TOWARD THE SYNTHESIS OF ALKALOIDS *VIA* DESYMMETRISATION

Inauguraldissertation

der Philosophisch-naturwissenschaftlichen Fakultät

der Universität Bern

vorgelegt von

Riccardo Piccardi

aus Italien

Leiter der Arbeit: Prof. Dr. P. Renaud

Departement für Chemie und Biochemie der Universität Bern

TOWARD THE SYNTHESIS OF ALKALOIDS *VIA* DESYMMETRISATION

Inauguraldissertation

der Philosophisch-naturwissenschaftlichen Fakultät

der Universität Bern

vorgelegt von

Riccardo Piccardi

aus Italien

Leiter der Arbeit: Prof. Dr. P. Renaud

Departement für Chemie und Biochemie der Universität Bern

Von der Philosophisch-naturwissenschaftlichen Fakultät angenommen

Bern, den 31. März 2005

Der Dekan:

Prof. Dr. P. Messerli

Acknowledgement

First of all I would like to thank Prof. Philippe Renaud for accepting me to work in his group. It has been a beautiful experience from the first moment, both from a professional and human point of view.

I would like also to thank Prof. J.L. Reymond and Y. Landais for having accepted to correct and judge this work.

Then I want to thank Prof. C. Leumann to have employed me in the departement.

Finally I want to thank Dr. Fabrice Denés for taking time to read this manuscript. I want to thank him also for the long professional discussions, which helped my clarify my thoughts. I want to thank him also for the nice time spent toghether. I have to say that he is not only an extremely good chemist, and he loves chemistry, but also a good friend, with whom it's nice to spend time.

Another person who deserves my gratitude is Eveline Kumli for helping with the delivery of this manuscript and also for the support during the last weeks of writing.

I want to thank then all the other members of the group, past and present. Starting from the italian connection, Dr. Barbara Becattini, and Dr. Andrea Romagnoli, to the old third floor, Dr. Phillipe Panchuad, Dr. Arnaud Pierre Schaffner and Dr. Xavier Salom-Roig, for the help, the discussions and the water-battles in summer. I would like to thank also Erich, Pascal and all the other on the first floor for the company and the good jokes. The same warm thoughts for the new entries in the group and Vincent, Alice, Monica, and Dedè. Good luck to everyone!

A particular thank to Florian and Renaud for the smoking cigar evening (when the next one?).

I thank also all the people from the Ausgabe: Simon, Ruch, Boh for their help and collaboration.

I will never forget this almost four years in Berne

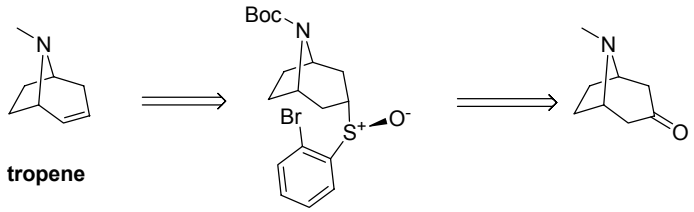
I want also to thank all the people I have met here in Berne for the nice time spent toghether. In particular I want to thank Romana for the help the support given expecially in the last months.

Infine un immenso grazie a tutta la mia famiglia.

Abstract

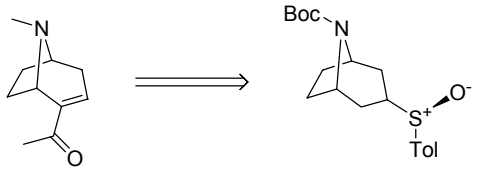
One of the most exciting challenges in organic chemistry is the possibility to synthesise molecules that contains chiral centres. This can be obtained in different ways. This work describes the possibility to use desymmetrisation of *meso* compounds for the synthesis of two classes of natural products.

First, the possibility to desymmetrise the tropane system in order to synthesis the natural occurring tropene is presented. A cascade 1,5-hydrogen abstraction-β-fragmentation of the sulfoxide is used as key step for this transformation.



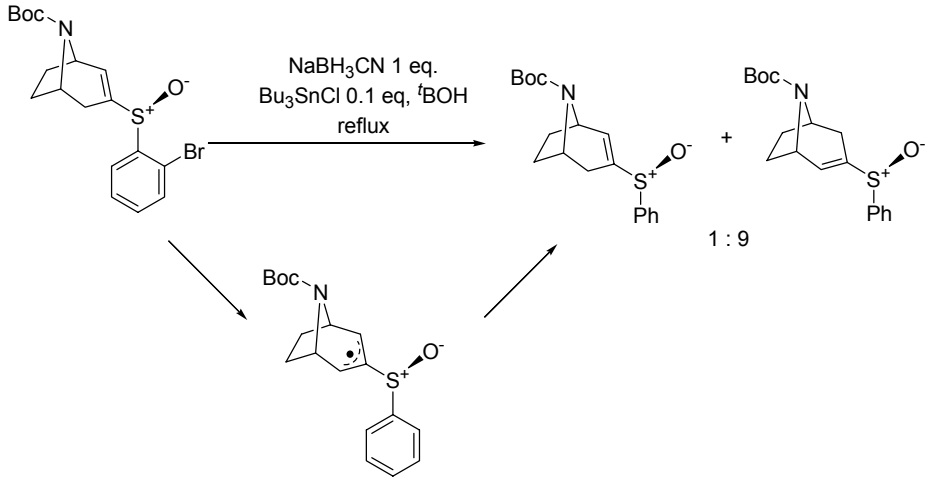
tropene

The synthesis of both enantiomerically pure enantiomers of ferruginine from vinyl sulfoxide is described in the second part of this work.

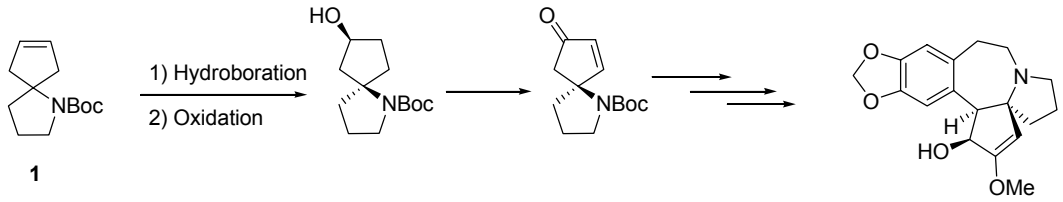


ferruginine

During this study, it has been investigated that 1,5-hygrogen abstraction can can be used to isomerise the vinyl sulfoxide intermediate.



The last part of this work is devoted the desymmetrisation of the bicycle **1** using an enantioselective hydroboration. The reaction leads to an intermediate that can be then used for the synthesis of cephalotaxine and other cephalotaxus alkaloids.



1

cephalotaxine

Abbreviations

Ac	Acetyl
AcOEt	Ethyl acetate
AIBN	2,2'-Azobis(isobutyronitrile)
Boc	*t*-Butoxy carbonyl
Bu	Butyl
Cat	Catechol
δ	chemical shift in parts per million downfield from TMS
d	doublet (in NMR)
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DMAP	4-dimethylaminopyridine
DME	Dimethoxyethane
dr	diastereoisomeric ratio
EI	Electronic Ionization
Et	Ethyl
EtOAc	Ethyl acetate
EtOH	Ethanol
Et_2O	Diethyl ether
FC	Flash column chromatography
GC	Gas Chromatography
GCMS	Gas Chromatography and Mass Spectroscopy
h	hour
hν	sun lamp irradiation
HRMS	High Resolution Mass Spectra
Hz	Hertz
i-	iso
IR	Infra Red
J	Coupling constant (in NMR)
m	multiplet (in NMR)
m-CPBA	*meta*-Chloroperbenzoic acid
Me	Methyl

MeOH	Methanol
MHz	Mega Hertz
min	minute
mp	melting point
MS	Mass Spectroscopy
m/z	mass to charge ratio
n-	normal
NBS	*N*-bromosuccinimide
NMR	Nuclear Magnetic Resonance
Ph	Phenyl
PhH	benzene
PhME	toluene
ppm	parts per million
Py	Pyridine
q	quartet (in NMR)
qu	quintuplet (in NMR)
R_f	Retention factor
rt	room temperature
t	triplet (in NMR)
t-	tert
t_R	Retention time
TBME	*tert*-butyl methyl ether
THF	Tetrahydrofurane
TLC	Thin layer chromatography
TMEDA	*N*,*N*,*N*′,*N*′-Tetramethylethylenediamine
TMS	Trimethylsilyl
Tol	*p*-tolyl

Table of Contents

Desymmetrisation

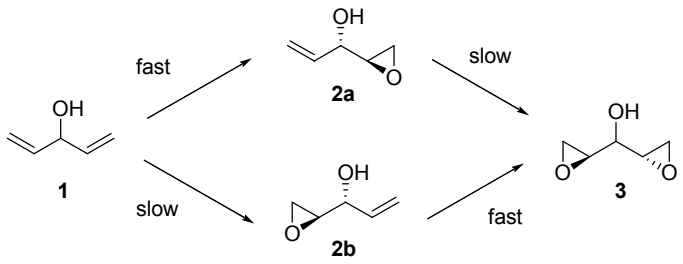
One of the most important challenges in organic synthesis is the formation of enantiopure compounds. Various methods can be used for this purpose; the possibility of introducing the chirality in prochiral or *meso* substrate introducing by selective modifications of enantiotopic groups will be discussed.

Desymmetrisation of prochiral or *meso* compound can be achieved in different way, normally using chiral reagents, catalysts or auxiliaries. Herein a brief, general and non-exhaustive presentation of desymmetrisation processes will be presented. Enzyme mediated desymmetrisations will not be considered.[1]

I. Desymmetrisation of *meso* alkenes

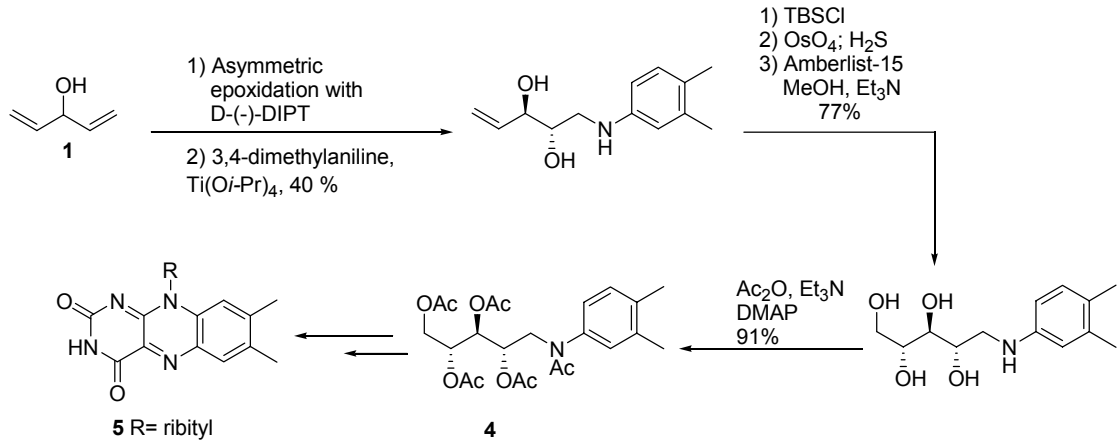
I.I. Sharpless Asymmetric epoxidation of meso dienes

One of the most interesting applications of desymmetrisation of *meso* dienes has been described by Schreiber[2]: Sharpless asymmetric epoxidation of the 1,4-pentadien-3-ol **1**, coupled to a kinetic resolution provides product with high level of enantioselectivity. The first epoxidation with diethyl tartrate occurs faster on one of the two prochiral double bonds (matched case) **2a**, while the second epoxidation on the other double bond is slower (mismatched case) (scheme 1) **2b**. Since the second epoxidation from **2b** is fast (matched case), the enantiomeric excess of **2a** increase with the reaction time.



Scheme 1

This type of strategy has been applied for the synthesis of (+)-and (-)-riboflavin **5** (scheme 2).[3]

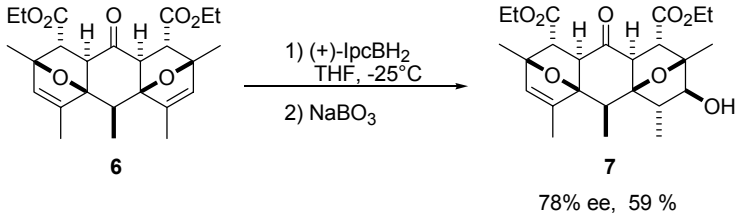


Scheme 2

The first step is an asymmetric epoxidation, the configuration of the tartrate inducing the desymmetrisation of the diene. After ring opening of the epoxide with the aniline derivative, dihydroxilation and subsequent acetylation, the precursor **4**, which has previously been converted to riboflavin, was obtained.[4]

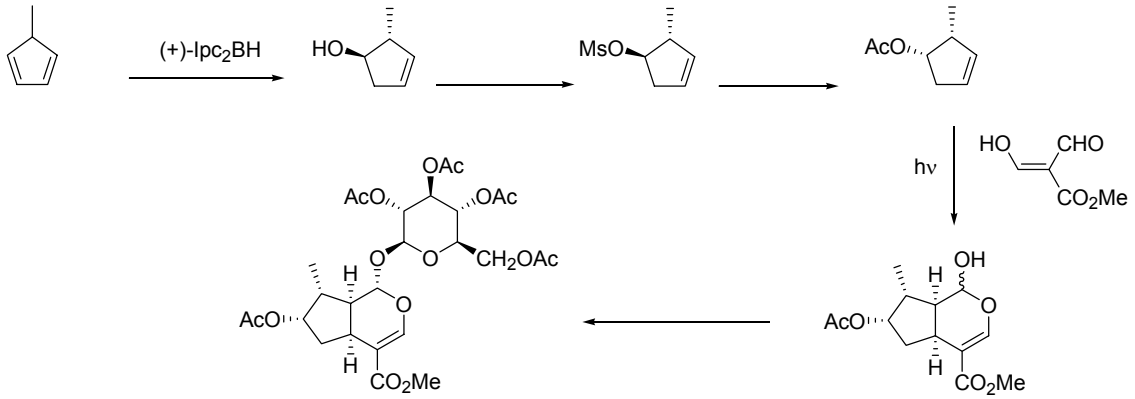
I.II. Asymmetric Hydroboration of meso dienes

The use of chiral boranes in order to desymmetrise *meso* dienes is known for long time. For example Vogel used a selective mono-hydroboration with $IpcBH_2$ to desymmterise the diene **6**. Oxidative work-up gave the desired alcohol in 59% yield and 78 % ee (scheme 3).[5,6]



Scheme 3

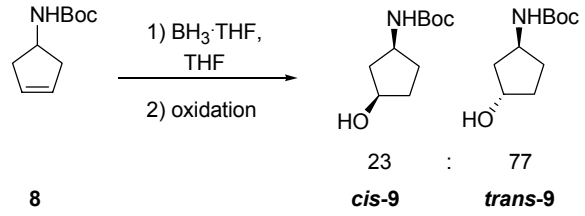
Hydroboration with Ipc_2BH has been applied for the synthesis of intermediates of various natural compounds. For instance has been used by Uskokovic and co-worker in the synthesis of loganin (scheme 4)[7] or for Corey's lactone intermediate for prostaglandin synthesis[8].



Scheme 4

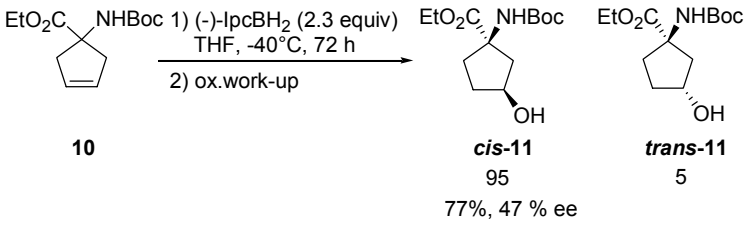
I.III.Asymmetric hydroboration of cyclic alkenes.

