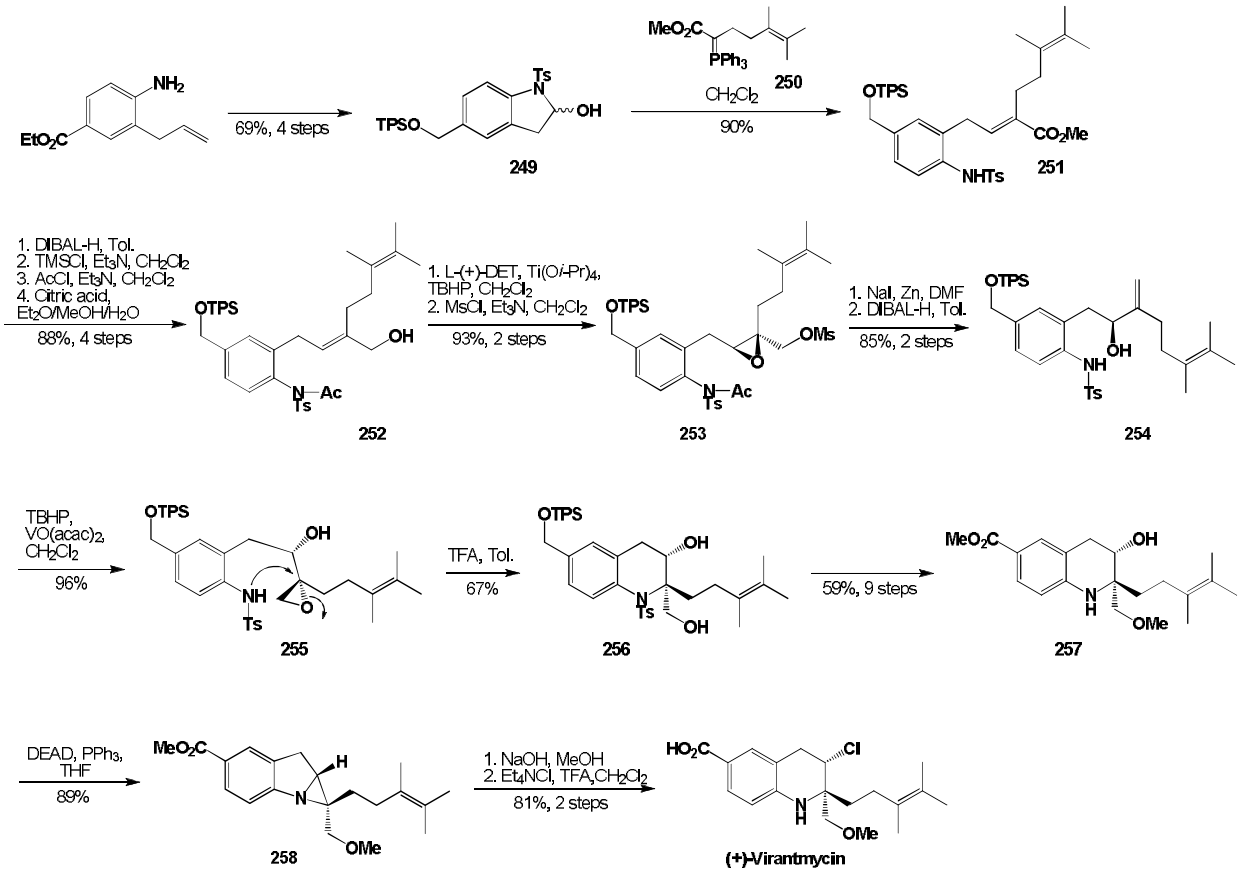
Scheme 97

Arylthiocarbamate **246**, prepared from 2-aminophenyl methanol, was submitted to an Appel-type reaction to afford the carbamate **247**. This product, in the presence of cesium carbonate (generation of a transient imino diene), experienced an intramolecular [4+2]-Diels-Alder cycloaddition to provide tricycle **248**, which, in turn, was iodinated to provide the Corey's intermediate **244** as a single isomer in 45% overall yield (4 steps).

2.3.2.2.Asymmetric syntheses

- Synthesis of (+)-Virantmycin

- The first asymmetric synthesis reported by Morimoto and co.[80] concerned the antipodal (+)-Virantmycin.



Scheme 98

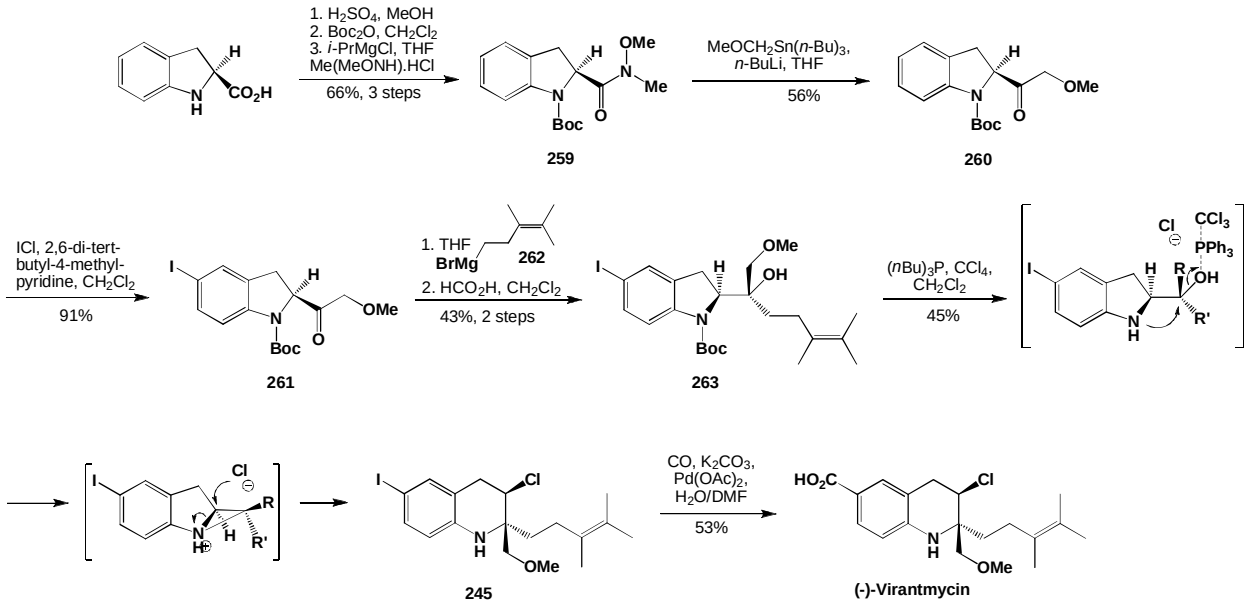
N-protected hemiacetal **249**, prepared from ethyl 4-amino-3-(2-propenyl)benzoate, was subjected to a Wittig reaction with phosphorane **250** to give (*E*)-α,β-unsaturated ester **251** with a high stereoselectivity (30:1). After ester reduction and amino bis-protection, the resulting allylic alcohol was subjected to a Sharpless asymmetric epoxidation using L-(+)-diethyl tartrate to furnish the optically active epoxy alcohol (92% ee), which was then mesylated to provide mesylate **253**. A two-step sequence transformed **253** into the allylic alcohol **254**, which underwent a vanadium (V)-catalyzed epoxidation to afford the erythro epoxy alcohol **255** as a

[80] Y. Morimoto, H. Shirahama. *Tetrahedron*. **1996**, *52*, 10631.

single diastereomer. This latter product was then treated with trifluoroacetic acid to selectively provide the tetrahydroquinoline **256**. After construction of the tetrahydroquinoline core in a stereoselective manner, manipulation of functional groups was performed next in nine steps. The resulting alcohol **257** was subjected to an intramolecular Mitsunobu reaction to furnish the aziridine **258**, which was transformed to (+)-Virantmycin **229** following a two-step sequence already reported (vide supra, Scheme 95). 27 steps were necessary to reach this molecule in an overall yield of 12%.

- Synthesis of (-)-Virantmycin

- The first enantioselective synthesis of (-)-Virantmycin was reported by Ori[76,81] from (*S*)-indoline-2-carboxylic acid.



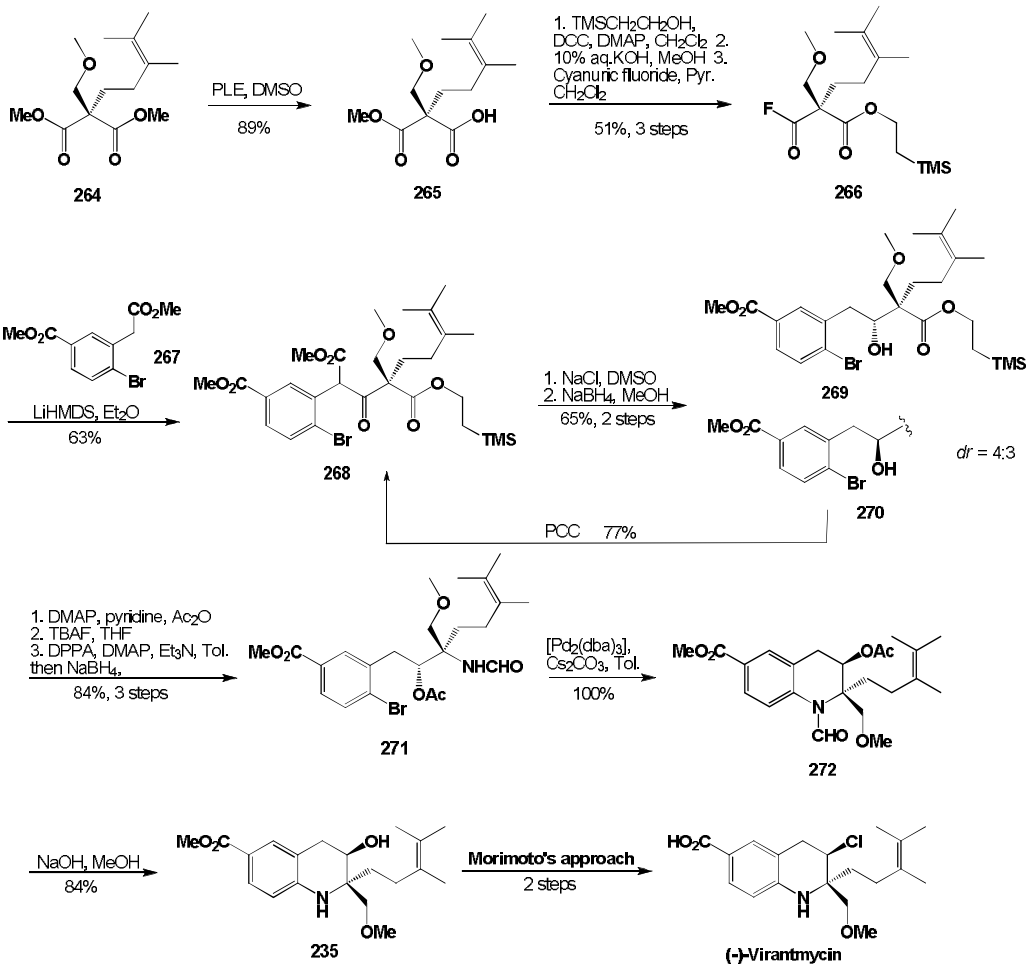
Scheme 99

2-Acylindoline **260**, prepared from (*S*)-(-)-indoline-2-carboxylic acid, was treated with iodine monochloride to afford the iodo derivative **261,** which, under the action of 2,3-dimethyl-3-pentenylmagnesium bromide **262** afforded the tertiary alcohol **263** with high diastereoselectivity (95:5). After Boc protecting group was removed on the separated major diastereomer, the resulting amino alcohol was subjected to a triphenylphosphane/CCl_4-mediated rearrangement

[81] M. Ori, N. Toda, K. Takami, K. Tago, H. Kogen, *Tetrahedron.* **2005**, *61*, 2075.

which proceeded through a transient aziridine immediately opened by a chloride anion to afford the 2,2,3-trisubstituted tetrahydroquinoline **245** as a single isomer. Finally, this product was carbonylated to give (-)-Virantmycin **229** in 3.4% overall yield (9 steps).

- Another approach using a highly enantioselective enzyme-mediated desymmetrization to synthesize both enantiomers of virantmycin was reported by Back and co.[82]



Scheme 100

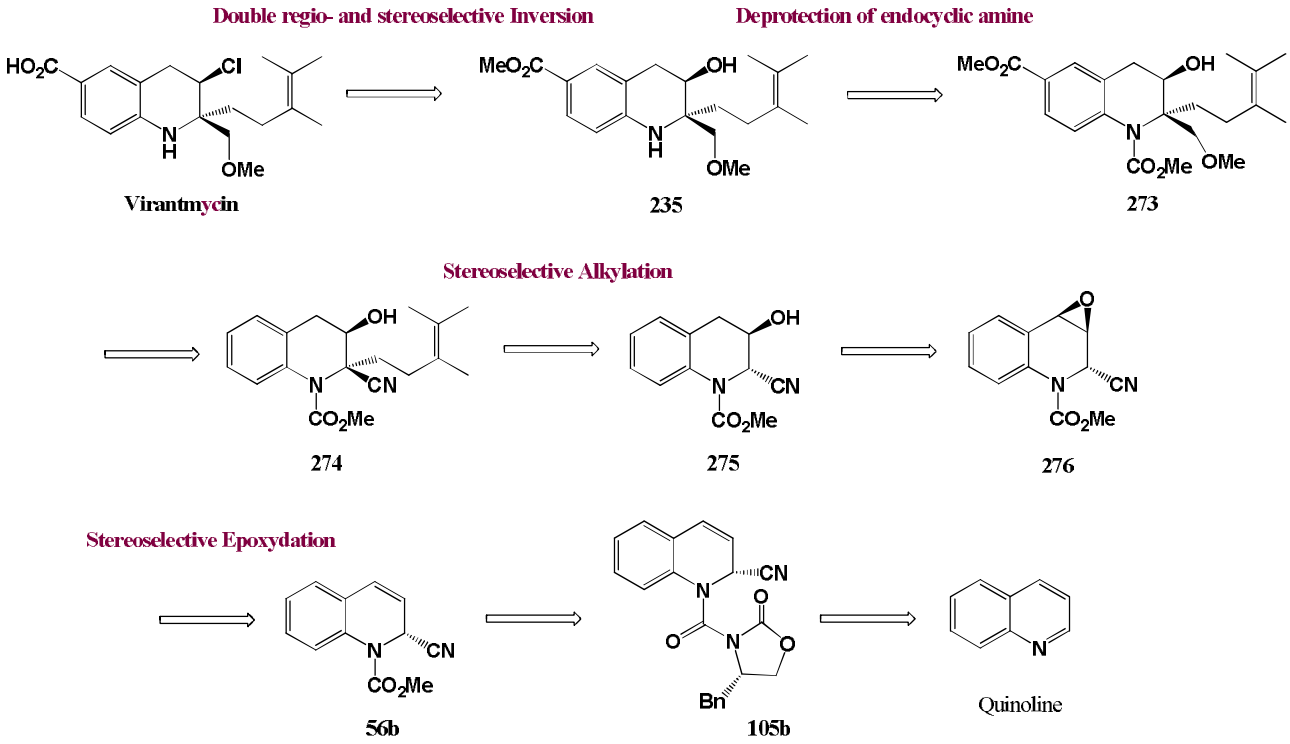
Half-ester **265** was obtained by desymmetrization of diester **264** with porcine liver esterase (PLE) in 95% ee. Half ester was then converted into acyl fluoride **266** in three steps, then was reacted with enolate of diester **267** to afford triester **268**. This latter compound was subjected to a selective Krapcho decarboxylation followed by reduction of the ketone group to furnish a mixture of diastereomeric alcohols **269** and **270** (*dr* = 4:3). The major isomer **269** was acetylated

[82] T. G. Back, J. E. Wulff, *Angew. Chem. Int. Ed.* **2004**, *43*, 6493.

and the trimethylsilylethyl ester group was excised with fluoride ion. The resulting carboxylic acid was subjected to a Curtius rearrangement through the action of DPPA to give, after a workup with sodium borohydride, the formamide **271**. Intramolecular Buchwald-Hartwig aryl amination next afforded the tetrahydroquinoline framework **272**. Deacetylation and concomitant deformylation of **272** furnished the free alcohol **235** which was then converted into (-)-Virantmyin **229** by the same method used previously by Morimoto.[77] This synthesis was achieved in 14 steps in 12% overall yield. Besides, an approach to the unnatural antipode, (+)-Virantmycin, was also performed following a similar process.

2.3.3. Our synthetic approach to Virantmycin

Inspired by these different syntheses, our approach to virantmycin is depicted in the following retrosynthetic Scheme 101.

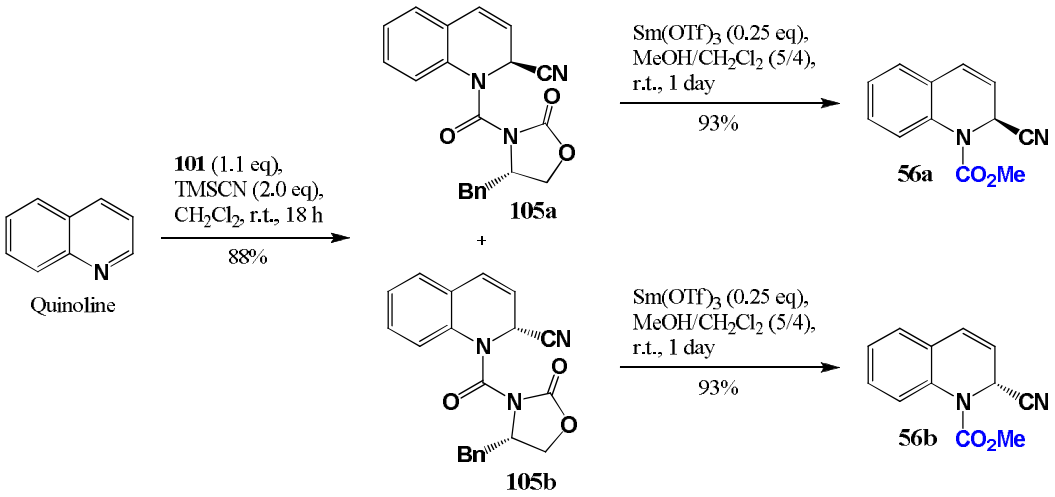


Scheme 101

Virantmycin would be derived from alcohol **235** by a stereoselective double inversion chlorination process. This alcohol could be itself obtained after deprotection of carbamate **273**, which in turn could be derived from compound **274** through introduction of an ester group at C6 following a procedure already reported by others (vide supra). Access to **274** could now be

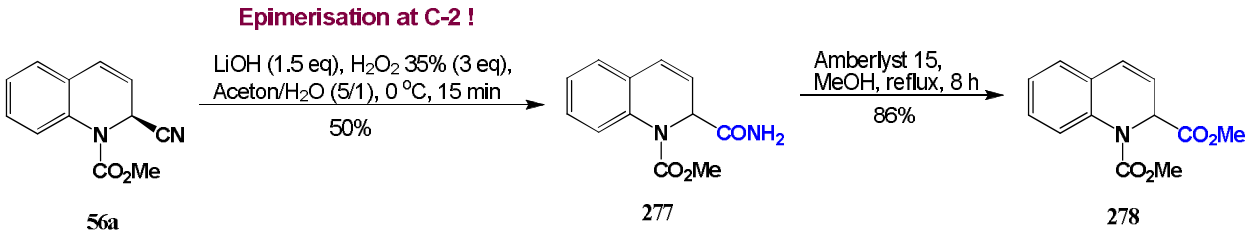
envisaged by a stereoselective alkylation of the Reissert derivative **275**, the synthesis of which could be executed from epoxide **276** through its regioselective opening. Finally, epoxide **276** would be derived from Reissert adduct **56b**, the product of the chiral auxiliary removal in **105b**.

The preparation of 1,2-dihydroquinoline **56a** and **56b** from quinoline through the chiral Reissert adducts **105a** and **105b** has been already reported earlier in the chapter dedicated to Sumanirole (Scheme 102).



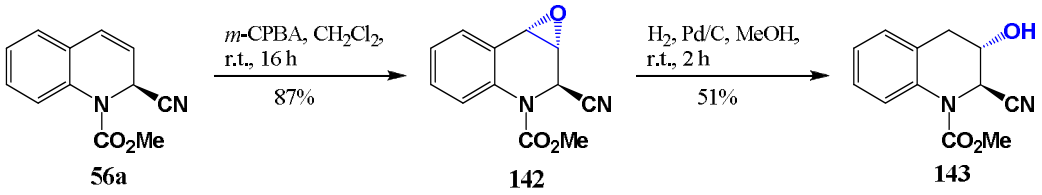
Scheme 102

For our preliminary study towards Virantmycin experimentations were carried out on isomer **56a**. We first envisaged the transformation of the cyano group to a methylester group. In order to limit the possibility of epimerization at C2 expected when using an acidic or a basic medium, a two-step sequence through an amide intermediate was considered (Scheme 103). However, we observed that these apparent smooth conditions also resulted in erosion of the chirality. Therefore, we abandoned this strategy and concentrated on the primary Reissert adduct.



Scheme 103

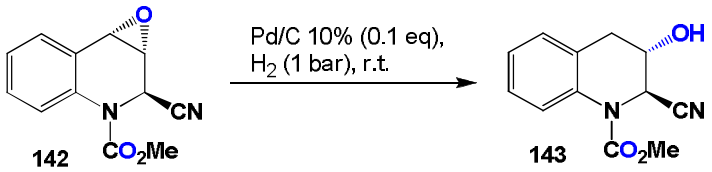
As previously reported in the part dedicated to Sumanirole synthesis, the stereoselective introduction of hydroxyl group at C3 was carried out through stereoselective epoxidation and regioselective opening of the resulting epoxide (Scheme 104, vide supra scheme 61). Accordingly, **56a** was treated with an excess of *m*-CPBA (1.5 equivalent) in CH_2Cl_2 to stereoselectively furnish compound **142** having its epoxide group in opposite to the cyano group. Because of its sensitivity under hydrolysis, epoxide **142** was not purified on silica gel but merely used crude in the subsequent hydrogenation reaction to give alcohol **143** as a single stereoisomer. After purification on silica gel, alcohol **143** was isolated pure in a yield of 44% over two steps.



Scheme 104

The low yield of this two-step transformation regarding to the high added value of the starting compound **56a**, and in particular the hydrogenation step, led us to briefly search for better conditions, in varying the nature of the solvent. Results were summarized in Table 8.

Table 8



N°	*Solvent*	*Reaction time (h)*	*Conversion (%)*[a]	*Yield (%)*[b]
1	CH_2Cl_2	24	0	/
2	THF	24	50	/
3	Dioxane	24	60	/
4	EtOAc/EtOH (1/1)	12	~90	39%
5	Dioxane	48	~85-90	56%

[a] Based on ^{1}H NMR spectrum

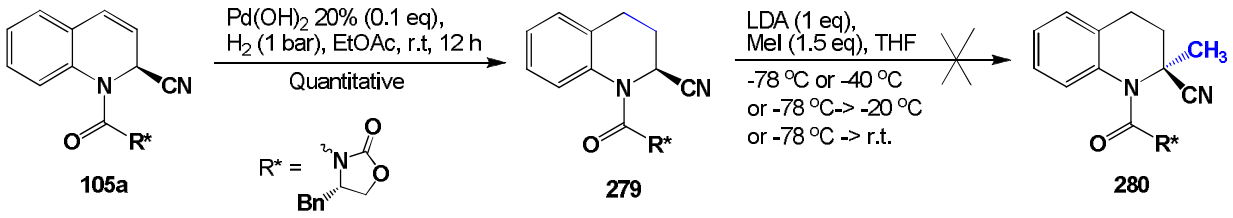
[b] Calculated over two steps: epoxidation and hydrogenation

Using CH_2Cl_2 as solvent gave a very poor result, the starting material being recovered unchanged after 24 h of stirring (entry 1). Better results were obtained in THF and dioxane, as the reaction took place with 50% conversion (entries 2 and 3). Using a mixture of ethyl acetate and methanol led to a still unsatisfactory 39% yield (entry 4). An even better result was recorded in dioxane when the reaction time was increased to 48 h (entry 5). In that case, the conversion was increased up to 85-90%, finally delivering alcohol **143** in an acceptable yield of 56% after purification by flash chromatography on silica gel.

Having the alcohol **143** in hand, the possibility of introducing a chain at C2 via a stereoselective process was next investigated. Initial tests were performed on 1,2,3,4-tetrahydroquinoline **279** lacking the hydroxy at C3 but bearing the chiral oxazolidinone group in order to induce stereoselectivity during the alkylation process. This latter was prepared by hydrogenation of the corresponding 1,2-dihydroquinoline **105a** and reactive methyl iodide was used as alkylating agent, following conditions described by Hurvois et al.[83] Deprotonation of **279** at low

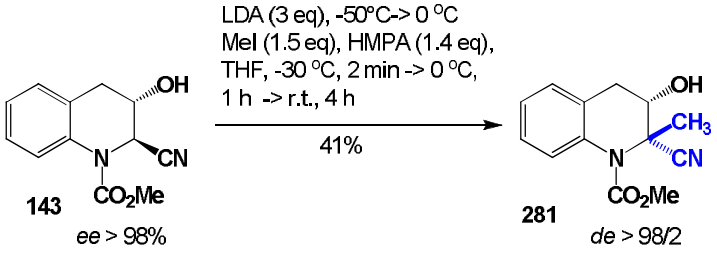
[83] S. Shahane, F. Louafi, J. Moreau, J.-P. Hurvois, J.-L. Renaud, P. van de Weghe, T. Roisnel. *Eur. J. Org. Chem.* **2008**, 4622.

temperature (between -78 °C and -30 °C) followed by addition of MeI at -78 °C did not afford the expected alkylated product (Scheme 105).



Scheme 105

This failure led us to study the alkylation reaction (MeI as the electrophilic partner) on optically pure tetrahydroquinoline **143** having a OH group at C3 (Scheme 106) to induce stereoselectivity. After much experimentation, we were pleased to observe that the treatment of **143** with three equivalents of LDA, and then with a mixture of MeI and HMPA, led to the desired product **281** in fair yield.

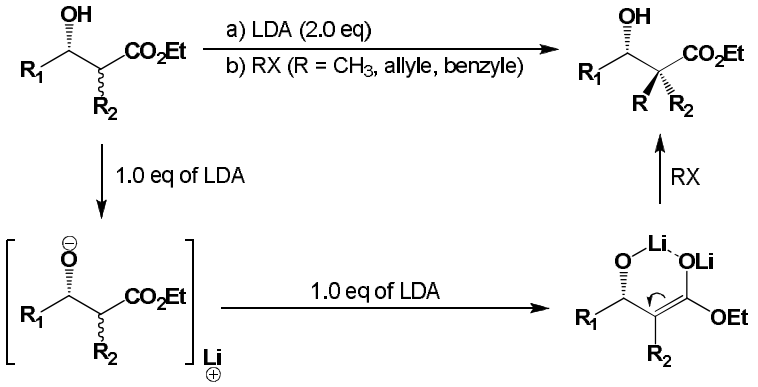


Scheme 106

After purification by flash chromatography on silica gel, a chiral HPLC analysis revealed that the reaction product **281** was formed as a single diastereoisomer (de > 98/2).

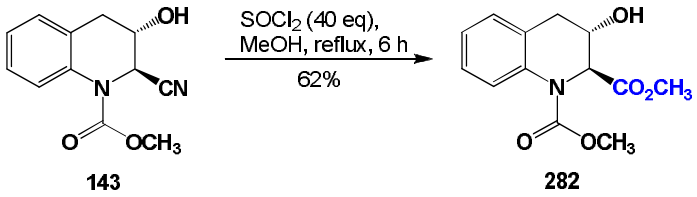
The stereochemistry of **281** at C2 could not be determined at this level. The closest example reported in the literature concerns the so-called Frater's alkylation[84] describing stereoselective alkylation of β-hydroxy esters. In the examples reported, the alkyl chain is introduced *trans* to the OH group and this was thought to be the result of the formation of a chelate intermediate which blocks one of the diastereotopic face of the double bond.

[84] (a) G. Frăter. *Tetrahedron Lett.*, **1981**, *22*, 425. (b) G. Frăter, W. Günther, H. Müller. *Helv. Chim. Acta.*, **1989**, *72*, 1846. (c) G. Frăter, W. Günther, H. Müller. *Tetrahedron*, **1984**, *40*, 1269.



Scheme 107

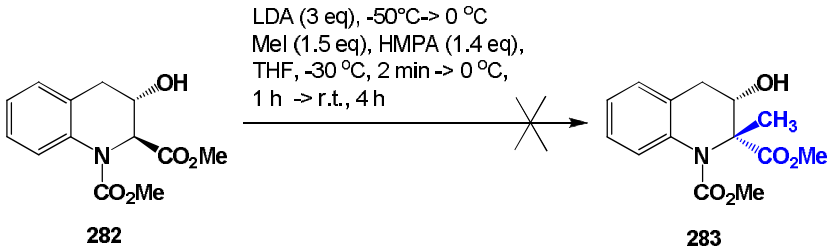
However, establishment of such a chelate is impossible in our case for geometrical reasons (CN is linear) so that the stereochemical result of the alkylation process cannot be safely deduced by simple analogy. We thus thought to explore alkylation of ester **282**, which was easily prepared from nitrile **143** by treatment with thionyl chloride in MeOH. Ester **282** was thus isolated in 62% yield (Scheme 108).



143 **282**

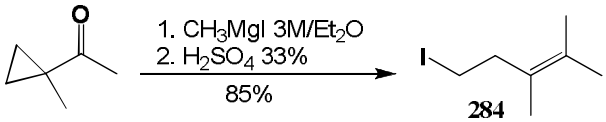
Scheme 108

The same conditions successfully used for alkylation of nitrile **143** were applied to ester **282**. However, and in striking contrast, only traces of what was supposed to be an alkylation product, were detected on the ^{1}H NMR spectrum. In fact, most of the starting material was recovered unchanged. Stirring at room temperature for a longer time or increasing the number of equivalents of HMPA did not improve the result but resulted mainly in extensive degradation of ester **282**.



Scheme 109

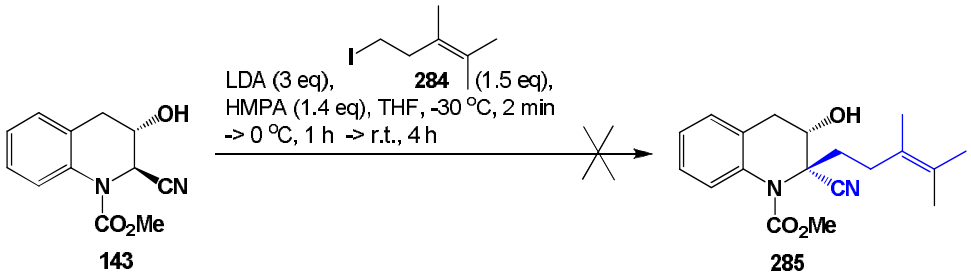
This failure forced us to continue our exploration starting from nitrile **143** in the hope that CN transformation in an ester group would be possible after alkylation was performed. Thus, after having successfully achieved alkylation of **143** with MeI, although in fair yield, we turned our attention to the most challenging task of alkylating **283** with the less reactive 5-iodo-2,3-dimethyl-2-pentene. This latter reagent was prepared in 85% yield by action of CH_3MgI on 1-methylcyclopropyl ketone (Scheme 110).[85]



Scheme 110

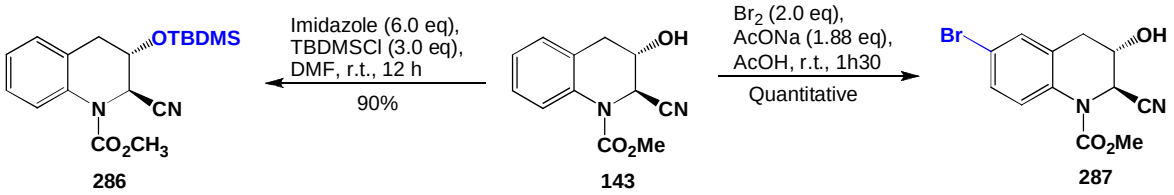
As it could have been feared, deprotonation of **143** and exposure of the resulting anion to 5-iodo-2,3-dimethyl-2-pentene **284**, in the same conditions as employed for MeI, did not lead to an alkylation product (Scheme 111). Several modifications of the reaction temperature as well as the reaction time or the amount of LDA and HMPA did not allow us to get a positive result and only led to a mixture of starting material and degradation products.

[85] (a) M. Machida, K. Oda, Y. Kanaoka. *Chem. Pharm. Bull*. **1984**, *32*, 75. (b) W. Biernacki, A. Gdula. *Synthesis.* **1979**, 37.



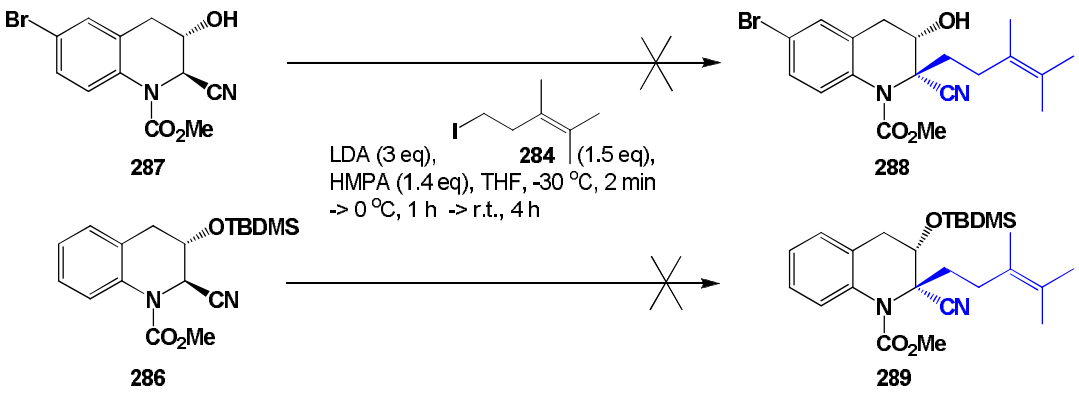
Scheme 111

Some others tetrahydroquinolines with a CN group at C2 were also submitted to alkylation reactions. For instance, we studied alkylation of deprotonated **286** and **287** with 5-iodo-2,3-dimethyl-2-pentene. **287** was prepared by bromination of **143** in mild conditions (Scheme 112) with the aim to perform later the methoxycarbonylation to access to Virantmycin. On the other hand, **286** was obtained after OH protection of **143** using *tert*-butyldimethylsilyl chloride in the presence of imidazole in DMF.