Hodgson reported the hydroboration of the cyclic alkene **8** using BH_3, (scheme 5).[9,10] In this case, the nitrogen atom is not able to complex the boron, thus the hydroboration generates a mixture of the two possible diasteroisomers.



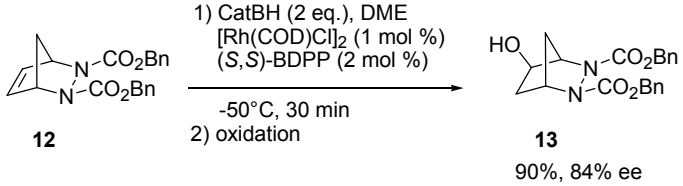
Sceme 5

For cyclopentene **10,** direct hydroboration with (+)-IpcBH$_2$ gave the enantioenriched alcohol with 74 % yield and 48% ee (Scheme 6).



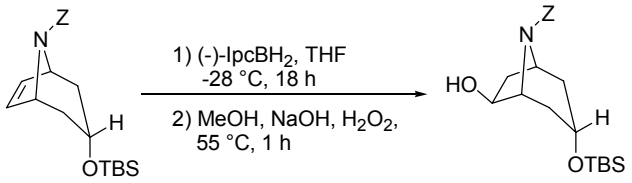
Scheme 6

More recently Bonin and Micouin reported the desymmetrisation of meso bicylic hydrazines **12** using catalytic asymmetric hydroboration. With [Rh(COD)Cl]$_2$ and (*S*,*S*)-BDPP, they were able to obtain 90% yield and 84% ee (Scheme 8).[11]



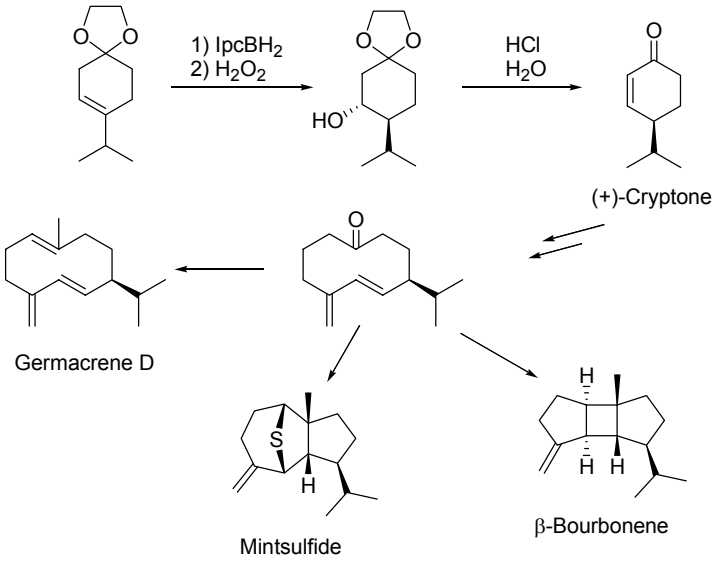
Scheme 7

Laschat reported the desymmetrization of tropinone derivatives *via* asymmetric hydroboration using $IpcBH_2$, obtaining very good enantioselectivities (Scheme 8).[12]



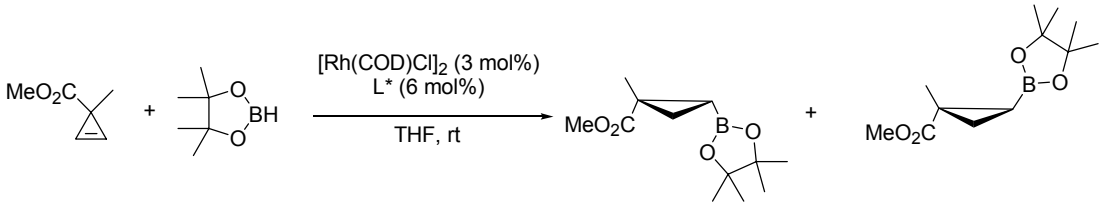
Sceme 8

$IpcBH_2$ found many applications in synthesis. For example Schreiber applied this reagent for the synthesis of (+)-cryptone[13] a precursor for different natural compounds (scheme 9).[14]



Scheme 9

Recently the hydroboration of cyclopropene derivatives using pinacolborane and rhodium catalyst bearing chiral phosphines has been reported (scheme 10).[15] The best results have been obtained with ligand such as (*R*)-BINAP and its derivates to-BINAP, NORPHOS, and PHANEPHOS: all of them afford good diasteroselectivity (up to 99:1) for the *cis* derivatives and good enantioselectivity (up to >99%) (table 1).



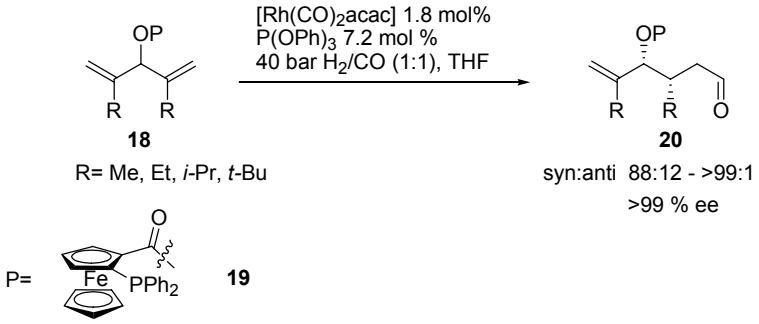
Scheme 10

Entry	Ligand	Time (h)	*cis*/*trans*	Yield (%)	*cis* ee (%) (config.)
1	(*R*)-BINAP	0.3	99/1	96	94 (*1S,2R)*
2	(*S,S*)-NORPHOS	1	98/2	86	>99 (*1R, 2S*)
3	(*R*)-PHANEPHOS	3	>99/1	89	>97 (*1R, 2S*)
4	(*S*)-Tol-BINAP	0.3	>99/1	94	>96 (*1R, 2S*)

Table 1. Hydroboration using pinacolborane

I.IV. Hydroformilation of dienes

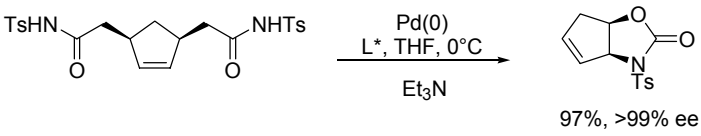
Recently Breit reported the possibility to desymmetrise *meso* diallylalcohols using an hydroformylation reaction.[16] The alcohol, bear a planar chiral directing group such as **19** (scheme 11). This group allow the discrimination of the two alkenes during the hydroformilation. Very good diasteroselectivity and enantioselectivity were obtained.



Scheme 11

I.V. Desymmetrisation of meso-biscarbamates

Trost in 1992 reported the possibility to synthesise bicyclic oxazolidinones starting from meso allylic biscarbamates, using chiral palladium catalyst (scheme 12).[17,18]

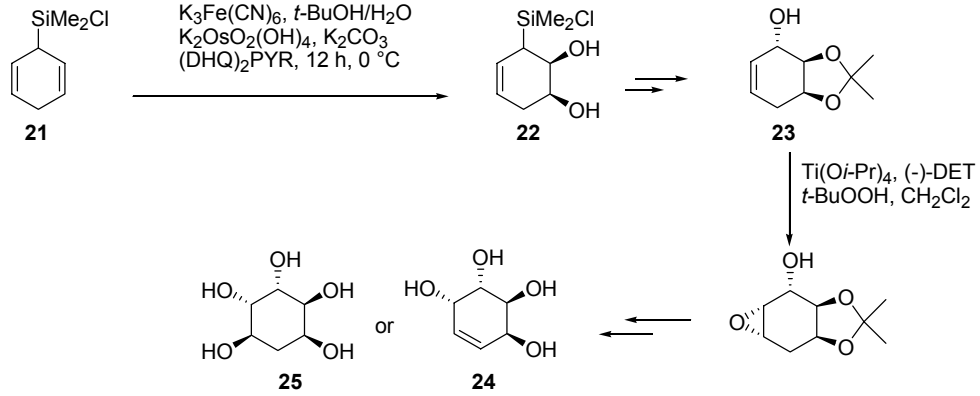


Scheme 12

I.VI.Cyclic dienes

Landais reported the possibility to desymmetrise silyl 2,5-cyclohexadienes **21** using the Sharpless asymmetric dihydroxylation.[19,20] The diol **22** is formed with good ee; this is converted in the triol **23** which after Sharpless epoxidation was converted in

(+)-conduritol **25** and (-)-2-deoxy-*allo*-inositol **24** (scheme 13).



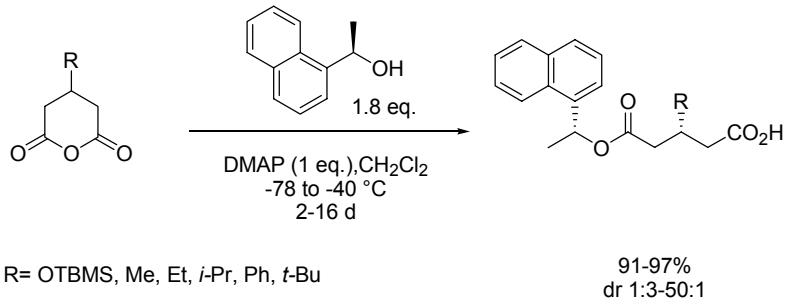
Scheme 13

II. Alcoholysis of cyclic anhydrides.[21,22]

A great interest has been given in particular to the desymmetrisation of *meso* and prochiral cyclic anhydrides. In this case an enantioselective alcoholysis generates the corresponding hemiester, a highly functionalised chiral product.

In 1956, Cohen reported the first attempt to desymmetrise a prochiral anhydride.[23] Using a chiral alcohol such as menthol he tried to desymmetrise a prochiral anhydride, such as 3-phenyl glutaric anhydride. However the two diastereoisomers were obtained in a close 1:1 ratio.

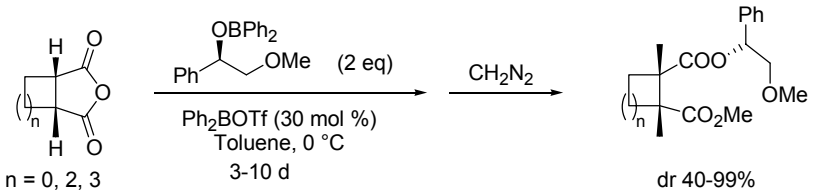
Only in 1985 Heathcock reported that the use of chiral alcohols as nucleophiles in the alcoholysis is synthetically useful.[24] The highest diastereoselectivity was obtained using with (*R*)-1-(1′-naphtyl)-2-ethanol as the chiral nucleophile in the desymmetrisation of 3-[(*tert*-butyldimethylsilyl)oxy] glutaric anhydride (92 % yield, dr 50:1) (scheme 14).



Scheme 14

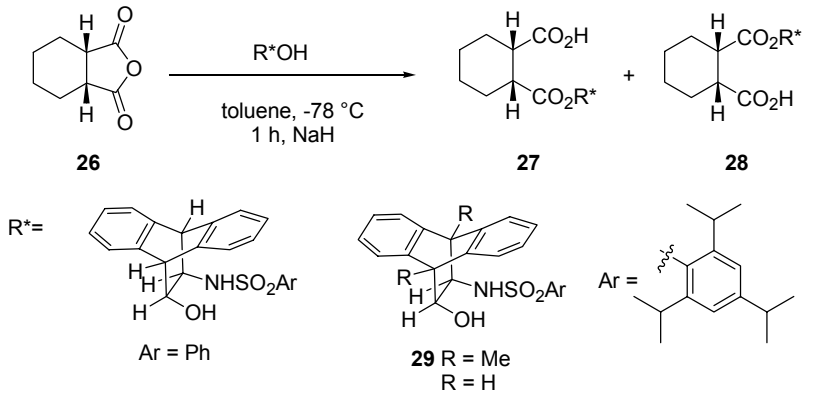
Mukaiyama used (*R*)-2-methoxy-1-phenylethanol diphenylborate as nucleophile, in presence of a catalytic amount of diphenylboryl triflate, to perform a diastereoselective alcoholysis (scheme 15).[25] With this method they obtained the

highest diastereoselectivity reported for **26**; desymmetrisation of a various *meso* bicyclic anhydrides affords the corresponding hemiester in moderate to excellent diastereoselectivities (40-99% dr) and good to excellent yields (75-95%). The best results were obtained for succinic and glutaric anhydrides fused with a six-membered ring. Replacement of the six-membered ring with one of a smaller size led to a decrease in the diastereoselectivity.



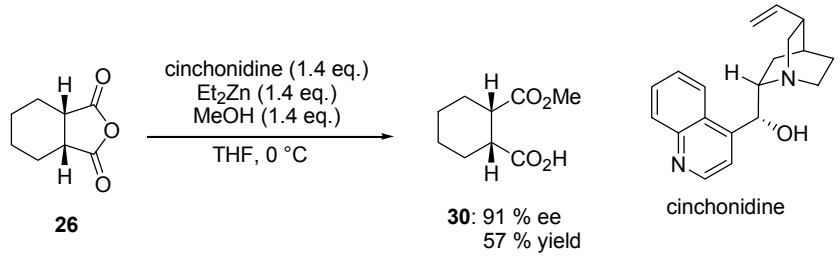
Scheme 15

Kunieda obtained very high diastereoselectivities in the ring opening of a variety of bi- and tricyclic anhydrides with the lithium or zinc salts of rigid chiral *N*-sulfonylamino alcohols (scheme 16).[26,27] The steric bulk of the sulfonyl group, the metal species used and the use of additives, all play a crucial role in the stereoselectivity. The highest diastereoselectivities were achieved using the lithium salts of the bulky amino alcohols **26** in presence of 5 equivalents of HMPA. When the zinc salt of **29** was used as nucleophile the sense of the asymmetric induction was found to be opposite to the one obtained using the corresponding lithium salt.



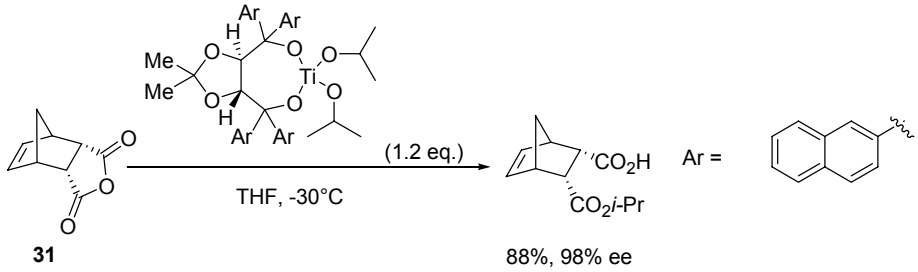
Scheme 16

Another possibility to realise an asymmetric alcoholysis is to use an achiral alcohol in presence of a chiral Lewis acid. Fujisawa reported the desymmetrisation of the anhydride **26** using a solution of cinchonidine and diethylzinc in the presence of MeOH.[28] This led to the formation of the desired hemiester **30** in an enantiomerical enriched form (scheme 17).



Scheme 17

These results have to be compared to the one obtained previously by Oda who reported earlier the use of cinchonidine for this type of desymmetrisation (*vide infra*).[29,30]

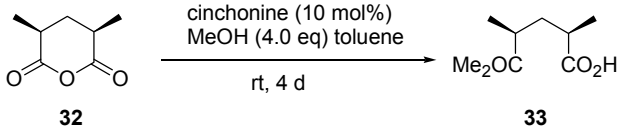


Scheme 18

Another example of Lewis acid catalysed alcoholysis is reported by Seebach in 1995.[31-35] Using Ti-TADDOLates he was able to obtain a 98% ee with an 88% yield in the case of the anhydride **31** (scheme 18).

A different approach, to catalyse the alcoholysis is to use Lewis base catalysts such as chiral amine, which can activate the nucleophilic alcohol via a general base catalysis mechanism or can activate the electrophilic anhydride via a nucleophilic mechanism.

The first example of using chiral amine has been reported by Oda, who used the cinchona alkaloids in catalytic quantity (10 mol%).[29,30] He was able to desymmetrise anhydride such as **32** with acceptable ee and excellent yields (scheme 19).

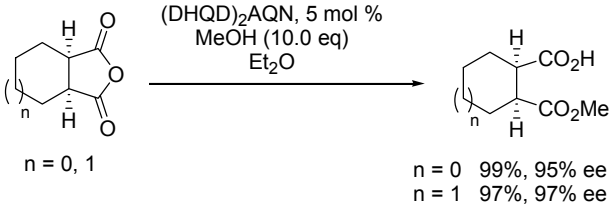


Scheme 19

Based on these results Bolm proposed the used stoichiometric amount of quinine and quinidine to promote the desymetrisation, obtaining up to 99% ee with up to 98% yield in the case of anhydride **32**.[36,37] This method has been used in natural

compound synthesis thus demonstrating the efficiency of the method.[38]

At the same time Deng reported the desymmetrisation of *meso* and prochiral cyclic anhydride with commercial available cinchona alkaloids derivatives, such as $(DHQD)_2AQN$.[39,40] Using 5-30 mol % of the catalyst, he was able to obtain the open derivative with good yield and excellent ee (90-95%) (scheme 20). Applying the same strategy but using the *quasi* enantiomer $(DHQ)_2AQN$, he was able to obtain the reverse enantiomer with very good yield and also very good enantioselectivity.

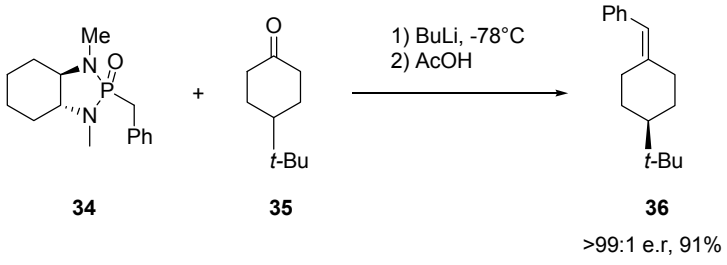


Scheme 20

III. Desymmetrisation of 4-alkyl-cyclohexanones

IV. Olefination of 4-alkylcyclohexanones

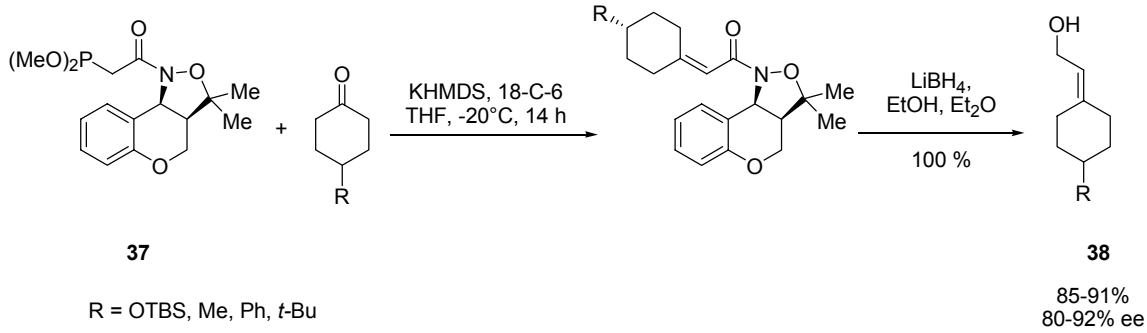
An example of desymmetrisation of cyclic ketones is the preparation of alkenes using Horner or Wadsworth-Emmons reactions using chiral phosphonates or phosphonamides. Hanessian employed the phosphonamide **34** to desymmetrise a different achiral ketones. For example treatment of the phosphonamide **34** with BuLi at –78°C, followed by treatment with 4-tert-butylcyclohexanone and acidic work-up provides the *exo*-alkene in 91% yield and 98% ee (scheme 21).[41,42]



Scheme 21

Masamune and Abiko reported the formation of chiral phosphonates in which the auxiliary is linked through an amide unit.[43] Treatment of the amide **37** with KHMDS in presence of a crown ether and the desired ketone at –78°C formed the

alkene **37** in good yield. Cleavage of the auxiliary using lithium borohydride affords the allylic alcohol with good to excellent ee's (scheme 22).



37

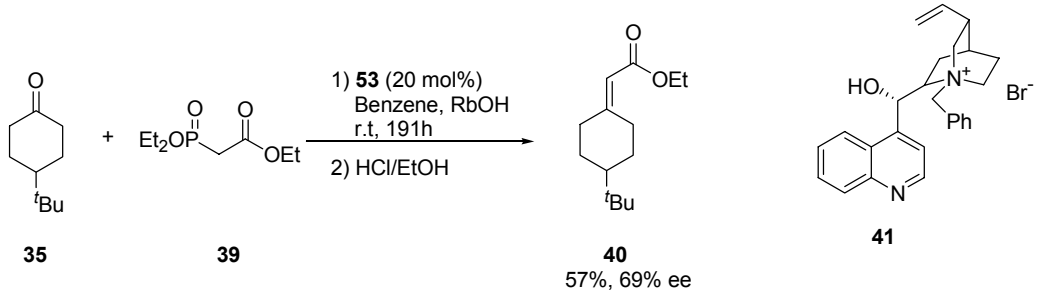
R = OTBS, Me, Ph, *t*-Bu

38

85-91%
80-92% ee

Scheme 22

Recently it has also been reported by Arai and Shioiri[44] a catalytic example of Horner-Wadsworth-Emmons reaction using the quaternary ammonium salt **41**, derived from cinchonine, the phosphonate **39** and rubidium hydroxide. In the case of **35,** this method affords the desired alkene in 57% yield and 69% ee (scheme 23).



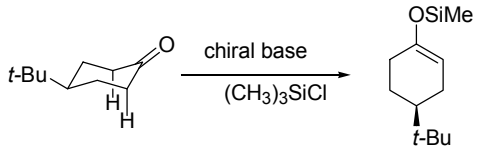
35 **39** **40**
57%, 69% ee

41

Scheme 23

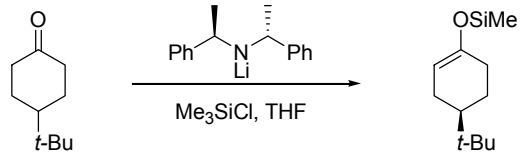
V. Formation of enol ethers

Both Simpkins[45] and Koga[46] reported independently the possibility to use chiral amide base in order to desymmetrise conformationally locked cyclohexanones. In such systems only the axial protons can be removed, thus the use of a suitable chiral base can discriminate the two protons generating only one enantiomer of silyl enol ether (scheme 24).



Scheme 24

For example Simpkins reported that **35** in presence of a chiral base yield the desired enol ether with very good ee (scheme 25).[45]

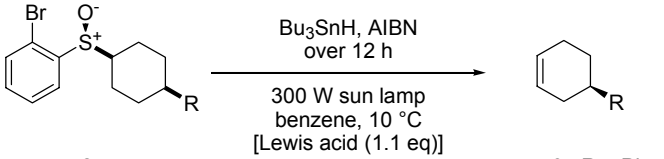


34

Scheme 25

VI. 1,5-H-abstraction

Renaud reported that radical fragmentation of chiral sulfoxide proved to be very efficient for the preparation of 4-substituted cyclohexenes starting from enantiopure *ortho*-bromophenyl sulfoxides.[47] The aryl radical formed at low temperature is able to abstract one of the two hydrogen atoms on the cycle, generating a radical in β-position, which undergoes fragmentation.



42

43 R = Ph
44 R = *t*-Bu

Scheme 26

Entry	Sulfoxide	Lewis acid	Product	Yield (%)	ee (%)
1	*trans* a	none	**42**	75	0
2	*cis*-a	none	**42**	65	70 (*R*)
3	*trans*-b	none	**43**	70	0
4	*cis*-b	none	**43**	70	80 (*R*)
5	*cis*-a	MAD	**42**	60	76 (*R*)
6	*cis*-a	MADPP	**42**	65	84 (*R*)
7	*cis*-a	MADP	**42**	57	86 (*R*)

Table 2. Effect of Lewis acid in the β-fragmentation

The selectivity of the elimination process is controlled by the diasteroselectivity of the hydrogen abstraction and it is rationalised by minimization of steric interactions between the sulfoxide oxygen and the cyclohexane ring. It has been found that only *cis*

derivatives can undergo selective abstraction this probably is due to conformational reasons.

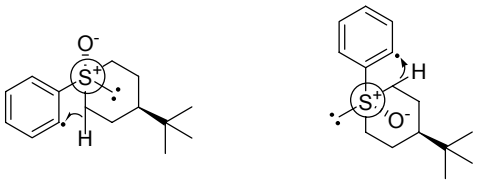
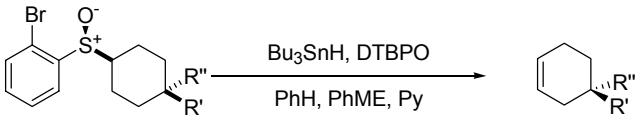


Figure 1

Further studies on this subject show that this method can be applied to a large variety of compound in an efficient way table 3.[48] It has been also shown that the introduction of 20mol% of pyridine helps the radical chain propagation thus increasing the yield as well the ee.



45 a R' = Ph, R'' = H
45 b R' = *t*-Bu, R'' = H
45 c R' = OH, R'' = H
45 d R' = Ph, R'' = OH
45 e R' = Ph_3Si, R'' = H

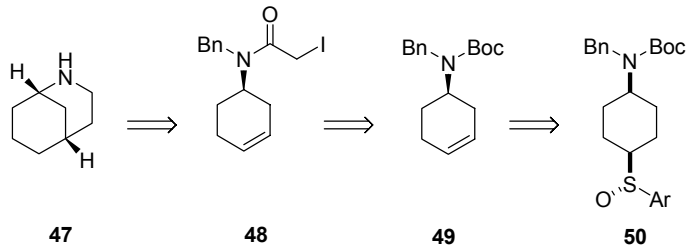
46 a R' = Ph, R'' = H
46 b R' = *t*-Bu, R'' = H
46 c R' = OH, R'' = H
46 d R' = Ph, R'' = OH
46 e R' = Ph_3Si, R'' = H

Scheme 27

Entry	Sulfoxide	Product	*R/S* conf.	Yield, %	e.e., %
1	*cis*-**45a**	**46a**	*R*	81	87
2	*cis*-**45b**	**46b**	*R*	85	96
5	*cis*-**45d**	**46d**	*R*	73	91[a]
9	*cis*-**45h**	**46h**	*R*	15	24
10	*trans*-**45h**	**46h**	---	17	*rac*
11	*cis*-**45i**	**46i**	*S*	36	71 (93)[c]
12	*trans*-**45i**	**46i**	---	23	*Rac*

Table !!!:[a] - e.e. was determined after transformation Ph_3Si – group to HO-; [b] e.e. was determined after reduction N-carbethoxy group to N-Me; [c] – in parentheses given e.e. after one crystallization from hexane

Bonjoch and co-workers have applied this method for the synthesis the morphane ring.[49] Two key steps of the synthesis relied on the formation in an enantiomerically enriched precursor **49** and the radical cyclization of **48,** which should lead to the morphane ring **47**.

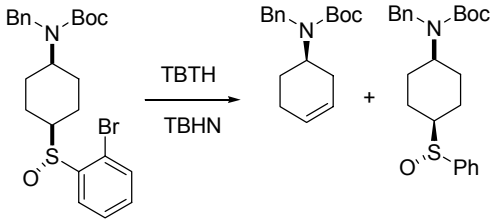


47 **48** **49** **50**

Scheme 28

The synthesis of the precursor has been achieved via 1,5 H abstraction from the correspondent sulfoxide **50**. The reaction run on the *cis* derivative, using TBTH and TBHN as radical initiator affords the desired compound in reasonable yield (50%) together with the reduced product (13%).

It was not possible to measure directly the enantiomeric excess, and it was necessary to synthesise the TAGIT (2,3,4,6-tetra-*O*-acetyl-b-D-glucopyranosyl isothiocyanate) derivative. Evaluation of the ee gave discordant values when measured *via* NMR or GCMS. NMR gave a value of 45% ee, while GCMS values gave a value of only 2 % ee.

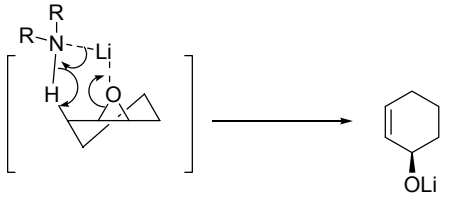


cis-**50** **51** **52**

Scheme 29

VII. Desymmetrisation of epoxides

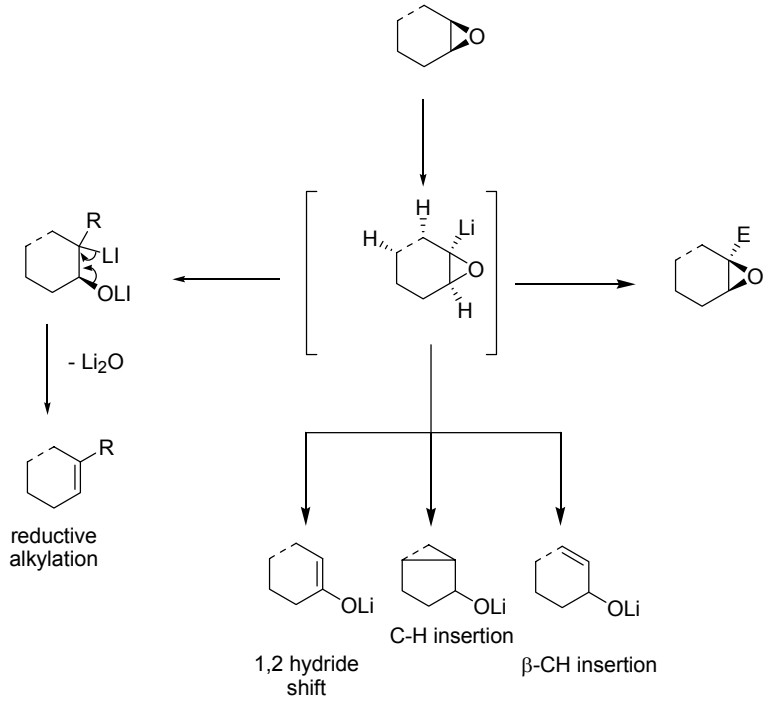
Reaction of a lithium amide with an epoxide bearing a proton in β position results in β-eliminations giving an allylic alcohol. The lithium amide is complexed to the oxygen atom in this way it direct the deprotonation (scheme 29).



Scheme 30

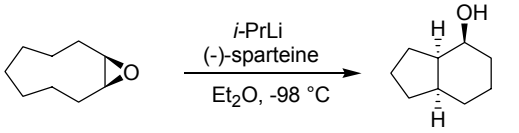
The reactivity of lithiated epoxides is quite various. Once the lithiated derivative is formed, it can follow three different pathways: in case of an excess of

lithium derivative it's possible to have reductive alkylation, while in presence of an electrophile the anion can be trapped, finally it can open to give or a 1,2-hydride shift, or CH insertions, or the β C-H insertion, that leads to enantioenriched allylic alcohols (scheme 30).