Scheme 112

However, and similarly to the behavior of nitrile **143**, no alkylation products could be detected after 5-iodo-2,3-dimethyl-2-pentene were added to deprotonated **286** and **287**. A mixture of starting material and degradation products were characterized in both cases after four hour of reaction.



Scheme 113

In conclusion, our preliminary efforts aimed at preparing Virantmycin came up against the impossibility of achieving the alkylation of nitrile **143**, or ester **282**, in the presence of an alkylating agent different from the simple and reactive MeI. This route was thus abandoned.

EXPERIMENTAL PART

2.4. Experimental Part

2.4.1. General Information

Chromatography

Reaction progress was monitored by thin layer chromatography (TLC) performed using Merck, Kieselgel 60 plates.

Column chromatography was performed using Merck Kieselgel 60 silica gel (40-63 μm).

Nuclear Magnetic Resonance (NMR)

NMR spectra were recorded on a BRUKER AC 300 at 300 MHz for ^{1}H and 75 MHz for ^{13}C at rt from samples in solution of suitable solvents. The references used are tetramethylsilane (TMS). The chemical shift values (δ) are expressed in parts per million (ppm) and coupling constants (J) in Hertz (Hz). Spectral coupling patterns are designated as follows: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet signal.

Polarimetry

Optical rotations were obtained with a digital polarimeter Perkin Elmer 341 at 20 °C and at a wavelength of 589 nm (c = g/100 mL).

Mass Spectroscopy

The mass spectra were performed by electron impact (EI, 70 eV) or chemical ionization (CI, 500eV) with NH_3 on a Hewlett Packard 5989A

HRMS were carried out either in Maldi, CI or EI mode (70ev).

Infrared Spectroscopy

IR spectra were recorded films for oily products and KBr platelets for solids on a Bruker Vector-22 Fourier transform spectrometer.

Chiral HPLC

Enantiomeric excess was determined by HPLC using a Daicel Chiralcel OD-H column (0.46 cm i.d. × 25 cm) with UV detection at 219 and 254 nm. 2-Propanol and hexanes were used as solvents, and the flow rate was set at 1.0 mL/min.

Melting points: were determined without correction.

Solvents

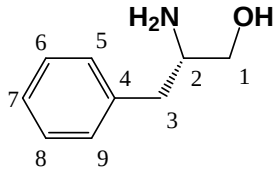
THF, CH_2Cl_2, toluene, DMF were of reagent grade and were dried through a solvent purification system. Acetonitrile were dried by distillation from calcium hydride. All other reagents were purified by distillation, the pressure being reduced if the boiling point of the compound was greater than 110 °C at atmospheric pressure.

Room temperature (r.t.) refers to 20-25 °C.

Reactions carried out under an inert atmosphere refer to the use of argon or nitrogen.

2.4.2. Synthesis and Physical Properties

(*S*)-2-Amino-3-Phenylpropan-1-ol **141**



$C_9H_{13}NO$

151.21 g/mol

MP = 91-93 °C

L-phenylalanine (25.00 g, 151 mmol) was added at ambient temperature to a solution of $NaBH_4$ (13.13 g, 347 mmol) in dry THF (150 mL) under nitrogen atmosphere, and the solution is cooled to 0 °C. A solution of I_2 (38.30 g, 151 mmol) in THF (150 mL) was added slowly (very exothermic reaction), and the resulting solution was heated at reflux for 18 h. After being cooled to 0 °C, MeOH (150 mL) was added slowly until the clear solution was observed and then stirred at the same temperature for 30 min. The solvent was evaporated *in vacuo* and the resulting paste was taken up with aqueous KOH (20%, 400 mL). The solution was stirred at room temperature for 5 h and then extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layer was washed with brine and dried over $MgSO_4$. The solvent was evaporated *in vacuo* to yield **141** as a white powder. A further crystallisation of this powder from toluene (60 mL) afforded white crystals (m = 16.9 g, yield = 74%).

^{1}H NMR ($CDCl_3$, 300MHz, δppm): 1.77 (s, 3 H, O*H*, NH_2), 2.53 and 2.79 (AB part of ABX system, 2 H, *J* = 13.5, 8.4, 5.1 Hz, H_3), 3.10-3.15 (m, 1 H, H_2), 3.38 and 3.64 (AB part of ABX system, 2 H, *J* = 10.5, 7.2, 3.9 Hz, H_1), 7.17-7.35 (m, 5 H, Ar-H).

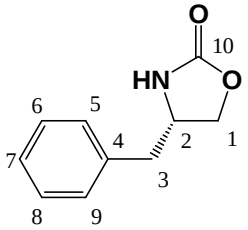
NMR ^{13}C ($CDCl_3$, 75MHz, δppm): 40.8 (C_3), 54.3 (C_2), 66.2 (C_1), 126.7 (C_7), 128.7 (C_6, C_8), 129.3 (C_5, C_9), 138.8 (C_4).

IR (KBr) (ν cm^{-1}): 3080 ($\nu_{C\text{-}Haro}$), 1339 ($\nu_{C\text{-}N}$), 1065 ($\nu_{C\text{-}O}$).

MS (EI) m/z (rel. int.) = 151 ($[M]^+$, <1), 120 (29), 91 (17), 60 (100).

Data were consistent with the literature (CAS: 3182-95-4).

(*S*)-4-Benzyloxazolidin-2-one **96**



$C_{10}H_{11}NO_2$

177.20 g/mol

MP = 90 °C

In a round-bottom flask fitted with a Dean-Stark apparatus, the phenylalaninol (11.06 g, 73 mmol) and K_2CO_3 (1.02 g, 7 mmol) were added to diethylcarbonate (22.2 mL, 183mmol). The stirred solution was heated at 140 °C for 4 hours (until completed recovery of EtOH in the Dean-Stark apparatus). The mixture was then diluted with water (200 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The organic phase was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give a white paste. A further recrystallisation from a biphasic system (petroleum ether/EtOAc, 1/4) afforded white crystals 96 in 68% yield (m = 8.80 g).

^{1}H NMR ($CDCl_3$, 300MHz, δppm): 2.87 (d, 2 H, *J* = 6.0 Hz, H_3), 4.08-4.22 (m, 1 H, H_2), 4.03-4.23 (m, 2 H, H_1), 5.25 (s, 1 H, NH), 7.10-7.40 (m, 5 H, Ar-H).

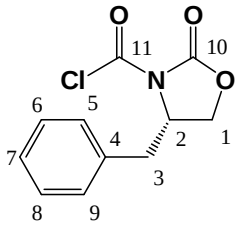
^{13}C NMR ($CDCl_3$, 75MHz, δppm): 41.5 (C_3), 53.9 (C_2), 67.9 (C_1), 127.4 (C_7), 129.1 (C_6, C_8), 129.2 (C_5, C_9), 136.1 (C_4), 159.6 (C_{10}).

IR (KBr) (ν cm^{-1}): 3288 (ν_{N-H}), 1751 ($\nu_{C=O}$).

MS (EI): m/z (rel. int.) = 177 ($[M]^+$, 3), 92 (100), 86 (85), 65 (17), 42 (44).

Data were consistent with the literature (CAS: 90719-32-7).

(*S*)-4-Benzyl-2-oxooxazolidin-3-carbonyl chloride **101**



$C_{10}H_{11}NO_3$

239.66 g/mol

MP = 85 °C

A solution of oxazolidinone 96 (2.0 g, 11.3 mmol) in dry toluene (50 mL) at 0 °C under nitrogen atmosphere was added NaH (60% suspension in oil) (0.5 g, 14.4 mmol). The mixture was stirred at room temperature for 3 h and then cooled to -17 °C (ice/salt), syringed to a 20% solution of phosgene in toluene (10 mL, 19.0 mmol) at the same temperature. The solution was allowed to warm to room temperature and then stirred for 18 h. After being filtered, the resulting solution was concentrated *in vacuo*. The paste was washed with a small amount of petroleum ether. The desired product 101 was obtained without further purification as a white powder in 80% yield (m = 2.07g, 80.5% wt/wt). A further recrystallisation from diethyl ether afforded white crystals.

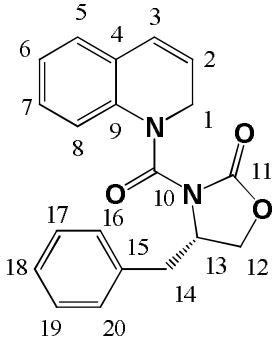
^{1}H NMR ($CDCl_3$, 300MHz, δppm): 2.90 and 3.36 (AB part of ABX system, 2 H, *J* = 13.5, 9.6, 3.3 Hz, H_3), 4.20 and 4.25 (AB part of ABX system, 2 H, *J* = 9.1, 7.2, 2.7 Hz, H_1), 4.69 (m, 1H, H_2), 7.16-7.40 (m, 5 H, Ar-H).

^{13}C NMR ($CDCl_3$, 75MHz, δppm): 37.9 (C_3), 58.1 (C_2), 65.4 (C_1), 127.8 (C_7), 129.2 (C_6, C_8), 129.4 (C_5, C_9), 134.0 (C_4), 145.2 (C_{10}), 149.9 (C_{11}).

IR (KBr) (ν cm^{-1}): 1836 (ν_{COCl}), 1737 ($\nu_{CO\ carbamate}$).

Data were consistent with the literature (CAS: 139149-49-8).

(*S*)-4-Benzyl-3-(1,2-dihydroquinoline-1-carbonyl)oxazolidin-2-one **48**



$C_{20}H_{18}N_2O_3$

M = 334.37 g/mol

MP = 111.6 °C

A solution of DIBAL-H 1M in hexane (13.6 mL, 13.6mmol) was added dropwise to a solution of quinoline (1.6 mL, 14 mmol) in CH_2Cl_2(18 mL) at 0 °C under an argon atmosphere. Stirring was continued for 1 h at 0 °C then the red solution was cannulated into a solution of carbamoyl chloride **101** (1.63 g, 6.8 mmol) in CH_2Cl_2 (2 mL) precooled at 0 °C. The resulting solution was stirred for 4 h while the temperature was raised progressively to 20 °C. The reaction mixture was then syringed into water (150 mL) at 0-5 °C. The resulting emulsion was kept under stirring for 30 min and then acidified to pH 4 with 4N HCl. After phase separation, the aqueous phase was extracted with methylene chloride (4 x 60 mL). The combined organics were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give a crude oil that was subjected to flash column chromatography (toluene/petroleum ether/diethylether 2:1:1; R_f = 0.26) to give compound **48** (1.39 g, 61% calculated based on carbamoyl chloride **X**) as a clear yellow oil. A further recrystallisation from a biphasic system (petroleum ether/EtOAc) afforded white crystals.

$[\alpha]_D^{20}$ = +7.7 (c = 0.5, $CHCl_3$)

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.92 and 3.26 (AB part of ABX system, 2 H, *J* = 13.5, 8.7, 3.3 Hz, H_{14}), 4.08-4.31 (m, 3 H, $1H_1$, $2H_{12}$), 4.40 (dd, 1 H, *J* = 17.0, 5.5 Hz, $1H_1$), 4.73-4.78 (m, 1 H, H_{13}), 5.99-6.04 (m, 1 H, H_2), 6.59 (dd, 1 H, *J* = 9.6, 2.4 Hz, H_3), 7.12-7.40 (m, 9 H, Ar-H).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 38.1 (C_{14}), 45.9 (C_{13}), 56.5 (C_{12}), 67.0 (C_1), 122.9 (Cq), 125.5 (C_2), 126.4 (C_3), 126.7 (Cq), 127.5 (C_5), 128.3 (C_6), 128.5 (C_7), 129.0 ($2\underline{C}H_{Ar}$), 129.2 (C_8), 129.5 ($2\underline{C}H_{Ar}$), 134.9 (C_{15}), 136.0 (C_8), 152.4 (C_{10}), 153.3 (C_{11}).

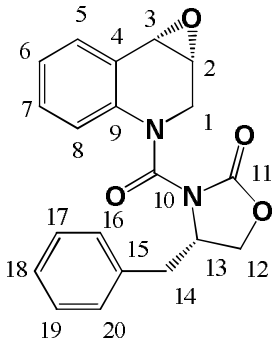
IR (KBr) (ν cm^{-1}): 1722 ($\nu_{C=O\ carbamate}$), 1685 ($\nu_{C=O\ urea}$), 1601-1454 ($\nu_{C=Caro}$), 1090, 1060 (ν_{C-O}).

MS (EI): m/z (rel. int.) = 334 (M^+, < 1), 130 (100), 91 (19).

HRMS (EI):

Calculated for $C_{20}H_{18}N_2O_3$: $[M]^+$ = 334.1317; found: $[M]^+$ = 334.1313

(*S*)-4-Benzyl-3-[(1a*R*,7b*S*)-1a,2,3,7b-tetrahydrooxireno[2,3-c]quinoline-3-carbonyl]oxazolidine-2-one **47**



$C_{20}H_{18}N_2O_4$

M = 350.37 g/mol

MP = 204-206 °C

To a solution of the 1,2-dihydroquinoline **48** (1.6 g, 4.78 mmol) in CH_2Cl_2 (250 mL) at 20 °C were successively added sodium bicarbonate (0.644 g, 6.22 mmol) and *m*-CPBA (70-75% pure, 1.5 g, 6.22 mmol). The reaction mixture was stirred for 18 h at 20 °C under a continuous flow of argon then washed with saturated aqueous sodium bicarbonate (250 mL). After phase separation, the aqueous phase was extracted with methylene chloride (3 x 160 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give a white powder consisting of a mixture of two diastereomeric epoxides **47** in a 9:1 ratio. The major diasteromer could be isolated in pure form after the mixture was subjected to silica gel column chromatography (CH_2Cl_2/AcOEt 9:1, R_f = 0.33).

$[\alpha]_D^{20}$ = +54.2 (c = 0.5, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.93 and 3.16 (AB part of ABX system, 2 H, *J* = 13.8, 8.4, 3.0 Hz, H_{14}), 3.55 and 4.38 (AB system, 2 H, *J* = 14.4 Hz, H_1), 3.90-3.92 (m, 1 H, H_2), 3.98 (d, 1 H, *J* = 4.2 Hz, H_3), 4.13 and 4.29 (AB part of ABX system, 2 H, *J* = 9.0, 8.8, 8.4 Hz, H_{12}), 4.57-4.75 (m, 1 H, H_{13}), 7.15-7.53 (m, 9 H, Ar-H).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 36.9 (C_{14}), 44.0 (C_1), 50.9 (C_2), 56.4 (C_{13}), 58.2 (C_3), 66.7 (C_{12}), 124.9 ($\underline{C}H_{Ar}$), 125.9 ($\underline{C}H_{Ar}$), 126.4 (Cq), 127.4 ($\underline{C}H_{Ar}$), 129.0 ($2\underline{C}H_{Ar}$), 129.3 (C_{18}), 129.8 ($2\underline{C}H_{Ar}$), 134.7 (C_{15}), 136.3 (Cq), 153.9 (C_{10}, C_{11}).

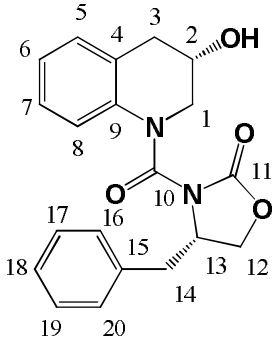
IR (KBr) (ν cm^{-1}): 1774 ($\nu_{C=O\ carbamate}$), 1675 ($\nu_{C=O\ urea}$), 1600, 1438 ($\nu_{C=Caro}$), 1118, 1066 (ν_{C-O}).

MS (EI): m/z (rel. int.) = 350 (M^+, 7), 322 (100), 174 (8).

HRMS (EI):

Calculated for $C_{20}H_{18}N_2O_4$: $[M]^+$ = 350.1267; found: $[M]^+$ = 350.1266

(*S*)-4-Benzyl-3-[(*S*)-3-hydroxy-1,2,3,4-tetrahydroquinoline-1-carbonyl]oxazolidin-2-one **167a**



$C_{20}H_{20}N_2O_4$

M = 352.38 g/mol

MP = 137-138 °C

10% Pd/C (0.668 g) was added to a solution of crude epoxides **47** (1.7 g) in a mixture of CH_2Cl_2/AcOEt (1:1). The mixture was stirred for 18 h under a pressure of hydrogen (8 bars) then filtered through a pad of Celite. The filter cake was rinsed with CH_2Cl_2/AcOEt (1:1), the filtrate concentrated *in vacuo* and the crude product purified by silica gel chromatography (petroleum ether/EtOAc 1:1, R_f = 0.39) to give alcohol **167a** (0.900 g, 54%) as white crystals.

$[\alpha]_D^{20}$ = -170.1 (c = 0.34, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.85 and 3.60 (AB part of ABX system, 2 H, *J* = 12.9, 10.2, 3.6 Hz, H_{14}), 2.99 and 3.15 (AB part of ABX system, 2 H, *J* = 18.0, 5.4, < 1 Hz, H_3), 3.38 and 4.41 (AB part of ABX system, 2 H, *J* = 12.6, < 1, < 1 Hz, H_1), 4.11 and 4.24 (AB part of ABX system, 2 H, *J* = 8.4, 8.4, 7.5 Hz, H_{12}), 4.28 (m, 1 H, H_2), 4.80 (m, 1 H, H_{13}), 7.00-7.40 (m, 9 H, Ar-H).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 34.7 (C_{14}), 37.0 (C_3), 50.6 (C_1), 55.2 (C_{13}), 62.9 (C_2), 67.2 (C_{12}), 120.3 ($\underline{C}H_{Ar}$), 124.2 ($\underline{C}H_{Ar}$), 125.2 ($\underline{C}H_{Ar}$), 126.5 ($\underline{C}H_{Ar}$), 128.0 (C_{18}), 128.1 ($2\underline{C}H_{Ar}$), 129.4 ($2\underline{C}H_{Ar}$), 133.9 (Cq), 138.0 (C_9), 152.9 (C_{10}), 154.1 (C_{11}).

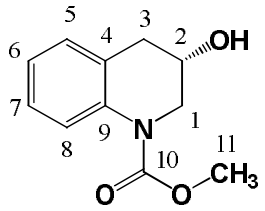
IR (film) (ν cm^{-1}): 3452 (ν_{O-H}), 1772 ($\nu_{C=O\ carbamate}$), 1683 ($\nu_{C=O\ urea}$), 1604, 1583, 1493, 1455 ($\nu_{C=Caro}$), 1220, 1074 (ν_{C-O}).

MS (EI): m/z (rel. int.) = 323 (M^+, 9), 132 (38), 130 (38), 118 (20), 117 (16), 91 (100).

HRMS (EI):

Calculated for $C_{20}H_{20}N_2O_4$: $[M]^+$ = 352.1423; found: $[M]^+$ = 352.1427

Methyl (3*S*)-3-hydroxy-3,4-dihydroquinoline-1(2*H*)-carboxylate **166**



$C_{11}H_{13}NO_3$

M = 207.23 g/mol

Samarium triflate (0.596, 0.95 mmol) was added to a solution of alcohol **167a** (1.34 g, 3.80 mmol) in anhydrous methanol. The mixture was stirred at 80 °C for 2 h then filtered through a pad of silica. The filter cake was rinsed with AcOEt, the filtrate concentrated *in vacuo* and the resulting crude product purified by silica gel chromatography (Petroleum ether/diethyl ether 1:4, R_f = 0.5) to give alcohol **166** as a clear yellow oil.

$[\alpha]_D^{20}$ = +6.0 (c = 0.10, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.82 and 3.10 (AB part of ABX system, 2 H, *J* = 16.3, 5.2, 5.2 Hz, H_3), 3.80 (s, 3 H, H_{11}), 3.82 (d, 2 H, *J* = 4.6 Hz, H_1), 4.31 (m, 1 H, H_2), 7.06 (t, 1 H, *J* = 8.2 Hz, H_6), 7.11 (d, 1 H, *J* = 8.2 Hz, H_5), 7.18 (t, 1 H, *J* = 8.2 Hz, H_7), 7.67 (d, 1 H, *J* = 8.2 Hz, H_8).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 36.0 (C_3), 50.5 (C_{11}), 53.1 (C_1), 65.0 (C_2), 123.8 (C_8), 124.3 (C_6), 126.3 (C_7), 126.7 (C_4), 129.5 (C_5), 137.5 (C_9), 155.8 (C_{10}).

IR (film) (ν cm^{-1}): 3429 (ν_{O-H}), 1699 ($\nu_{C=O}$), 1600, 1582, 1463, 1441 ($\nu_{C=Caro}$).

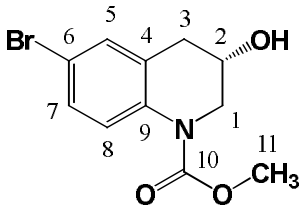
MS (EI): m/z (rel. int.) = 207 (M^+, 100), 178 (20), 147 (36), 130 (41), 118 (59), 91 (57), 77 (22).

HRMS (EI):

Calculated for $C_{11}H_{13}NO_3$: $[M]^+$ = 207.0895; found: $[M]^+$ = 207.0894

NB: (4*S*)-benzyl oxazolidin-2-one was recovered with a yield of 66%.

Methyl (3*S*)-6-bromo-3-hydroxy-3,4-dihydroquinoline-1(2*H*)-carboxylate **168**



$C_{11}H_{12}BrNO_3$

M = 286.12 g/mol

To a solution of alcohol **166** (0.228 g, 1.39 mmol) in acetic acid were successively added anhydrous AcONa (0.214 g, 1.88 mmol) and Br_2 (0.071 mL, 1.39 mmol). The mixture was stirred for 1 h at 20 °C then quenched with water (30 mL) and extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was taken up in cyclohexane and the solution concentrated in vacuo in order to azeotropically remove traces of AcOH. The crude bromo alcohol **168** (orange amorphous solid) was used in the next step without further purification.

$[\alpha]_D^{20}$ = -11.0 (c = 0.33, $CHCl_3$)

^{1}H NMR (300MHz, $CDCl_3$, δ ppm): 2.78 and 3.05 (AB part of ABX system, 2 H, *J* = 16.8, 5.1, 2.8 Hz, H_3), 3.71-3.88 (m, 2 H, H_1), 3.79 (s, 3 H, H_{11}), 4.28 (m, 1 H, H_2), 7.24-7.30 (m, 2 H, H_5, H_7), 7.56 (d, 1 H, *J* = 8.7 Hz, H_8).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 35.7 (C_3), 50.3 (C_{11}), 53.3 (C_1), 64.4 (C_2), 117.1 (Cq), 125.4 ($\underline{C}H_{Ar}$), 128.8 (Cq), 129.6 ($\underline{C}H_{Ar}$), 132.0 ($\underline{C}H_{Ar}$), 136.7 (Cq), 155.6 (C_{10}).

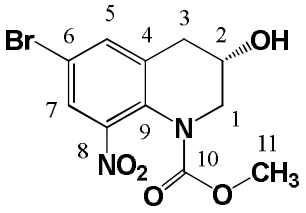
IR (KBr) (ν cm^{-1}): 3413 (ν_{O-H}), 1709 ($\nu_{C=O}$), 1600, 1580, 1486, 1442 ($\nu_{C=Caro}$), 817 (ν_{C-Br}).

MS (EI): m/z (rel. int.) = 285/287 (M^+, 100), 117 (58), 90 (20).

HRMS (EI):

Calculated for $C_{11}H_{12}BrNO_3$: $[M]^+$ = 285.0001; found: $[M]^+$ = 285.0001

Methyl (3*S*)-6-bromo-3-hydroxy-8-nitro-3,4-dihydroquinoline-1(2*H*)-carboxylate **169**



$C_{11}H_{11}BrN_2O_5$

M = 331.12 g/mol

MP = 123 °C

To a solution of sodium nitrate (0.041 g, 0.48 mmol) in trifluoroacetic acid (2 mL) was added bromo alcohol **168**. The resulting solution was stirred at 20 °C for 30 min then concentrated in vacuo. AcOEt (20 mL) and water (10 mL) were then added to the residue. After separation, the organic layer was washed sequentially with saturated aqueous sodium bicarbonate (10 mL), 1M NaOH (10 mL) and water (10 mL), then dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (CH_2Cl_2/EtOAc 3:2, R_f = 0.5) to give the nitro compound **169** (0.132, 84%) as a white solid.

$[\alpha]_D^{20}$ = +25.4 (c = 0.41, $CHCl_3$).

^{1}H NMR (400 MHz, C_6D_6, δ ppm): 2.16 and 2.23 (AB part of ABX system, 2 H, *J* = 16.4, 5.2, 4.8 Hz, H_3), 3.30 (m, 2 H, H_1), 3.38 (s, 3 H, H_{11}), 3.59, (m, 1 H, H_2), 6.84 (d, 1 H, *J* = 2.4 Hz, H_5), 7.64 (d, 1 H, *J* = 2.4 Hz, H_7).

^{13}C NMR (100 MHz, C_6D_6, δ ppm): 35.6 (C_3), 50.7 (C_1), 53.1 (C_2), 65.1 (C_{11}), 117.3 (Cq), 126.1 ($\underline{C}H_{Ar}$), 131.3 (Cq), 134.0 (Cq), 136.0 ($\underline{C}H_{Ar}$), 145.1 (Cq), 154.9 (C_{10}).

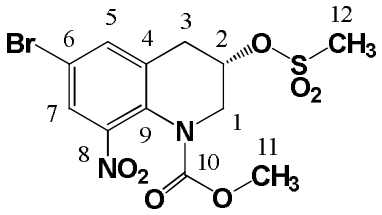
IR (film) (ν cm^{-1}): 3441 (ν_{O-H}), 1700 ($\nu_{C=O}$), 1601, 1528, 1471, 1452, 1441 ($\nu_{C=Caro}$), 1370 (ν_{NO2}).

MS (EI): m/z (rel. int.) = 330/332 (M+, 8), 284/286 (66), 201 (48), 173 (51), 117 (100).

HRMS (EI):

Calculated for $C_{11}H_{11}N_2O_5Br$: $[M]^+$ = 329.9851; found: $[M]^+$ = 329.9854

Methyl (3*S*)-6-bromo-3-[(methylsulfonyl)oxy]-8-nitro-3,4-dihydroquinoline-1(2*H*)-carboxylate **165**



$C_{12}H_{13}BrN_2O_7S$

M = 409.21 g/mol

MP = 160 °C

To a stirred solution of alcohol **169** (0.282 g, 0.85 mmol) in anhydrous CH_2Cl_2 (16 mL) kept at 20 °C under nitrogen (16 mL) were successively added freshly distilled NEt_3 (0.360 mL, 2.56 mmol) and mesyl chloride (0.132 mL, 1.71 mmol). After stirring was continued for 45 min, CH_2Cl_2 (90 mL) was added to the reaction mixture which was then washed sequentially with saturated aqueous sodium bicarbonate and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (CH_2Cl_2/AcOEt 9:1; R_f = 0.46) to give mesylate **165** (0.320 g, 92%) as a yellow solid.

$[\alpha]_D^{20}$ = +34.0 (c = 0.20, $CHCl_3$).

^{1}H NMR (400MHz, C_6D_6, δ ppm): 2.19 (s, 3 H, H_{12}), 2.20 and 2.47 (AB part of ABX system, 2 H, *J* = 12.6, 3.3, 3.0 Hz, H_3), 3.36 (bs, 4 H, $1H_1$, $3H_{11}$), 3.90 (bs, 1 H, $1H_1$), 4.66 (m, 1 H, H_2), 4.74 (s, 1 H, H_5), 7.62 (s, 1 H, H_7).

^{13}C NMR (100 MHz, C_6D_6, δ ppm): 33.5 (C_{12}), 38.2 (C_3), 48.1 (C_2), 53.1 (C_1), 73.1 (C_{11}), 117.7 (Cq), 126.6 ($\underline{C}H_{Ar}$), 131.0 (Cq), 132.0 (Cq), 135.8 ($\underline{C}H_{Ar}$), 145.0 (Cq), 154.1 (C_{10}).

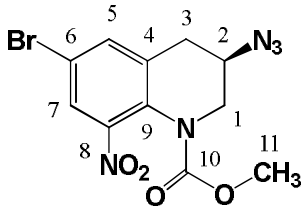
IR (KBr) (ν cm^{-1}): 1721 ($\nu_{C=O}$), 1601, 1471, 1460, 1452 ($\nu_{C=Caro}$), 1528, 1369 (ν_{NO2}), 1350, 1310, 1170 (ν_{SO2}).

MS (EI): m/z (rel. int.) = 408/410 (M^+, 13), 362/364 (88), 207/209 (57).

HRMS (EI):

Calculated for $C_{12}H_{13}N_2O_7SBr$: $[M]^+$ = 407.9627; found: $[M]^+$ = 407.9630

Methyl (3*R*)-3-azido-6-bromo-8-nitro-3,4-dihydroquinoline-1(2*H*)-carboxylate **164**



$C_{11}H_{10}BrN_5O_4$

M = 356.13 g/mol

To a solution of mesylate **165** (0.250 g, 0. 61 mmol) in anhydrous DMF (11 mL) kept at 20 °C under nitrogen was added sodium azide (0.199 g, 3.06 mmol). The resulting solution was stirred for 1 h at 20 °C then quenched with water (50 mL). After separation, the aqueous phase was extracted with Et_2O (2 x 50 mL). The combined organic layers were dried over $MgSO_4$ then concentrated *in vacuo*. The crude product was purified by silica gel chromatography (petroleum ether then petroleum ether/Et_2O 3:2; R_f = 0.34) to give azide **164** (0.140g, 65%) as an orange oil.

$[\alpha]_D^{20}$ = +58.4 (c = 0.51, $CHCl_3$).

^{1}H NMR (400 MHz, C_6D_6, δ ppm): 2.02 and 2.08 (AB part of ABX system, 2 H, *J* = 17.0, 5.2, 5.2 Hz, H_3), 3.04 (m, 1 H, H_2), 3.38 (s, 3 H, H_{11}), 3.50 (bs, 2 H, H_1), 6.73 (s, 1 H, H_5), 7.63 (s, 1 H, H_7).

^{13}C NMR (100 MHz, C_6D_6, δ ppm): 32.9 (C_3), 48.1 (C_2), 53.6 (C_{11}), 56.0 (C_1), 117.8 (Cq), 127.0 (C_7), 131.6 (Cq), 133.2 (Cq), 136.0 (C_5), 145.6 (Cq), 154.6 (C_{10}).

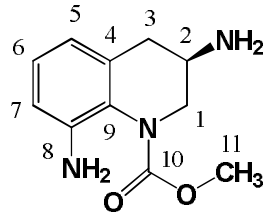
IR (KBr) (ν cm^{-1}): 2106 (ν_{N3}), 1717 ($\nu_{C=O}$), 1539, 1363 (ν_{NO2}).

MS (EI): m/z (rel. int.) = 355/357 (M+, 31), 309/311 (42), 209/211 (35), 89/90 (100).

HRMS (EI):

Calculated for $C_{11}H_{10}N_5O_4Br$: $[M]^+$ = 354.9916; found: $[M]^+$ = 354.9923

Methyl (3*R*)-3,8-diamino -3,4-dihydroquinoline-1(2*H*)-carboxylate **163**



$C_{11}H_{15}N_3O_2$

M = 221.26 g/mol

20% $Pd(OH)_2/C$ (0.025 g) was added to a solution of azide **164** (0.2 g, 1. 52 mmol) in ethanol (13 mL) and the resulting mixture was stirred for 18 h under hydrogen (1 bar). The reaction mixture was then filtered through a pad of Celite, the filter cake rinsed with ethanol and the ethanolic filtrate concentrated *in vacuo*. The crude residue was taken up in saturated aqueous sodium bicarbonate (5 mL). The solution was extracted with CH_2Cl_2 (5 x 20 mL), the combined organic layers were dried over Na_2SO_4 then concentrated *in vacuo*. The crude diamino ester derivative **163** (0.1 g, 99%) was used in the next step without further purification as a brown oil.

$[\alpha]_D^{20}$ = +25.1 (c = 0.31, $CHCl_3$)

^{1}H NMR (400MHz, C_6D_6, δ ppm): 2.13 and 2.65 (AB part of ABX system, 2 H, *J* = 15.8, 7.2, 6.2 Hz, H_3), 2.99 (m, 1 H, H_2), 3.47 (s, 3 H, H_{11}), 3.72 (bs, 2 H, H_1), 6.36 (d, 1 H, *J* = 7.2 Hz, H_5 or H_7), 6.45 (d, 1 H, *J* = 7.2 Hz, H_5 or H_7), 6.88 (t, 1 H, *J* = 7.2 Hz, H_6).

^{13}C NMR (100 MHz, C_6D_6, δ ppm): 38.5 (C_3), 49.3 (C_2), 53.2 (C_1), 54.1 (C_{11}), 116.5 (C_5 or C_7), 119.6 (C_5 or C_7), 127.2 (C_6), 128.0 (C_9), 133.6 (Cq), 143.0 (Cq), 156.0 (C_{10}).

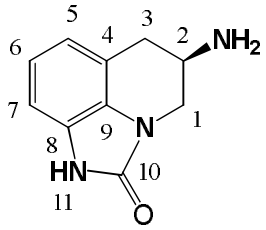
IR (KBr) (ν cm^{-1}): 3425 ($\nu_{N\text{-}H\ aniline}$), 3361 ($\nu_{N\text{-}H\ aliphatic\ amine}$), 1692 ($\nu_{C=O}$).

MS (EI): m/z (rel. int.) = 221 (M^+, 100), 204 (24), 133 (32).

HRMS (EI):

Calculated for $C_{11}H_{15}N_3O_2$: $[M]^+$ = 221.1164; found: $[M]^+$ = 221.1167

(5*R*)-5-Amino-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2*H*)-one **170**



$C_{10}H_{11}N_3O$

M = 189.21 g/mol

MP = 153 °C

To a solution of crude diamino ester **163** (0.250 g, 1.13 mmol) in dry THF (3 mL) was added a 20% (w/w) solution of *t*-BuOK in THF (3.4 mL, 5.65 mmol). After the reaction medium was stirred for 3.5 h at 20 °C, water and AcOEt were added. After separation, the aqueous phase was extracted with AcOEt (5 x 20 mL). The combined organic layers were dried over Na_2SO_4 then concentrated *in vacuo*. The crude amino derivative derivative **170** (0. 210 g, 98%) was used in the next step without further purification as a brown powder.

$[\alpha]_D^{20}$ = -7.1 (c = 0.16, $CHCl_3$).

^{1}H NMR (300 MHz, DMSO-d_6, δ ppm): 2.50 (m, 1 H, $1H_3$), 2.91 (dd, 1 H, *J* = 15.9, 3.3 Hz, $1H_3$), 3.52 (bs, 2 H, $1H_1$, $1H_2$), 3.86 (m, 1 H, $1H_1$), 6.77 (d, 1 H, *J* = 6.8 Hz, H_5 or H_7), 6.79 (d, 1 H, *J* = 8.9 Hz, H_5 or H_7), 6.88 (dd, 1 H, *J* = 8.9, 6.8 Hz, H_6), 10.6 (s, 1 H, H_{11}).