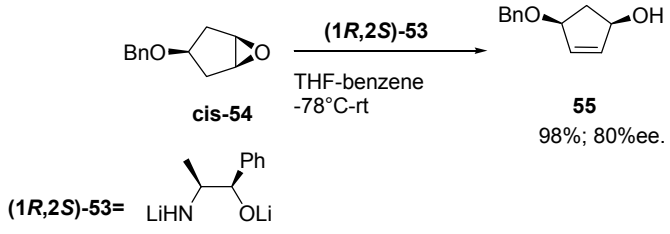
Scheme 30

Hodgson reported for example an enantioselective base-induced transannular rearrangements of medium-sized cycloalkene oxide (scheme 31).[50]



Scheme 31

Murphy rearranged the epoxide *cis*-**54** using the di-lithiated chiral base **(1*R*, 2*S*)-53**, derived from norephedrine and produced the allylic alcohol **55** with good ee.[51,52]



Scheme 32

VIII. References

(1) Schoffers, E.; Golebiowski, A.; Johnson, C. R. *Tetrahedron* **1996**, *52*, 3769-3826.
(2) Poss, C. S.; Schreiber, S. L. *Accounts of Chemical Research* **1994**, *27*, 9-17.
(3) Smith, D. B.; Wang, Z.; Schreiber, S. L. *Tetrahedron* **1990**, *46*, 4793-4808.
(4) Yoneda, F.; Sakuma, Y.; Shinomura, K. *Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry (1972-1999)* **1978**, 348-351.
(5) Marchionni, C.; Vogel, P.; Roversi, P. *Tetrahedron Letters* **1996**, *37*, 4149-4152.
(6) Marchionni, C.; Vogel, P. *Helvetica Chimica Acta* **2001**, *84*, 431-472.
(7) Partridge, J. J.; Chadha, N. K.; Uskokovic, M. R. *Journal of the American Chemical Society* **1973**, *95*, 532-540.
(8) Partridge, J. J.; Chadha, N. K.; Uskokovic, M. R. *Journal of the American Chemical Society* **1973**, *95*, 7171-7172.
(9) Hodgson, D. M.; Thompson, A. J.; Wadman, S.; Keats, C. J. *Tetrahedron* **1999**, *55*, 10815-10834.
(10) Hodgson, D. M.; Thompson, A. J.; Wadman, S. *Tetrahedron Letters* **1998**, *39*, 3357-3358.
(11) Luna, A. P.; Ceschi, M. A.; Bonin, M.; Micouin, L.; Husson, H. P.; Gougeon, S.; Estenne-Bouhtou, G.; Marabout, B.; Sevrin, M.; George, P. *Journal of Organic Chemistry* **2002**, *67*, 3522-3524.
(12) Cramer, N.; Laschat, S.; Baro, A.; Frey, W. *Synlett* **2003**, 2175-2177.
(13) Hawley, R. C.; Schreiber, S. L. *Synthetic Communications* **1990**, *20*, 1159-1165.
(14) Schreiber, S. L.; Hawley, R. C. *Tetrahedron Letters* **1985**, *26*, 5971-5974.
(15) Rubina, M.; Rubin, M.; Gevorgyan, V. *Journal of the American Chemical Society* **2003**, *125*, 7198-7199.
(16) Breit, B.; Breuninger, D. *Journal of the American Chemical Society* **2004**, *126*, 10244-10245.
(17) Trost, B. M.; Patterson, D. E. *Journal of Organic Chemistry* **1998**, *63*, 1339-1341.
(18) Trost, B. M.; Van Vranken, D. L.; Bingel, C. *Journal of the American Chemical Society* **1992**, *114*, 9327-9343.
(19) Rahman, N. A.; Landais, Y. *Current Organic Chemistry* **2002**, *6*, 1369-1395.
(20) Angelaud, R.; Landais, Y. *Journal of Organic Chemistry* **1996**, *61*, 5202-5203.
(21) Willis, M. C. *Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry* **1999**, 1765-1784.
(22) Tian, S.-K.; Chen, Y.; Hang, J.; Tang, L.; McDaid, P.; Deng, L. *Accounts of Chemical Research* **2004**, *37*, 621-631.
(23) Altschul, R.; Bernstein, P.; Cohen, S. G. *Journal of the American Chemical Society* **1956**, *78*, 5091-5095.
(24) Rosen, T.; Heathcock, C. H. *Journal of the American Chemical Society* **1985**, *107*, 3731-3733.
(25) Ohshima, M.; Mukaiyama, T. *Chemistry Letters* **1987**, 377-380.
(26) Imado, H.; Ishizuka, T.; Kunieda, T. *Tetrahedron Letters* **1995**, *36*, 931-934.
(27) Hashimoto, N.; Kawamura, S.; Ishizuka, T.; Kunieda, T. *Tetrahedron Letters* **1996**, *37*, 9237-9240.
(28) Shimizu, M.; Matsukawa, K.; Fujisawa, T. *Bulletin of the Chemical Society of Japan* **1993**, *66*, 2128-2130.
(29) Hiratake, J.; Yamamoto, Y.; Oda, J. i. *Journal of the Chemical Society, Chemical Communications* **1985**, 1717-1719.

(30) Hiratake, J.; Inagaki, M.; Yamamoto, Y.; Oda, J. *Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry (1972-1999)* **1987**, 1053-1058.
(31) Seebach, D.; Beck, A. K.; Schmidt, B.; Wang, Y. M. *Tetrahedron* **1994**, *50*, 4363-4384.
(32) Seebach, D.; Jaeschke, G.; Wang, Y. M. *Angewandte Chemie, International Edition in English* **1995**, *34*, 2395-2396.
(33) Jaeschke, G.; Seebach, D. *Journal of Organic Chemistry* **1998**, *63*, 1190-1197.
(34) Seebach, D.; Beck, A. K.; Imwinkeiried, R.; Roggo, S.; Wonnacott, A. *Helvetica Chimica Acta* **1987**, *70*, 954-974.
(35) Seebach, D.; Dahinden, R.; Marti, R. E.; Beck, A. K.; Plattner, D. A.; Kuehnle, F. N. M. *Journal of Organic Chemistry* **1995**, *60*, 1788-1799.
(36) Bolm, C.; Dinter, C. L.; Seger, A.; Hoecker, H.; Brozio, J. *Journal of Organic Chemistry* **1999**, *64*, 5730-5731.
(37) Bolm, C.; Gerlach, A.; Dinter, C. L. *Synlett* **1999**, 195-196.
(38) Starr, J. T.; Koch, G.; Carreira, E. M. *Journal of the American Chemical Society* **2000**, *122*, 8793-8794.
(39) Choi, C.; Tian, S.-K.; Deng, L. *Synthesis* **2001**, 1737-1741.
(40) Chen, Y.; Tian, S.-K.; Deng, L. *Journal of the American Chemical Society* **2000**, *122*, 9542-9543.
(41) Hanessian, S.; Delorme, D.; Beaudoin, S.; Leblanc, Y. *Journal of the American Chemical Society* **1984**, *106*, 5754-5756.
(42) Hanessian, S.; Beaudoin, S. *Tetrahedron Letters* **1992**, *33*, 7655-7658.
(43) Abiko, A.; Masamune, S. *Tetrahedron Letters* **1996**, *37*, 1077-1080.
(44) Arai, S.; Hamaguchi, S.; Shioiri, T. *Tetrahedron Letters* **1998**, *39*, 2997-3000.
(45) Cain, C. M.; Cousins, R. P. C.; Coumbarides, G.; Simpkins, N. S. *Tetrahedron* **1990**, *46*, 523-544.
(46) Shirai, R.; Tanaka, M.; Koga, K. *Journal of the American Chemical Society* **1986**, *108*, 543-545.
(47) Imboden, C.; Villar, F.; Renaud, P. *Org. Lett.* **1999**, *1*, 873-875.
(48) Kuznetsov, N.; Renaud, P., Unpubblished results.
(49) Villa, X.; Bonjoch, J.; Barcellona, 2003.
(50) Cope, A. C.; Lee, H.-H.; Petree, H. E. *Journal of the American Chemical Society* **1958**, *80*, 2849-2852.
(51) Milne, D.; Murphy, P. J. *Journal of the Chemical Society, Chemical Communications* **1994**, 675.
(52) Milne, D.; Murphy, P. J. *Journal of the Chemical Society, Chemical Communications* **1993**, 884-886.

Total synthesis of (+)- and (-)-ferruginine

I. Tropane alkaloids.

Plants of the family of Solanaceae produce a large variety of alkaloids. Among them there are the tropane alkaloids, which possess an 8-azabicyclo[3.2.1]-octane skeleton. These alkaloids are present in solanaceous plants as hebane (*Hyosciamus niger*), the thorn apple (*Datura Stramonium*) and the nightshade (*Atropa belladonna*), and also in a less extent in Erytroxylaceae and Convolvulaceae.

Hyoscyamine **1** and scopolamine **2** have attracted a lot of attention due to their use in the Middles ages as hallucinogens. Another important example is the racemic hyoscyamine **1**, atropine that causes the dilatation of the eye pupils at 1 in 130000 parts in water, and that is largely used in ophthalmic as a pupil dilatory agent. Scopolamine **2** remains a significant pre-medication administered before surgery under general anaesthetic to arrest salival and mucous secretions.

Cocaine **3** was first isolated from the leaves of Peruvian *Erythroxylon coca* plant from Niemann in 1860. The plant was known for its local anaesthetic properties but it also stimulates the central nervous system and improves physical endurance. These are attractive properties and led to drug being widely administrated in Europe in various medicatins before the addictive properties of cocaine were fully realised.

Ecgonine **4**, is obtained by hydrolysis of cocaine.

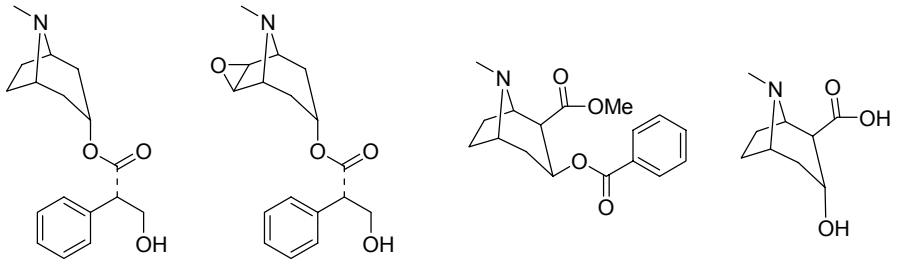
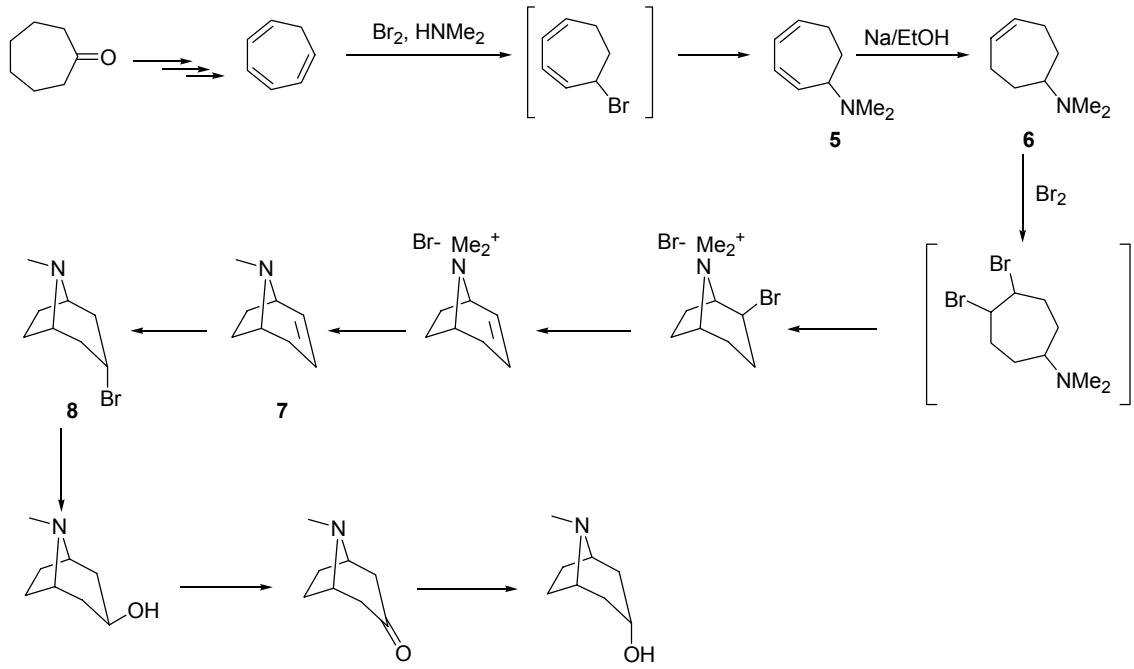


Figure 1

The elucidation of the structure of the tropane alkaloids was secured by Willstaeter, who extensively studied the tropane alkaloids. The first total synthesis of the tropane ring was also reported by Willstaetter in 1901 (Scheme 1).[1] Considering the years when this has been carried out, this synthesis is a masterpiece of organic

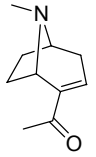
synthesis. A shorter synthesis was described by Robinson in 1912.[2]

The synthesis of α-tropine, that was isolated by Kraut in 1863 after boiling a sample of atropine with $BaSO_4$ solution, started from cycloheptatriene, which was synthesised from cycloheptanone (scheme 1). Treatment with bromine and dimethylamine afforded the dimethylaminocycloheptadiene **5**. Reduction with Na in EtOH, gave **6.** After bromination, cyclisation gave the first synthesis of the tropane skeleton. Alkali treatment afforded **7,** which was therefore transformed in **8** by HBr addition. The bromide was then transformed in the β-alcohol by heating the product in a sealed vessel at 200°C with sulfuric acid. Oxidation and then reduction with alcoholic sodium afforded the good stereoisomer.



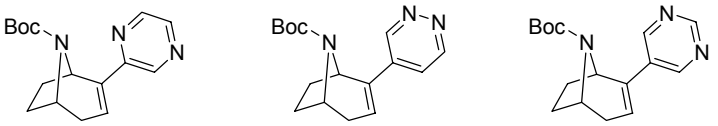
Scheme 1

(+)-Ferruginine (+)-**9** has been isolated from two arboreal species *Darlingia Darlingiana* and *Darlingia Ferruginea* in 1979.[3,4] It's a potent neurotoxin, while its unnatural isomer has shown interesting activities as nAChR agonist.[5] In order to find analogues showing a better activity in binding the nAChR and also to get more information concerning the receptor itself.[5-11]



(+)-9
Ferruginine

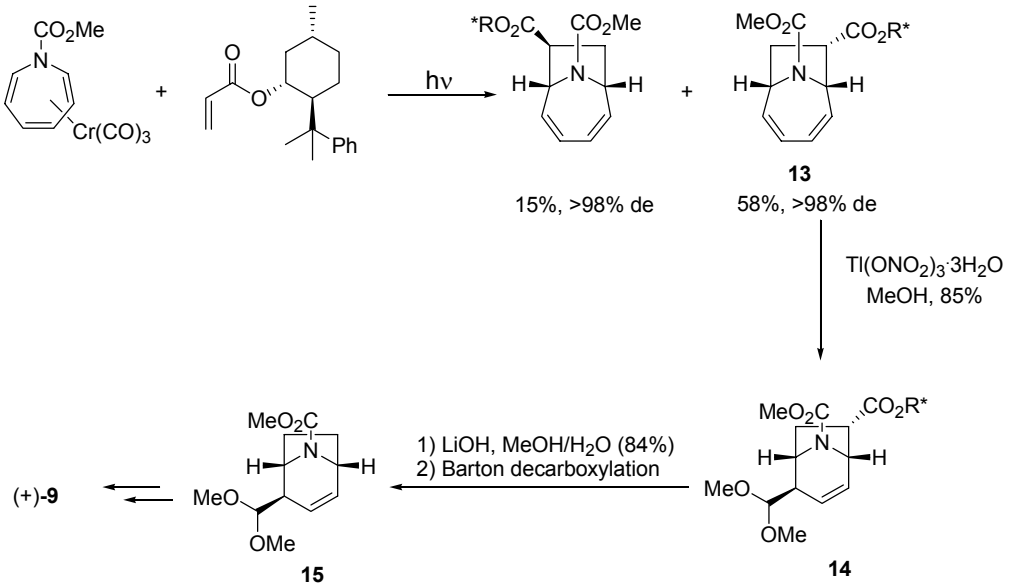
Many synthesis have been reported in literature. For example Gundisch and Seitz reported the synthesis of three diazine analogs, which possess in vitro affinity towards two different nAChR subtypes. Only **12** showed a better affinity than (-)-**9**.[11]



10 **11** **12**

II. Feruginine synthesis

The first synthesis of (-)-**9** was reported by Rigby and co-worker in 1995.[12] Using a chromium(0) promoted [6π+2π] cycloaddition with a vinyl acrylate containing a chiral auxiliary they synthesised the adduct **13** with 98% dr. This was submitted to a ring contraction using a thallium (III) salt leading to compound **14**. After Barton decarboxylation, the intermediate **15** was transformed into (+)-**9** (scheme 2).



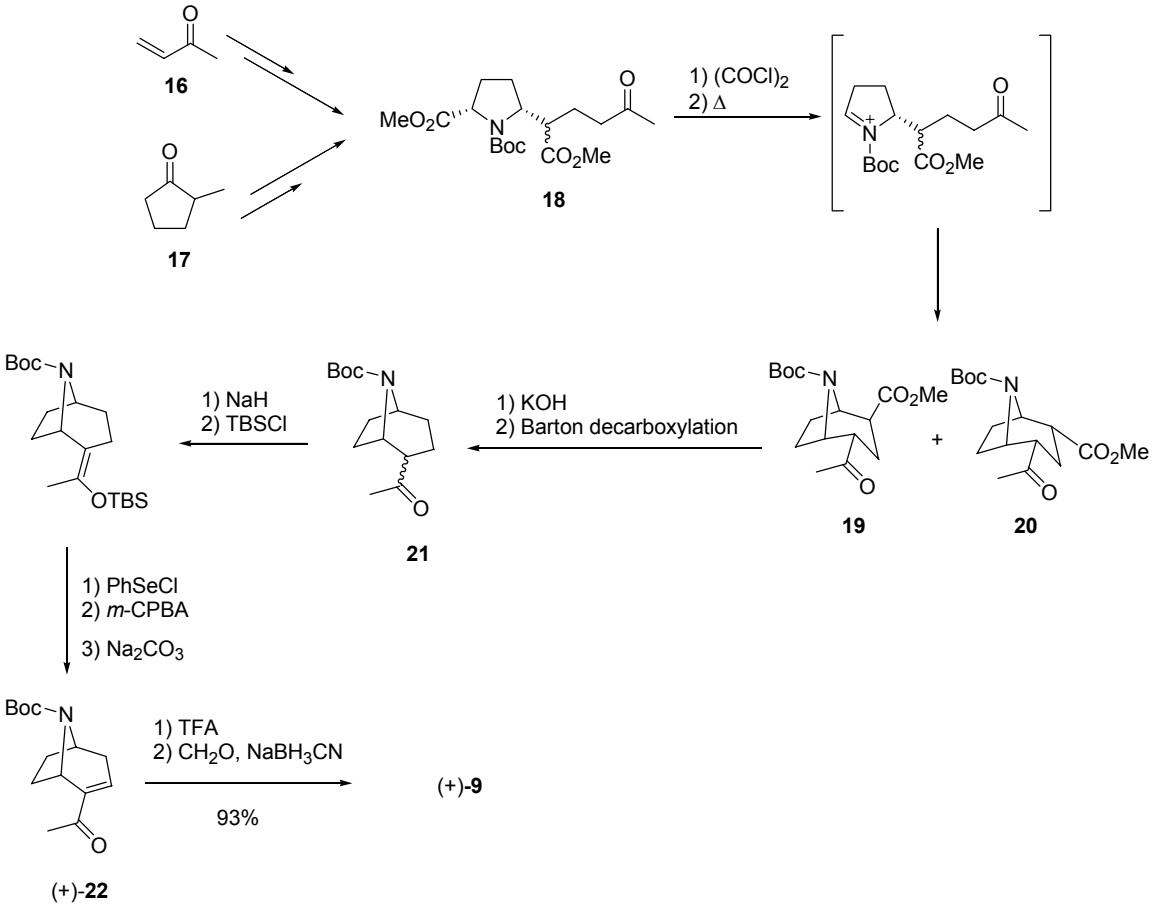
13 **14** **15**

Scheme 2

In 1996 Rapoport reported the synthesis of both (+) and (-)-**9**.[13] They synthesised compound **18** in two different ways starting either from the vinyl methyl ketone **16** or from the methyl cyclopentanone **17**. Intramolecular cyclisation of the

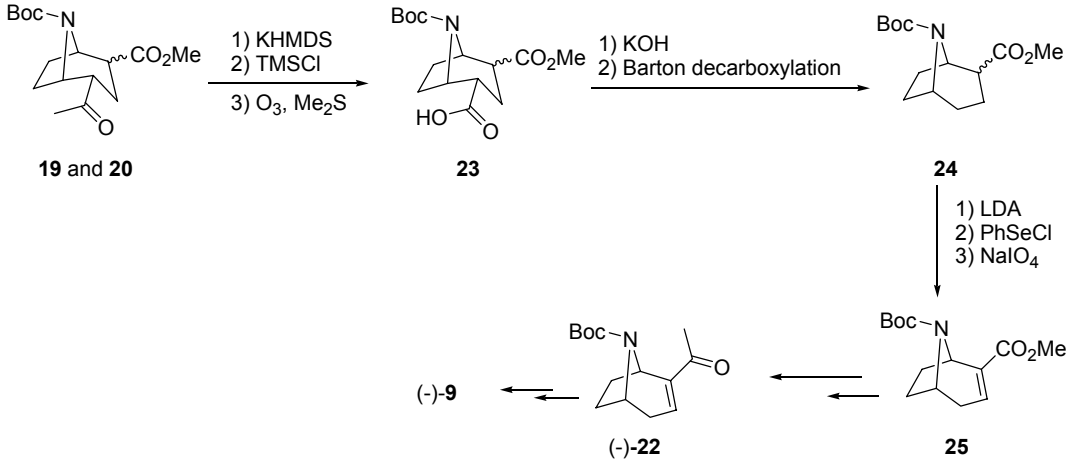
iminium ions generated from the keto esters **18** afforded the tropanic systems **19** and **20**. The Boc-protected derivatives are then submitted to Barton decarboxylation to give **21**. The enolised derivatives were then submitted to addition of PhSeCl and subsequent oxidation/elimination to give (+)-*N*-Boc-norferruginine **22**, which was then transformed into (+)**-9** (scheme 3).

The enantiomer (-)**-9** was obtained from **19** and **20.** Ozonolysis of the enolic form of the methyl ketone yielded the acid **23**. Once again Barton decarboxylation



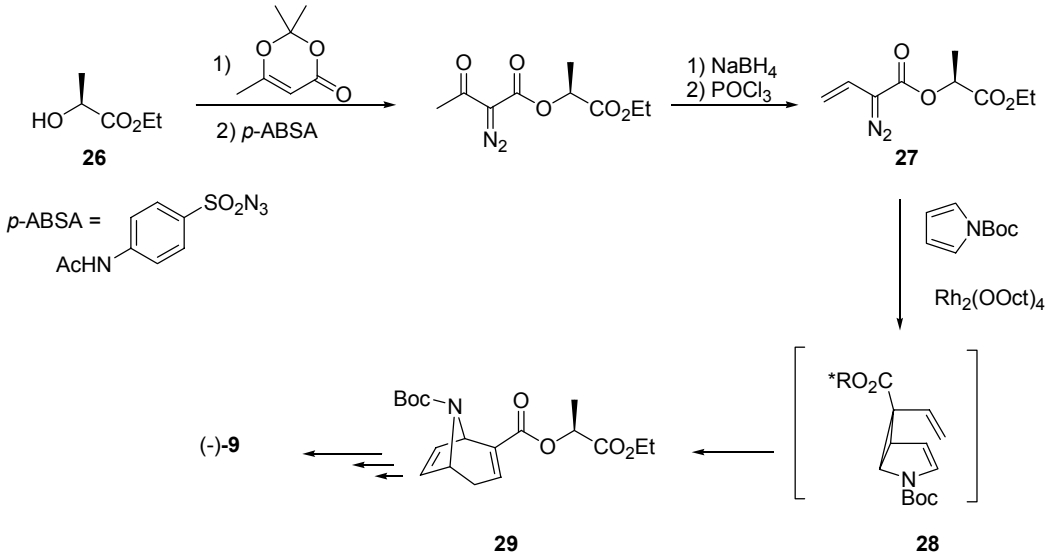
Scheme 3

afforded the esters **24**. Introduction of PhSeCl, and subsequent oxidation/elimination gave the α,β-unsaturated ester, which was transformed into the corresponding (-)-*N*-Boc-norferruginine **22**, and finally into (-)**-9** (scheme 4).



Scheme 4

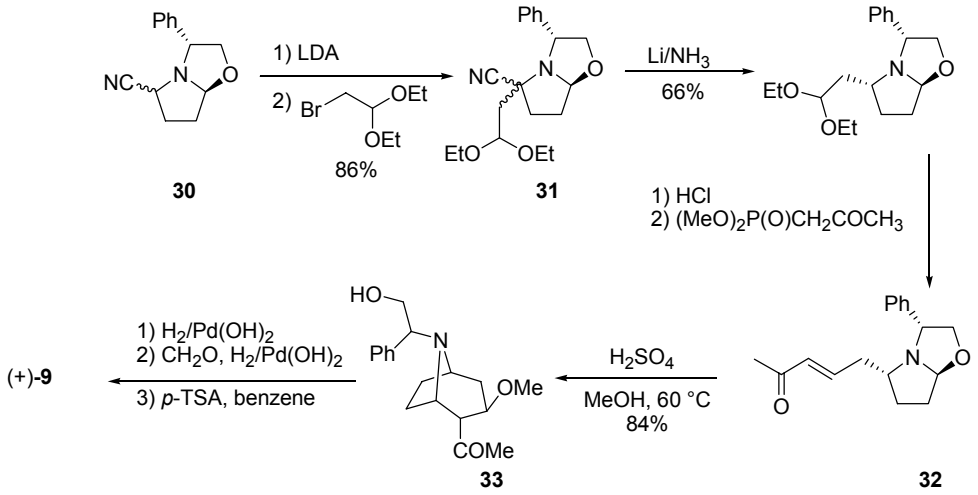
Davies and co-workers reported in 1997 the possibility to use a tandem rhodium (II)-catalysed cyclopropanation followed by a Cope rearrangement to create the tropane skeleton (scheme 5).[14] They prepared the vinyldiazomethane **27** starting from the chiral alcohol **26**. Reaction of N-Boc-pyrrole with **27** in presence of Rh(II) octanoate afforded the intermediate **28** which then evolved spontaneously through a Cope rearrangement to the tropanic system **29**. Ferruginine (-)**-9** was then obtained after several steps from **29** (scheme 5).



Scheme 5

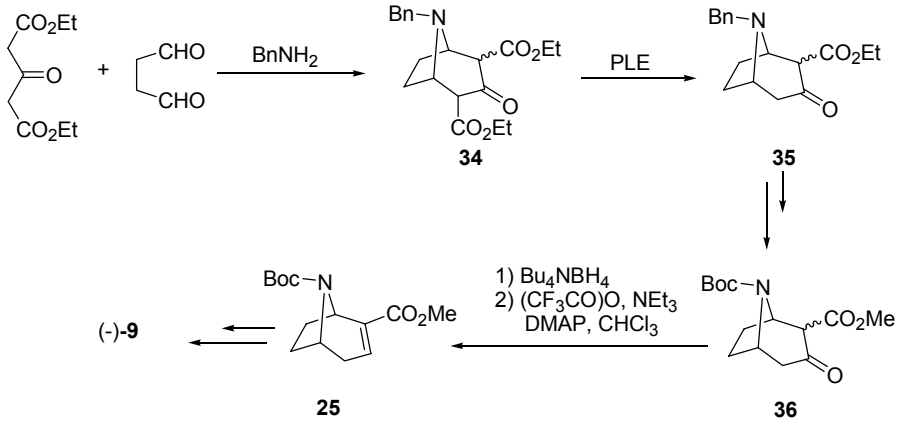
In the same year Husson and Royer reported the synthesis of **9** (scheme 6).[15] They started from the bicycle **30**, which can be prepared from phenylglycinol dimethoxytetrahydrofuran and potassium cyanide. Alkylation with bromoacetaldehyde diethylacetal affords **31** as a mixture of diastereoisomers.

Decyanation gave only one disatereoisomer. After hydrolysis of the acetal and Horner-Wasdworth-Emmons reaction the intermediate **32** was obtained. Treatment with sulfuric acid in methanol afforded **33**, which after deprotection, methylation and treatment with *p*-toluenesulfonic acid gave (+)**-9**.



Scheme 6

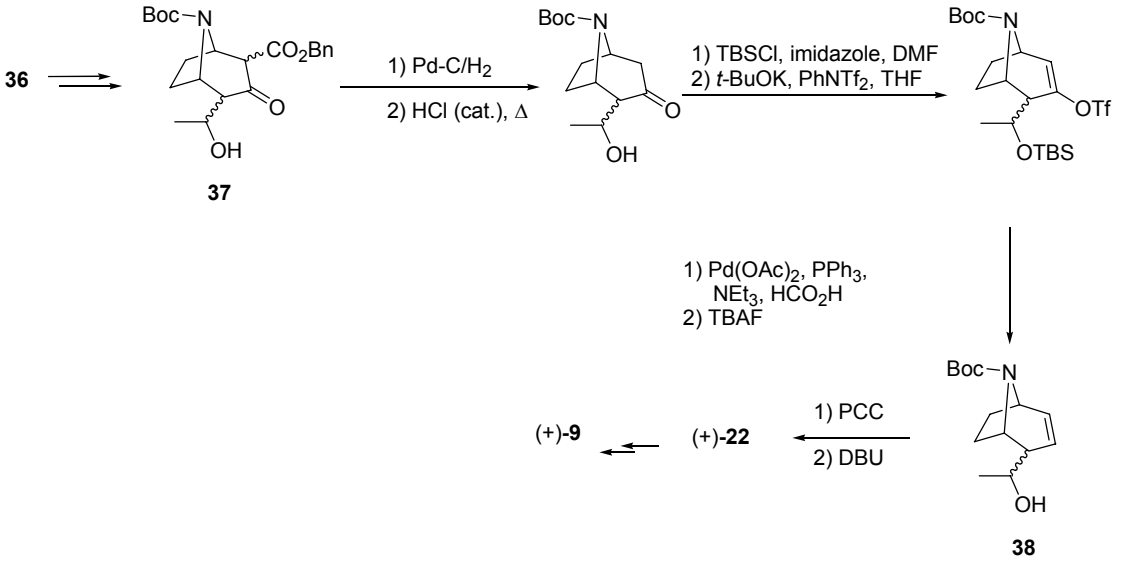
More recently Node and co-workers reported the synthesis of **9** using a PLE-catalysed asymmetric dealkoxycarbonylation (scheme 7).[16] Following the procedure reported by Robinson for the synthesis of tropinone they prepared the diethyl dicarboxylate **34**. Subsequent PLE-catalysed asymmetric dealkoxycarbonylation gave the derivative **35**. Reduction of the ketone followed by elimination of the corresponding triflate gave **24**, reported already by Rapoport.