^{13}C NMR (75 MHz, DMSO-d_6, δ ppm): 29.3 (C_3), 45.6 (C_1, C_2), 106.3 (C_5 or C_7), 117.7 (Cq), 119.0 (C_5 or C_7), 120.5 (C_6), 126.3 (Cq), 127.1 (Cq), 135.6 (C_{10}).

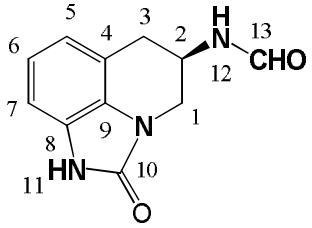
IR (KBr) (ν cm^{-1}): 3300 (ν_{N-H}), 1684 ($\nu_{C=O}$).

MS (EI): m/z (rel. int.) = 189 (M^+, 100), 171 (35), 147 (30).

HRMS (EI):

Calculated for $C_{10}H_{11}N_3O$: $[M]^+$ = 189.0902; found: $[M]^+$ = 189.0903

(5*R*)-5-(Formylamino)-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2*H*)-one **171**



$C_{11}H_{11}N_3O_2$

M = 217.22 g/mol

MP = 215 °C

To a solution of amine **170** (0.170 g, 0.9 mmol) in acetonitrile (0.9 mL) was added a preformed 1:1 mixture of Ac_2O and HCO_2H (0.28 mL) and Ac_2O (0.570 mL). The resulting solution was stirred under argon for 2 h at 20 °C then concentrated *in vacuo*. To the residue was added MeOH (15 mL) and the solution was stirred for 1 h at 20 °C. After concentration *in vacuo*, the crude product was purified by silica gel chromatography (CH_2Cl_2 / MeOH 95:5; R_f = 0.12) to give formamide **171** (0.150 g, 77 %) as an orange solid.

$[\alpha]_D^{20}$ = -153 (c = 0.14, $CHCl_3$).

^{1}H NMR (300 MHz, DMSO-d_6, δ ppm): 2.86 and 3.07 (AB part of ABX system, 2 H, *J* = 18.0, 6.0, 3.0 Hz, H_3), 3.70 and 3.90 (AB part of ABX system, 2 H, *J* = 12.0, 6.0, 3.0 Hz, H_1), 4.46 (m, 1 H, H_2), 6.79 (d, 1 H, *J* = 9.0 Hz, H_5 or H_7), 6.87 (d, 1 H, *J* = 8.8 Hz, H_5 or H_7), 6.96 (dd, 1 H, *J* = 9.0, 8.8 Hz, H_6), 8.02 (s, 1 H, H_{13}), 8.33 (d, 1 H, *J* = 6.0 Hz, H_{12}), 10.74 (s, 1 H, H_{11}).

^{13}C NMR (75 MHz, DMSO-d_6, δ ppm): 29.1 (C_3), 41.4 (C_2), 42.0 (C_1), 106.6 (C_5 or C_7), 116.1 (Cq), 119.3 (C_5 or C_7), 120.7 (C_6), 126.5 (Cq), 126.9 (Cq), 153.7 (C_{10}), 160.9 (C_{13}).

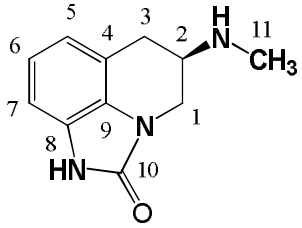
IR (KBr) (ν cm^{-1}): 1727, 1576 ($\nu_{C=O}$).

MS (EI): m/z (rel. int.) = 217 (M+, 16), 171 (100).

HRMS (EI):

Calculated for $C_{11}H_{11}N_3O_2$: $[M]^+$ = 217.0851; found: $[M]^+$ = 217.0859

(5*R*)-5-(Methylamino)-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-1(2*H*)-one (*R*)-**1**



$C_{11}H_{13}N_3O$

M = 203.24 g/mol

MP = 297 °C (salt HCl)

To a stirred solution of formamide **171** (0.130 g, 0.6 mmol) in anhydrous THF (0.330 mL) was added dropwise a 2M solution of $BH_3.Me_2S$ complex in THF (0.670 mL, 1.4 mmol). Stirring was continued for 3 h at 20 °C under argon. After concentration of the reaction mixture a solution of 2N HCl in Et_2O (2.5 mL) and MeOH (2 mL) were added. The resulting solution was heated at reflux for 2 h. After cooling to 20 °C, the solution was concentrated *in vacuo*. The solid residue was triturated with a 1:1 mixture of MeOH/Et_2O then filtered to give (*R*)-**1**.HCl as a brown solid (0.77 g, 63%).

$[\alpha]_D^{20}$ = -33.5 (c = 0.10, MeOH).

^{1}H NMR (300 MHz, D_2O, δ ppm): 2.70 (s, 3 H, H_{11}), 3.13 and 3.27 (AB part of ABX system, 2 H, *J* = 17.3, 2.8, 2.5 Hz, H_3), 3.96 and 4.17 (AB part of ABX system, 2 H, *J* = 13.3, 2.9, < 1 Hz, H_1), 3.99 (m, 1 H, H_2), 6.95 (d, 1 H, *J* = 8.0 Hz, H_5 or H_7), 6.98 (d, 1 H, *J* = 8.0 Hz, H_5 or H_7), 7.05 (dd, 1 H, *J* = 8.0 Hz, H_6).

^{13}C NMR (75 MHz, D_2O, δ ppm): 25.9 (C_3), 31.0 (C_{11}), 39.3 (C_1), 52.2 (C_2), 108.7 (C_5 or C_7), 113.9 (Cq), 120.5 (C_5 or C_7), 122.7 (C_6), 126.0 (2Cq), 155.0 (C_{10}).

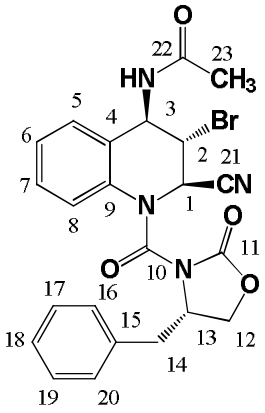
IR (KBr) (ν cm^{-1}): 1680 ($\nu_{C=O}$).

MS (EI): m/z (rel. int.) = 203 (M^+, 100), 171 (28), 162 (30).

HRMS (EI):

Calculated for $C_{11}H_{13}N_3O$: $[M]^+$ = 203.1059; found: $[M]^+$ = 203.1062

(2*R*,3*S*,4*R*)-3-bromo-1-{[(4*S*)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]carbonyl}-4-(2-oxopropyl)-1,2,3,4-tetrahydroquinoline-2-carbonitrile **223**



$C_{23}H_{21}BrN_4O_4$

M = 497.34 g/mol

Tetrahydroquinoline **108a** (0.481 g, 1.0 mmol), acetic anhydride (94 µL, 1.0 mmol) and a substoichiometric amount of 10% Pd/C (0.212 g, 0.2 mmol) were added to a mixture of EtOH/EtOAc (40 mL, 1:1) under hydrogen atmosphere and stirred at r.t. for 12 h. After filtration and evaporation of solvent *in vacuo*, the residue was purified by flash column chromatography on silica gel (CH_2Cl_2/EtOAc: 7/3, R_f = 0.41) to yield amide **223** (0.149 g, 0.30 mmol, 30 %) as a yellow solid.

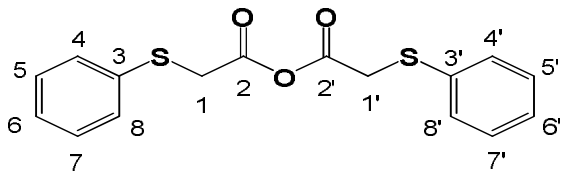
^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.05 (s, 3 H, H_{23}), 2.71 and 3.47 (AB part of ABX system, 2 H, *J* = 13.1, 10.8, 3.4 Hz, H_{14}), 4.18 and 4.29 (AB part of ABX system, 2 H, *J* = 9.0, 8.9, 8.4 Hz, H_{12}), 4.77-4.87 (m, 2 H, H_2, H_{13}), 5.32 (d, 1 H, *J* = 3,0 Hz, H_1), 5.38 (dd, 1 H, *J* = 7.3, 1.8 Hz, H_3), 6.52 (d, 1 H, *J* = 7.3 Hz, N<u>H</u>), 7.18-7.21 (m, 2 H, H_{16}, H_{20}), 7.27-7.39 (m, 7 H, Ar-H).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 23.2 (C_{23}), 38.5 (C_{14}), 47.7 (C_2), 50.0 (C_1), 51.5 (C_3), 57.0 (C_{13}), 68.2 (C_{12}), 115.3 (C_{21}), 124.5 (C_8), 127.2 (C_6), 127.7 (C_{18}), 129.1 (2<u>*C*</u>H$_{Ar}$), 129.3 (2<u>*C*</u>H$_{Ar}$), 129.4 (C_7), 129.9 (C_5), 134.1 (Cq), 134.8 (2Cq), 152.5 (C_{10}), 153.3 (C_{11}), 169.8 (C_{22}).

IR (ν cm^{-1}): 3366 (ν_{N-H}), 3028 (ν_{C-Haro}), 1782, 1685 ($\nu_{C=O}$), 1492, 1455 ($\nu_{C=Caro}$), 1219 ($\nu_{C-Oester}$), 763, 703 (ν_{C-Haro}).

MS (CI): m/z = 514, 516 $[M+NH_4]^+$, 497, 499 $[M+H]^+$, 464, 455, 416.

(Phenylsulfanyl)acetic anhydride **224**



$C_{16}H_{14}O_3S_2$

M = 318.41 g/mol

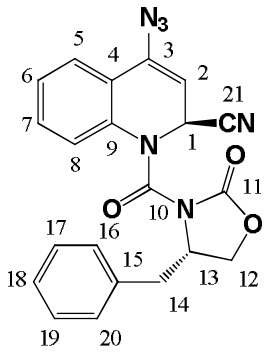
N,*N*-Dicyclohexylcarbodiimide (0.620 g, 3.0 mmol) was added to a solution of phenylthioacetic acid (0.840 g, 5.0 mmol) in CH_2Cl_2 (50 mL). The reaction solution was stirred at r.t. for 2 h. After filtration, the filtrate was quenched with water (100 mL) and the resulting solution was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. After addition of pentane (100 mL), the mixture was filtered and then evaporated *in vacuo* to afford the product **224** as a colourless power (0.516 g, 1.62 mmol, 54%).

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 3.68 (s, 4 H, H_1, H_1'), 7.25-7.34 (m, 6 H, Ar-H), 7.40-7.44 (m, 4 H, Ar-H).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 36.6 (4C, C_1, C_1'), 127.4 (2C, C6, C6'), 129.3 (4$\underline{C}H_{Ar}$), 130.2 (4$\underline{C}H_{Ar}$), 134.6 (2C, C_3, C_3'), 174.6 (2C, C_2, C_2').

IR (ν cm^{-1}): 3058 ($\nu_{C\text{-}Haro}$), 1819, 1747 ($\nu_{C=O}$), 1583, 1482, 1439 ($\nu_{C=Caro}$).

(2*S*)-1-{[(4*S*)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]carbonyl}-1,2-dihydroquinoline-2-carbonitrile **226a**



$C_{21}H_{16}N_6O_3$

M = 400.39 g/mol

MP = 153 °C

A solution of azido bromo **108a** (0.240 g, 0.5 mmol) and triethylamine (0.34 ml, 2.5 mmol) in toluene (5 mL) was stirred at r.t. for 12 h. Evaporation of solvent *in vacuo* gave a mixture of two diastereoisomers (0.170 g, 0.425 mmol, 85%, *dr* = 56/44). Isomer **226a** and isomer **226b** were successfully separated by chromatography on silica gel (PE/EtOAc, 7:3) and then recrystallized to give products as yellow crystals.

$[\alpha]_D^{20}$**:** -325.6 (c = 1.00, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.98 and 3.39 (AB part of ABX system, 2 H, *J* = 13.4, 9.2, 3.4 Hz, H_{14}), 4.16 and 4.30 (AB part of ABX system, 2 H, *J* = 9.5, 8.9, 8.4 Hz, H_{12}), 4.79 (m, 1 H, H_{13}), 5.64 (d, 1 H, *J* = 6.8 Hz, H_2), 5.86 (d, 1 H, *J* = 6.8 Hz, H_1), 6.99 (dd, 1 H, *J* = 8.0, 1.7 Hz, H_8), 7.21-7.40 (m, 7 H, Ar-H), 7.53-7.56 (m, 1 H, H_5).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 37.3 (C_{14}), 44.5 (C_1), 56.6 (C_{13}), 67.4 (C_{12}), 102.4 (C_2), 115.6 (C_{21}), 121.3 (C_8), 122.8 (Cq), 124.4 (C_5), 126.3 (C_6), 127.9 (C_{18}), 129.4 (2$\underline{C}H_{Ar}$), 129.5 (2$\underline{C}H_{Ar}$), 130.4 (C_7), 134.5 (Cq), 134.7 (Cq), 139.7 (Cq), 151.4 (C_{10}), 152.1 (C_{11}).

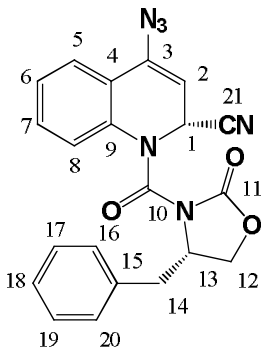
IR (ν cm^{-1}): 3062, 3025 ($\nu_{C\text{-}Haro}$), 2961 ($\nu_{C\text{-}Hsat}$), 2235 (ν_{CN}), 1783 ($\nu_{C=Ocarbamate}$), 1675 ($\nu_{C=Ourea}$), 1603, 1556, 1490, 1456 ($\nu_{C=Caro}$).

MS (CI): 418 $[M+NH_4]^+$, 401 $[M+H]^+$.

HRMS (ESI+):

Calculated for $C_{21}H_{16}N_6O_3Na$: $[M+Na]^+$ = 423.1176; found: $[M+Na]^+$ = 423.1171

(2*R*)-1-{[(4*S*)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]carbonyl}-1,2-dihydroquinoline-2-carbonitrile **226b**



MP = 130 °C

$[\alpha]_D^{20}$**:** +357.8 (c = 1.04, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.90 and 3.68 (AB part of ABX system, 2 H, *J* = 13.5, 9.9, 3.6 Hz, H_{14}), 4.18 and 4.25 (AB part of ABX system, 2 H, *J* = 9.0, 6.6, 2.9 Hz, H_{12}), 4.58 (m, 1 H, H_{13}), 5.72 (d, 1 H, *J* = 6.9 Hz, H_2), 5.86 (d, 1 H, *J* = 6.9 Hz, H_1), 7.21-7.40 (m, 8 H, Ar-H), 7.56 (dd, 1 H, *J* = 7.7, 1.6 Hz, H_5).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 38.1 (C_{14}), 44.6 (C_1), 58.1 (C_{13}), 66.9 (C_{12}), 102.7 (C_2), 115.7 (C_{21}), 120.3 (C_8), 122.7 (Cq), 124.6 (C_5), 126.3 (C_6), 127.6 (C_{18}), 129.3 (2$\underline{C}H_{Ar}$), 129.6 (2$\underline{C}H_{Ar}$), 130.5 (C_7), 134.9 (Cq), 135.2 (Cq), 139.6 (C_3), 151.2 (C_{10}), 151.5 (C_{11}).

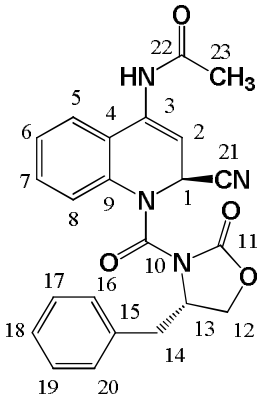
IR (ν cm^{-1}): 3057, 3024 ($\nu_{C\text{-}Haro}$), 2917 ($\nu_{C\text{-}Hsat}$), 1788 ($\nu_{C=Ocarbamate}$), 1696 ($\nu_{C=Ourea}$), 1605, 1495, 1457 ($\nu_{C=Caro}$).

MS (CI): 418 $[M+NH_4]^+$.

HRMS (ESI+):

Calculated for $C_{21}H_{16}N_6O_3Na$: $[M+Na]^+$ = 423.1176; found: $[M+Na]^+$ = 423.1170

(2*S*)-1-{[(4*S*)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]carbonyl}-4-(2-oxopropyl)-1,2-dihydroquinoline-2-carbonitrile **228a**



$C_{23}H_{20}N_4O_4$

M = 416.43 g/mol

MP: 133 °C

A solution of azido bromo **223** (72 mg, 0.145 mmol) and triethylamine (0.1 mL, 0.72 mmol) in toluene (5 mL) was stirred at r.t. for 12 h. After evaporation of solvent *in vacuo*, the mixture of two diastereoisomers (48.3 mg, 0.116 mmol, 80%, *dr* = 69/31) was submitted to chromatography on silica gel (CH_2Cl_2/EtOAc, 7:3) and the major product **228a** was isolated as a yellow powder.

$[\alpha]_D^{20}$**:** -101 (c = 0.21, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 1.91 (s, 3 H, H_{23}), 3.04 and 3.64 (AB part of ABX system, 2 H, *J* = 13.2, 10.6, 4.2 Hz, H_{14}), 4.31 (d, 1 H, *J* = 5.8 Hz, $1H_{12}$,), 4.34 (d, 1 H, *J* = 3.8 Hz, $1H_{12}$), 4.85 (m, 1 H, H_{13}), 5.83 (dd, 1 H, *J* = 8.5, 7.5 Hz, H_1), 6.59 (d, 1 H, *J* = 7.5 Hz, H_2), 7.14 (d, 1 H, *J* = 8.7 Hz, Ar-H), 7.28-7.44 (m, 6 H, Ar-H), 7.58 (dd, 1 H, *J* = 7.5, 1.3 Hz, Ar-H), 8.27 (d, 1 H, *J* = 8.1 Hz, Ar-H).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 23.4 (C_{23}), 37.2 (C_{14}), 44.1 (C_1), 58.2 (C_{13}), 69.3 (C_{12}), 114.0 (C_{21}), 118.1 (C_3), 121.5 ($\underline{C}H_{Ar}$), 127.5 ($\underline{C}H_{Ar}$), 127.7 ($\underline{C}H_{Ar}$), 128.6 ($\underline{C}H_{Ar}$), 128.8 (Cq), 129.1 ($2\underline{C}H_{Ar}$), 129.3 ($\underline{C}H_{Ar}$), 129.7 ($\underline{C}H_{Ar}$), 130.4 (C_2), 134.9 (2Cq), 136.9 (Cq), 149.3 (C_{10}), 153.8 (C_{11}), 169.7 (C_{22}).

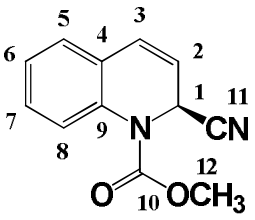
IR (ν cm^{-1}): 3378 (ν_{N-H}), 3027 (ν_{C-Haro}), 2235 (ν_{CN}), 1774, 1701, 1676 ($\nu_{C=O}$).

MS (CI, F:-c): m/z = 416 $[M]^+$.

HRMS (ESI+):

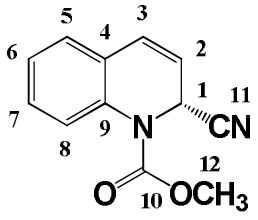
Calculated for $C_{23}H_{20}N_4O_4Na$: $[M+Na]^+$ = 439.1377; found: $[M+Na]^+$ = 439.1377

(*S*)-Methyl 2-cyanoquinoline-1(2*H*)-carboxylate **56a**



$C_{12}H_{10}N_2O_2$

M = 214.22 g/mol



MP = 92 °C

$[\alpha]_D^{20}$**:** -456.3 (c = 0.93, $CHCl_3$)

MP = 88 °C

$[\alpha]_D^{20}$**:** +409.4 (c = 1.00, $CHCl_3$)

To a solution of Reissert compound **105a** (1.078 g, 3.0 mmol) in CH_2Cl_2 (18 mL) was added $Sm(OTf)_3$ (0.448 g, 0.75 mmol). The resulting solution was stirred at r.t. for 1 h. After addition of MeOH (23 mL), the reaction mixture was stirred for 12 h and concentrated *in vacuo*. The crude residue was purified by chromatography on silica gel (petroleum ether/EtOAc, 4:1) to give the product **56a** as white solid (0.598 g, 2.79 mmol, 93%). A further crystallization of this powder from a biphasic system (petroleum ether/EtOAc) afforded **56a** as colorless crystals.

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 3.88 (s, 3 H, H_{12}), 5.97 (dd, 1 H, *J* = 9.22, 6.29 Hz, H_2), 6.13 (d, 1 H, *J* = 6.29 Hz, H_1), 6.74 (d, 1 H, *J* = 9.22 Hz, H_3), 7.18-7.19 (m, 2 H, H_5, H_6), 7.30-7.36 (m, 1 H, H_7), 7.64 (d, 1 H, *J* = 7.72 Hz, H_8).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 43.3 (C_1), 54.2 (C_{12}), 116.1 (C_{11}), 119.2 (C_2), 124.2 (C_8), 125.7 (C_6), 127.5 (C_5), 129.2 (C_7), 129.9 (C_3), 133.4 (2Cq), 153.7 (C_{10}).

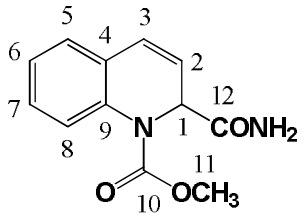
MS (EI): m/z (rel. int.) = 214 $[M]^+$ (100), 199 (17), 188 (95), 169 (37), 155 (77).

IR (ν cm^{-1}): 3068 ($\nu_{C\text{-}Haro}$), 1709 ($\nu_{C=O}$).

HRMS (EI):

Calculated for $C_{12}H_{10}N_2O_2$: $[M]^+$ = 214.0742; Found: $[M]^+$ = 214.073.

Methyl 2-carbamoylquinoline-1(2*H*)-carboxylate **277**



$C_{12}H_{12}N_2O_3$

M = 232.24 g/mol

MP = 119 °C

To a solution of nitrile **56a** (0.359 g, 1 mmol) in acetone (10 mL) at 0 °C was added a mixture of LiOH / H_2O_2 (35% in water) / water (60 mg / 0.5 mL / 2 mL) under vigorous stirring. The reaction solution was stirred for 15 min and then concentrated *in vacuo*. The residue was taken up with water and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by chromatography on silica gel (EtOAc) gave the product **277** as a white powder (0.116 g, 0.5 mmol, 50%).

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 3.86 (s, 3 H, H_{11}), 5.41 (bs, 1 H, NH), 5.64 (dd, 1 H, *J* = 6.5, 1.1 Hz, H_1), 5.92 (bs, 1 H, NH), 6.20 (dd, 1 H, *J* = 9.5, 6.5 Hz, H_2), 6.31 (d, 1 H, *J* = 9.5 Hz, H_3), 7.08-7.14 (m, 2 H, Ar-H), 7.22-7.28 (m, 1 H, Ar-H), 7.60 (d, 1 H, *J* = 8.0 Hz, H_8).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 53.8 (C_{11}), 56.2 (C_1), 123.8 (C_8), 124.5 (C_2), 125.2 ($\underline{C}H_{Ar}$), 126.4 (Cq), 126.7 (C_3), 127.2 ($\underline{C}H_{Ar}$), 128.3 ($\underline{C}H_{Ar}$), 134.1 (Cq), 155.3 (C_{10}), 172.5 (C_{12}).

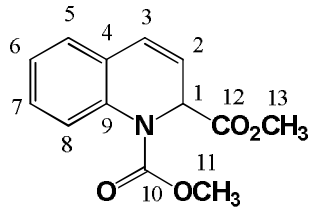
IR: (ν cm^{-1}) 3418 (ν_{N-H}), 2955 (ν_{C-Hsat}), 1705 ($\nu_{C=Oester}$), 1677 ($\nu_{C=Oamide}$), 1600, 1571, 1556, 1493 ($\nu_{C=Caro}$).

MS (CI): m/z = 250 $[M+NH_4]^+$, 233 $[M+H]^+$, 216, 188, 173.

HRMS (Maldi-PEG200):

Calculated for $C_{12}H_{12}N_2O_3Na$: $[M+Na]^+$ = 255.0740; Found: $[M+Na]^+$ = 255.0747.

Dimethyl quinoline-1,2(2*H*)-dicarboxylate **278**



$C_{13}H_{13}NO_4$

M = 247.25 g/mol

MP: 71 °C

Amide **277** (0.605 g, 2.61 mmol) was placed in the presence of Amberlyst resin (3.2 g), covered by MeOH (10 mL). The reaction solution was refluxed with strong stirring for 8 h. Then, the mixture was cooled to r.t., filtered and washed successively with MeOH (10 mL) and EtOAc (10 mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo* to afford the product **278** as colourless crystals (0.555 g, 2.24 mmol, 86%). R_f = 0.38 (PE/EtOAc, 4:1).

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 3.67 (s, 3 H, H_{13}), 3.84 (s, 3 H, H_{11}), 5.72 (d, 1 H, *J* = 6.8 Hz, H_1), 6.11 (dd, 1 H, *J* = 9.2, 6.8 Hz, H_2), 6.53 (d, 1 H, *J* = 9.2 Hz, H_3), 7.05-7.07 (m, 2 H, Ar-H), 7.22-7.28 (m, 1 H, Ar-H), 7.73 (bs, 1 H, Ar-H).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 52.5 (C_{13}), 53.5 (C_{11}), 55.3 (C_1), 122.7 (C_2), 123.5 ($\underline{C}H_{Ar}$), 124.4 ($\underline{C}H_{Ar}$), 125.6 (Cq), 126.7 ($\underline{C}H_{Ar}$), 126.9 (C_3), 128.4 ($\underline{C}H_{Ar}$), 134.9 (Cq), 154.7 (C_{10}), 170.0 (C_{12}).

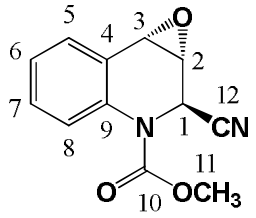
IR: (ν cm^{-1}) 3065, 3039 ($\nu_{C\text{-}Haro}$), 2961, 2941 ($\nu_{C\text{-}Hsat}$), 1756, 1690 ($\nu_{C=O}$), 1602, 1574, 1490 ($\nu_{C=Caro}$).

MS (CI): m/z = 265 $[M+NH4]^+$, 248 $[M+H]^+$.

HRMS (Maldi-PEG200):

Calculated for $C_{13}H_{14}NO_4$: [M+H] = 248.0917; Found: [M+H] = 248.0925.

Methyl (1a*R*,2*R*,7b*S*)-2-cyano-1a,7b-dihydrooxireno[*c*]quinoline-3(2*H*)-carboxylate **142**



$C_{12}H_{10}N_2O_3$

M = 230.22 g/mol

MP: 90 °C

To a solution of Reissert compound **56a** (0.562 g, 2.62 mmol) in CH_2Cl_2 (10 mL) at 20 °C was added *m*-CPBA (0.680 g, 3.94 mmol) in small portions. After being stirred at r.t. under argon for 14 h, the resulting solution was filtered on a pad of Celite and washed with CH_2Cl_2. The filtrate layer was washed successively with a saturated $NaHCO_3$ solution (3 x 20 mL) and brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (PE/EtOAc 7:3) to give epoxide **142** as white solid (0.513 g, 2.23 mmol, 85%).

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 3.81 (s, 3H, H_{11}), 4.01 (d, 1 H, *J* = 4.0 Hz, H_3), 4.15 (dd, 1 H, *J* = 4.0, 2.6 Hz, H_2), 6.04 (br.s, 1 H, H_1), 7.26 (t, 1 H, *J* = 8.1 Hz, Ar-H), 7.41-7.48 (m, 3 H, Ar-H).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 43.1 (C_1), 50.8 (C_3), 54.4 (C_{11}), 59.4 (C_2), 114.9 (C_{12}), 124.4 (Cq), 126.5 ($\underline{C}H_{Ar}$), 129.9 (3$\underline{C}H_{Ar}$), 133.8 (Cq), 155.0 (C_{10}).

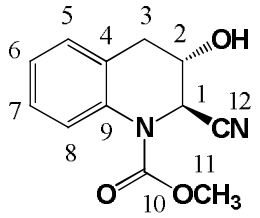
IR (ν cm^{-1}): 2242 (ν_{CN}), 1710 ($\nu_{C=O}$).

MS (CI): m/z = 248 $[M+NH_4]^+$, 231 $[M+H]^+$.

HRMS (Maldi-PEG200):

Calculated for $C_{12}H_{11}N_2O_3$ $[M+H]^+$ = 231.0764; Found: $[M+H]^+$ = 231.0762.

Methyl (2*R*,3*S*)-2-cyano-3-hydroxy-3,4-dihydroquinoline-1(2*H*)-carboxylate **143**



$C_{12}H_{12}N_2O_3$

M = 232.24 g/mol

Epoxide **142** (2.61 g, 11.3 mmol) and 10% Pd/C (1.20 g, 1.13 mmol) were added to a mixture of EtOAc-EtOH 1:1 (50 mL) and stirred at r.t. under hydrogen atmosphere for 12 h. After filtration through a pad of Celite, the filtrate was evaporated *in vacuo* and the crude residue was purified by chromatography on silica gel (PE/EtOAc 1:1, R_f = 0.36) to give compound **143** as brown oil (1.023 g, 4.4 mmol, 39% from Reissert compound **105a**).

$[\alpha]_D^{20}$**:** -41.6 (c = 0.94, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.80 and 3.18 (AB part of ABX system, 2 H, *J* = 16.6 Hz, 5.3 Hz, 4.8 Hz, H_3), 3.37 (sl, 1 H, OH), 3.83 (s, 3 H, H_{11}), 4.31 (ddd, 1 H, *J* = 5.3, 5.0, 4.8 Hz, H_2), 5.31 (d, 1 H, *J* = 5.0 Hz, H_1), 7.12-7.27 (m, 3 H, Ar-H), 7.57 (d, 1 H, d, *J* = 8.2 Hz, H_8).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 33.6 (C_3), 50.8 (C_1), 54.1 (C_{11}), 67.8 (C_2), 117.1 (C_{12}), 124.6 (C_8), 125.6 (C_4), 125.8 (C_5), 127.2 (C_7), 129.3 (C_6), 134.4 (C_9), 155.1 (C_{10}).

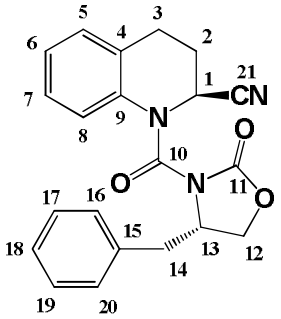
IR (ν cm^{-1}): 3337 (ν_{OH}), 2958 ($\nu_{C\text{-}Hsat}$), 2248 (ν_{CN}), 1710 ($\nu_{C=O}$), 1608, 1587, 1493 ($\nu_{C=Caro}$), 1247, 1202 ($\nu_{C\text{-}Oester}$).

MS (CI): m/z = 250.00 $[M+NH_4]^+$, 233.02 $[M+H]^+$.

HRMS (Maldi-PEG200):

Calculated for $C_{12}H_{12}N_2O_3Na$ $[M+Na]^+$ = 255.0740; Found: $[M+Na]^+$ = 255.0736.

(2*S*)-1-{[(4*S*)-4-methyl-2-oxo-1,3-oxazolidin-3-yl]carbonyl}-1,2,3,4-tetrahydroquinoline-2-carbonitrile **279**



$C_{21}H_{19}N_3O_3$

M = 361.39 g/mol

MP = 177 °C

To a solution of 1,2-dihydroquinoline **105a** (1.900 g, 5.29 mmol) in EtOAc (50 mL) was added 20% $Pd(OH)_2$ (0.371 g, 0.53 mmol). The mixture was stirred at r.t. under hydrogen atmosphere for 12 h. After filtration through a pad of Celite, the filtrate was evaporated *in vacuo* to give compound **279** as as white solid (1.893 g, 5.24 mmol, 99%).

$[\alpha]_D^{20}$**:** -158.7 (c = 1.15, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.13 (ddd, 1 H, *J* = 20.0, 7.9, 6.3 Hz, $1H_3$), 2.60 (ddd, 1 H, *J* = 20.0, 6.3, 6.3 Hz, $1H_3$), 2.80-2.97 (m, 3 H, H_2, $1H_{14}$), 3.52 (dd, 1 H, *J* = 13.2, 3.5 Hz, $1H_{14}$), 4.09 and 4.24 (AB part of ABX system, 2 H, *J* = 9.8, 8.9, 8.3 Hz, $1H_{12}$), 4.73-4.84 (m, 1 H, H_{13}), 5.26 (dd, 1 H, *J* = 7.6, 6.3 Hz, H_1), 6.91-6.94 (m, 1 H, Ar-H), 7.12-7.16 (m, 2 H, Ar-H), 7.20-7.22 (m, 1 H, Ar-H), 7.23-7.40 (m, 5 H, Ar-H).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 24.9 (C_2), 29.3 (C_1), 37.7 (C_{14}), 45.2 (C_1), 56.7 (C_{13}), 67.7 (C_{12}), 118.0 (C_{21}), 122.2 ($\underline{C}H_{Ar}$), 126.5 ($\underline{C}H_{Ar}$), 127.1 ($\underline{C}H_{Ar}$), 127.8 ($\underline{C}H_{Ar}$), 128.6 ($\underline{C}H_{Ar}$), 129.3 ($4\underline{C}H_{Ar}$), 131.9 (Cq), 134.8 (Cq), 136.2 (Cq), 152.3 (C_{10}), 152.6 (C_{11}).

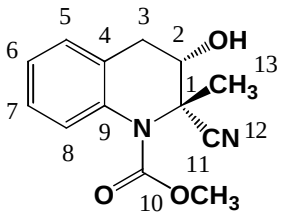
IR (ν cm^{-1}): 3069, 3030 ($\nu_{C\text{-}Haro}$), 2938, 2855 ($\nu_{C\text{-}Hsat}$), 2240 (ν_{CN}), 1784 ($\nu_{C=Ocarbamate}$), 1672 ($\nu_{C=Ourea}$), 1605, 1587, 1491, 1455 ($\nu_{C=Caro}$).

MS (EI): m/z (rel. int.) = 361 ($[M]^+$, 26), 204 (17), 157 (58), 91 (100).

HRMS (Maldi-PEG400):

Calculated for $C_{21}H_{19}N_3O_3Na$: $[M+Na]^+$ = 384.1319; Found: $[M+Na]^+$ = 384.1328.