Scheme 7

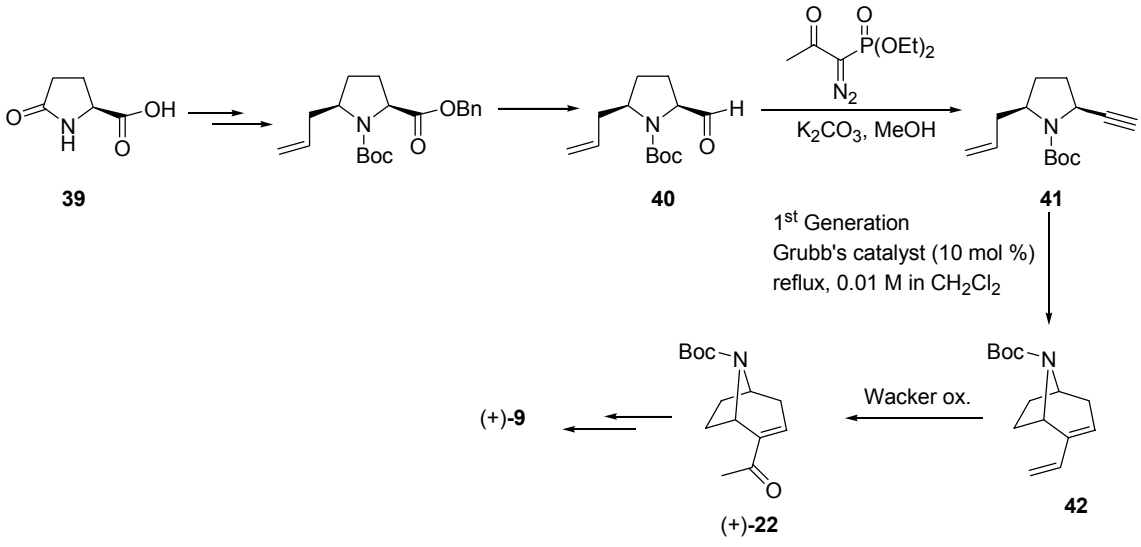
On the other hand aldolisation with **36** and acetaldehyde afforded the keto-alcohol **37**, which, after decarboxylation, was protected with TBSCl. Formation of the

enol triflate, Pd(0)-catalysed reduction of the triflate with formic acid, and deprotection of the alcohol gave **37**. Oxidation and treatment with DBU yield (+)**-22**. Deprotection and methylation gave (+)**-9** (scheme 8).



Scheme 8

In 2004 Aggarwal reported the use of enyne ring-closing metathesis.[17] Starting from L-pyroglutamic enyne **41** was synthesised. Ring-closing metathesis with Grubb's first generation catalyst afforded the diene **42**, which gave after Wacker oxidation **(+)-22** (scheme 9).

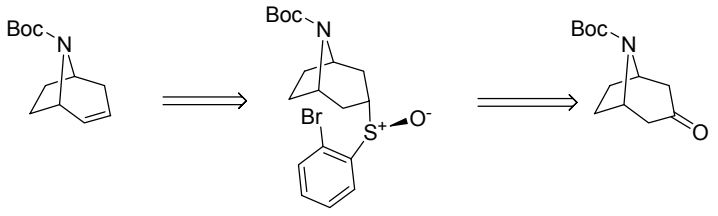


Scheme 9

III. Objective of the work

Based on previous result obtained in the laboratory on the β-fragmentation of

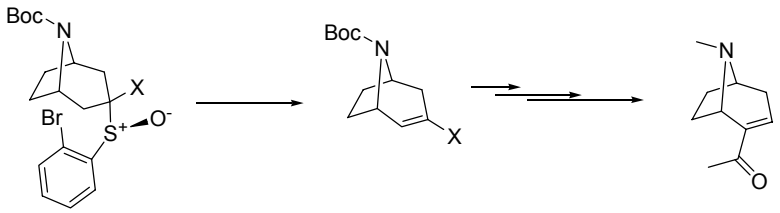
sulfoxide, we thought to synthesis **9** using as key step radical fragmentation of sulfoxide to desymmetrise the meso tropinone. Compound **43** should give 1,5-hydrogen abstraction followed by β-fragmentation affording tropene in an enantioenriched way (scheme 10).



43 **44**

Scheme 10

If the tropane system is suitable for the β-fragmentation of the sulfoxide, it should be possible to introduce on the carbon bearing the sulfoxide a substituent like a sulphide or, even better, a sulfone that after the fragmentation will help to introduce the methyl ketone moiety (scheme 11).



45 **(+)-9**

Scheme 11

This would be an interesting substrate in order to introduce further functionalities an in particular could be used for the synthesis of ferruginine.

IV. Sulfoxides in Asymmetric Synthesis

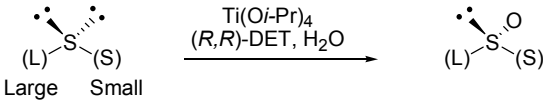
The use of sulfoxide in asymmetric synthesis is widely spread due to the easy preparation of enantiopure, or enantioenriched derivatives and to the easily removal without loss of the stereochemical integrity. This makes the sulfoxide a particular interesting chiral auxiliary.

IV.I.I. Preparation of optically active sulfoxides.[18]

Three are the main method used for the preparation of optically active sulfoxides: a) resolution of racemic mixtures, but this method is of limited used and generally suffers of lack of generality; b) oxidation of sulfides with chiral systems; c) asymmetric synthesis.

Oxidative procedure.

Many methods are reported for the synthesis of chiral sulfoxides via oxidation, and a lot of reviews cover this field.[19-22] One of the most efficient methods is the one reported by Kagan[23-25], which uses a Sharpless type reagent, i.e. Ti(O*i*-Pr)$_4$/DET/H_2O in a ratio 1:2:1 and as peroxide the tert-butyl hydroxyperoxide (TBHP) or cumene hydroperoxide (CHP)[26,27]. Using this combination of reagents Kagan was able to obtain good yield of sulfoxides with very good enantioselectivities (table).



Scheme 12

Entry	Sulfide	Hydroperoxide	Yield(%)	ee (%)	Ref.
1	Me-S-(*p*-Tol)	TBHP	90	89	24
2	Bu-S-(*p*-Tol)	TBHP	75	75	24
3	Me-S-(1-Napht)	TBHP	98	89	28
4	Cycloprop-S-(*p*-Tol)	TBHP	73	95	28
5	Me-S-(*p*-Tol)	CHP	93	96	26
6	Me-S-(*o*-Anisyl)	CHP	97	93	26

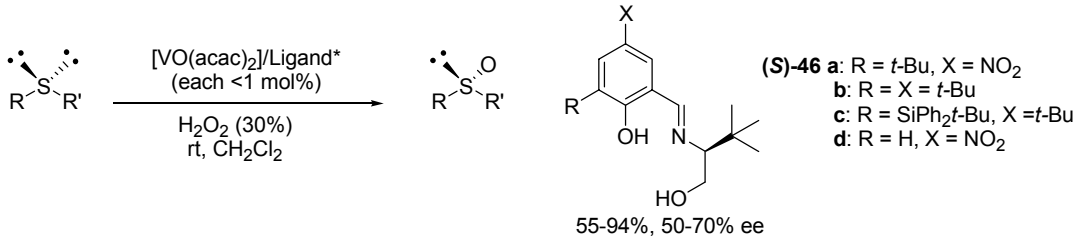
Table 1: reaction condition performed at –20°C, at 5 mmol scale. Ti(O*i*-Pr)$_4$/ (*R,R*)DET/H_2O, 1:2:1

At the same time Modena[29] reported a similar reagent Ti(iPrO)4/DET in a ratio of 1: 4 and the reaction was carried out in anhydrous condition with TBHP.

Entry	Sulfide	Yield(%)	ee (%)	Ref.
1	Me-S-(*p*-Tol)	46	64 (*R*)	30}.98
2	Me-S-(*p*-Tol)	60[a]	88 (*R*)	30}.98
3	Bu-S-(*p*-Tol)	99	34 (+)	30}.98
4	Me-S-CH_2Ph	70[a]	46 (+)	30}.98
5	(*p*-ClC_6H_4)-S-$(CH_2)_2$OH	41	14 (-)	30}.98

Table 2: reaction performed with 1 equivalent of Ti complex at –20°C in toluene. Ti(O*i*-Pr)$_4$/ (*R,R*)DET, 1:4
a) Reaction run in dichloromethane at –77°C

An other interesting reagent has been reported more recently by Bolm[31] who used a vanadium catalyst preformed *in situ* from VO(acac)$_2$ and the ligands **46**. These catalysts present an interesting improvement since it use a cheap oxidant H_2O_2 and the reaction can be carried out at room temperature and without using inert atmosphere, since the humidity or the oxygen do not effect the outcome.

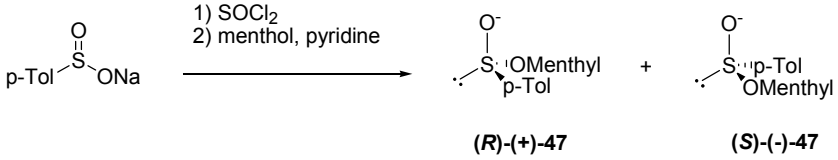


Scheme 13

Asymmetric synthesis

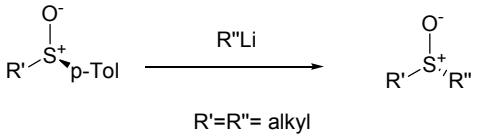
The most efficient asymmetric synthesis of chiral sulfoxides has been reported by Andersen.[32] The key step is the addition of a Grignard derivative onto a diastereomerically pure sulfinate ester. The addition of the Grignard onto the sulfinate ester proceeds with complete inversion of configuration of the sulfur atom, thus starting from an enantiopure sulfinate ester an enantiopure sulfoxide is formed.

The synthesis of the sulfinate has been reported for the first time by Phillips and subsequently improved by Solladié, can be achieved starting from the sulfinic salt, which is transformed in the correspondent chloride.[33] Subsequent addition of the menthylate affords the desired sulfinate ester **47** as a mixture of two diastereoisomers. The two diastereoisomers can be equilibrated/epimerized in acidic media and the less soluble (*S*)-(-) diastereoisomer is isolated by crystallization. [34,35]



Scheme 14

Using Andersen's method is possible to prepare aromatic sulfinate can be obtained, thus no dialkyl sulfoxides can be prepared with this method. This problem was solved by Johnson who observed that the addition of alkyl lithium derivatives onto an arylsulfoxide gives the nucleophylic substitution on the sulphur atom with complete inversion of configuration.[36]



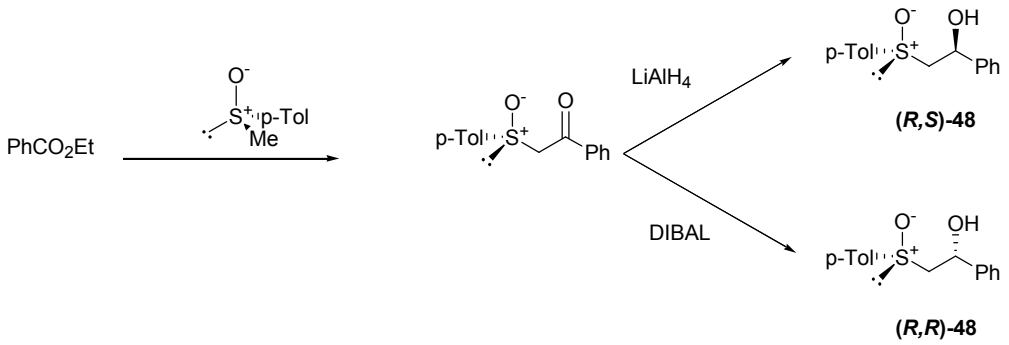
Scheme 15

IV.I.II. Applications

Reduction of alcohols

In 1982 Solladié reported a highly efficient asymmetric reduction of β-ketosulfoxides, prepared from the condensation of the anion of the methyl-(R)-*p*-tolylsulfoxide with different esters.[37] Depending from the source of hydride used, he

was able to obtain one or the other diasteroisomeric alcohol. The absolute configuration was determined by transformation to the known benzoate.



Scheme 16

Subsequently, Solladié reported that addition of equimolar amount of $ZnCl_2$ anhydrous to the substrate solution prior to the DIBAL reduction afford the opposite diastereoisomer respect to the one obtained employing DIBAL alone.[38] In this case The zinc goes to chelate the two oxygen atoms, thus the hydride attacks the keto-group from the less hindered face of the prochiral carbonyl group (figure 2A).

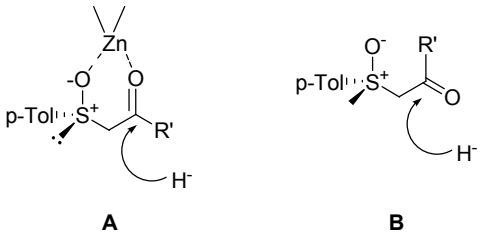


Figure 2

When the reaction is carried out with $LiAlH_4$ the more stable conformation is B and the attack of the hydride comes from the less hindered face (figure 2B). When the reaction is carried out with DIBAL but without a Lewis acid A is the favoured one, since C, and D suffer of unfavourable R'/*i*-Bu 1,3 diaxial interactions, while B suffer of an unfavourable R/*i*-Bu 1,3 diaxial interaction (figure 3).[39]