Methyl (2*S*,3*S*)-2-cyano-3-hydroxy-2-methyl-3,4-dihydroquinoline-1(2*H*)-carboxylate **281**



$C_{13}H_{14}N_2O_3$

M = 246.26 g/mol

MP = 82 °C

A solution of nitrile derivative **143** (0.390 g, 1.68 mmol) in THF (5 mL) was cooled to -50 °C and added to a THF solution (5 mL) of LDA (prepared from 2.25 M *n*-BuLi in hexane (2.24 mL, 5.04 mmol) and diisopropylamine (0.78 mL, 5.54 mmol) at -50 °C over a 5' period. The reaction mixture was stirred at -10 °C for 25 min, and then at 0 °C for 5 min, followed by the dropwise addition of a solution of methyl iodide (0.16 mL, 2.52 mmol) in HMPA (0.41 mL, 2.35 mmol) at -30 °C over a period of 2 min. The mixture was stirred at 0 °C for about 1 h. The ice bath was then removed and the mixture was allowed to continue stirring at r.t. for 4 h. The reaction was quenched with saturated aqueous NH_4Cl, extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by chromatography on silica gel (PE /EtOAc, 3:2) to afford the product **281** as a brown solid (0.170 g, 0.69 mmol, 41%, *ed* > 98:2).

$[\alpha]_D^{20}$**:** -25.1 (c = 0.70, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 1.92 (s, 3 H, H_{13}), 2.82 (bs, 1 H, OH), 2.88 and 3.01 (AB part of ABX system, *J* = 14.1, 10.4, 3.3 Hz, H_3), 3.63 (dd, 1 H, *J* = 10.2, 3.1 Hz, H_2), 3.88 (s, 3 H, H_{11}), 7.07-7.15 (m, 2 H, Ar-H), 7.20-7.25 (m, 1 H, Ar-H), 7.41 (d, 1 H, *J* = 8.1 Hz, Ar-H).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 24.3 (C_{13}), 34.7 (C_3), 53.6 (C_{11}), 75.2 (C_2), 118.7 (C_{12}), 125.0 ($\underline{C}H_{Ar}$), 125.4 ($\underline{C}H_{Ar}$), 127.4 ($\underline{C}H_{Ar}$), 128.0 (2Cq), 128.3 ($\underline{C}H_{Ar}$), 134.7 (Cq), 154.5 (C_{10}).

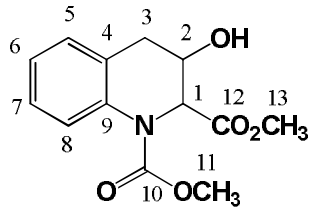
IR (ν cm^{-1}): 3353 (ν_{OH}), 2954, 2852 ($\nu_{C\text{-}Hsat}$), 2247 (ν_{CN}), 1712 ($\nu_{C=Ocarbamate}$), 1588, 1494, 1439 ($\nu_{C=Caro}$).

MS (CI): m/z = 264 $[M+NH_4]^+$, 247 $[M+H]^+$, 220, 187.

HRMS (Maldi-PEG200):

Calculated for $C_{13}H_{15}N_2O_3$ $[M+H]^+$ = 247.1077; Found $[M+H]^+$ = 247.1073.

Dimethyl 3-hydroxy-3,4-dihydroquinoline-1,2(2*H*)-dicarboxylate **282**



$C_{13}H_{15}NO_5$

M = 265.26 g/mol

Thionyl chloride (8 mL) was added slowly at -10 °C to a solution of nitrile **143** (0.635 g, 2.75 mmol) in methanol (20 mL). The reaction mixture was allowed to warm to r.t. and then refluxed for 3 h. The solvent was removed *in vacuo* and the residue was triturated with a saturated aqueous $NaHCO_3$ (50 mL). After extraction with Et_2O (2 x 20 mL), the combined organic layer was washed with brine (50 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* and then the residue was purified by flash chromatography on silica gel (PE/EtOAc, 1:1) to afford the product **282** as a yellow oil (0.453 g, 1.71 mmol, 62%).

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.77 and 2.96 (AB part of ABX system, 2 H, *J* = 14.8, 8.2, 4.4 Hz, H_3), 3.73 (s, 3 H, H_{13}), 3.81 (s, 3 H, H_{11}), 4.14-4.21 (m, 1 H, H_2), 4.92 (d, 1 H, *J* = 5.9 Hz, H_1), 7.07 (td, 1 H, *J* = 7.5, 1.1 Hz, Ar-H), 7.12 (dd, 1 H, *J* = 7.5, 2.1 Hz, Ar-H), 7.24 (td, 1 H, *J* = 8.2, 2.1 Hz, Ar-H), 7.68 (d, 1 H, *J* = 8.2 Hz, Ar-H).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 34.5 (C_3), 52.8 (C_{13}), 53.6 (C_{11}), 63.5 (C_1), 69.4 (C_2), 124.2 ($\underline{C}H_{Ar}$), 125.0 ($\underline{C}H_{Ar}$), 127.0 (Cq), 127.3 ($\underline{C}H_{Ar}$), 128.7 ($\underline{C}H_{Ar}$), 136.3 (Cq), 155.4 (C_{10}), 171.4 (C_{12}).

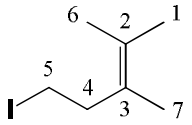
IR (ν cm^{-1}): 3360 (ν_{OH}), 2956, 2850 ($\nu_{C\text{-}Hsat}$), 1670 ($\nu_{C=O}$), 1607, 1586, 1493, 1442 ($\nu_{C=Caro}$).

MS (CI): 283 $[M+NH_4]^+$, 266 $[M+H]^+$.

HRMS (Maldi-PEG200):

Calculated for $C_{13}H_{15}NO_5Na$ $[M+Na]^+$ = 288.0842; Found $[M]^+$ = 288.0853.

5-Iodo-2,3-dimethylpent-2-ene **284**



$C_7H_{13}I$

M = 224.08 g/mol

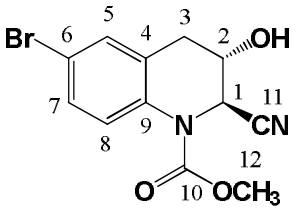
To a solution of methyl 1-methylcyclopropyl ketone (0.548 mL, 5.0 mmol) in Et_2O (15 mL), 3M methyl magnesium iodide in Et_2O (15 mL, 5.0 mmol) was added dropwise at r.t. with stirring. The mixture was stirred at the same temperature for 2 h. The Grignard adduct thus formed is slowly added to a stirred and cooled (0 °C) solution of concentrated sulfuric acid (15 mL) in water (30 mL) at a rate of maintain the temperature below 10 °C. After the addition was complete, stirring was continued for 12 h. The ethereal layer was separated, and the aqueous layer was extracted with Et_2O (2 x 15 mL). The combined ethereal phases were decolorized by the addition of 5% $Na_2S_2O_3$, neutralized with 5% $NaHCO_3$, washed with brine and dried with $MgSO_4$. The solvent was evaporated and the residue was distilled *in vacuo* to afford the product **284** as a colorless liquid (0.952 g, 4.25 mmol, 85%).

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 1.63 (s, 3 H, H_7), 1.65 (s, 6 H, H_1, H_6), 2.62 (dd, 2 H, J = 8.3, 7.9 Hz, H_4), 3.12 (dd, 2 H, J = 9.3, 7.9 Hz, H_5).

MS (EI): m/z (rel. int.) = 225 ($[M]^+$, 44), 169 (19), 127 (91), 55 (100).

Data were consistent with the literature (CAS: 216320-01-3).

Methyl 6-bromo-2-cyano-3-hydroxy-3,4-dihydroquinoline-1(2*H*)-carboxylate **287**



$C_{12}H_{11}BrN_2O_3$

M = 311.13 g/mol

To a solution of alcohol **143** (0.485 g, 2.09 mmol) and AcONa (0.322 g, 3.93 mmol) in glacial acetic acid (4.1 mL) was added Br_2 (0.214 mL, 4.18 mmol). After being stirred at r.t. for 1h30, the resulting solution was taken up with a saturated solution of $Na_2S_2O_3$ (50 mL), extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Acetic acid was then removed via an azeotropic distillation with cyclohexane to give the product **287** as a colourless oil without further purification.

$[\alpha]_D^{20}$**:** -32.5 (c = 1.03, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.86 and 3.25 (AB part of ABX system, 2 H, *J* = 17.1 Hz, 4.7 Hz, 4.5 Hz, H_3), 3.87 (s, 3 H, H_{12}), 4.42 (ddd, 1 H, *J* = 4.7, 4.6, 4.5 Hz, H_2), 5.40 (d, 1 H, *J* = 4.6 Hz, H_1), 7.30 (d, 1 H, *J* = 2.2 Hz, H_5), 7.37 (dd, 1 H, *J* = 8.8, 2.2 Hz, H_7), 7.53 (d, 1 H, *J* = 8.8 Hz, H_8).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 33.0 (C_3), 50.3 (C_1), 54.2 (C_{11}), 66.8 (C_2), 116.6 (C_{11}), 118.6 (C_6), 126.0 (C_8), 127.8 (C_4), 130.1 (C_7), 131.9 (C_5), 133.4 (C_9), 154.5 (C_{10}).

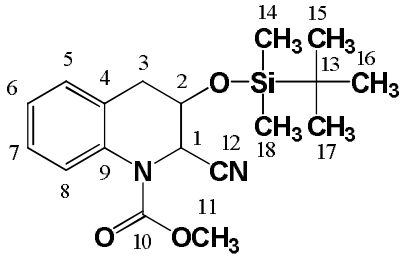
IR (ν cm^{-1}): 3452 (ν_{OH}), 2958 ($\nu_{C\text{-}Hsat}$), 2248 (ν_{CN}), 1713 ($\nu_{C=O}$), 1596, 1484, 1443 ($\nu_{C=Caro}$).

MS (CI): m/z = 330, 328 $[M+NH_4]^+$, 312, 310 $[M+H]^+$, 284, 250, 233.

HRMS (Maldi-PEG400)**:**

Calculated for $C_{12}H_{11}BrN_2O_3Na$: $[M+Na]^+$ = 332.9845; Found: $[M+Na]^+$ = 332.9854.

Methyl 3-((tert-butyldimethylsilyl)oxy)-2-cyano-3,4-dihydroquinoline-1(2*H*)-carboxylate **286**



$C_{18}H_{26}N_2O_3Si$

M = 346.50 g/mol

MP = 90 °C

A solution of alcohol **143** (0.464 g, 2.0 mmol) in DMF (8mL) was added imidazole (0.817 g, 12 mmol) and then TBDMSCl (0.904 g, 6.0 mmol). The resulting solution was stirred at r.t. for 12 h. After dilution with EtOAc (50 mL), the resulting solution was washed with water (3 x 50 mL) and then with brine. The combined organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (petroleum ether/EtOAc, 9:1) to afford the product **286** as a colourless powder (0.628 g, 1.8 mmol, 90%).

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 0.14 (d, 6 H, *J* = 3.5 Hz, H_{14}, H_{18}), 0.87 (s, 9 H, H_{15}, H_{16}, H_{17}), 2.76 and 3.08 (AB part of ABX system, 2 H, *J* = 15.9, 6.5, 4.5 Hz, H_3), 3.84 (s, 3 H, H_{11}), 4.30 (m, 1 H, H_2), 5.20 (d, 1 H, *J* = 5.0 Hz, H_1), 7.13 (dd, 1 H, *J* = 4.9, 1.1 Hz, Ar-H), 7.22-7.28 (m, 2 H, Ar-H), 7.54 (d, 1 H, *J* = 8.0 Hz, Ar-H).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 18.0 (C_{14}, C_{18}), 25.6 (C_{15}, C_{16}, C_{17}), 35.0 (C_3), 51.4 (C_1), 53.9 (C_{11}), 69.5 (C_2), 117.6 (C_{12}), 125.0 ($\underline{C}H_{Ar}$), 125.7 ($\underline{C}H_{Ar}$), 126.5 (Cq), 127.2 ($\underline{C}H_{Ar}$), 129.0 ($\underline{C}H_{Ar}$), 134.8 (Cq), 154.8 (C_{10}).

IR (ν cm^{-1}): 2957, 2931 ($\nu_{C\text{-}Hsat}$), 1722 ($\nu_{C=O}$), 1253 ($\nu_{Si\text{-}CH3}$).

MS (CI): 364 $[M+NH_4]^+$, 347 $[M+H]^+$.

HRMS (ESI+):

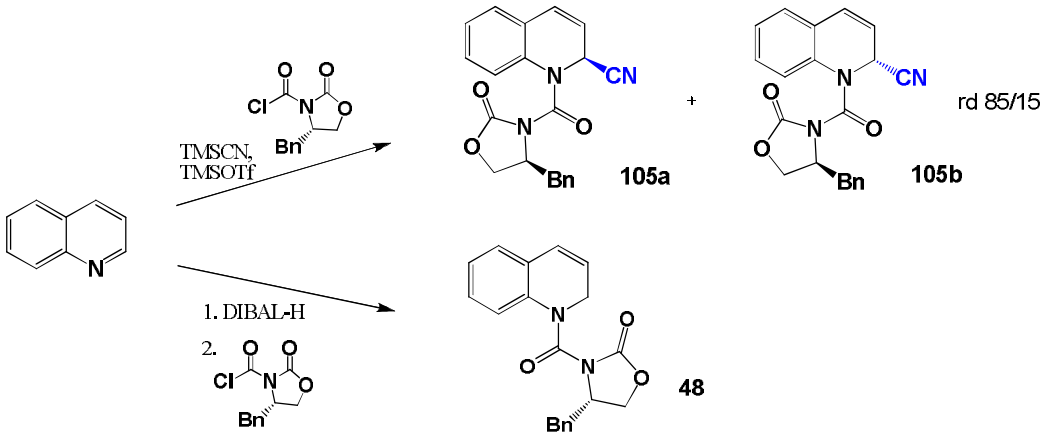
Calculated for $C_{19}H_{26}N_2O_3Si$: $[M+H]^+$ = 347.1786; found: $[M+H]^+$ = 347.1782

GENERAL CONCLUSIONS

GENERAL CONCLUSIONS

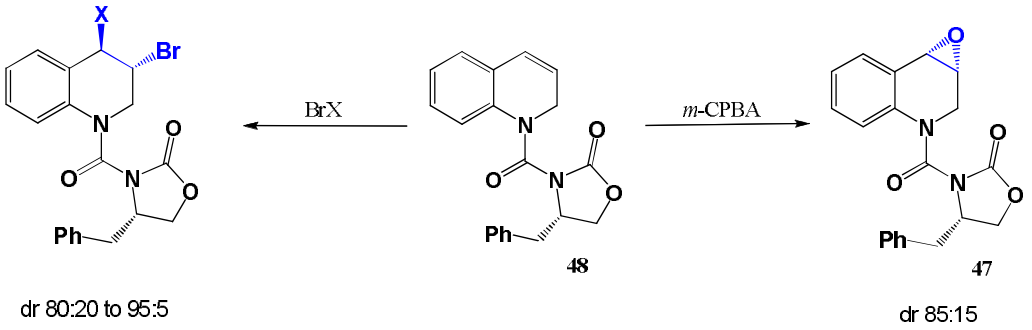
Our work mainly aimed at developing a simple and efficient method to prepare chiral non racemic 1,2,3,4-tetrahydroquinolines diversely substituted at C2, C3 and C4 positions. Our initial motivation can be found in the fact that substituted 1,2,3,4-THQ display a wide range of biological activities and, also, in the fact that the 1,2,3,4 THQ skeleton can be found in a small number of natural compounds exhibiting interesting pharmacological properties.

Our approach to the problem of preparing substituted 1,2,3,4-THQ in an asymmetric manner was based on the rapid elaboration of 1,2-dihydroquinolines bearing a chiral auxiliary attached at N1. Based on earlier work, we chose a 4-benzyloxazolin-2-one moiety as the chiral inducer. This latter was fixed at N1 through the formation of a transient quaternary salt, which was subsequently treated with TMSCN to deliver Reissert adducts **105a** and **105b** or after a preliminary reduction of quinoline (DIBAL-H) to give 1,2-DHQ **48** (Scheme 114).



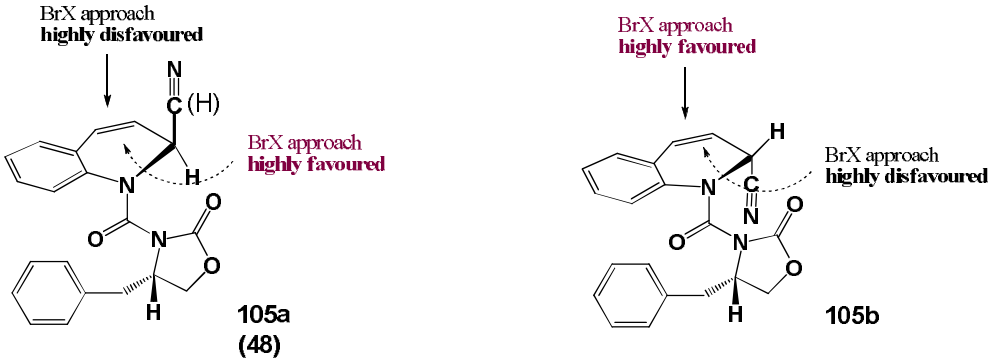
Scheme 114

In a first part of the study we demonstrated that addition of electrophiles of the type Br-X on the unsaturated C3-C4 double bond of 1,2-DHQ **48** could be achieved with good diastereo-selectivities in spite of the fact that the chiral auxiliary is remote from the reacting double bond. These results do not detract with our earlier observation that epoxidation of **48** (*m*-CPBA) could be done with an encouraging diastereoselectivity of 85/15 (Scheme 115).



Scheme 115

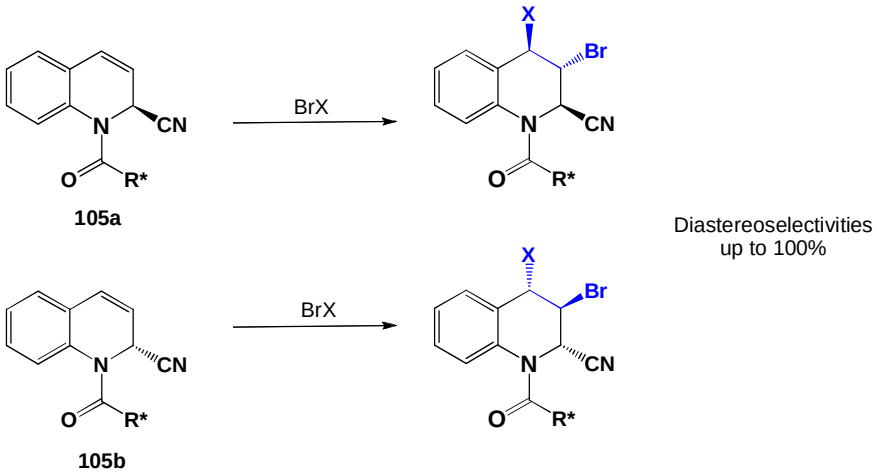
An interpretation of these results was offered first based on X-Ray observations, then later confirmed by theoritical calculations. It thus appeared that the chiral information borne by the oxazolidin-2-one motif is relayed to the C3-C4 double bond via a conformational bias. In other words, the particular conformation of the 1,2-DHQ ring in **48** places a hydrogen substituent at C2 in a quasi axial position on the top face of the molecule, whereby favouring the Br-X approach from the bottom face of the C3-C4 double bond. Reaction of Br-X reagents with diastereomeric 1,2-DHQ **105a** and **105b,** having a CN substituent at C2, is somewhat different. In that case, the steric course of the reaction is governed by the configuration of the C2 center. We thus observed that approach of the electrophilic reagents occurred opposite to the CN substituent (Scheme 116).



Scheme 116

The chiral auxiliary is not a simple spectator group, since it influences the conformation of the 1,2-THQ ring. Indeed, the CN group occupied an axial position in both diastereomers **105a** and **105b**, thus favouring the electrophile approach from the opposite direction and, consequently, the formation of the corresponding adducts (Scheme 117). Because a CN group (although not

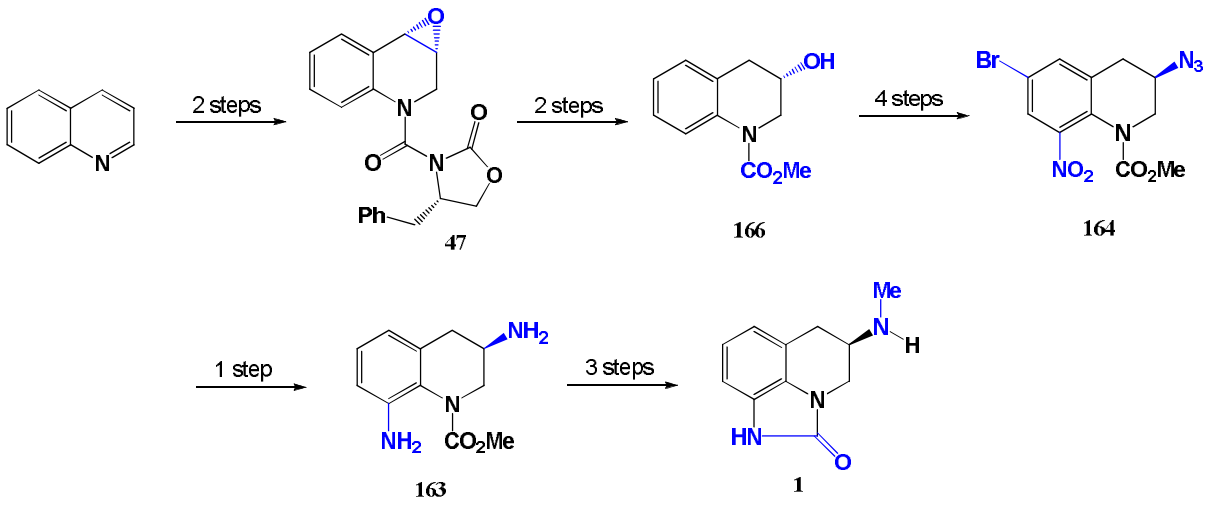
very cumbersome) is bulkier than a hydrogen atom, the diastereoselectivities were better (c.a. 100%) with Reissert adducts than with 1,2-THQ **48** (Scheme 115).



Scheme 117

To complete this methodological study, we delineated the structural elements of the chiral auxiliary necessary for obtaining good diastereoselectivities in the C2-C3 addition reactions. It thus appeared that a five-membered ring (oxazolidin-2-one or oxazolidine) as well as the nature of the substituent at C'4 of the chiral ring are a requisite for obtaining good stereochemical results.

The second part of our thesis work is concerned with synthetic applications. We first concentrated our efforts on the synthesis of Sumanirole, a highly selective D2 receptor full agonist. This unnatural compound was developed for the treatment of Parkinson's disease and restless leg syndrome. While this compound, for not obvious reasons, has never been approved for medical use, it remains a valuable tool for research to identify neurobiological mechanisms that are based on a dopamine D2-linked mechanism of action. Our synthesis was accomplished in 12 steps from quinoline and in an overall yield of 4.3%. The salient features of this synthesis are the diastereoselective epoxidation of the *m*-CPBA-mediated epoxidation of the C3-C4 double bond of **48** as well as a spectacular hydrogenation reaction allowing the transformation of three different groups (Scheme 118).



Scheme 118

In addition to this successfull synthetic work, preliminary synthetic efforts have been made to develop an asymmetric synthesis of two natural alkaloids, i.e.Virantmycin and Martinellic acid. Virantmycin, a chlorine-containing antiviral antibiotic isolated from a strain of *Streptomyces nitrosporeus* possesses antifungal activity and potent inhibitory activity against various RNA and DNA viruses. Martinellic acid, a pyrroloquinoline alkaloid isolated from the root bark of the tropical plant *Martinella iquitosensis*, represents the first example of a nonpeptidic compound to be identified as a bradykinin receptor antagonist. The Reissert adduct **56a** was used as the starting compound of the two synthetic approaches. Although, in both series, a relatively important set of transformations has been accomplished from this compound, we were not able to make decisive advances due to the various, and yet unsolved, problems encountered.

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REFERENCES

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RESUME FRANCAIS

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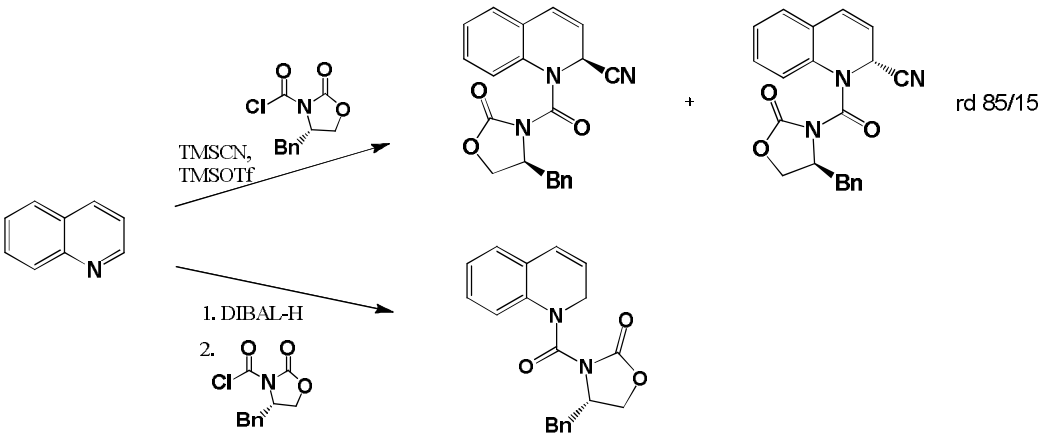
Introduction Générale

Les composés hétérocycles, et plus particulièrement les hétérocycles azotés, représentent la plus importante classe de molécules développées dans le milieu pharmaceutique et agrochimique. Environ 60% des molécules utilisées comme médicaments sont des hétérocycles. Parmi eux, les 1,2,3,4-tétrahydroquinoléines ont fait l'objet de nombreuses investigations ces dernières années pour l'étendue de leurs propriétés biologiques. De plus, le squelette 1,2,3,4-tétrahydroquinoléine peut être rencontré dans de nombreux médicaments ainsi que dans nombre de molécules naturelles possédant des propriétés biologiques intéressantes.

Nous nous sommes récemment intéressés au développement de nouvelles approches asymétriques de 1,2,3,4-tétrahydroquinoléines diversement substituées avec comme objectif principal l'application de notre méthodologie pour la synthèse totale de molécules naturelles (ou non-naturelles) possédant des propriétés pharmaceutiques avérées.

Il y a quelques années, nous avons montré que des structures de type Reissert dérivées de quinoléine ou d'isoquinoléine pouvaient être synthétisées avec des diastéréosélectivités pouvant aller jusque 70% en soumettant la quinoléine (isoquinoléine) à un chlorure d'acide chiral dérivé d'une oxazolidin-2-one chirale en présence de cyanure de triméthylsilyle (TMSCN). Nous avons montré, au cours d'une autre étude, qu'une 1,2-dihydroquinoléine chirale pouvait être obtenue de façon similaire en utilisant le Dibal-H permettant de générer intermédiairement un aminoalane capable de réagir avec le même chlorure d'acide chiral.



Ces résultats nous ont conduits à nous demander si divers additions électrophiles stéréosélectives pouvaient être envisagées sur chaque 1,2-dihydroquinoléine. Si tel était le cas, nous pourrions atteindre de nouvelles 1,2,3,4-tétrahydroquinoléines pouvant être transformées par la suite en molécules d'intérêt. Alors que nous sommes assez confiants quant à l'addition électrophile sur les dérivés de type Reissert grâce à l'effet directionnel probable engendré par le groupement nitrile, nous étions moins sereins concernant l'addition sur la simple 1,2 dihydroquinoléine étant donnée la distance importante entre la double liaison réagissant et le centre de chiralité inducteur.

Dans le premier chapitre de la thèse, nous présenterons les résultats de cette étude méthodologique montrant que diverses additions électrophiles peuvent être effectuées sur des dérivés de type Reissert avec d'excellentes diastéréosélectivités. De façon plus surprenante, nous montrerons que les mêmes additions peuvent être effectuées sur des 1,2-dihydroquinoléines ne comportant pas de groupement CN en C2 avec des stéréosélectivités intéressantes.

Le deuxième chapitre de la thèse consiste en l'application de la méthodologie développée à la synthèse multi-étapes. Nous décrirons dans un premier temps une nouvelle synthèse originale du Sumanirole, composé non-naturel possédant des propriétés antiparkinsoniennes intéressantes. Des études préliminaires destinées à la synthèse de deux alcaloïdes naturels, la Virantmycine et l'acide martinellique, seront également décrites.

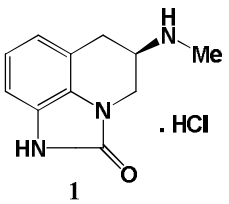
CHAPITRE I : Contrôle à distance d'additions électrophiles sur la double liaison C3-C4 de 1,2-dihydroquinoléines chirales

I.1. Revue bibliographique

Les composés hétérocycliques azotés représentent la plus grande famille de composés dans l'industrie pharmaceutique et agrochimique. Parmi eux, les 1,2,3,4-tétrahydroquinoléines (1,2,3,4-THQs) ont fait l'objet de recherches intensives ces dernières années. L'intérêt marqué pour ce type de composés réside dans la présence du squelette 1,2,3,4-tétrahydroquinoléique dans de nombreux produits naturels d'intérêt biologique ainsi que dans de nombreux médicaments. En conséquence, de nombreuses méthodologies de synthèse de dérivés de 1,2,3,4-THQ ont été rapportées dans la littérature ces dernières années.[1] Dans le cadre de synthèses totales envisagées au laboratoire, nous nous sommes particulièrement intéressés aux 1,2,3,4-THQs comportant un groupement NHR ou NR1R2 en position C3 ou C4. Nous donnerons ici un rapide aperçu des méthodes connues pour obtenir ce type de composés.

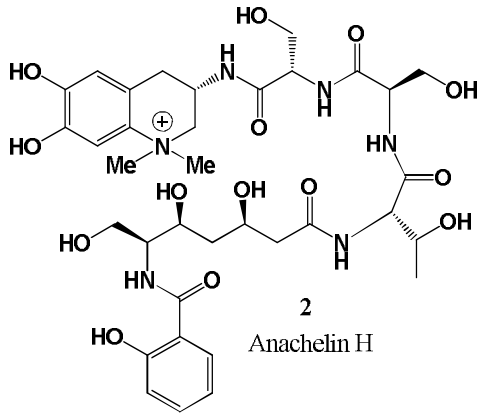
I.1.1. Tétrahydroquinolines comportant un groupement NHR ou NR_1R_2 en C_3

Le sumanirole (PNU-95666E) **1** et l'anachelin-H **2** appartiennent à cette famille de molécules (Figure 1). Le sumanirole, agoniste des récepteurs D2 a été développé pour le traitement de la la maladie de Parkinson.[2] L'anachelin H [3] isolé de la cyanobacterie *Anabaena cylindrical* est un excellent chélatant du fer.



1

Sumanirole



2

Anachelin H

Figure 1: 1,2,3,4-THQs comportant un groupement NHR en C_3

[1] (a) A. R. Katritzky, S. Rachwal, B. Rachwal, *Tetrahedron*, **1996**, *52*, 15031-15068. (b) V. Sridharan, P. A. Suryavanshi, J. C. Menéndez, *Chem. Rev*. **2011**, *111*, 7157.
[2] (a) R. F. Heier, L. A. Dolak, J. N. Duncan, D. K. Hyslop, M. F. Lipton, I. J. Martin, M. A. Mauragis, M. F. Piercey, N. F. Nichols, P. J. K. D. Schreur, M. W. Smith, M. W. Moon, *J. Med. Chem.* **1997**, *40*, 639. (b) R. B. McCall, K. L. Lookingland, P. J. Bédard, R. M. Huff, *J. Pharmacol. Exp. Ther*. **2005**, *314*, 1248.
[3] (a) Y. Ito, K. Ishida, S. Okada, M. Murakami, *Tetrahedron*, **2004**, *60*, 9075. (b) K. Gademann, Y. Bethuel, *Org. Lett*. **2004**, *6*, 4707. (c) K. Gademann, Y. Bethuel, *Angew. Chem. Int. Ed.* **2004**, *43*, 3327. (d) Y. Bethuel, K. Gademann, *J. Org. Chem.* **2005**, *70*, 6258.

I.1.2. Tétrahydroquinoléines comportant un groupement NHR ou NR_1R_2 en C_4

Les 2-méthyltétrahydroquinoléines **3** et **4** possèdent par exemple des activités plus ou moins importantes dans le domaine de la résistance multi-drogue (MDR),[4] considérée comme l'obstacle majeur dans la lutte contre le cancer. Les *trans*-2-carboxy-4-amidotétrahydroquinoléines **5** ont également été identifiées comme des antagonistes de récepteurs NMDA.[5] Le torcetrapib (CP 529,414) **6** [6] a pour sa part été développé pour traiter les problèmes d'hypercholestérolémie et prévenir certaines maladies cardiovasculaires.

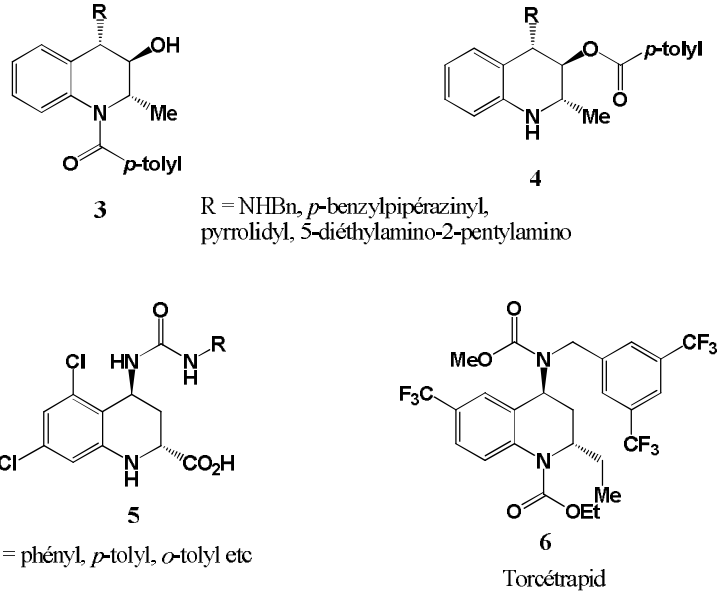


Figure 2: 1,2,3,4-THQs comportant un groupement NHR en C_4

Etant donné le faible nombre de tétrahydroquinoléines substituées en C_3 et C_4 par un groupement aminé, les synthèses énantiosélectives connues n'en sont que plus rares.

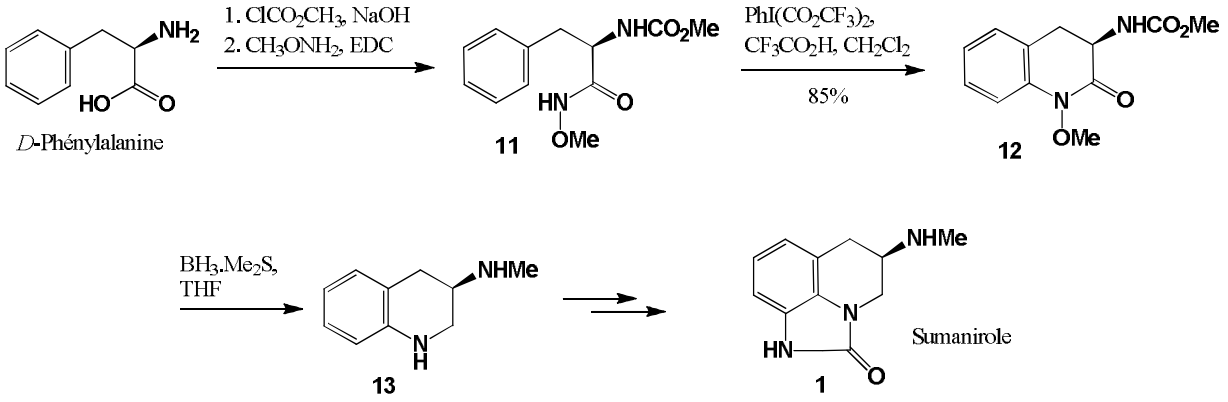
I.1.3. Introduction énantiosélective d'un groupement NHR en C_3

Cette installation peut être effectuée soit par substitution nucléophile intramoléculaire ou par réduction et cyclisation intramoléculaire.

A titre d'exemple, la substitution nucléophile intramoléculaire peut permettre la formation de la liaison N-C_{8a} pour la synthèse du sumanirole (Schéma 1). La cyclisation à l'aide du $PhI(CO_2CF_3)_2$ du *N*-méthoxyamide **11,** préparé à partir de la *D*-phénylalanine en 2 étapes, permet

[4] R. Hiessböck, C. Wolf, E. Richter, M. Hitzler, P. Chiba, M. Kratzel, G. Ecker. *J. Med. Chem.***1999**, *42*, 1921.
[5] P. D. Leeson, R. W. Carling, K. W. Moore, A. M. Moseley, J. D. Smith, G. Stevenson, T. Chan, R. Baker, A. C. Foster, S. Grimwood, J. A. Kemp, G. R. Marshall, K. Hoogsteen, *J. Med. Chem.* **1992**, *35*, 1954.
[6] (a) M. Guinó, P. H. Phua, J-C. Caille, K. K. Hii, *J. Org. Chem.* **2007**, *72*, 6290. (b) H. Liu, G. Dagousset, G. Masson, P. Retailleau, J. Zhu, *J. Am. Chem. Soc.* **2009**, *131*, 4598.

d'isoler la dihydroquinolone **12**[7]. La réduction de **12** avec BH_3 mène à la 3-(*N*-méthylamino)-1,2,3,4-tétrahydroquinoléine **13**, intermédiaire de synthèse du Sumanirole **1**.[8]



SS**chéma 1**: Synthèse de la (3*R*)-3-méthylamino-1,2,3,4-tétrahydroquinoléine

La séquence réduction-cyclisation intramoléculaire peut être illustrée par l'exemple suivant décrivant la synthèse d'un intermédiaire avancé de l'anachéline H (schéma 2) à partir de la L-DOPA. Le composé nitré **27**, préparé à partir de la *L*-DOPA en 4 étapes,[9] est réduit et cyclisé en dérivé tétrahydroquinoléique **28** en présence de Fe/AcOH. La fonction amine est ensuite déprotégée en présence de Pd(0) et le groupement carbonyle réduit en présence de borane.[3d]

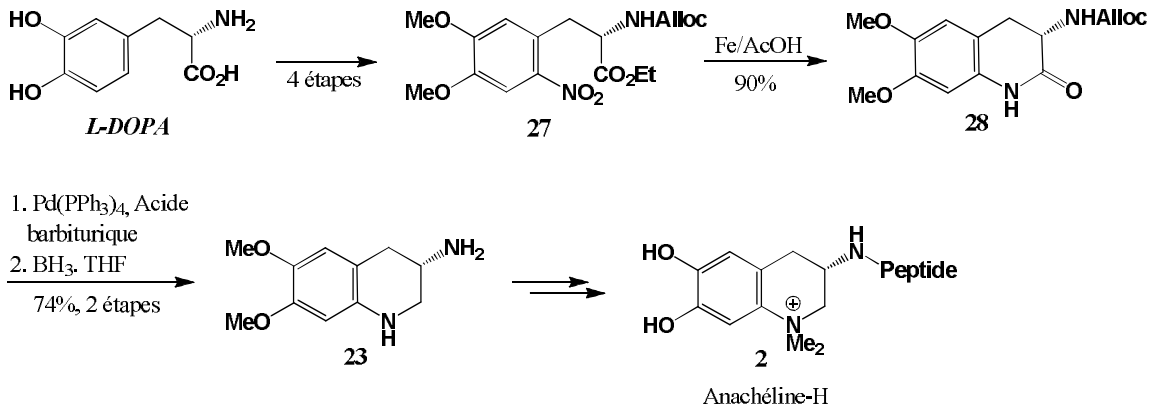


Schéma 2

I.1.4. Introduction asymétrique d'un groupement NHR en C_4

L'introduction d'un groupement NHR en C4 peut être effectuée en amont de la formation du cycle quinoléique, cette cyclisation pouvant être effectuée *via* la formation de la liaison N-C_2,

[7] A. G. Romero, W. H. Darlington, M. W. McMillan, *J. Org. Chem.***1997**, *62*, 6582.
[8] P. G. M. Wuts, *Curr. Opin. Drug Discovery Dev.* **1999**, *2*, 557.
[9] T. Kolasa, M. J. Miller. *J. Org. Chem.* **1990**, *55*, 4246.

C_2-C_3, C_3-C_4 ou C_4-C_{4a}. Nous décrirons dans ce résumé la plus récente des 4 illustrant la cyclisation par formation de la liaison C_2-C_3 (Schéma 3).

Afin de mettre au point une synthèse générale d'alcaloïdes dérivés de la martinelline, l'addition d'amidures de lithium chiraux sur divers esters α-β-insaturés a été étudiée.[10] L'ester α-β-insaturé **34** est tout d'abord synthétisé *via* un couplage de Heck suivi d'une oléfination de Wittig à partir de la 2-iodoaniline. L'addition conjuguée de l'amidure de lithium homochiral **35** entraine la cyclisation par addition conjuguée de l'énolate intermédiaire **36** pour mener aux dérivés 4-amino-tétrahydroquinoléiques **37**.

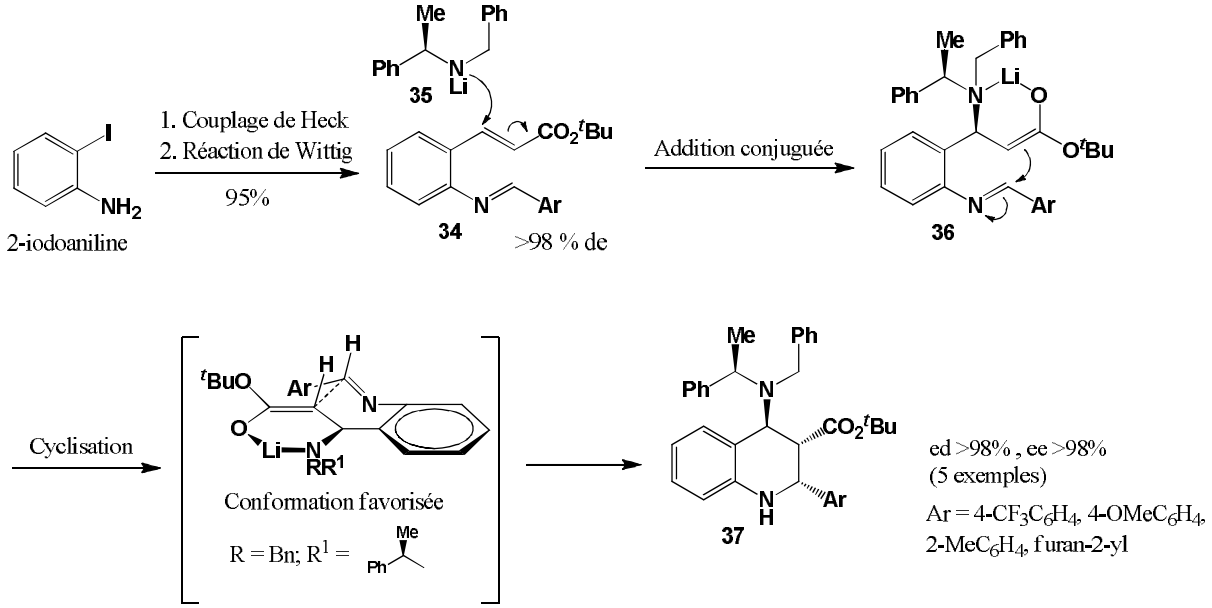


Schéma 3: Séquence addition conjuguée-cyclisation

Pour notre part, au cours d'une étude de la synthèse du Sumanirole **1**, nous nous sommes penchés sur une nouvelle approche rétrosynthétique dans laquelle l'époxydation d'une 1,2 dihydroquinoléine chirale pouvait être effectuée de manière diastéréosélective (Schéma 4) afin d'introduire un groupement aminé en C_3 du noyau quinoléique.

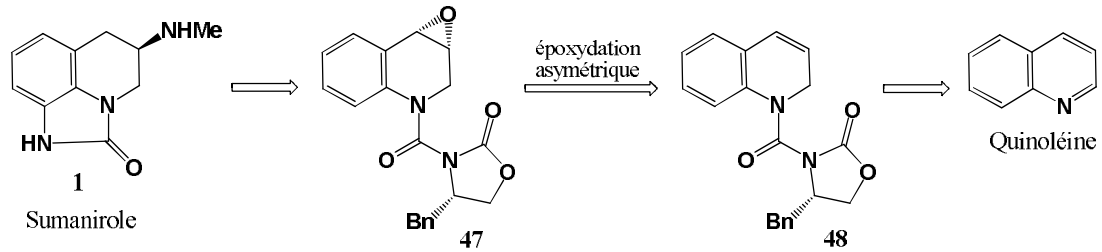


Schéma 4

[10] S. G. Davies, N. Mujtaba, P. M. Roberts, A. D. Smith, J. E. Thomson, *Org. Lett.* **2009**, *9*, 1959.

La présence d'une entité 4-benzyloxazolidin-2-one-3-carbonyle en tant qu'auxiliaire de chiralité positionné sur l'atome d'azote d'une 1,2-dihydroquinoléine permet en effet de contrôler la stéréosélectivité de l'époxydation de la double liaison C_3-C_4. Même si celle-ci n'est pas très élevée, la sélectivité reste raisonnable (*rd* = 9/1) étant donnée la distance entre l'auxiliaire chiral et la double liaison réagissant (Schéma 5).

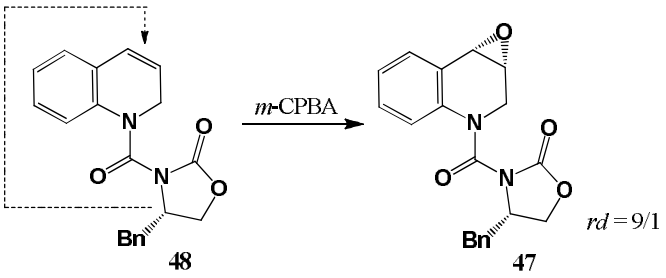


Schéma 5

I.2. Addition électrophile d'entités Br-X sur la 1,2-dihydroquinoléine 48

Dans le but de trouver une explication cohérente à la stéréosélectivité observée au cours de cette réaction d'époxydation, d'autres réactifs électrophiles comme le dibrome, le NBS ont été mis en réaction avec cette 1,2-dihydroquinoléine chirale.

II.2.1. Dibromation

A notre connaissance, très peu de publications décrivent la dihalogénation de 1,2-dihydroquinoléines. Les seuls travaux mentionnant des aspects stéréochimiques lors de l'addition sont rapportés par Willamson et Ward (Schéma 6).[11] Les auteurs mentionnent que la dichloration de la tétrahydroquinoléine **49** mène, avec un excellent rendement, à un adduit dichloré **50** de configuration relative *syn* compte tenu des constantes de couplages observées en RMN. La participation des doublets de l'atome d'oxygène du groupement trifluoroacétyle a été évoquée par les auteurs pour expliquer la stéréochimie relative *syn* entre les deux atomes de chlore.

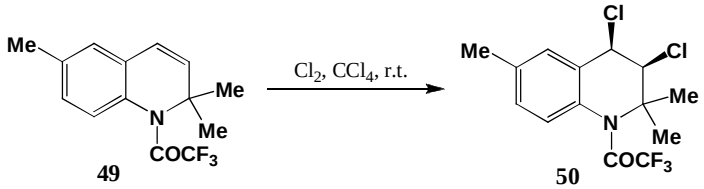


Schéma 6

[11] N. M. Williamson, A. D. Ward. *Tetrahedron*, **2004**, *61(1)*, 155-165.

Nous nous sommes donc, en toute logique, orientés tout d'abord vers la dibromation de la *N*-acyl-1,2-DHQ **48** chirale. Suivant les conditions expérimentales utilisées, nous avons observé un mélange de dérivés bromés à l'issue des différents essais effectués (Schéma 7 et Tableau 1).

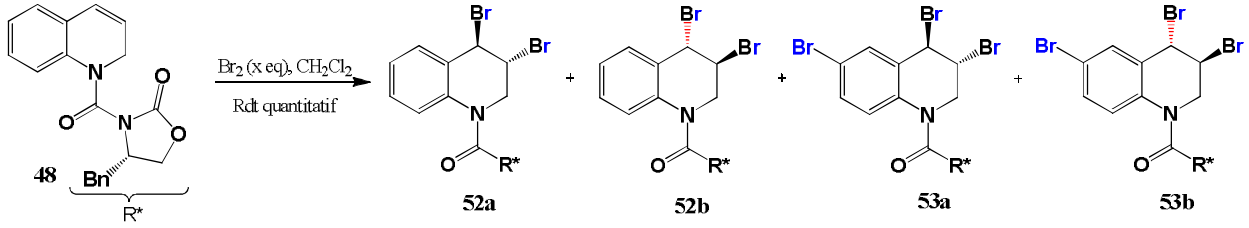


Schéma 7

Table 1: Bromation de la dihydro-1,2-quinoléine **48**

Essai	*Reactif*	*Equi.*	*Conditions*	*52a (%)*	*52b (%)*	*53a (%)*	*53b (%)*
1	Br_2	1.0	0 °C → t.a., 2 h	30.1	-	59.2	10.7
2	Br_2	3.0	0 °C → t.a., 2 h	-	-	89.3	10.7
3	Br_2	10.0	0 °C → t.a., 2 h	-	-	89.7	10.3
4	$(CH_3)_4NBr_3$	3.0	0 °C → t.a., 2 h	-	-	85	15
5*	Br_2	1.0	0 °C → t.a., 2 h	84.0	13,0	0	3.0
6*	Br_2	2.0	0 °C → t.a., 2 h	40.4	0.8	47.4	12.2
7*	Br_2	3.0	0 °C → t.a., 2 h	-	-	90.1	9.9
8	Br_2	1.0	-78 °C, 3 h	28.6	-	67.7	4.76
9*	Br_2	1.0	-78 °C, 3 h	94.6	5.4	-	-

Les ratios sont déterminés à partir des spectres RMN ^{1}H du mélange réactionnel brut.

(*): Br_2 a été dilué dans le CH_2Cl_2 (solution 1M) et additionné à une solution 0.2 M de **48** dans le CH_2Cl_2.

Deux conclusions principales peuvent être tirées à partir de ces expériences :

- La substitution de l'atome d'azote avec un groupement électroattracteur (acyloxazolidinone) n'est pas suffisante pour éviter une bromation excessive en position C_6 du noyau quinoléique. Ce problème peut facilement être évité en utilisant 1 seul équivalent de dibrome en solution (1M) dans le CH_2Cl_2.
- De relativement bonnes diastéréosélectivités en faveur des composés **52a** (ou **53a**) ont été observées. Effectuer la réaction en abaissant la température du milieu réactionnel ainsi qu'en utilisant une solution diluée de dibrome entraine une augmentation de la stéréosélectivité.

Concernant les configurations absolues des centres stéréogènes créés en C_3 et C_4, celles-ci ont été déterminées dans un premier temps sur les dérivés tribromés **53a** et **53b**. En RMN ^{1}H, les constantes de couplage ^3J H_3-H_4 des 4 composés s'avèrent proches de 0 Hz. L'équation de Karplus suggère qu'une telle valeur est observée lorsque l'angle dièdre H_3-C_3-C_4-H_4 est proche de 90°. L'utilisation de modèles moléculaires nous montre que cette valeur ne peut être atteinte que lorsque les 2 atomes de brome sont en position *trans*-diaxiale, comme l'ont confirmé les

structures aux rayons X des dérivés **53a** et **53b**. Ces résultats sont donc en contradiction avec ceux obtenus par Williamson et Ward (Schéma 6).

Les configurations absolues des centres C_3 and C_4 pour les composés **52a**, **52b**, **53a** et **53b** sont donc bien celles décrites dans le schéma 7. Contrairement à l'hypothèse de Willliamson et Ward, la réaction se déroulerait via la formation d'un pont bromonium **55** qui serait régio- et stéréo-sélectivement ouvert par l'approche de Br^- en C_4 pour mener aux adduits majoritaires **52a** et **53a**. La formation d'un carbocation benzylique intermédiaire **54** peut également être envisagée par ouverture du pont bromonium **55** (Schéma 8).

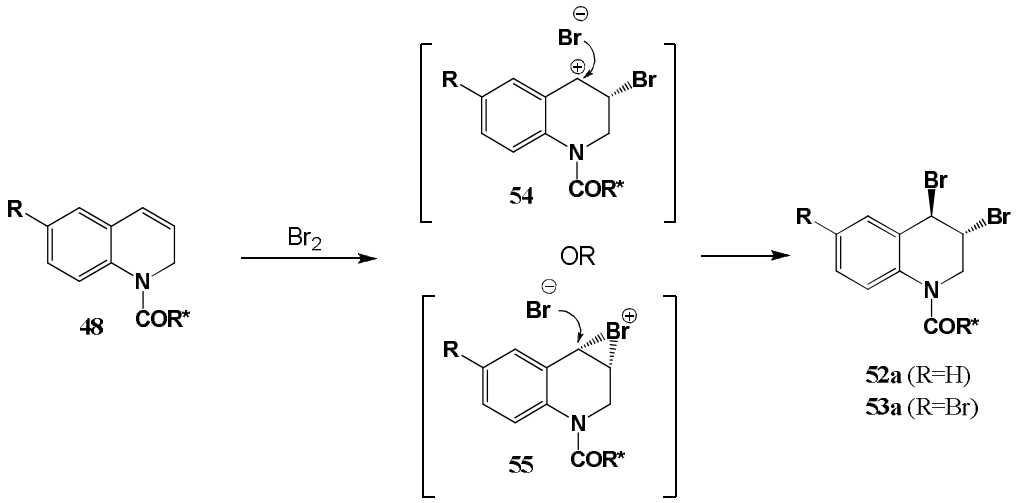


Schéma 8

Ce point sera discuté plus en détail plus loin dans la thèse, mais nous pouvons d'ores et déjà noter que la stéréochimie du bromonium **55** est identique à celle de l'époxyde majoritaire **47** isolé lors de l'époxydation de la dihydroquinoléine **48** à l'aide du *m*-CPBA.

I.2.2. Bromohydroxylation

Après avoir étudié la dibromation de la dihydroquinoléine chirale **48**, nous nous sommes intéressés à la bromohydroxylation. Là encore, les rares publications dans le domaine ne mentionnaient aucune information stéréochimique.

La bromohydroxylation a été effectuée par ajout de NBS à une solution de **48** dans un mélange THF/H_2O (1:1). Les différentes conditions opératoires employées nous ont permis de mettre en évidence quatre adduits dans des proportions variables (Schéma 9 et Tableau 2).

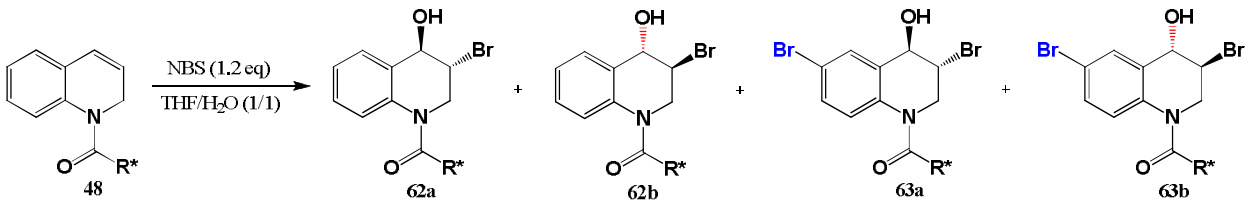


Schéma 9

Tableau 2

Essai	*NBS (éq.)*	*Conditions*	*62a (%)*	*62b (%)*	*63a (%)*	*63b (%)*	*Rdt[b] (%)*
1[a]	1.1	0 °C, 5 min → t.a., 2 h	73		27		70.6
2	1.1	0 °C, 1 h → t.a., 1 h	80.6	19.4			77.9

Les ratios sont déterminés à partir des spectres RMN ^{1}H du mélange réactionnel brut.
[(a)] ratio déterminé après chromatographie sur gel de silice; [(b)] rendement combiné en diastéréoisomères.

La prolongation du temps réactionnel à 0 °C permet facilement d'éviter la formation de composés dibromés **63a** et **63b**. Ces conditions permettent d'atteindre une sélectivité de 4:1 pour les composés **62a** et **62b**. Le diastéréoisomère majoritaire montrant une constante de couplage ^3J H_3-H_4 en RMN ^{1}H proche de 0 Hz suggère, comme dans le cas précédent, une stéréochimie relative *anti* entre l'atome de brome et le groupement hydroxyle. Cette stéréochimie a été confirmée par la formation non équivoque des époxydes **64** et **47** de stéréochimie connue, à partir du mélange de bromhydrines obtenu (Schéma 10).

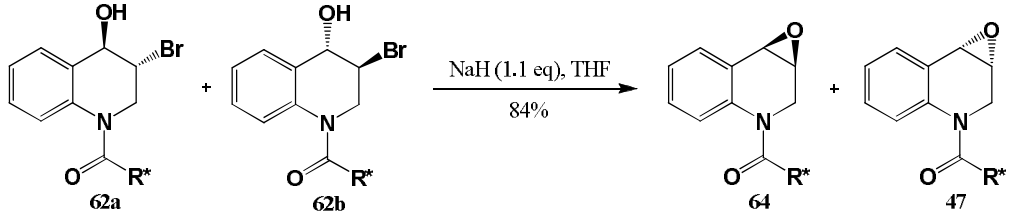


Schéma 10

I.2.3. Bromométhoxylation

Comme pour la bromohydroxylation, très peu de travaux mentionnent la bromométhoxylation de dérivés dihydroquinoléiques et aucun ne discute d'aspects stéréochimiques.

La bromométhoxylation de la 1,2-dihydroquinoléine **48** est effectuée dans le méthanol en présence d'un léger excès de NBS (Schéma 11). Un contrôle de la température du milieu réactionnel et du nombre d'équivalents de NBS permet d'éviter les réactions de sur-bromation.

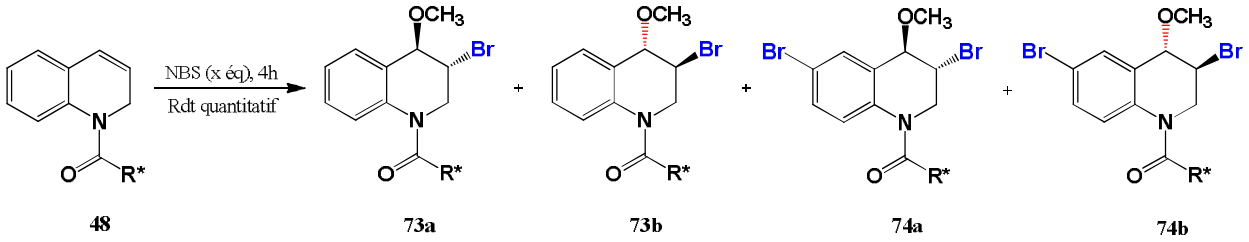


Schéma 11

Tableau 3

essai	*NBS (éq.)*	*Conditions*	*73a (%)*	*73b (%)*	*74a (%)*	*74b (%)*
1	1.1	0 °C, 1 h → t.a., 4 h	85	15	-	-
2	1.1	t.a., 4 h	86	14	-	-
3	3.0	t.a., 4 h	-	-	85	15

Les ratios sont déterminés à partir des spectres RMN ^{1}H du mélange réactionnel brut.

Les diastéréoisomères majoritaires **73a** et **74a** ont été purifiés par recristallisation

Un changement de conditions opératoires n'apporte pas de modification significative sur la stéréosélectivité de la réaction. L'observation de constantes de couplage ^3J H_3-H_4 proches de 2,4 Hz pour les différents diastéréoisomères majoritaires obtenus suggère, comme pour les cas précédents, un arrangement stéréochimique *anti* entre les groupements Br et méthoxy. Ceci a été confirmé par des analyses aux rayons X effectuées pour les dérivés **73a** et **74a**.

I.2.4. Bromoazidation

De nombreuses méthodes de synthèse de 1,2,3,4-THQs comportant un groupement aminé en C_4 ont été publiées et résumées dans la thèse. Dans la continuité de notre travail, nous nous proposons d'accéder à ce type de molécules à partir de la dihydroquinoléine **48** (Schéma 12), soit par :

a) Substitution nucléophile en C_4 sur le dérivé tribromé **53a**

b) Ouverture de l'époxyde **47** par un nucléophile azoté

c) Bromoamidation ou bromoazidation de la 1,2-dihydroquinoléine **48**

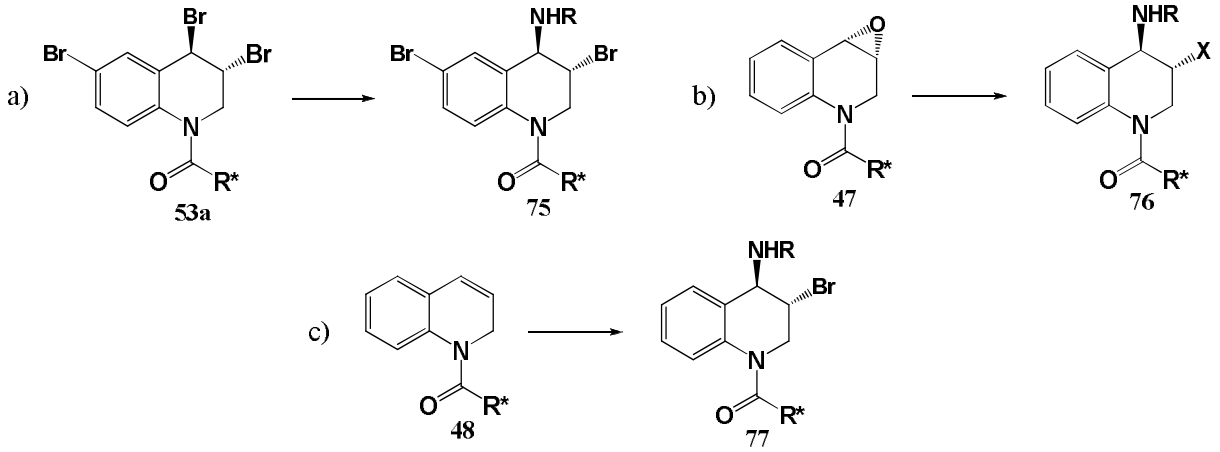
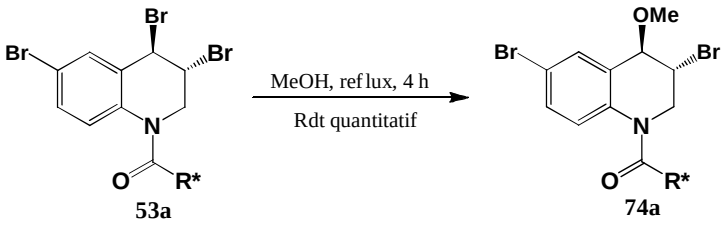


Schéma 12

*a) Substitution nucléophile en C_4 sur le dérivé tribromé **53a***

A partir du dérivé tribromé **53a**, il peut être facilement anticipé de par sa position benzylique que l'atome de brome en position C_4 soit plus nucléofuge que celui en C_3. En effet, celui-ci peut facilement être substitué par un groupement méthoxy au reflux du méthanol (Schéma 13).



53a **74a**

Schéma 13

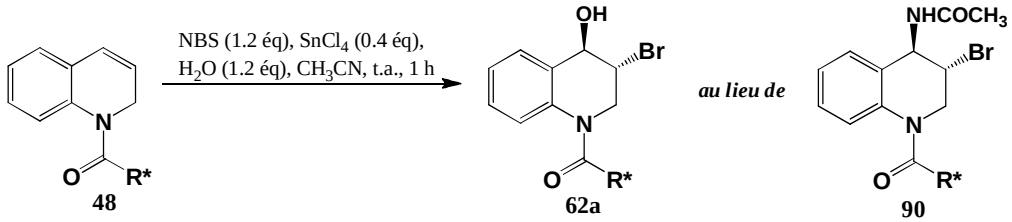
Malheureusement, ni l'utilisation d'ammoniac en solution dans l'éthanol à 50 °C, ni l'utilisation d'azoture de sodium dans le DMF n'ont permis d'isoler les dérivés tétrahydroquinoléiques attendus. Seuls les dérivés azotés de structure 1,2 dihydroquinoléique ont été observés, entrainant une perte de l'information stéréochimique en C_3 et C_4. Cette voie a donc été abandonnée.

*b) Ouverture de l'époxyde **47** par un nucléophile azoté*

Les différents essais d'ouverture de l'époxyde **47** en présence d'ammoniac, de benzylamine ou d'azoture de sodium n'ont mené qu'à des produits de dégradation. Une coupure de l'auxiliaire chiral a été observée lors de l'utilisation d'azoture de sodium.

*c) Bromoamidation et bromoazidation de la 1,2-dihydroquinoléine **48***

L'utilisation des conditions de Corey[12] pour former le bromoamide **90** a conduit principalement à la formation de la bromhydrine **62a** obtenue précédemment au cours des réactions de bromohydroxylation (Schéma 14).



48 **62a** **90**

Schéma 14

[12] (a) Y. –Y. Yeung, S. Hong, E. J. Corey. *J. Am. Chem. Soc.* **2006**, *128*, 6310-6311. (b) Y. –Y. Yeung, S. Hong, E. J. Corey. *J. Am. Chem. Soc.* **2006**, *128*, 9644-9645.

Cet échec nous a conduits à envisager la bromoazidation de **48** sous l'action de NBS et $TMSN_3$ en présence d'un acide de Lewis (Schéma 15).

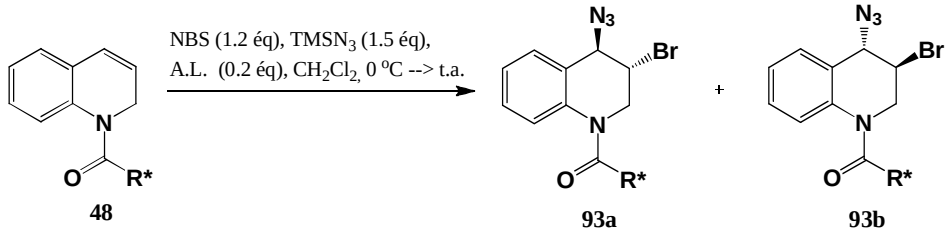


Schéma 15

Les meilleurs résultats sont reportés dans le tableau 4.

Tableau 4

Essai	***Conditions***	***93a (%)***	***93b (%)***	***Rdt(%)***
1	$Zn(OTf)_2$, 12 h	82	18	89
2	$Sm(OTf)_3$, 12 h	83	17	99
3	48 h	72	28	80

Les ratios sont déterminés à partir des spectres RMN ^1H du mélange réactionnel brut.

Le diastéréoisomère majoritaire **93a** a été purifié par recristallisation

Ces différents résultats permettent de conclure que la nature de l'acide de Lewis employé influe peu sur la stéréosélectivité de la réaction. Par contre, l'absence d'acide de Lewis ralentit fortement le cours de la réaction (essai 3). Le diastéréoisomère majoritaire **93a** à pu être isolé par cristallisation et sa stéréochimie a pu être déterminée sans ambiguïté par une analyse par diffraction aux rayons X. Une nouvelle fois, la valeur de la constante de couplage ^3J H_3-H_4 (1,7 Hz) pour les deux diastéréoisomères suggère un arrangement *trans*-diaxial des groupements Br et N_3, ceci ayant bien été confirmé sur le cliché aux rayons X de **93a**.

Pour achever l'introduction de la fonction amine en position C_4, il s'avère nécessaire de réduire la fonction azoture. Cette réduction est effectuée par hydrogénation catalysée au Pd/C en présence d'Ac_2O afin de piéger l'amine au fur et à mesure de sa formation (schéma 16). Effectuer la réaction sans anhydride acétique entraîne une dégradation du milieu réactionnel.

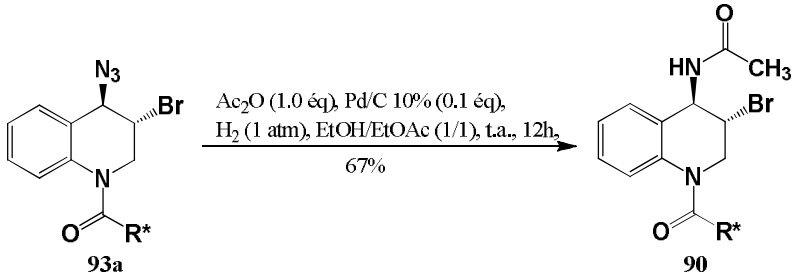


Schéma 16

En résumé, nous avons donc montré qu'outre l'époxydation, nous pouvions procéder à des réactions de bromation, bromohydroxylation, bromométhoxylation et bromoazidation avec des stéréosélectivités comparables à celle obtenue initialement lors de l'étape d'époxydation de la 1,2-dihydroquinoléine **48** (diastéréosélectivité de 80:20 à 95:5 – tableau 5) pour mener à des adduits de configuration relative *anti* (Schéma 17). Il est intéressant de noter que la formation de ces adduits passe très certainement par l'ouverture du même intermédiaire bromonium.