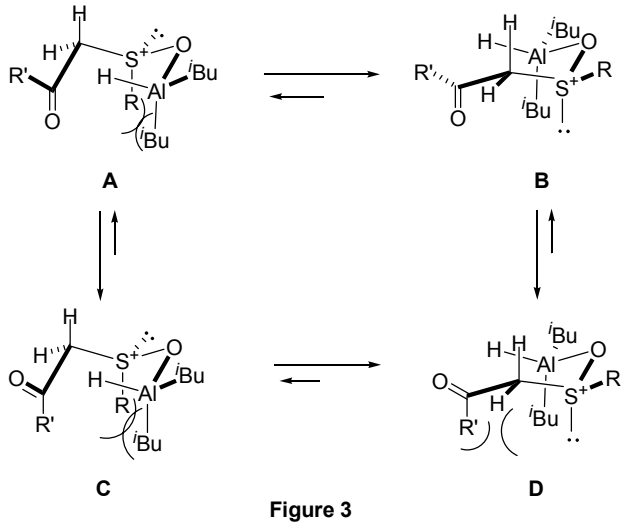
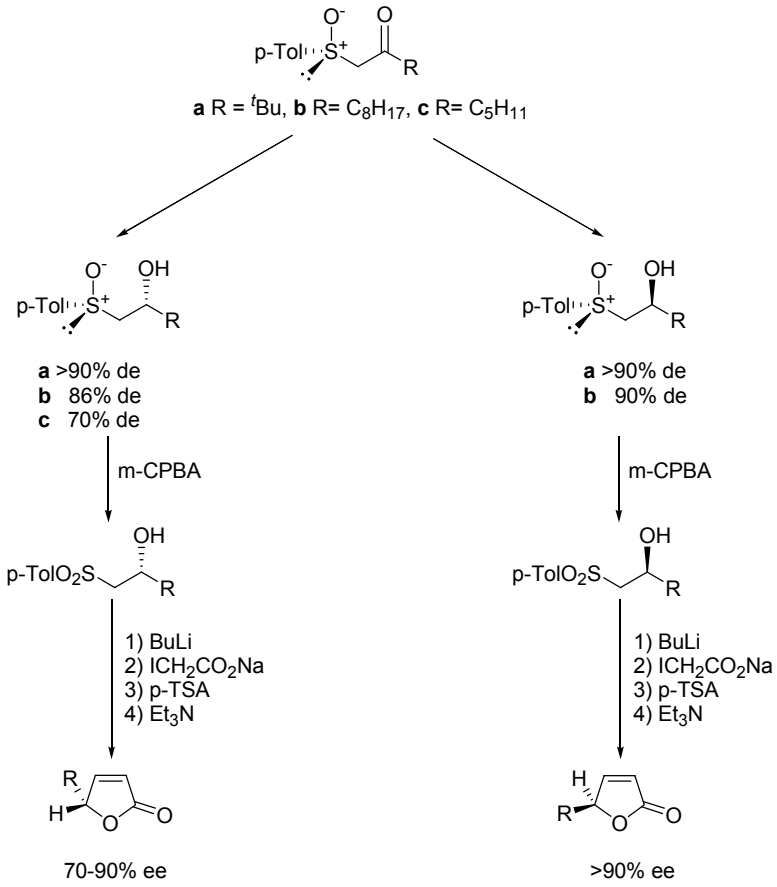


Figure 3

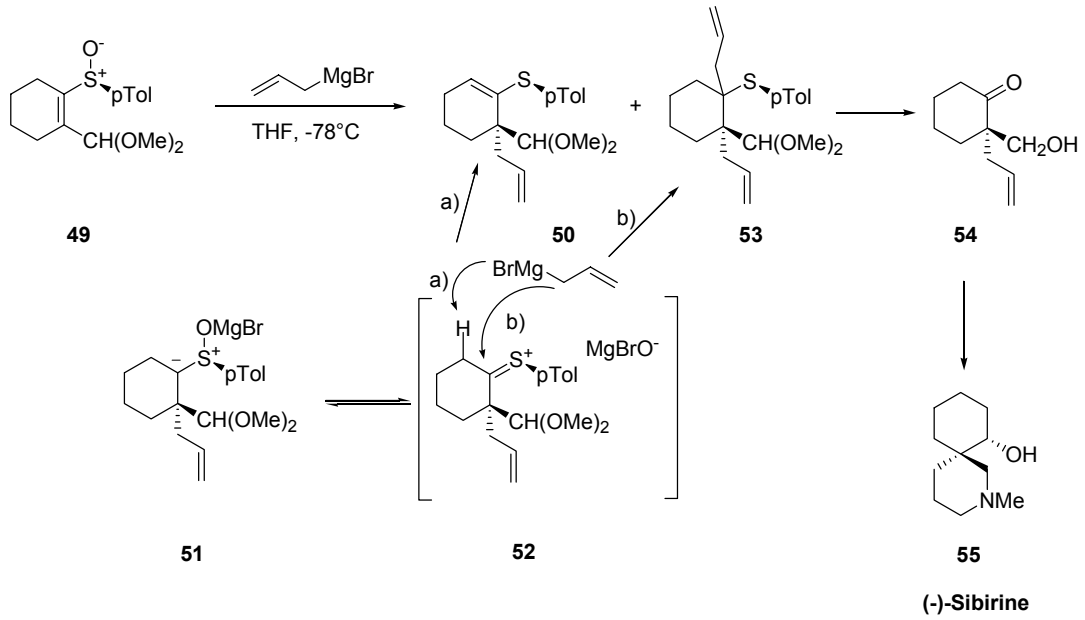
In 1986 it has been reported the synthesis of various butanolides using β-reduction of ketosulfoxide.[40] Butanolides are compounds widely found as subunit of naturally occurring products (scheme 19).[41-44]



Scheme 17

Conjugate additions

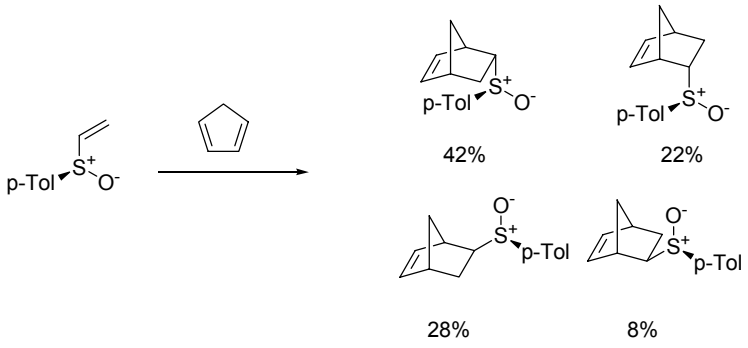
It is also possible to have conjugate addition onto vinylic sulfoxides, for example (-)-sibirine **55** has been synthesised via addition of allyllmagnesiumbromide onto **49**, giving a vinylic sulfide of 96%ee **50**.[45,46] The nucleophilic addition to **49** affords the ylide intermediate **51,** which evolves to the sulfonium cation **52**. Deprotonation by the Grignard reagent affords the vinylic sulfoxide, while a second attack by the Grignard affords the bis-allylated compound **53**. Subsequent deprotonation of the aldehyde, reduction of the alcohol and Pummerer-type reaction afford the ketoalcohol **54**, which after various steps is converted in **55**.



Scheme 18

Diels-Alder

The first report on the use of enantiomerically pure sulfinyl dienophiles in Diels-Alder cycloaddition was by Maignan and Raphael, who utilised (+)-(*R*)-*p*-tolyl vinyl sulfoxide as an optically active dienophile.[47] A mixture of *exo* and *endo* diastereoisomers was formed as a result of a poor selectivity.



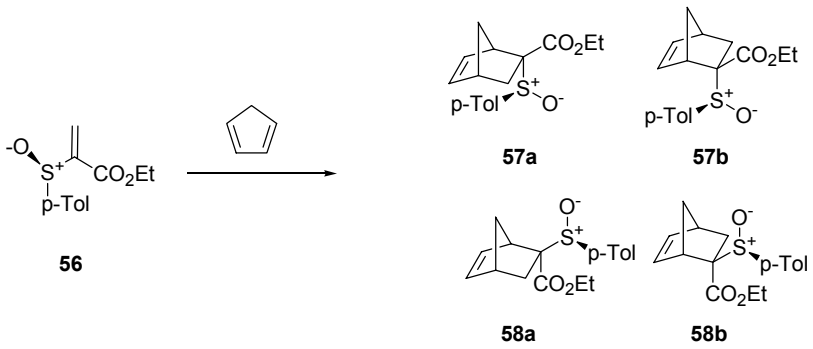
Scheme 19

It was found that simple, unactivated enantiomerically pure vinyl sulfoxide such as the *p*-tolyl vinyl sulfoxide, without further substitution on the double bond, are not effective in inducing diastereoselectivity in asymmetric Diels-Alder reactions.

In case of substituted vinyl sulfoxides the diastereoselectivity depends from the conformation of the compound. Normally the addition onto the dienophile occurs from the less hindered face, i.e. *syn* to the lone-pair electrons on the sulphur.

Koizumi and co-workers reported the use of the optically active derivative **56**

as a chiral dienophile. It exhibits high reactivity and diastereoselectivity in cycloaddition reaction with antracene and cyclopentadiene, affording compounds **57** and **58**, although the *endo-exo* selectivity was low (table1).[48] The addition of $ZnCl_2$ to the reaction with cyclopentadiene afford the opposite selectivity, this due to the complete change of the conformation due to the chelation of the two oxygen atom to the Zn.



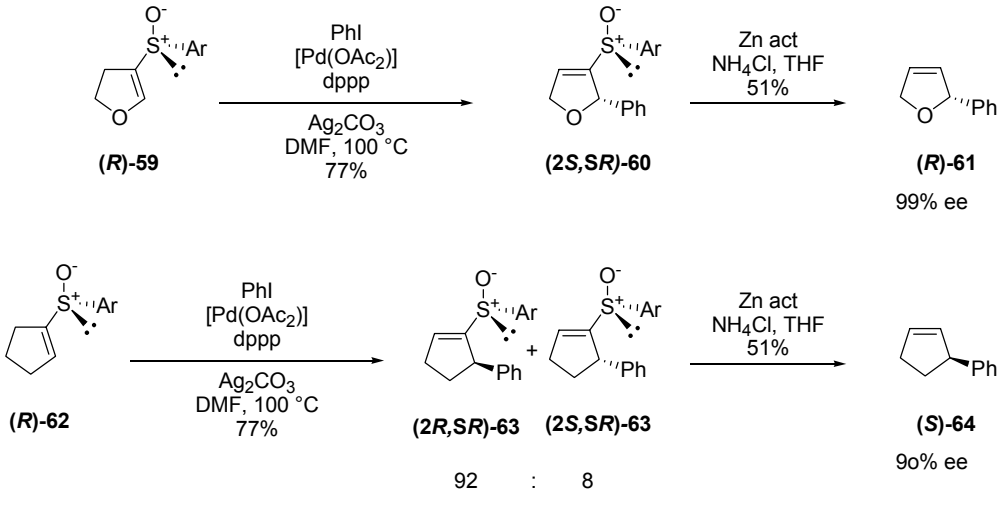
Scheme 20

Lewis Acid	Solvent	Ratio of diastereomeric cycloadducts (*endo* CO_2Et) a:b	(*exo* CO_2Et) a:b	**57**:**58**
None	PhH	64:11	23:2	3.0:1
$ZnCl_2$	CH_2Cl_2	2:77	2:19	3.8:1

Table3. Selectivity of vinyl sulfoxide in Diels Alder reactions

Heck reactions

Recently, Carretero reported the capacity of sulfoxide to control the stereochemical outcome of Heck reactions.[49] They synthesised compound **59** and **62** and they run the Heck coupling with iodobenzene in presence of $Pd(OAc)_2$, dppp and Ag_2CO_3. Cleavage of the sulfoxide generates the compounds with high ee (scheme 23).

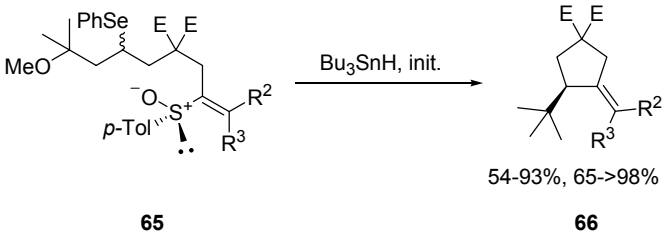


Scheme 21

Radical cyclisation

Malacria and co-workers reported recently an asymmetric intramolecular vinylation using enantiopure sulfoxides as chiral auxiliaries.[50]

The cyclisation occurs with good ee: once that the radical is formed this adds onto the vinyl sulfoxide to give after β-fragmentation only **66** (scheme 22).



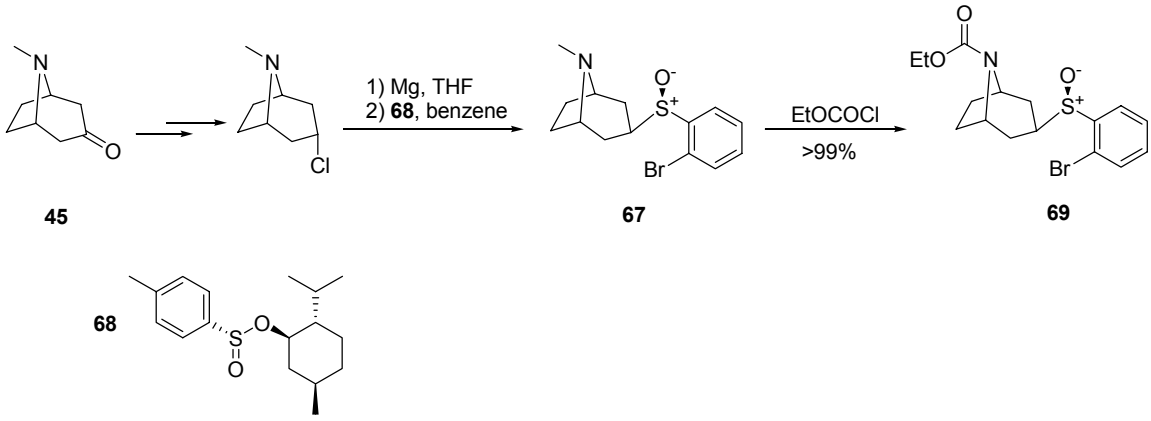
65 **66**

Scheme 22

V. Results and discussion

V.I. Desymmretisation of tropanone

A previous work run by Kuznetsov in this research group was devoted to the study of radical fragmentation of sulfoxides, among the various examples he studied the ortho-substituted sulfoxide **69**, which was synthesised starting from the tropinone **45**. After reduction of tropinone and formation of the chloride the *exo* sulfoxide **67** has been synthesised and protected into the corresponding ethylcarbamate **69** (scheme 26).[51]

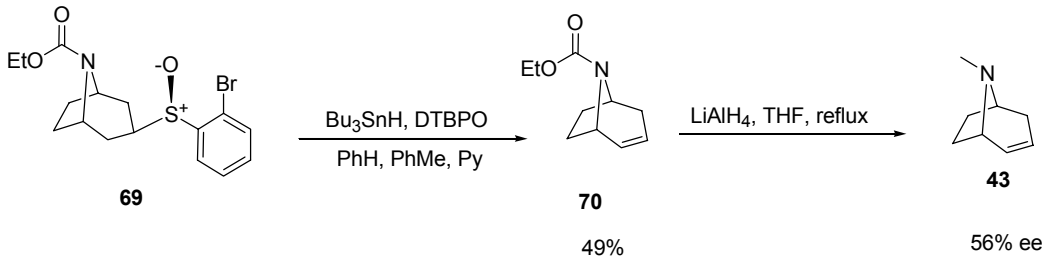


45 **67** **69**

68

Scheme 23

The cascade 1,5-hydrogen abstraction- β-fragmentation gave the desired **70.** The determination of the enantiomeric excess was effectuated on **43**, which was obtained by simple reduction with $LiAlH_4$. The whole process gave 56% ee and 46% yield (scheme 27).[51]

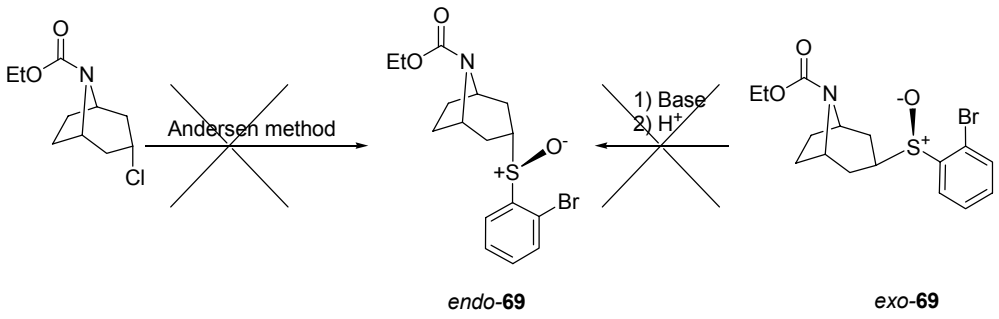


Scheme 24

Supported by this encouraging result, the subsequent step in order to improve the ee was to run the cascade 1,5-hydrogen abstraction-β-fragmentation with the *endo* derivative. Previous studies run in this research group have proven that the spatial configuration of the sulfoxide is important for the selectivity of the 1,5-hydrogen abstraction, and therefore it was expected that the *endo* derivative would produce a better ee.