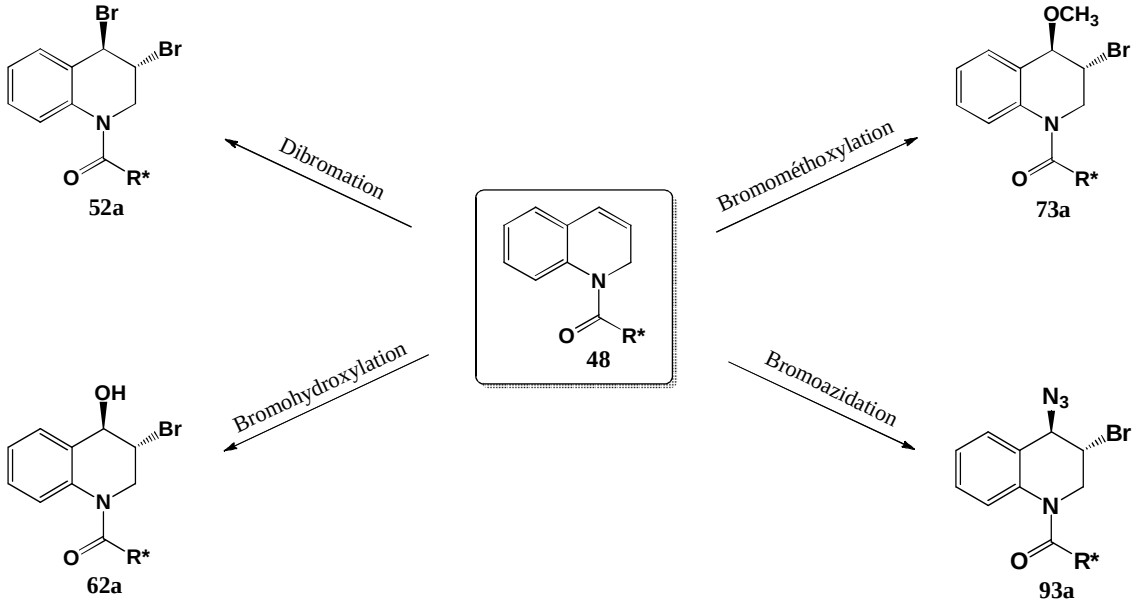
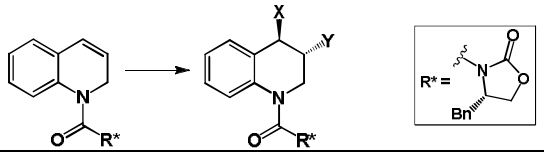


Schéma 17

Tableau 5



Essai	***Réactif***	***Conditions***	***X***	***Y***	***Rdt (%)***	***Ratio***
1	Br_2	Br_2 (1.0 éq), CH_2Cl_2, -78 °C, 3 h,	Br	Br	99	95/5
2	Id.	$(CH_3)_4NBr_3$ (3.0 éq), CH_2Cl_2, 0 °C → t.a., 2 h	Br	Br	99	85/15
3	Aq. NBS	NBS (1.1 éq), THF/H_2O (1/1), 0 °C, 1 h → t.a., 1 h	OH	Br	78	81/19
4	NBS/MeOH	NBS (1.1 éq), MeOH, t.a., 4 h	OCH_3	Br	99	86/14
5	NBS/$TMSN_3$	NBS (1.2 éq), $TMSN_3$ (1.5 eq), $Sm(OTf)_3$ (0.2 éq), CH_2Cl_2, 0 °C → t.a., 12 h	N_3	Br	97	83/17

Avant d'aborder en détail le mécanisme de ces additions, il apparaît nécessaire d'obtenir des informations sur la conformation préférentielle de l'auxiliaire chiral vis à vis du noyau quinoléique ainsi que sur la nature des éléments présents sur l'auxiliaire chiral permettant d'atteindre de telles sélectivités.

I.3. Aperçu mécanistique de l'addition électrophile sur la 1,2-dihydroquinoléine 48.

Nous avons précédemment montré que la 1,2-dihydroquinoléine **48** réagissait avec différents agents électrophiles de type BrX pour donner les adduits correspondant avec des diastéréosélectivités allant de 80:20 à 95:5. Deux points importants peuvent être soulignés à ce stade de l'étude :

- Les adduits majoritaires ou minoritaires sont tous des adduits de configuration relative *anti*.
- La configuration absolue du nouveau centre stéréogène formé en C_3 peut être interprétée par la formation du bromonium intermédiaire **55** qui résulte de l'approche de Br_2 par la face inférieure de la double liaison C_3-C_4 (Schéma 18).

  Nous pouvons aussi rappeler que:

  + l'époxydation de **48** par le *m*-CPBA permet d'obtenir diastéréosélectivement l'époxyde **47** qui possède la même stéréochimie que le bromonium **55** proposé.

  + La formation d'adduits *anti* exclue l'assistance du carbonyle exocyclique dans l'ouverture du bromonium comme cela avait été avancé par Williamson et Ward[11] lors de leurs essais de dihalogénation (cf. schéma 6).

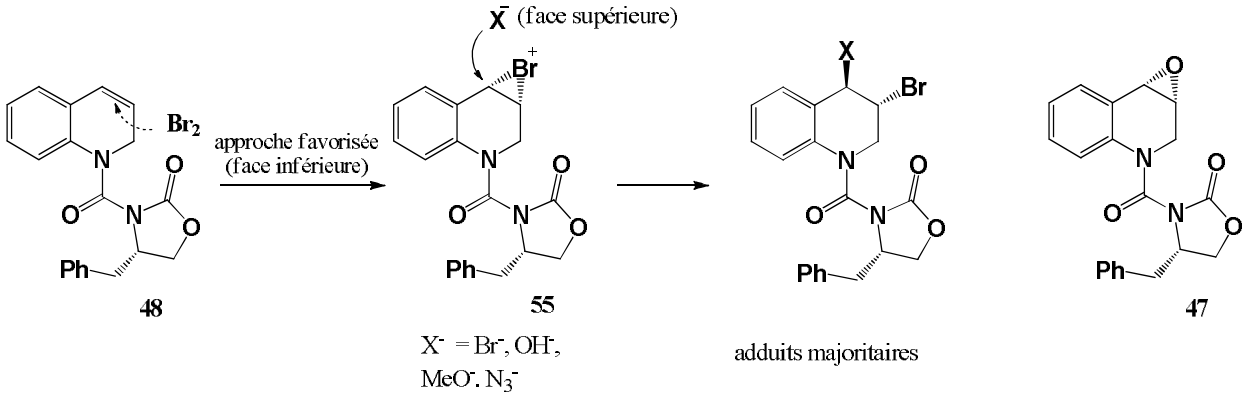
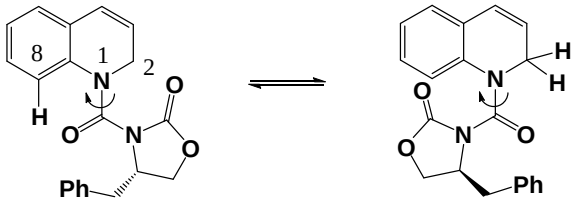


Schéma 18

Afin de comprendre l'origine de la diastéréosélectivité au cours de ces réactions, il est nécessaire de répondre à la question : *pourquoi le dibrome approche par la face inférieure de la double liaison réagissant?*

Tout d'abord, il est important de noter que la 1,2-dihydroquinoléine présente une forte mobilité conformationnelle autour des liaisons N_1-CO et CO-N (de l'oxazolidinone). En l'absence d'acide de Lewis et pour des raisons de répulsion des moments dipolaires, la partie N-acyloxazolidinone peut se positionner suivant les modèles représentés sur le schéma 19. Seule la rotation autour de la liaison N_1-CO peut donc être prise en considération et mener à deux conformations préférentielles **48 Cf1** et **48 Cf2**, les deux cycles quinoléine et oxazolidinone résidant dans des plans différents pour minimiser les interactions stériques avec les protons H_2 et H_8.



48 Cf1 **48** Cf2

Schéma 19

Ceci étant, ces conformations montrent toujours un certain éloignement entre le centre stéréogène et la double liaison réagissant et n'expliquent pas la raison de l'approche préférentielle de Br_2 par la face inférieure.

Une analyse par diffraction aux rayons X de **48** nous a montré que la structure, à l'état solide, adoptait la conformation **48 Cf1** (figure 3). Cette structure nous a également permis de mettre en évidence une légère pyramidalisation de l'atome d'azote du noyau quinoléine, le doublet de l'atome d'azote pointant vers la face supérieure, ainsi que le positionnement d'un des protons H_2 en position quasi-axiale.

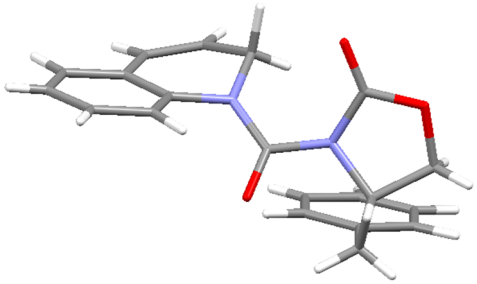
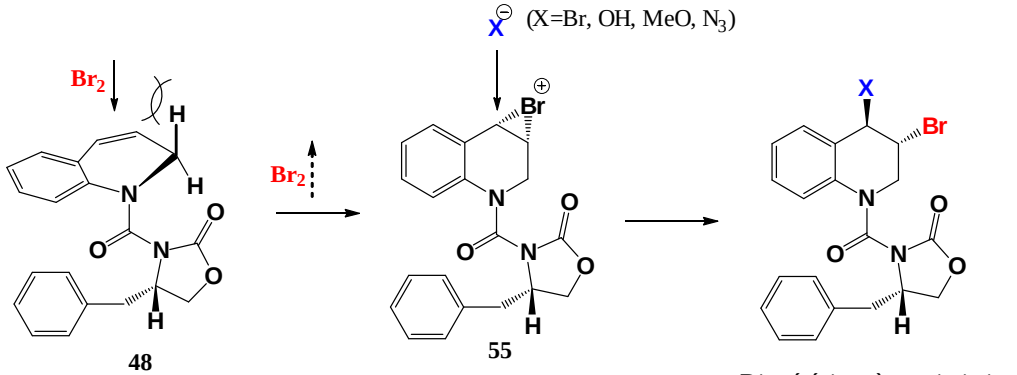


Figure 3

Ce proton en position quasi-axiale pourrait éventuellement gêner l'approche du dibrome par la face supérieure et ainsi favoriser son approche par la face inférieure. En d'autres termes, l'information stéréochimique présente sur l'oxazolidinone serait transmise à la double liaison C_3-C_4 par l'intermédiaire de simples contraintes conformationnelles (Schéma 20).



48 **55**

Approche face inférieure (Br_2)

Diastéréoisomère majoritaire

Schéma 20

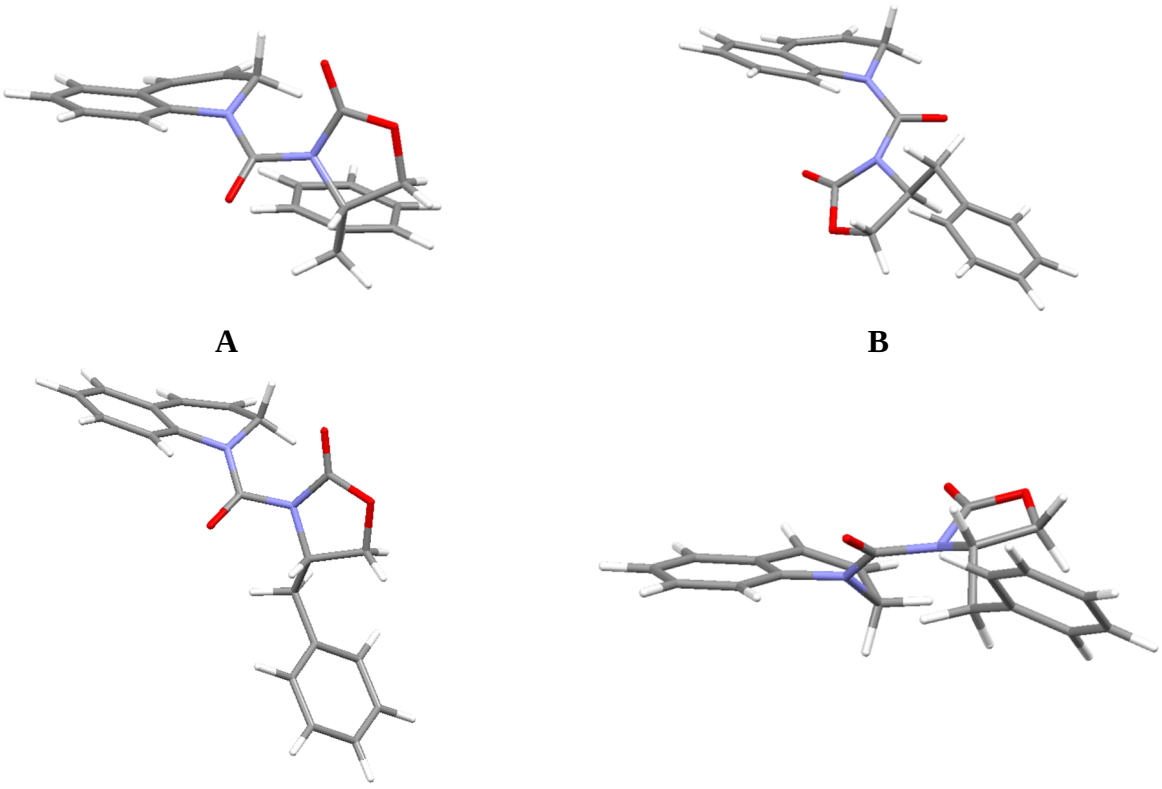
Afin d'identifier les conformations les plus probables en solution ainsi que la géométrie adoptée par l'état de transition, nous avons entrepris différents calculs théoriques.

I.3.1. Calculs théoriques

Pour ces calculs, nous avons privilégié le programme Gaussien et sélectionné la fonction M06-2X.

I.3.1.1. Analyse conformationnelle des réactants

Une étude a tout d'abord été menée pour identifier les conformations préférentielles adoptées par le substrat en solution (CH_2Cl_2) et quatre minima ont été identifiés avec les valeurs relatives d'énergies libres suivantes (G in kcal.mol^{-1}): 0,00 (A), 0,47 (B), 0,90 (C) and 2,69 (D) (Figure 4).



A **B**

C **D**

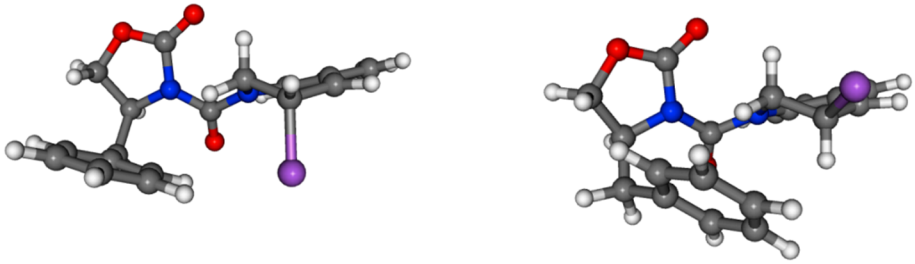
Figure 4

Ces calculs permettent de montrer que le conformère A possédant une géométrie proche de celle observée sur la structure aux rayons X pourrait dominer en phase liquide. En effet, la distribution selon Boltzmann serait de 60% pour le conformère A et 27% et 13% pour les conformères B et C, respectivement.

Il est intéressant de noter que pour les conformères A, B et C un atome d'hydrogène H_2 se retrouve dans une orientation quasi-axiale.

I.3.1.2. Identification de l'état de transition

Pour chacun des 3 conformères A, B et C, nous avons cherché les 2 états de transition correspondant à l'attaque de Br_2 par la face inférieure et la face supérieure. Nous avons rapidement constaté que la formation d'un pont bromonium entrainait des tensions au niveau de l'état de transition et que l'ion Br^+ s'additionnait plutôt en C_3. De plus, l'intermédiaire cationique **A-1** correspondant à l'approche de Br^+ par la face inférieure s'avère plus stable de 2,65 $kcal.mol^{-1}$ que l'intermédiaire cationique **A-2** correspondant à une approche de Br^+ par la face supérieure (figure 5).



A-1 **A-2**

Figure 5: Intermédiaires cationiques résultant de l'attaque de Br^+

Nous avons ensuite analysé les états de transitions tenant compte à la fois de la rupture de la liaison Br-Br et de la création du lien C-Br. Une fois encore les résultats ont permis de montrer que la rupture du lien Br-Br et la création du lien C-Br était plus favorisées sur la face inférieure avec une différence d'énergie de 4,40 $kcal.mol^{-1}$, comme nous avions pu le constater expérimentalement. Les calculs effectués à partir des conformations B et C ont donné des résultats analogues à ceux obtenus à partir du conformère A. Nous pouvons donc en conclure que l'atome d'hydrogène H_2 en position axiale guide bien la réaction en gênant l'attaque du Br^+ sur la face supérieure, comme nous avions pu l'imaginer au regard de la structure obtenue par diffraction aux rayons X de la dihydroquinoléine **48**.

I.4. Détermination des éléments structuraux de l'auxiliaire chiral nécessaires à l'obtention d'une bonne diastéréosélectivité.

Dans le but d'identifier les éléments structuraux de l'auxiliaire chiral indispensables à l'obtention de bonnes diastéréosélectivités, nous avons étudié l'addition de NBS dans le méthanol sur diverses dihydroquinoléines comportant principalement des variations structurales sur la partie oxazolidinone. Nous souhaitions évaluer:

- l'influence stérique ou stéréoélectronique du groupement benzyle sur l'oxazolidinone.
- l'importance du cycle oxazolidinone
- la probable influence électronique que provoquerait un substituant électrodonneur ou électroattracteur en position C_6 du cycle dihydroquinoléique.

Pour cette étude les dihydroquinoléines **48a** à **48g** (figure 6) ont été synthétisées et engagées dans une réaction de bromométhoxylation.

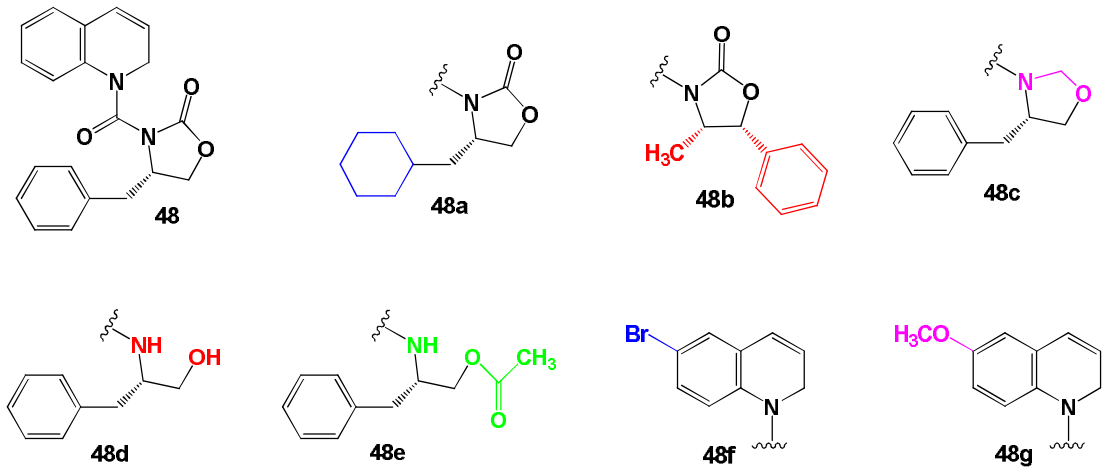
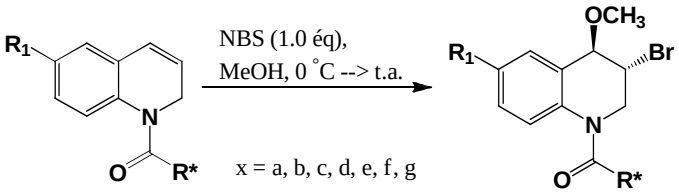


Figure 6

Tous les résultats de bromométhoxylation sont reportés dans le tableau 6.

Tableau 6: addition électrophile de NBS dans le MeOH sur les 1,2-dihydroquinoléines **48x**



48x **102x**

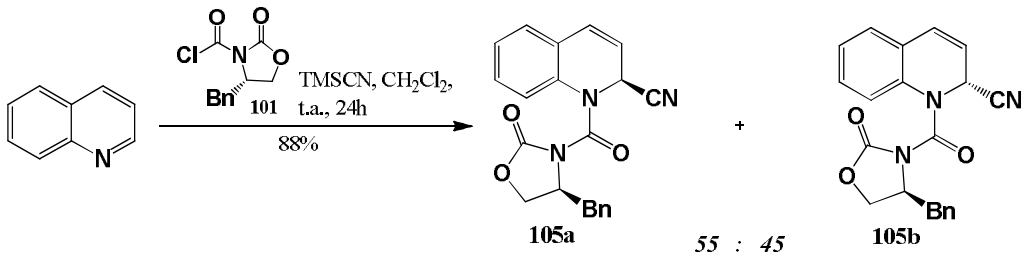
Essai	*Substrat*	*Produit*	*R_1*	*t (h)*	*Rdt (%)*	*rd*
1	**48**	**73a**	H	4	93	86/14
2	**48a**	**102a**	H	4	79	92/08
3	**48b**	**102b**	H	4	90	75/25
4	**48c**	**102c**	H	2	72	82/18
5	**48d**	**102d**	H	48	59	55/45
6	**48e**	**102e**	H	6	92	63/37
7	**48f**	**102f**	Br	3	71	86/14
8	**48g**	**102g**	OCH_3	2	80	84/16

Les configurations des composés **102x** ont été déterminées soit par diffraction aux rayons X d'adduits majoritaires ou minoritaires, soit par synthèse non équivoque de certains d'entre eux à partir de composés de stéréochimie connue suivie d'une comparaison des spectres RMN ^{1}H et ^{13}C.

A partir de ces résultats, nous pouvons affirmer que la présence du cycle à 5 chaînons (oxazolidine ou oxazolidinone) ainsi que la taille du substituant présent en position C'4 paraissent indispensables à l'observation de bonne diastéréosélectivités lors de cette réaction d'addition électrophile ; l'effet stéréoélectronique (empilement π) du groupement benzyle n'a pas montré d'influence significative sur la stéréosélectivité de la réaction.

I.5. Addition électrophile de composés de type BrX aux composés de type Reissert 105a and 105b

Comme nous avons pu conclure précédemment, la présence de l'oxazolidinone chirale sur la structure dihydroquinoléique **48**, entraînerait l'orientation quasi-axiale d'un proton en position C_2 défavorisant l'attaque du brome par la face supérieure de la double liaison réagissant. Le remplacement de ce proton par un groupement plus encombrant pourrait ne pas changer l'équilibre conformationnel et induire une meilleure diastéréosélectivité lors des réactions d'additions électrophiles de dérivés de type Br-X. Afin de vérifier cette hypothèse nous avons décidé d'effectuer ces additions électrophiles sur les composés de type Reissert **105a** et **105b** comportant un groupement CN en position C_2 ; ceux-ci ayant été étudiés préalablement au laboratoire et étant facilement accessibles à partir de la quinoléine (schéma 21). [13]



Scheme 21

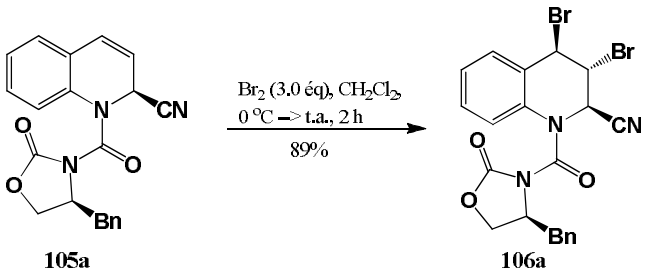
Les structures aux rayons X des deux diastéréoisomères **105a** et **105b** facilement séparables par chromatographie sur gel de silice montrent pour les deux composés un positionnement quasi-axial du groupement CN mais une conformation de type Cf2.

L'addition électrophile de Br_2, l'addition de NBS dans le méthanol ainsi que l'addition de $TMSN_3$ ont été effectuées sur chacun des diastéréoisomères **105a** et **105b**.

I.5.1. Dibromation

Le premier essai de dibromation en présence de 3 équivalents de Br_2, a permis d'atteindre une parfaite diastéréosélectivité en faveur du diastéréoisomère **106a** (Schéma 22). La valeur de la constante de couplage ^3J H_3-H_4 en RMN ^{1}H (J = 2,4 Hz) suggère une stéréochimie relative *anti* entre les deux atomes de brome.

[13] M. Pauvert, S. Collet, M-J. Bertrand, A. Guingant, M. Evain, *Tetrahedron Lett*. **2005**, *46*, 2983.



Scheme 22

Dans les mêmes conditions, le diastéréoisomère **105b** conduit à un seul diastéroisomère qui, caractérisé par diffraction aux rayons X, a confirmé d'une part la stéréochimie relative *anti* entre les deux atomes de brome, mais également la stéréochimie relative *anti* entre le groupement CN et l'atome de brome en C_3. Ce résultat peut être expliqué par l'attaque électrophile du brome par la face opposée à celle comportant le groupement CN.

I.5.2. Bromométhoxylation

La bromométhoxylation du dérivé **105a** a été effectuée en présence d'un équivalent de NBS dans le méthanol (Schéma 23). Comme précédemment la réaction s'est révélée totalement diastéréosélective, menant à l'adduit **107** caractérisé sans ambiguïté par diffraction aux rayons X.

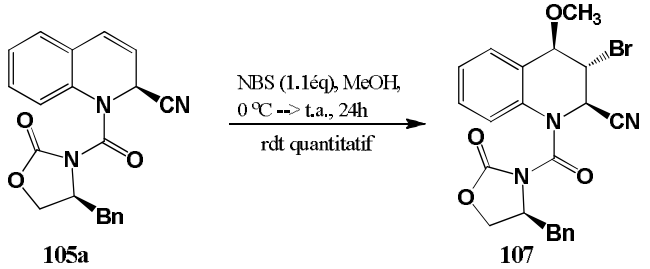
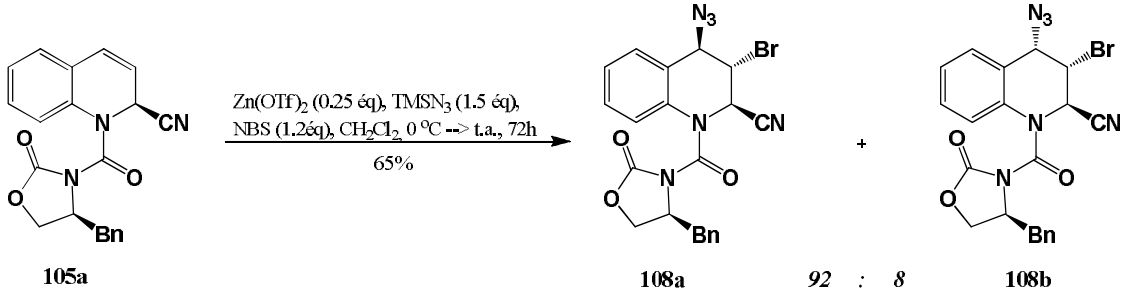


Schéma 23

I.5.3. Bromoazidation

L'adduit de Reissert **105a** a ensuite été soumis à un mélange de NBS et $TMSN_3$ en présence de triflate de Zinc ($ZnOTf_2$) (Schéma 24). Dans ce cas, un mélange de diastéréoisomères **108a** et **108b** a été obtenu (rd 92 :8) La moins bonne diastéréosélectivité peut être due à la présence de l'acide de Lewis qui perturbe l'équilibre conformationnel du dérivé de Reissert de départ.



Scheme 24

En conclusion, ces derniers résultats montrent qu'un substituant plus encombrant en position 2 du noyau 1,2-dihydroquinoléique influence davantage la diastéréosélectivité lors de l'addition *trans* de dérivés de type BrX sur la double liaison C_3-C_4. Ces résultats confirment également que le substituant en C_2 orienté de façon quasi-axiale relaie l'information stéréochimique apportée par l'auxiliaire chiral fixé sur l'atome d'azote. Dans le chapitre suivant, nous tenterons de profiter de ces résultats pour développer la synthèse de produits naturels.

CHAPITRE II : Synthèse d'alcaloïdes en série 1,2,3,4-tétrahydroquinoléine

II.1 Synthèse totale du Sumanirole

II.1.1 Introduction

La maladie de Parkinson correspond à la deuxième maladie neurodégénérative la plus répandue après la maladie d'Alzheimer. Elle touche environ 0,3 % de la population des pays industrialisés. Elle touche principalement les personnes âgées avec 1% des individus de plus de 60 ans et 4% des individus de plus de 80 ans. [14] La disparition des neurones dopaminergiques qui fabriquent et utilisent la dopamine, neurotransmetteur impliqué dans le contrôle des mouvements, est la principale cause d'apparition de la maladie de Parkinson. Il n'y a, à l'heure actuelle, aucun traitement permettant de combattre cette maladie. Certains traitements existent pour atténuer les effets de la maladie, mais n'ont aucun effet sur la progression de la maladie. Le traitement le plus connu consiste en l'utilisation de *L*-Dopa, précurseur des neurotransmetteurs tels que la dopamine, la norépinéphrine et l'épinéphrine (Figure 7). L'inconvénient de ce traitement est qu'il baisse en efficacité après quelques années.

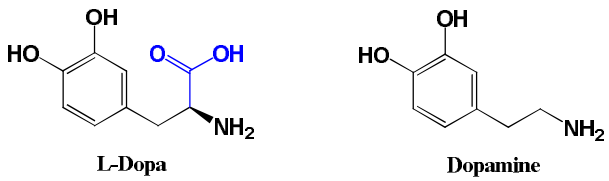


Figure 7

Une méthode alternative de traitement consiste à utiliser des agonistes de la dopamine qui se fixent sur certains récepteurs D2 post-synaptiques. Le plus connu d'entre eux est l'apomorphine. Ces agonistes sont moins efficaces que la L-Dopa, mais ont moins d'effets délétères sur le long terme. Néanmoins, ils provoquent de nombreux effets secondaires tels que nausées, somnolence, hypotension orthostatique. Diverses études de relations structure-activité ont montré que le motif rigide phényléthylamine présent dans la structure de l'apomorphine, ainsi que le motif rigide pyrroéthylamine présent dans le pergolide et l'apocriptine sont à l'origine de l'activité dopaminergique de ces molécules.

[14] L. M. de Lau, M. M. Breteler. *Lancet Neurol.* **2006**, *5(6)*, 525–35

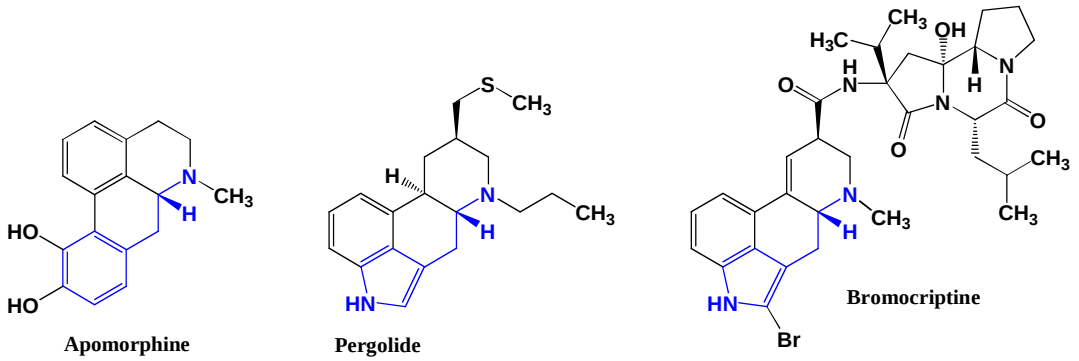
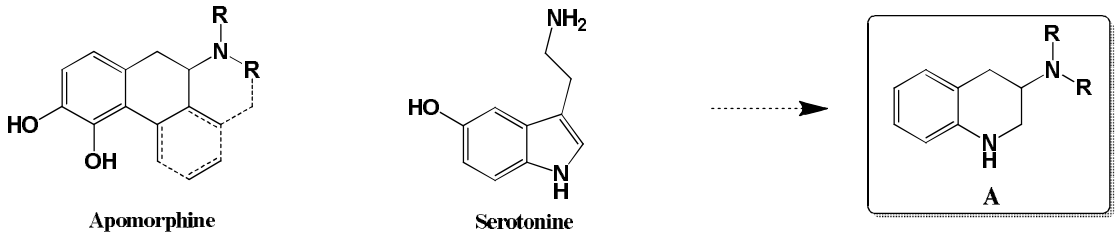


Figure 8

A partir d'études effectuées sur l'apomorphine ainsi que sur la sérotonine, neuromodulateur incontournable du système nerveux central, Moon[2a,15] et al. ont décidé de synthétiser des analogues non-hydroxylés de tétrahydronaphtylamines possédant un hétéroatome sur le cycle tétraline (Scheme 25).



Scheme 25

Divers analogues tricycliques ont alors été synthétisés puis testés pour leur activité dopaminergique.

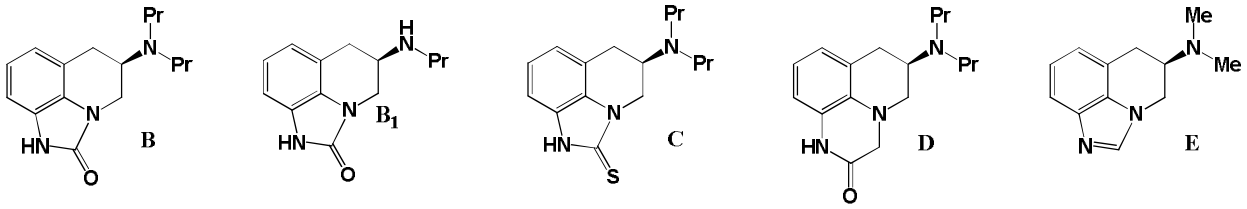
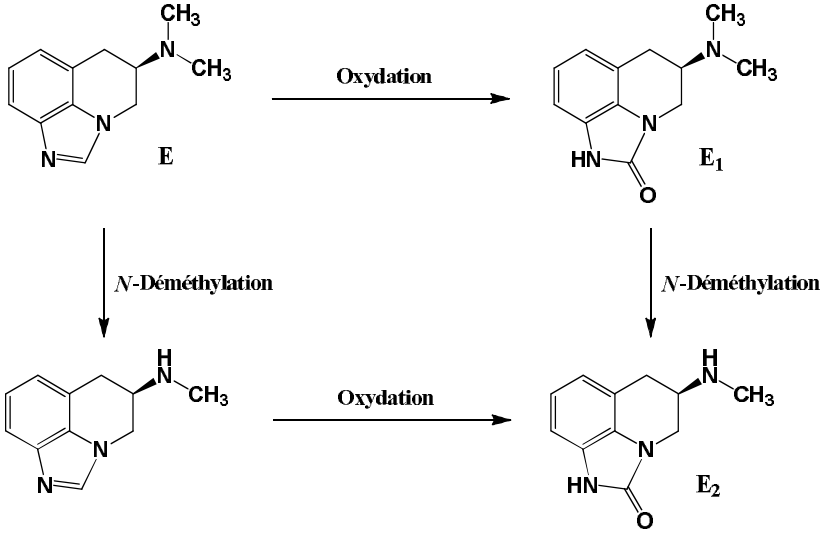


Figure 9

Tous ces composés possèdent une activité dopaminergique significative in vivo, Les composés **B** et **E** étant les plus prometteurs En 1993, Moon a montré que le composé **B** était métabolisé en composé **B1**, meilleur candidat pour le développement d'une drogue pour des raisons de biodisponibilité.

[15] M. W. Moon, J. K. Morris, R. F. Heier, C. G. Chidester, W. E. Hoffmann, M. F. Piercey, J. S. Althaus, P. F. Von Voigtlander, D. L. Evans, L. M. Figur, R. A. Lahti. *J. Med. Chem.* **1992**, *35*, 1076-1092.

Après d'autres investigations, il est apparu que le composé **E** était métabolisé en dérivés imidazoquinoléine **E1** et **E2** (Schéma 26), chacun possédant de bonnes activités dopaminergiques sur récepteurs D2.



Scheme 26

Parmi ces composés, seul le composé **E2** possède de bonnes activités *in vitro* et *in vivo*. Ce composé, le Sumanirole, a ensuite fait l'objet de nombreuses études biologiques et synthétiques dans le but de préparer une molécule optiquement active avec le meilleur rendement global. En juin 2004, la société Pfizer, qui possède le brevet d'application de cette molécule, décide soudainement d'arrêter l'étude clinique en phase III. Les raisons officielles invoquées étaient que le Sumanirole ne se distinguait pas suffisamment des autres drogues déjà disponibles sur le marché.

II.1.2 Revue bibliographique

Avant de présenter notre propre synthèse du Sumanirole, nous présentons ici une vue générale des synthèses déjà décrites dans la littérature. Ce bref résumé présente uniquement les synthèses non-racémiques de la molécule. En s'attachant simplement au mode d'introduction de la chiralité, les différentes synthèses peuvent être classées dans 3 groupes distincts (Figure 10).

- Dédoublement d'un mélange racémique à mi-parcours à l'aide de l'acide *L*-tartrique ou du (*R*)-naproxen. [16,17]

- Synthèse au départ d'un substrat chiral optiquement actif (*D*-Phénylalanine).[7]

- Recours à une époxydation de Jacobsen ou d'une dihydroxylation de Sharpless asymétriques. [18,19]

[16] M .W. Moon, J. K. Morris, R. F. Heier, C. G. Chidester, W. E. Hoffmann, M. F. Piercey, J. S. Althaus, P. F. Von Voigtlander, D. L. Evans, L. M. Figur, R. A. Lahti. *J. Med. Chem.* **1992**, *35*, 1076.
[17] P. G. M. Wuts. *Curr. Opin. Drug Discov. Devel.* **1999**, *2*, 557.

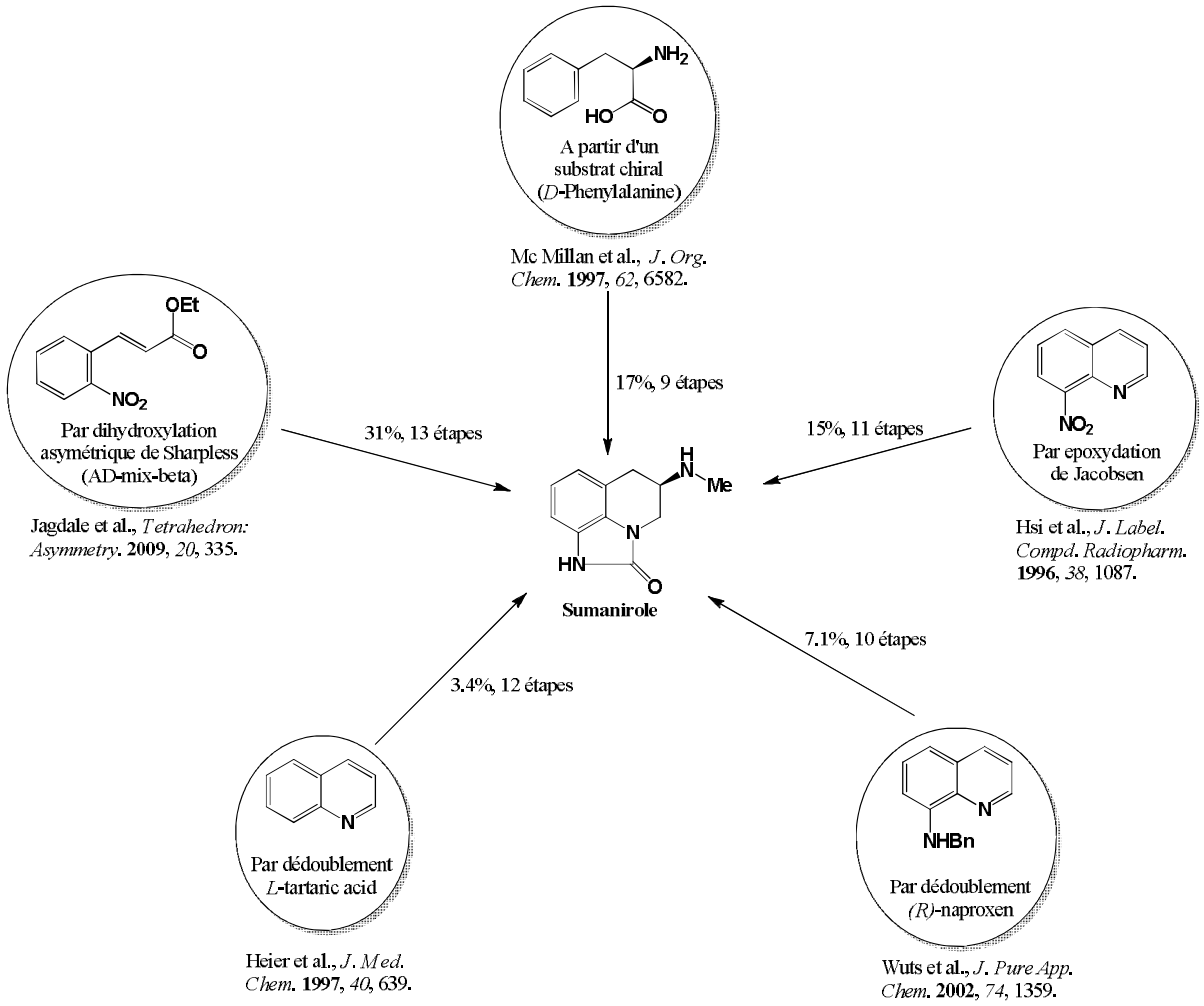


Figure 10

II.1.3 Résultats préliminaires obtenus au laboratoire

Une étude préalable a été effectuée au laboratoire utilisant les composés **105a** et **105b** comme substrats de départ éventuels (Schéma 27).[13] Nous pensions que la présence du groupement cyano permettrait de contrôler la stéréosélectivité de la réaction d'époxydation de la double liaison en C3-C4 et qu'il pourrait ensuite être éliminé tel quel ou après une transformation en dérivé carboxylique, en fin de synthèse.

[18] R. F. Heier, M. W. Moon, W. T. Stolle, J. A. Easter, R. S. P. Hsi. *J. Label. Compd. Radiopharm.* **1996**, *38*, 1087-1098.
[19] (a) A. R. Jagdale, R. S. Reddy, A. Sudalai, *Tetrahedron: Asymmetry*. **2009**, *20*, 335. (b) A. R. Jagdale, R. S. Reddy, A. Sudalai, *Org. Lett.* **2009**, *11 (4)*, 803.

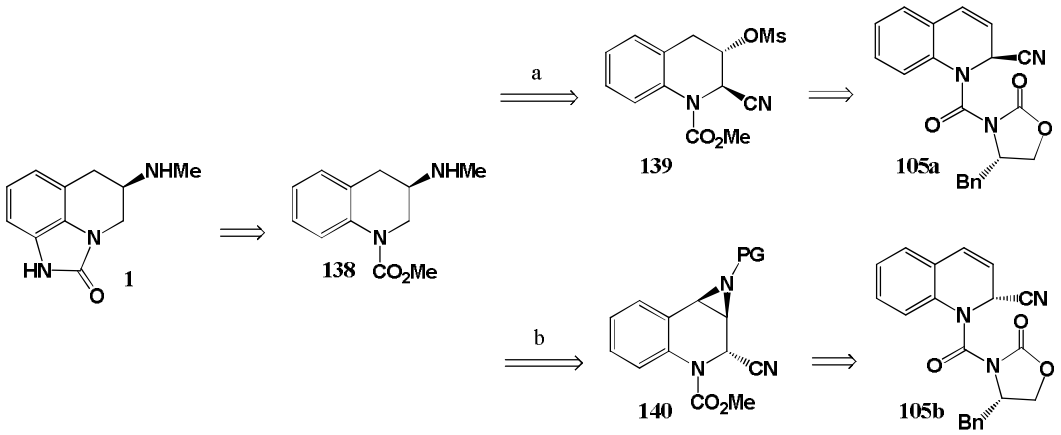


Schéma 27

II.1.3.1. *Préparation des adduits de type Reissert 105a et 105b*

Les adduits **105a** et **105b** ont été synthétisés au laboratoire en série optiquement active suivant une séquence de quatre étapes à partir de la *L*-phénylalanine, acide aminé commercial et bon marché (schéma 28).

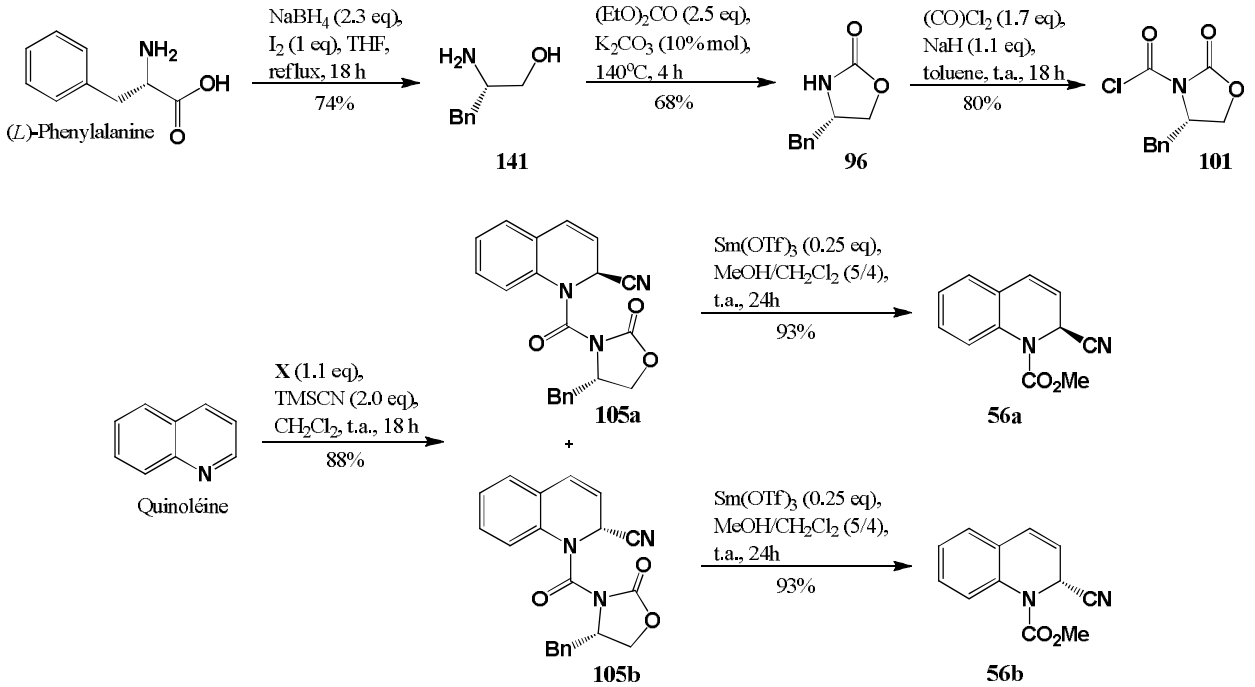


Schéma 28

Le phénylalaninol **141,** préparé par réduction de la *L*-phénylalanine en présence de borohydrure de sodium et de diode, est mis en réaction avec le carbonate de diéthyle pour mener à la (*S*)-4-benzyloxazolidin-2-one **96** avec un rendement global de 74%. La déprotonation de **96** par l'hydrure de sodium génère un nitranion qui est piégé par le phosgène pour mener au chlorure d'acide **101** avec un rendement de 80%. Après formation du sel d'acyl quinolinium par réaction du chlorure d'acide **101** avec la quinoléine, l'addition de cyanure de triméthylsilyle mène à un

mélange de diastéréoisomères **105a** et **105b** qui peuvent être séparés facilement par chromatographie sur gel de silice. Pour finir, l'auxiliaire chiral est facilement éliminé à l'aide de triflate de Samarium dans un mélange de dichlorométhane et de méthanol. L'auxiliaire chiral est récupéré sous sa forme oxazolidin-2one en fin de chromatographie.

II.1.3.2. *Introduction stéréosélective d'un groupement méthylamino en C3*

Toutes les réactions qui suivent ont été réalisées à partir d'un mélange racémique de **56**.

- Introduction indirecte par l'intermédiaire d'un époxyde

L'adduit de Reissert racémique **56** est mis en réaction avec l'acide métachloroperbenzoïque (*m*-CPBA) pour mener à l'époxyde **142** qui est ensuite réduit par hydrogénation catalysée au Pd/C pour mener à l'alcool **143** avec un rendement modéré (Schéma 29).

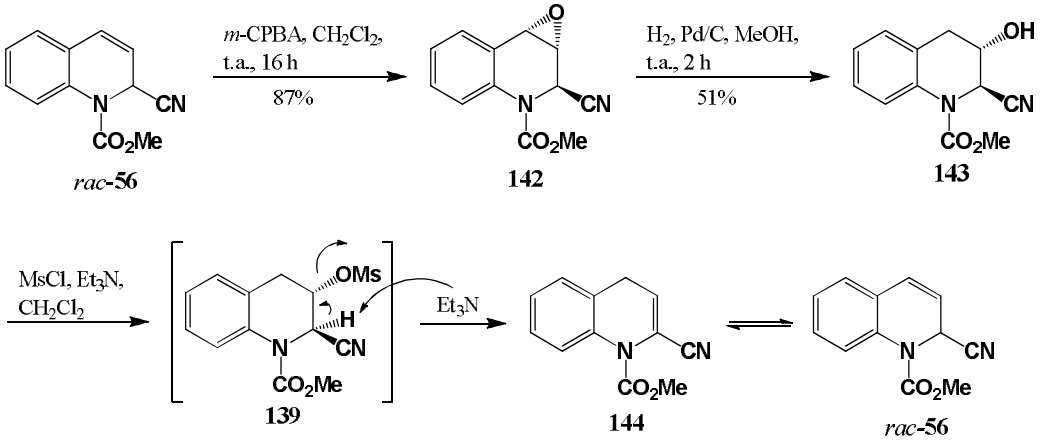


Schéma 29

La position *anti* de l'époxyde vis-à-vis du groupement nitrile a été déterminée par analogie avec un dérivé analogue (N-COPh au lieu de NCO_2Me) obtenu lors d'une étude préalable. L'hydroxynitrile **143** traité par le chlorure de méthanesulfonyle en présence de triéthylamine n'a pas mené au mésylate intermédiaire attendu, mais a mené directement aux dérivés **144** et **56** de départ, certainement dû à l'acidité du proton en α du groupement nitrile. Ce mauvais résultat nous a conduits à abandonner cette voie de synthèse.

- Stratégies basées par une introduction directe d'un cycle aziridine
  - ✓ Introduction d'un groupement amino en C3 *via* la formation d'une aziridine tosylée intermédiaire

L'adduit de Reissert racémique **56** est mis en réaction avec le *N*-tosyliminobenzyliodinane (PhINTs) en présence d'acétylacetonate de cuivre (II) ($Cu(acac)_2$) et permet d'obtenir l'aziridine **147** avec un rendement de 50 à 80% selon la pureté du PhINTs utilisé. Les meilleurs rendements ont été enregistrés lorsque 7 équivalents de PhINTs sont utilisés. L'aziridine **147** est ensuite réduite par hydrogénation en présence du catalyseur de Pearlman pour mener à l'amine tosylée **148** avec un rendement de 75% (Schéma 30).

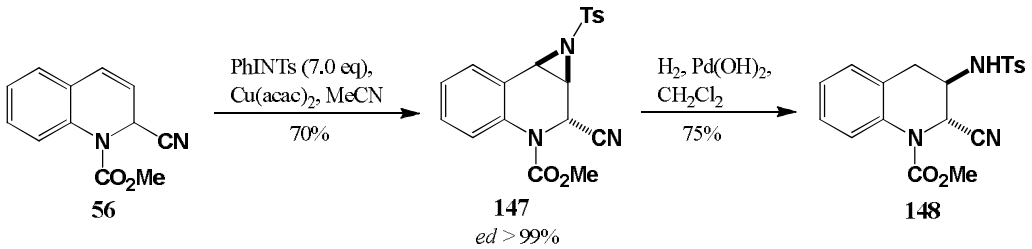


Schéma 30

La disposition *anti* entre le cycle aziridine et le groupement nitrile a été déterminée par analogie après une analyse par diffraction aux rayons X effectuée sur un dérivé analogue obtenu dans les même conditions (N-COPh au lieu de NCO_2Me).

Différents essais de réduction de l'amine tosylée en présence de sodium dans l'ammoniac liquide n'ont pas permis d'obtenir l'amine libre attendue mais plutôt un mélange de produits ; la seule amine libre caractérisée provenant de la réduction de la fonction nitrile dans ces conditions. Etant données ces difficultés de déprotection de la fonction amine, nous avons envisagé une nouvelle stratégie en remplaçant le groupement tosyle par un groupement nosyle (*para*-nitrobenzenesulfonyle) ou un groupement SES (triméthylsilyléthylsulfonyle), connus pour être plus facilement déprotégés.

- ✓ Introduction d'un groupement amino en C3 *via* la formation d'une aziridine nosylée intermédiaire

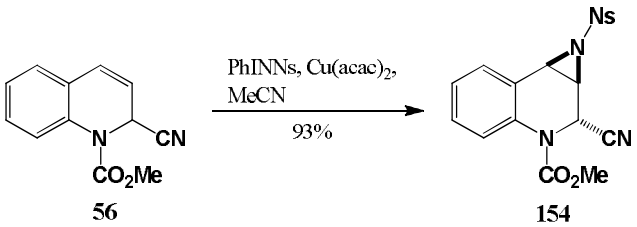


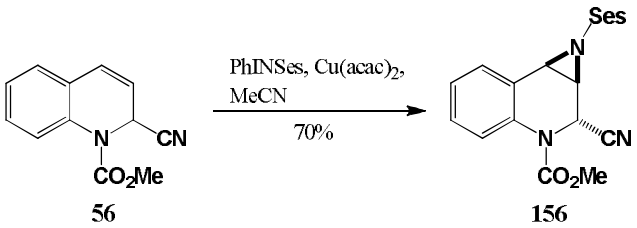
Schéma 31

Le dérivé de Reissert racémique **56** est mis en réaction avec le PhINs dans les mêmes conditions que précédemment. L'aziridine **154** est alors obtenue avec un excellent rendement sous la forme d'un seul diastéréoisomère possédant une stéréochimie présumée *anti* au regard des résultats précédents.

Comme dans le cas de l'aziridine tosylée **148**, l'aziridine nosylée **154** n'a pu être déprotégée en présence du catalyseur de Pearlman.

- ✓ Introduction d'un groupement amino en C3 *via* la formation d'une aziridine-SES intermédiaire

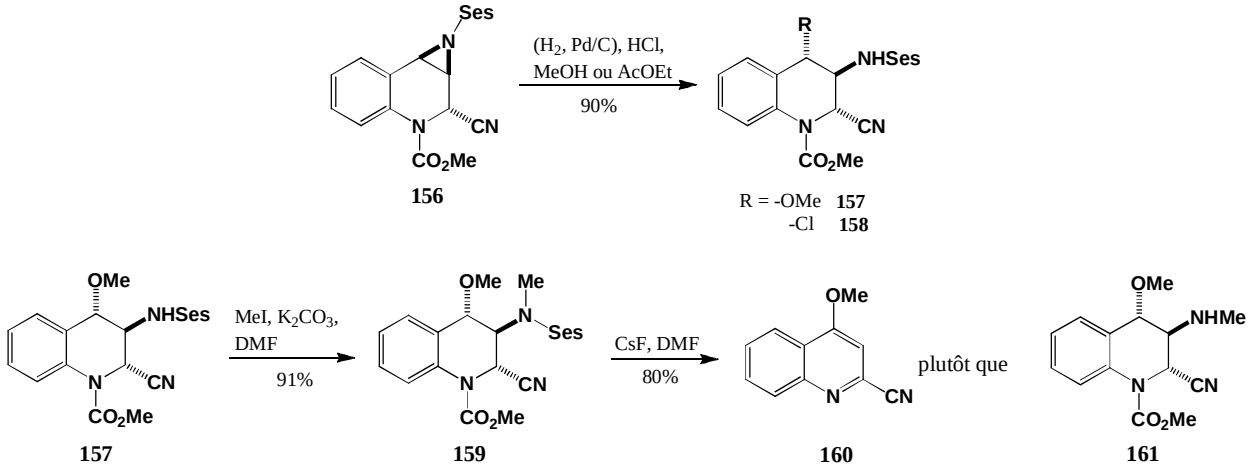
Le dérivé de Reissert racémique **56** est mis en réaction avec le PhINSes en présence de $Cu(acac)_2$ et permet d'obtenir l'aziridine désirée avec un rendement de 70% sous la forme d'un seul diastéréoisomère (Schéma 32).



56 **156**

Schéma 32

Comme pour l'aziridine nosylée, l'aziridine Ses n'a pu être déprotégée par hydrogénation en présence de catalyseur de Pearlman ou de Pd/C. La réduction en milieu acide a permis d'isoler les composés **157** et **158** (Schéma 33). Ces composés auraient pu être satisfaisants si nous avions pu nous débarrasser des groupements introduits en position benzylique par des procédés connus de la littérature. La méthylation de l'amine et la déprotection du groupement Ses devaient également être envisagés pour atteindre notre cible synthétique. La méthylation de la fonction amine a été effectuée avec succès en présence de MeI et de K_2CO_3. La coupure du groupement Ses en présence de CsF n'a pas permis d'isoler le produit attendu **161**, mais un produit totalement aromatisé **160** avec perte des centres asymétriques créés.



156 **157** **159** **160** **161**

Schéma 33

La formation de ce composé totalement aromatisé **160** peut être expliqué par la basicité des ions fluorures. La déprotonation en position α du groupement nitrile entrainerait une élimination de l'amine exocyclique. La déprotection de l'amine intracyclique suivie d'une étape d'oxydation (déshydrogénation) conduirait ensuite au composé **160**.

L'accumulation de ces différents échecs nous a conduits à abandonner cette voie qui nous aurait permis de valoriser le composé de Reissert **56** et à proposer une nouvelle voie pour atteindre notre cible, le Sumanirole.

II.1.4 Synthèse totale du Sumanirole

II.1.4.1. *Rétrosynthèse*

En profitant des résultats mentionnés précédemment concernant l'époxydation de la dihydroquinoléine chirale **48**, nous proposons une nouvelle stratégie de synthèse (Schéma 34).

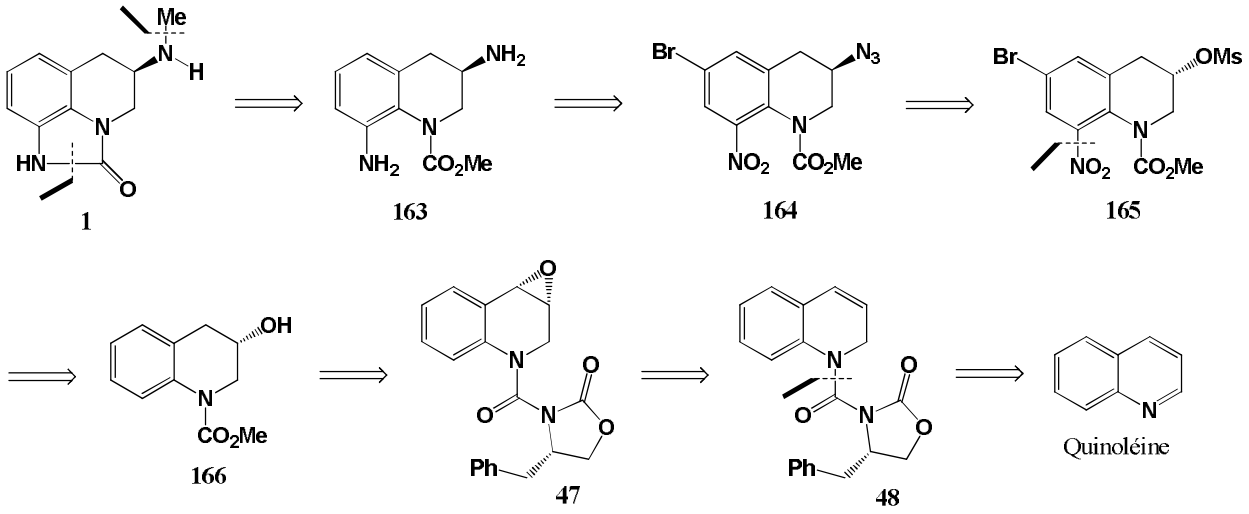


Schéma 34

Le sumanirole (*R*)-**1** proviendrait de la diamine **163** synthétisée à partir la tétrahydroquinoléine **164**, elle-même obtenue par substitution nucléophile du mésylate **165**. La tétrahydroquinoléine tétrasubstituée **165** serait synthétisée à partir de l'alcool **166** issu de l'ouverture régiosélective de l'époxyde **47** obtenu par époxydation diastéréosélective de la dihydroquinoléine **48** mentionnée au début du chapitre I.

II.1.4.2. *Synthèse du Sumanirole en 12 étapes*

Suivant cette stratégie, la synthèse de la dihydroquinoléine **48** a tout d'abord été effectuée en s'inspirant des travaux préalables de Minter et Slatter[20] qui ont décrit la réduction de la quinoléine à l'aide du Dibal-H et piégeage de l'aminoalane subséquent avec un large excès de chloroformate de méthyle. L'utilisation du chlorure d'acide chiral **101** pour piéger l'aminoalane formé nous a permis, dans notre cas, d'isoler la dihydroquinoléine chirale **48** avec un rendement correct (61%).

[20] D. E. Minter, P. L. Stotter. *J. Org. Chem.* **1981**, *46*, 3965.

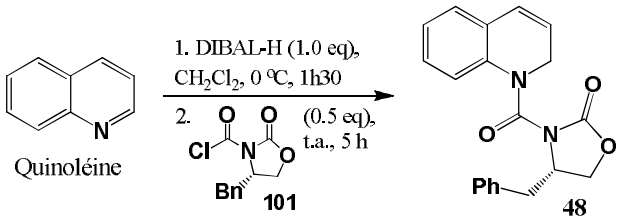


Schéma 35: Réduction/Acylation

Un travail d'optimisation de cette étape a été effectué afin d'atteindre un tel résultat. Le ratio entre quinoléine et chlorure d'acide a été optimisé ainsi que l'ordre et la vitesse d'addition. Les conditions optimales utilisées correspondent à une addition lente de l'aminoalane sur le chlorure d'acide à 0 °C suivie d'une remontée à température ambiante et d'une agitation durant 5 heures.

Avec la dihydroquinoléine chirale en main, nous pouvons procéder à l'étape d'époxydation diastéréosélective. Celle-ci est effectuée à l'aide du *m*-CPBA en présence de bicarbonate de sodium et permet d'obtenir un mélange de diastéréoisomères dans un ratio de 9:1 (Schéma 36). La configuration absolue du diastéréoisomère majoritaire **47** a été déterminée sans ambiguïté à partir d'une analyse par diffraction aux rayons X.

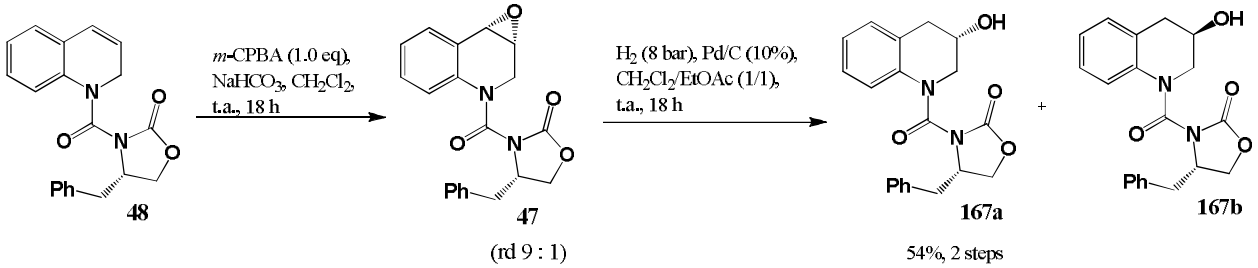


Schéma 36: Epoxydation/Réduction

Le mélange de diastéréoisomères est ensuite directement engagé dans une étape d'hydrogénation sous pression d'hydrogène et catalysée au Pd/C. Les deux diastéréoisomères sont aisément séparés à ce stade par chromatographie sur gel de silice pour mener à l'alcool désiré **167a**.

A ce stade, nous décidons de remettre à plus tard l'introduction de l'amine en C3, mais préférons nous concentrer sur l'introduction du cycle imidazolone. Afin d'éviter toute réaction parasite avec l'auxiliaire chiral, nous décidons de nous en débarrasser à ce stade. La coupure de celui-ci est effectuée en présence de triflate de samarium dans le méthanol. Ceci nous permet d'isoler le carbamate **166** avec un rendement de 66% ainsi qu'un excès énantiomérique supérieur à 98% (Schéma 37).

L'alcool est ensuite bromé en position 6 à l'aide du dibrome en présence d'acide acétique puis nitré en position 8 pour mener au composé **169** avec un rendement sur deux étapes de 70%.

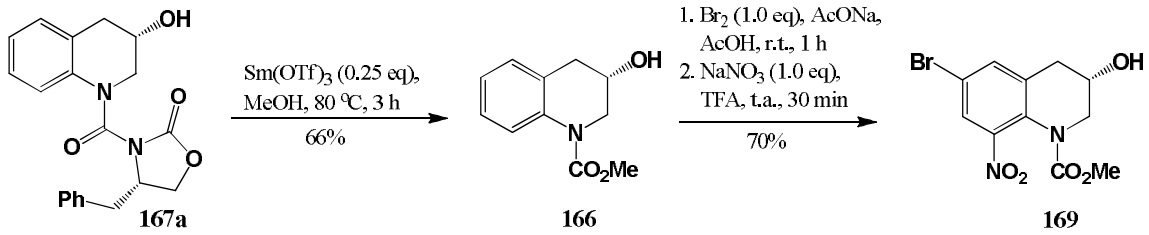


Schéma 37

Les préparatifs d'installation du cycle imidazolone étant effectués, l'introduction du groupement méthylamino en C3 peut à nouveau être entreprise. L'alcool **169** est traité à l'aide du chlorure de mésyle en milieu basique puis transformé en azoture **164**. Un hydrogénolyse dans des conditions choisies permet de réduire de manière efficace en une seule étape, le groupement azoture, le groupement nitro et de couper la liaison C-Br (Schéma 38).

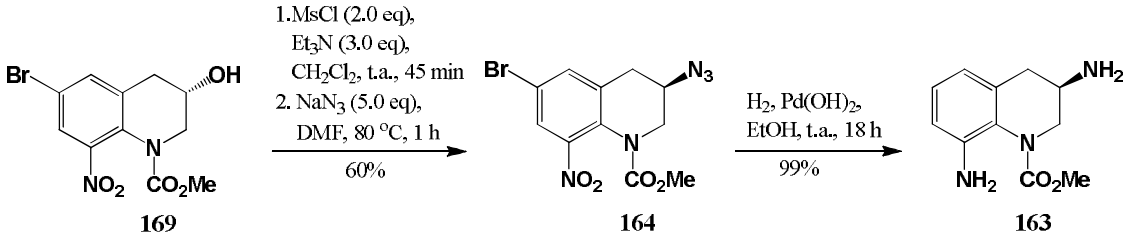


Schéma 38

La construction du cycle imidazolone est effectuée en présence d'un excès de *t*BuOK avec un excellent rendement.

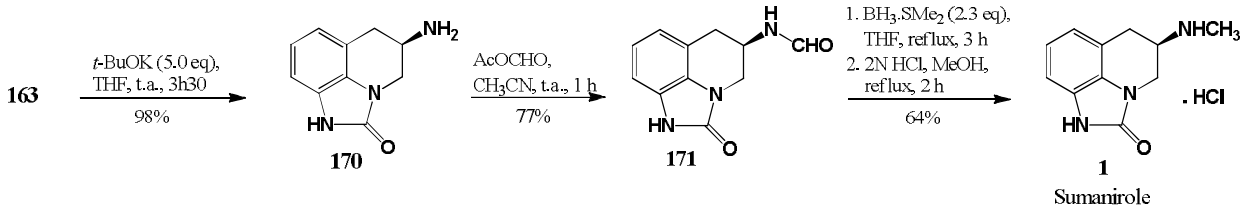


Schéma 39

Pour terminer la synthèse, la monométhylation de l'amine primaire est effectuée en deux étapes distinctes. L'amine est tout d'abord formylée en présence de l'anhydride formique et acétique puis réduite en présence de BH_3 pour mener au Sumanirole. Celui-ci est isolé et caractérisé sous sa forme chlorhydrate.

Finalement, nous avons effectué la synthèse du (*R*)-Sumanirole en 20 étapes à partir de la quinoléine avec un rendement global de 4,3%. L'étape d'époxydation diastéréosélective de la 1,2-dihydroquinoléine chirale **48** constitue l'étape clé de cette synthèse. L'hydrogénation concomitante de 3 groupements mérite également d'être soulignée dans cette synthèse.

II.2 Approche de la synthèse de l'acide Martinellique

II.2.1 Introduction

L'acide martinellique et la martinelline sont deux alcaloïdes pyrroloquinoléiques isolés en 1995 par les laboratoires Merck à partir d'écorces de racines d'une plante tropicale, *Martinella iquitosensis*. Ces alcaloïdes sont les premiers exemples de composés non-peptidiques identifiés comme des antagonistes au niveau des récepteurs à la bradykinine B1 et B2. D'un point de vue structural, ces alcaloïdes possèdent un squelette pyrrolo[3,2,c]quinoléique qui n'ont pas été décrits jusqu'alors. Leurs propriétés biologiques conjuguées à leur structure originale en ont fait des cibles synthétiques très attractives. Plusieurs groupes de recherche ont développé différentes méthodes pour synthétiser ces composés en version racémique ainsi qu'en version chirale non-racémique.

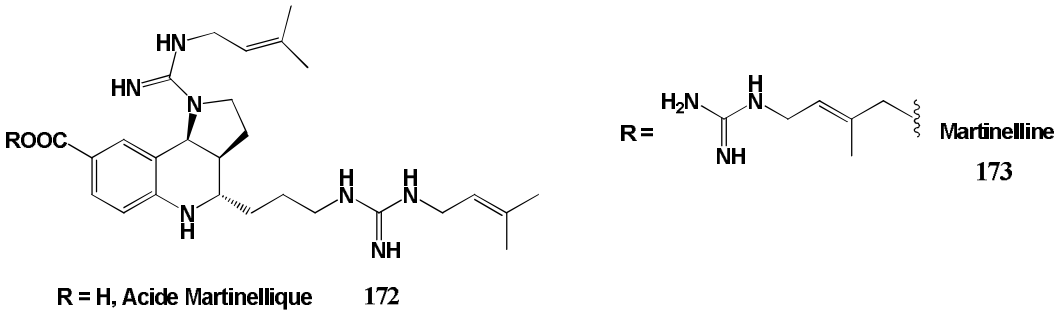


Figure 11

II.2.2 Revue bibliographique

La plus majorité des synthèses passé par l'intermédiaire de Ma **174** (Figure 12) et nous nous limitons dans cette thèse à la description des synthèses passant par cet intermédiaire.

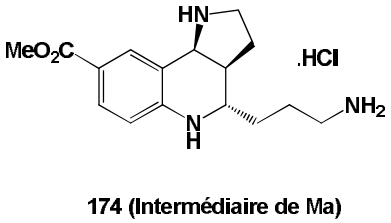


Figure 12

II.2.3 Résultats de notre étude préliminaire pour la synthèse de l'acide martinellique

Comme nous avons pu le décrire dans le premier chapitre, l'addition électrophile d'azoture de triméthylsilyle sur le dérivé de Reissert **105a** a permis d'obtenir sélectivement un mélange de produits d'addition (rd 92/8) dont le diastéréoisomère majoritaire **108a** pouvait être facilement séparé (Schéma 40).

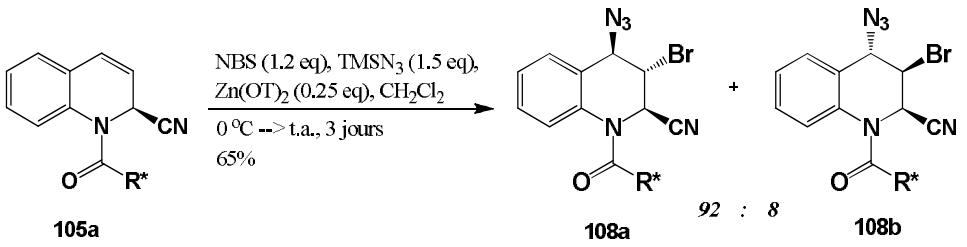


Schéma 40

Nous avons dès lors pensé utiliser ce composé **108a** comme point de départ d'une nouvelle synthèse de l'acide martinellique. La stratégie envisagée est présentée sur le schéma rétrosynthétique suivant.

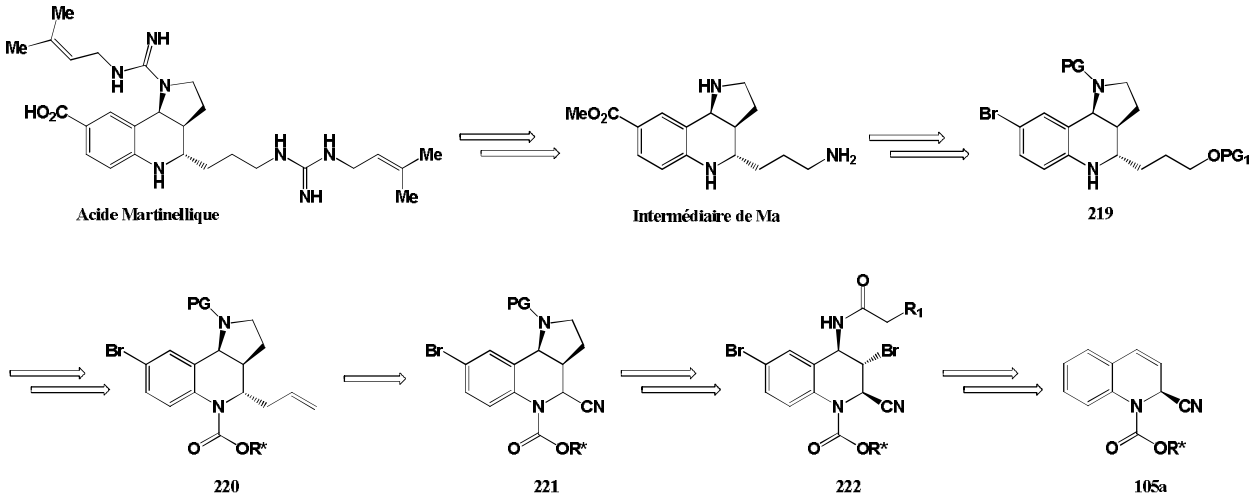
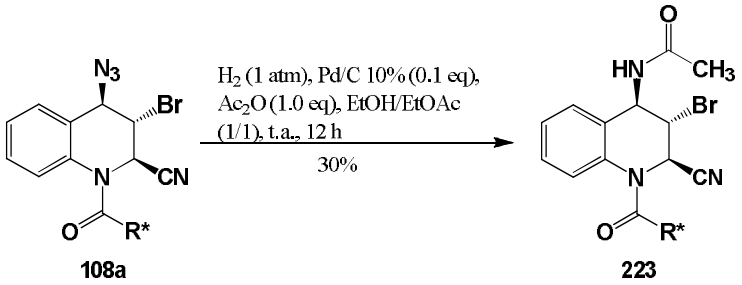


Schéma 41

L'acide martinellique proviendrait de l'intermédiaire de Ma qui pourrait lui-même provenir du bromoalcool **219** après manipulation des divers groupes fonctionnels. Le composé **219** serait envisagé à partir du dérivé allylique **220** obtenu à partir du nitrile **211** à travers la formation intermédiaire de l'ion iminium correspondant. La formation du cycle pyrrolidine serait effectuée à partir du composé dibromé **222**. L'essentiel de notre travail dans cette étude a consisté à tenter de synthétiser cet intermédiaire **222** à partir de l'adduit de Reissert **105a** décrit préalablement.

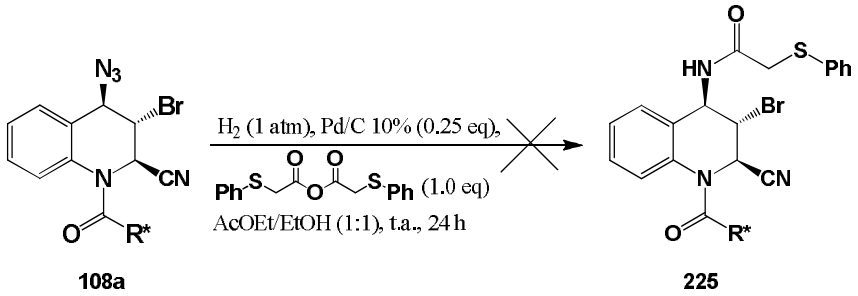
Pour atteindre notre cible, nous avons appliqué au composé **108a** les conditions de réduction/acylation utilisées sur le composé analogue ne comportant pas de groupement nitrile (chapitre I – Schéma16). Nous avons ainsi pu isoler le composé **223** avec un rendement légèrement inférieur au cas précédent, certainement dû à une réduction partielle du groupement nitrile (Schéma 42).



108a 223

Schéma 42

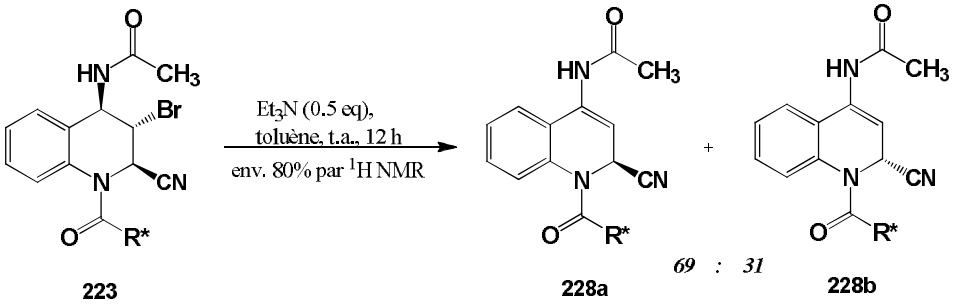
La formation du tricycle pouvait alors être envisagée, mais l'acidité des protons du groupement méthyle du groupe acétamido s'est révélée insuffisante. Afin d'exacerber cette acidité, nous avons envisagé la synthèse du dérivé **225** à l'aide de l'anhydride phénylthioacétique (Schéma 43).



108a 225

Schéma 43

Les diverses conditions opératoires appliquées n'ont jamais permis d'isoler le produit attendu **225**. Nous avons alors envisagé la déshydrobromation du composé **223** en position C2-C3 qui permettrait une addition plus aisée de l'énolate sur l'aminoacrylonitrile.



223 228a 69 : 31 228b

Schéma 44

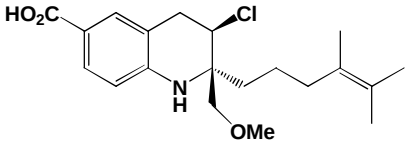
Le traitement du composé **223** en milieu basique a conduit à un mélange des 2 diastéréoisomères **228a** et **228b**. La formation de la double liaison en position benzylique issue de la déshydrobromation en position C3-C4 paraît plus favorisée qu'en position C2-C3. Des résultats similaires ont été obtenus à partir du dérivé **108a**.

En conclusion de cette étude préliminaire, il apparait que composé bromo-acétamido **223** peut être synthétisé à partir du dérivé de Reissert **108a**, mais sa transformation en dérivé tricyclique **221** ne peut pas être effectuée par addition conjuguée intramoléculaire sur un acrylonitrile formé intermédiairement. Ces travaux n'ont donc pas été poursuivis.

II.3 Approche de la synthèse de la Virantmycine

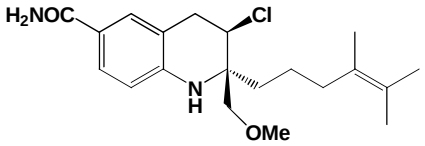
II.3.1 Introduction

La (-)-Virantmycine **229**, antibiotique antiviral isolé d'une souche de *Streptomyces nitrosporeus* en 1980 est une tétrahydroquinoléine substituée en C3 par un groupement chloré. Elle possède de fortes activités inhibitrices sur les virus à ADN et ARN ainsi qu'une activité antifongique. Plus tard, en 1996, les benzastatines C et D, isolées de *Streptomyces sp*. et dont les structures sont proches de la virantmycine, ont démontré une activité inhibitrice contre la toxicité au glutamate et la peroxydation de lipides. Ces trois produits naturels possèdent une structure unique tétrahydroquinoléique 2,2-disubstituée avec deux centres asymétriques tertiaire et quaternaire contigus.

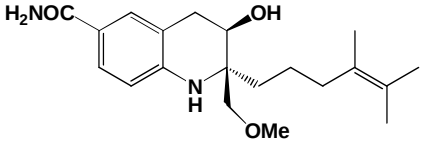


229

Virantmycin



Benzastatin C



Benzastatin D

Figure 13

II.3.2 Revue bibliographique

La construction stéréosélective du centre quaternaire chiral de la virantmycine représente l'enjeu le plus important dans les différentes synthèses décrites. De plus, la présence d'un centre tertiaire asymétrique vicinal n'en rend la synthèse totale que plus difficile. La première synthèse racémique a été décrite en 1986[21] et il a fallu attendre une dizaine d'année pour que la première

[21] (a) M. L. Hill, R. A. Raphael, *Tetrahedron Lett.* **1986**, *27*, 1293. (b) M. L. Hill, R. A. Raphael. *Tetrahedron* **1990**, *46*, 4587.

synthèse énantiosélective soit proposée. [22] Les différentes synthèses proposées sont détaillées dans la thèse.

II.3.3 Notre approche de la synthèse de la Virantmycine

Inspiré par les différentes synthèses décrites dans la littérature, notre approche à la synthèse de la virantmycine est décrite dans le schéma rétrosynthétique ci-dessous.

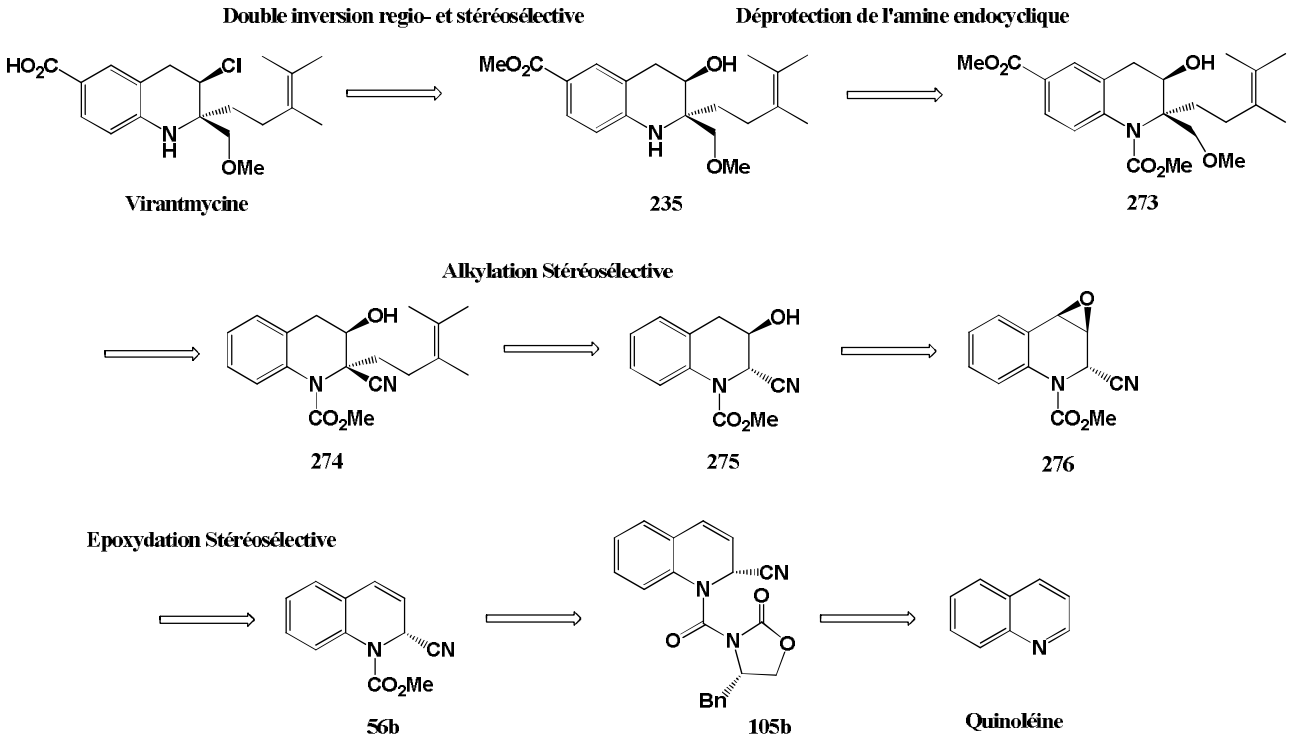


Schéma 45

La virantmycine proviendrait de l'alcool **235** à la suite d'une chloration par double inversion stéréosélective. Cet alcool pourrait être obtenu après déprotection du carbamate **273** qui proviendrait lui-même du composé **274** après introduction d'un groupement ester en C6. Ce dernier serait synthétisé par alkylation stéréosélective de l'alcool **275**, lui-même provenant de l'époxyde **276**. Cet époxyde serait obtenu à partir de l'adduit de Reissert **56b** obtenu à la suite de la coupure de l'auxiliaire chiral du composé **105b**.

Pour notre étude préliminaire, nous avons choisi de partir du dérivé **56a**. Nous avons envisagé dans un premier temps la transformation du groupement cyano en groupement ester. Malgré les précautions mises en place, nous avons constaté une épimérisation au niveau du centre stéréogène (Schéma 46).

[22] M. Ori, N. Toda, K. Takami, K. Tago, H. Kogen. *Angew. Chem. Int. Ed.* **2003**, *42*, 2540.

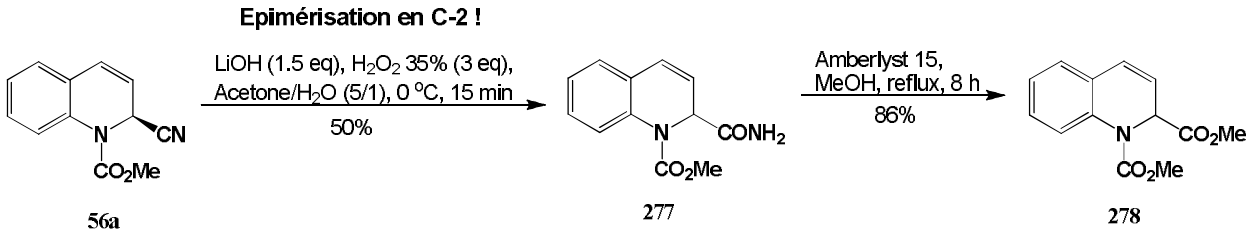


Schéma 46

L'introduction du groupement hydroxyle en C3 a été envisagée de la même façon que pour la synthèse du Sumanirole. L'adduit de Reissert **56a** est traité par le *m*-CPBA pour fournir avec une totale stéréosélectivité l'époxyde **142** avec le cycle époxyde opposé au groupement cyano. L'époxyde **142** est ensuite hydrogéné pour mener au cyano alcool **143** sous la forme d'un seul diastéréoisomère (Schéma 47).

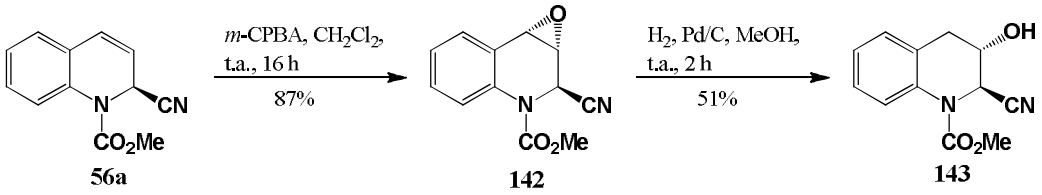


Schéma 47

Diverses optimisations ont été entreprises au niveau l'étape d'hydrogénation pour mener à un rendement de 56% en utilisant le dioxane comme solvant.

Avec l'alcool **143** en main, nous avons ensuite envisagé l'introduction stéréosélective de la chaîne en C2. Après plusieurs tentatives, nous avons obtenu le composé **281** sous la forme d'un seul diastéréoisomère après traitement de **143** par la LDA suivi de l'addition de MeI en présence de HMPA (Schéma 48). La configuration absolue du centre stéréogène quaternaire n'a pu être déterminée à ce stade.

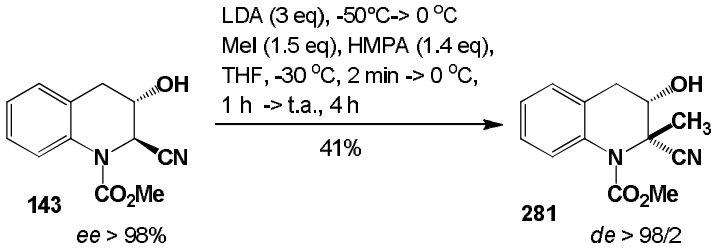


Schéma 48

Afin de mieux prévoir la configuration du centre stéréogène quaternaire généré par formation d'un chélate avec la fonction alcool, nous avons ensuite envisagé l'étape d'alkylation sur l'alcool ester **282**. Celui-ci a été obtenu après réaction de l'alcool **143** en présence de $SOCl_2$ dans le méthanol (Schéma 49).

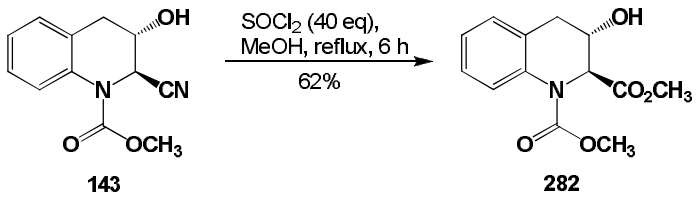


Schéma 49

Les mêmes conditions d'alkylation appliquées à l'ester **282** n'ont malheureusement pas permis d'isoler de composé alkylé en C2. Nous avons donc poursuivi nos investigations à partir du dérivé **143** en espérant pouvoir convertir le groupement cyano en groupement ester après l'étape d'alkylation. L'alkylation à l'aide du 5-iodo-2,3-diméthylpent-2-ène **284** n'a malheureusement pas pu nous mener au dérivé attendu **285** (Schéma 50).

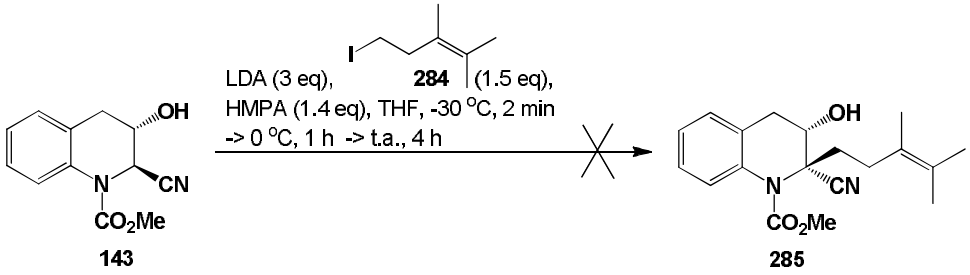


Schéma 50

Les cyano quinoléines **286** et **287** obtenues à partir du cyanoalcool **143** (Schéma 51) ont également été soumises aux mêmes conditions d'alkylation et n'ont pu mener aux dérivés alkylés correspondant.

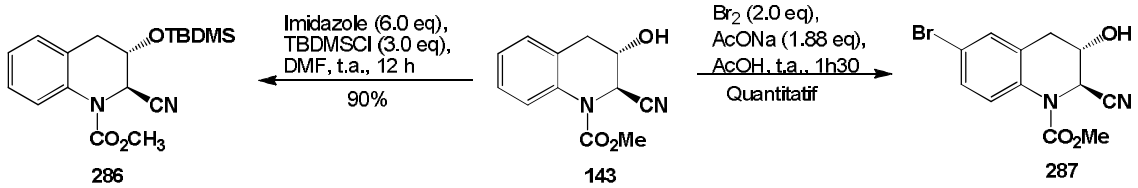


Schéma 51

Face à ces échecs répétés en termes d'alkylation à l'aide d'un dérivé halogéné élaboré, nous n'avons pas poursuivi nos investigations dans le domaine.

Notre travail a consisté principalement à développer une méthodologie de synthèse simple et efficace de 1,2,3,4-tétrahydroquinoléines diversement substituées en C2, C3 et C4 en série chirale non-racémique. Notre motivation initiale provenait du fait que nombre de 1,2,3,4-tétrahydroquinoléines développent diverses activités biologiques intéressantes et que ce squelette tétrahydroquinoléique se retrouve dans un petit nombre de produits naturels possédant des propriétés pharmaceutiques avérées.

Notre stratégie de synthèse de telles-structures repose dans un premier temps sur l'obtention de 1,2-dihydroquinoléines possédant un auxiliaire chiral dérivé de la 4-benzyloxazolin-2-one lié à l'atome d'azote du noyau quinoléique.

Dans une première partie nous avons montré que l'addition électrophile de dérivés de type BrX sur la double liaison C3-C4 de la 1,2-dihydroquinoléine **48** pouvait être effectuée avec de bonnes diastéréosélectivités en dépit du fait que l'auxiliaire chiral se trouve éloigné de la double liaison réagissante. Ces résultats sont cohérents avec des résultats obtenus préalablement lors de l'époxydation de cette même 1,2-dihydroquinoléine (Schéma 52).

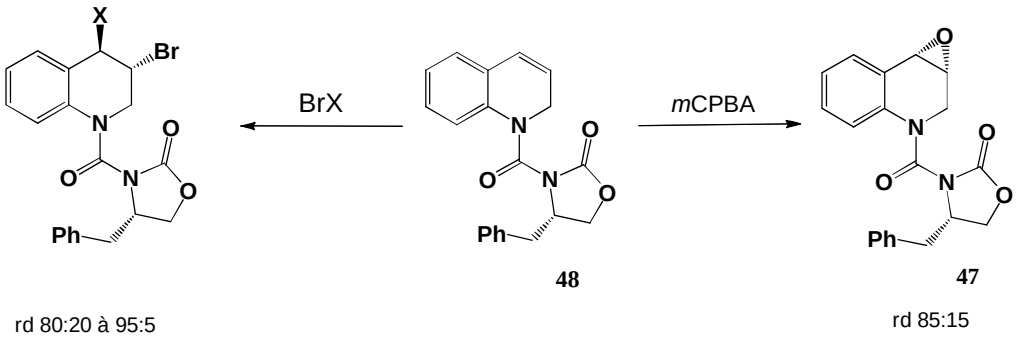


Schéma 52

Une interprétation de ces résultats a été faite à la suite d'analyses aux rayons X de différentes structures puis confirmée par des calculs théoriques. Il apparaît que la chiralité apportée par le motif oxazolidin-2-one soit transmise à la double liaison en C3-C4 par le biais d'une conformation privilégiée au niveau du noyau quinoléique. En d'autres termes, une contrainte conformationnelle au niveau de la 1,2-dihdroquinoléine **48** positionne un atome d'hydrogène en C2 en position quasi-axiale sur la face supérieure de la molécule favorisant une approche de l'ion Br^+ par la face inférieure de la double liaison. Les mêmes réactions effectuées à partir des 1,2-dihydroquinoléines **105a** et **105b** possédant un groupement CN en position C2 mènent à des résultats légèrement différents. Dans ce cas, la stéréosélectivité est essentiellement due à la configuration absolue en C2 et nous observons donc une attaque électrophile à l'opposé du groupement cyano (Schéma 53).

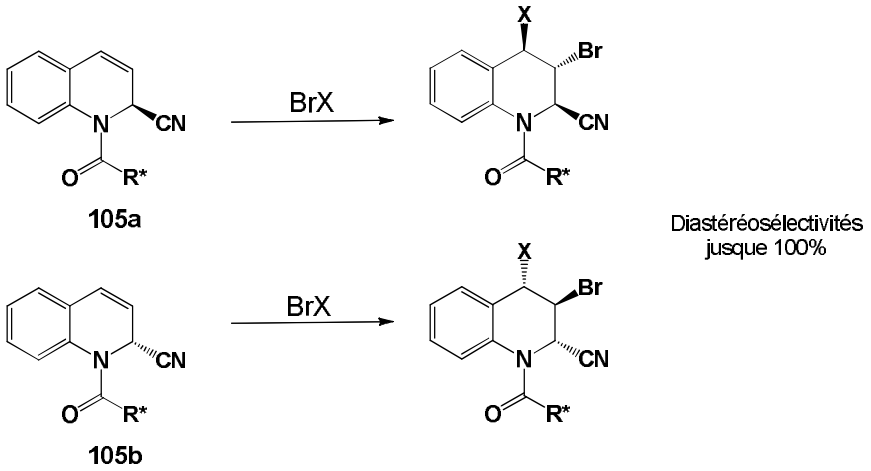


Schéma 53

Pour compléter cette étude méthodologique, nous avons cherché à déterminer quelles étaient les éléments essentiels à l'obtention de ces bonnes diastéréosélectivités lors de ces réactions d'addition en C3-C4. Il est apparu qu'une structure cyclique (oxazolidin-2-one ou oxazoline), ainsi que la nature du substituant en C'4 de l'auxiliaire chiral étaient importants pour obtenir de bonnes diastéréosélectivités.

La deuxième partie de notre travail concerne diverses applications synthétiques des résultats obtenus précédemment. Nous avons tout d'abord envisagé la synthèse du Sumanirole, agoniste des récepteurs D2. Notre synthèse est effectuée en 12 étapes à partir de la quinoléine avec un rendement global de 4,3%. Les étapes clés de cette synthèse sont d'une part l'époxydation diastéréosélective de la 1,2-dihydroquinoléine **48**, puis l'étape d'hydrogénation permettant de transformer 3 groupements en une seule étape (Schéma 54).

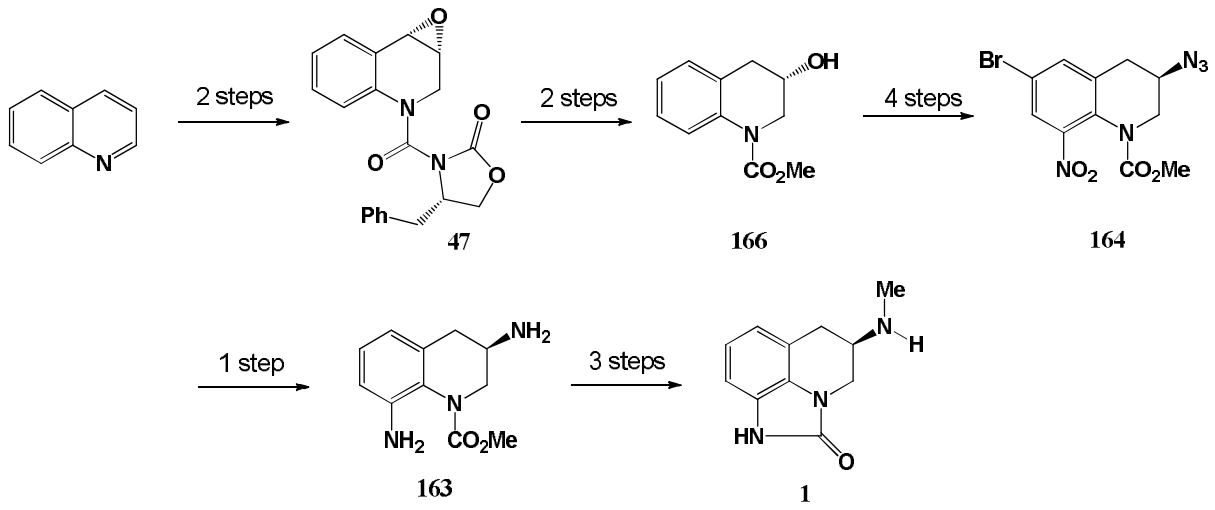


Schéma 54

A la suite de cette synthèse, des études préliminaires ont été effectuées pour développer une nouvelle synthèse asymétrique de 2 alcaloïdes naturels, la virantmycine et l'acide martinellique. Les adduits de Reissert **56a** et **56b** ont été utilisés comme composés de départ pour les deux approches. Malgré l'obtention de quelques résultats intéressants, nous n'avons pu mener à bien les synthèses envisagées à l'origine.

Research in the field of 1,2,3,4-tetrahydroquinoline derivatives : Total synthesis of Sumanirole Synthetic approach to Virantmycine and Martinellic acid

We have been interested in developing a new asymmetric strategy to reach 1,2,3,4-tetrahydroquinolines. At the beginning of the study, we made the two following observations : 1) a chiral Reissert compound (e.g. 2-cyano-1,2-dihydroquinoline) could be prepared in reasonable diastereoselectivity (up to 70%), under the action of TMSCN on a transient quinolinium salt bearing a chiral 4-benzyl-2-oxazolidinone-derived moiety attached at N1 and, 2) a chiral 1,2-dihydroquinoline could be obtained by *in situ* reduction (Dibal-H) of the transient chiral quinolinium salt mentioned above. The first part of the thesis reports on the addition of various electrophiles onto the 3,4-double bond of the two chiral 1,2-dihydroquinolines previously prepared. Diastereoselectivities up to 90% were obtained in spite of the fact that the chiral oxazolidinone moiety is far remote from the reactive double bond. Results were rationalized with the support of *ab initio* calculations. Interestingly, a conformational relay between the chiral moiety and the reactive 3,4-double bond was highlighted. In the second part of the thesis, results of the methodological study were applied in the field of multi-step synthesis. First of all, a total synthesis of Sumanirole, an unnatural compound exhibiting interesting anti-parkinsonian activities, was carried out in twelve steps and in an overall yield of 4.3%. Synthetic advances towards the syntheses of two natural alkaloids, Virantmycin and Martinellic acid, were also accomplished.

Depuis quelques années, nous nous intéressons au développement de nouvelles stratégies permettant d'accéder à des structures de type 1,2,3,4-tétrahydroquinoléine en série chirale non-racémique. Au début de cette nouvelle étude, nos observations étaient les suivantes : 1) un composé de Reissert (e.g. 2-cyano-1,2-dihydroquinoléine) peut être préparé, avec une diastéréosélectivité raisonnable (jusque 70%), par action du TMSCN sur un sel de quinoléinium portant une structure de type 4-benzyl-2-oxazilidinone chirale en N1 et 2) une dihydroquinoléine chirale peut être obtenue par une réduction *in situ* (Dibal-H) de ce même sel de quinoléinium chiral. La première partie de cette thèse présente l'addition de divers électrophiles sur la double liaison en position C3-C4 des deux dihydroquinoléines chirales mentionnées ci-dessus. D'étonnantes diastéréosélectivités pouvant atteindre 90% ont été observées compte-tenu de la distance importante entre l'auxiliaire chiral et la double liaison. Les résultats ont été rationalisés à l'aide de calculs *ab initio*. De façon intéressante, un relai conformationnel entre l'auxiliaire chiral et la double liaison réactive a été mis en évidence. La seconde partie est consacrée à l'application de cette méthodologie à la synthèse multi-étapes de composés comportant un motif tétrahydroquinoléique. La synthèse totale du sumanirole, composé non-naturel possédant des propriétés anti-parkinsoniennes intéressantes, a été effectuée en 20 étapes avec un rendement global de 4,3%. Diverses approches synthétiques de la virantmycine et de l'acide martinellique, ont également été entreprises.

Key-words

1,2,3,4-tetrahydroquinoline
Asymmetric synthesis
Diastereoselectivity
Sumanirole
Virantmycin
Martinellic acid