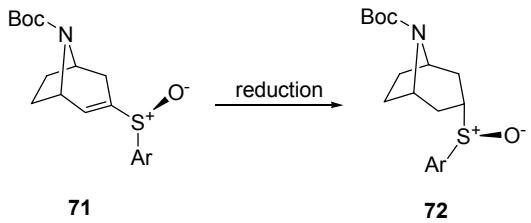
In order to test the cascade 1,5-hydrogen abstraction-β-fragmentation this part of our project aimed firstly to synthesise of the *endo*-derivative. Unfortunately every attempt to obtain it failed: only the *exo* derivative was isolated.

Deprotonation/protonation experiments did not give the desired result (scheme 25).[51]



Scheme 25

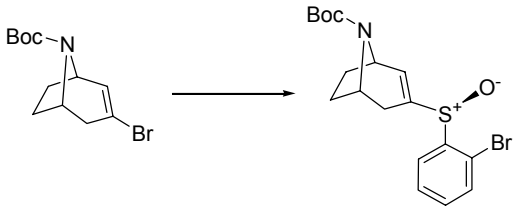
A different approach to synthesise the *endo* derivative was the reduction of the vinyl sufoxide **71** (scheme 26).



Scheme 26

The enantiopure vinyl sulfoxide can be synthesised using the vinyl bromide **73**

(scheme 27).

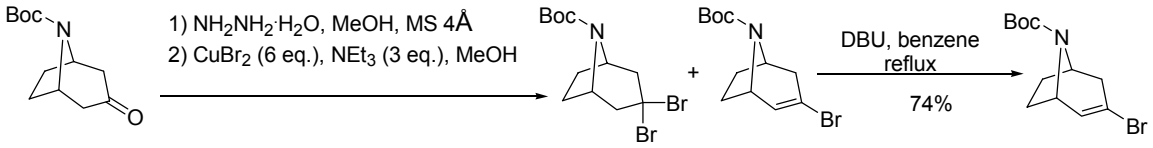


73 **74**

Scheme 27

Takeda describes that an hydrazone can be transformed in the corresponding geminal dibromide using copper (II) halide and triethylamine, while Marchand describe that in the same conditions the geminal dibromide derivative is not isolated, but spontaneously eliminate HBr to afford the vinylbromide.[52,53]

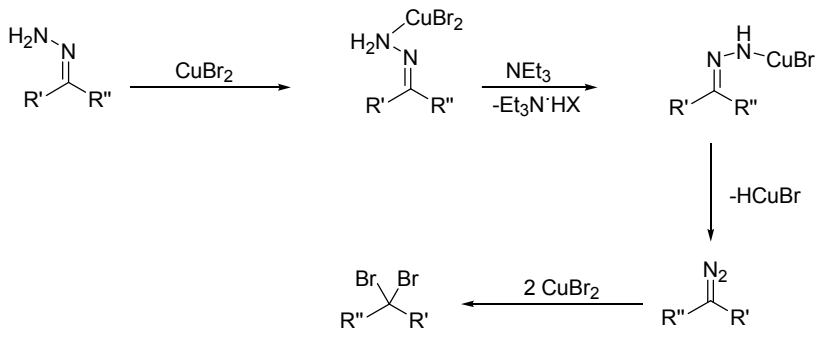
Using the same condition the hydrazone deriving from **75** gave a mixture of **76** and **73**. Subsequent base elimination run on the mixture of **76** and **73** afforded the pure **73** with good yield for the three steps (scheme 31).



75 **76** **73** **73**

Scheme 28

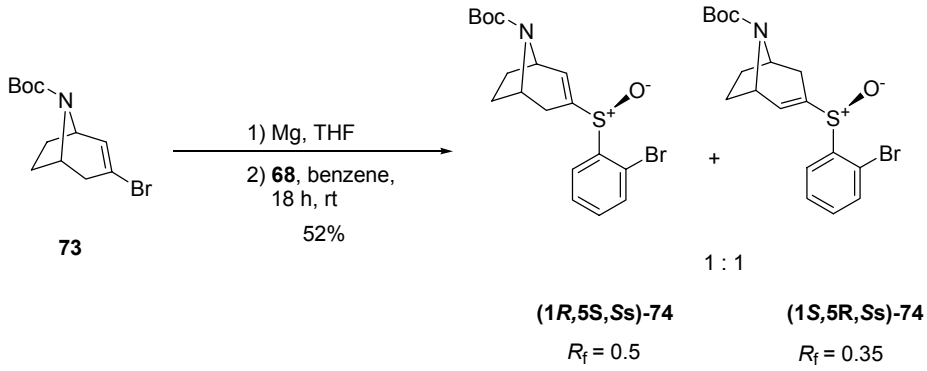
In this reaction copper bromide and triethylamine catalyse the formation of the diazoderivative, which then evolves, in presence of copper bromide, to the geminal dibromide (scheme 29).



Scheme 29

So following the Andersen's method the sulfoxide **77** was synthesised as a 1 : 1

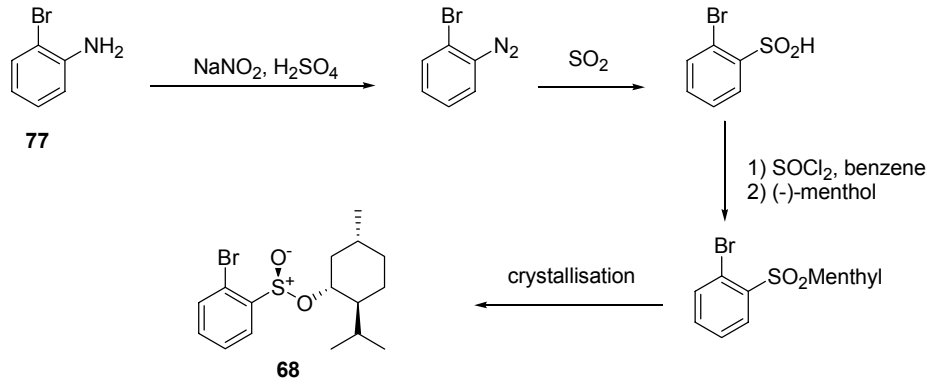
mixture of two diastereoisomers.[32] These were easily separable using FC (Fluka, LOBAR) and were isolated in a 54% combined yield. The facility of separation of the two diastereoisomers (R_f = 0.5 and 0.35, TBME/hexane, 2:1) opened the way to different strategies for the synthesis of **9.**



Scheme 30

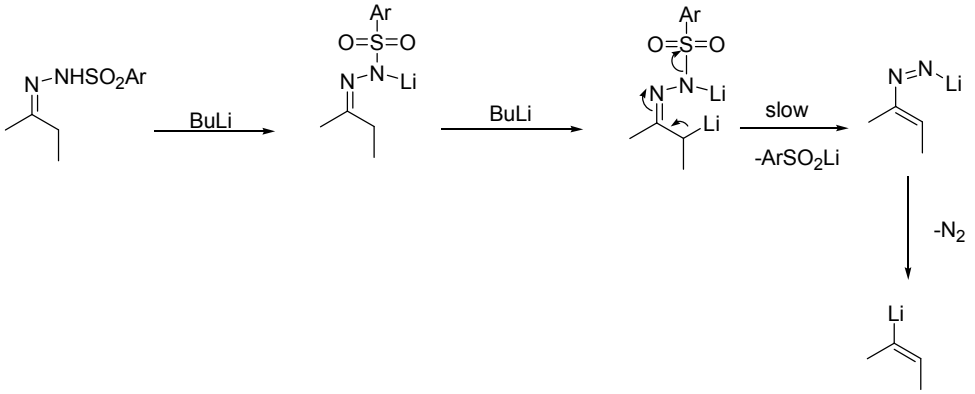
For the synthesis of **74** it was necessary to prepare the sulfinate **68**, which was synthesised following literature procedure.[54] Formation of the diazonium salt form and addition of SO_2 gave the sulfinic acid that was then transformed into the sulfinate **68.** After crystallisations and acid isomerisation the enantiopure sulfinate was obtained (scheme 31)**.**[54]

In order to increase the overall yield of this process the possibility to prepare the sulfoxide in two steps from the ketone using the Shapiro reaction was investigated.[55-57]



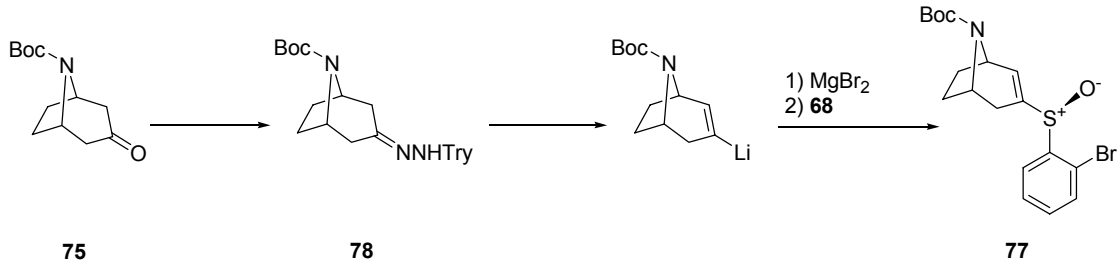
Scheme 31

In the Shapiro reaction, treatment with two equivalents of BuLi or LDA leads to the elimination of the sulfone as sulfinic acid and to the vinylic diazo-derivative, which looses spontaneously N_2. The lost of the sulfone is the slow and in order to increase the speed of the reaction bulky groups are used on the aromatic rings (scheme 32).



Scheme 32

In order to run the Shapiro reaction on our system it has been chosen to synthesis the trisylhydrazone, since from the literature this hydrazone is one that give best results. Shapiro reaction run onto the trysilhydrazone gave the vinyllithium derivative. After lithium-magnesium exchange the mixture was added onto the sulfinate **68** (scheme 33).



75 **78** **77**

Scheme 33

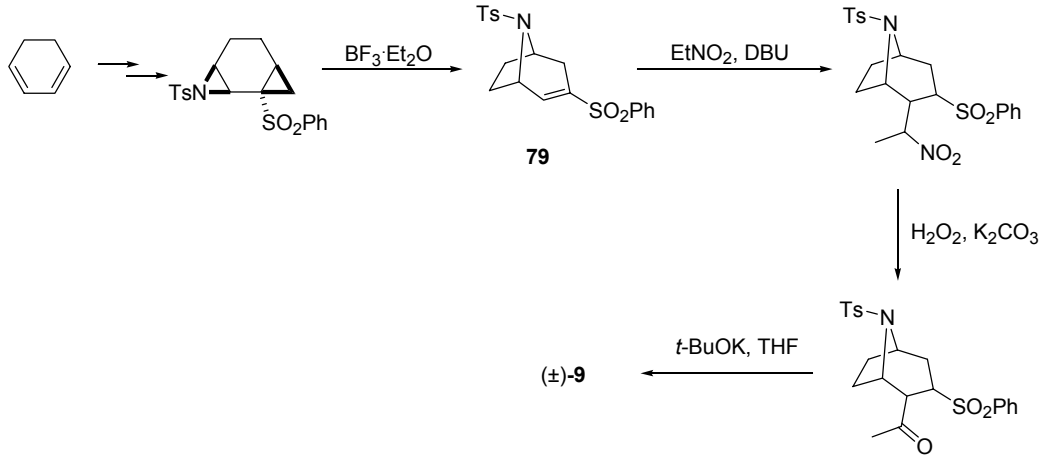
After many trials in order to optimise the reaction conditions only 21 % yield of the two diastereoisomers was obtained. The low yield induced us to give up this way and continue with the original strategy.

Once that the vinyl sulfoxide was obtained the reduction of the double bond with Pd on charcoal was tested, but it revealed to be unsuccessful.

On the other hand, the feasibility of resolution of the two diastereoisomers revealed to be interesting and it will be discussed in the next paragraph.

V.II. Formal synthesis of (+) and (-)-feruginine

Bäckvall reported the racemic synthesis of ferruginine 9 using a conjugate addition onto the vinyl sulfone 79 (scheme 34).[58]

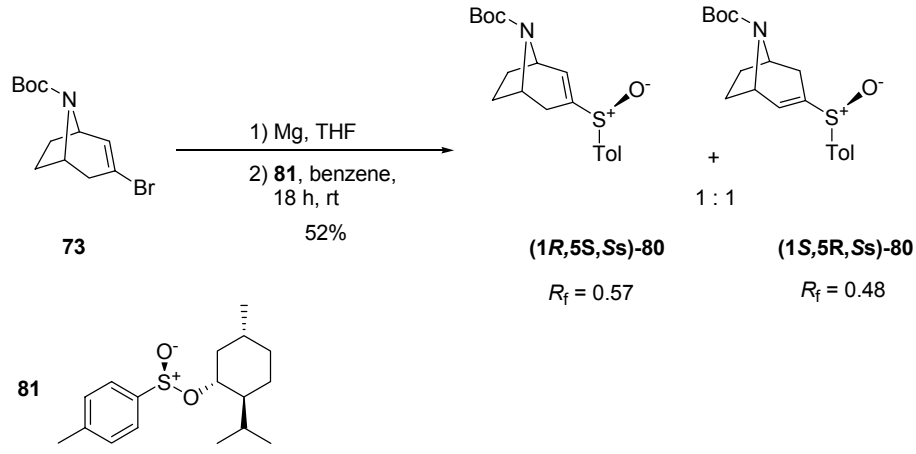


Scheme 34

Taking into account this, a fast and easy synthesis of **9** can derive from our strategy. In fact resolution of the vinyl sulfoxide lead to two diastereomerically pure compounds that after oxidation would yield to the enantiomerically pure vinyl sulfone that could be then used to continue the synthesis following Bäckvall approach.

In order to synthesise ferruginine the vinyl sulfoxide **80** was prepared: the *p*-tolyl derivative was chosen since it is commercially available and the presence of the bromine atom on the aromatic ring is not necessary to the synthesis itself.

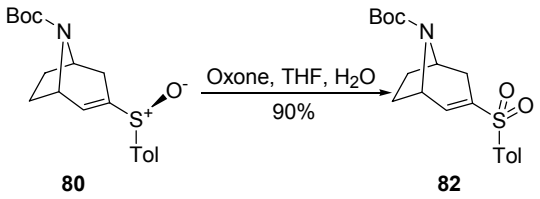
Following the same procedure used for **74** it was possible to synthesise **80** with 54 % yield as a mixture of two diasteroisomers. As for **74** the two diastereoisomers are easily and completely separable (R_f = 0.57 and 0.48, hexane/EtOAc, 3:1) (scheme 35).



Scheme 35

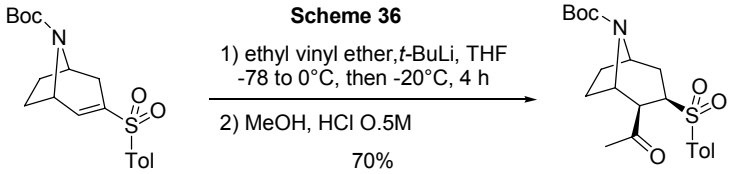
Each diastereoisomer was use to prepare (+) and (-) ferruginine. Here it will be described the synthesis only on the diastereoisomer that leads to the natural product. The same strategy has been applied to synthesise the other enantiomer obtaining the same results in terms of product and yields.

Oxidation of the vinyl sulfoxide to the corresponding vinyl sulfone can be easily achieved with good yield using Oxone® (scheme 36).



80 **82**

Scheme 36

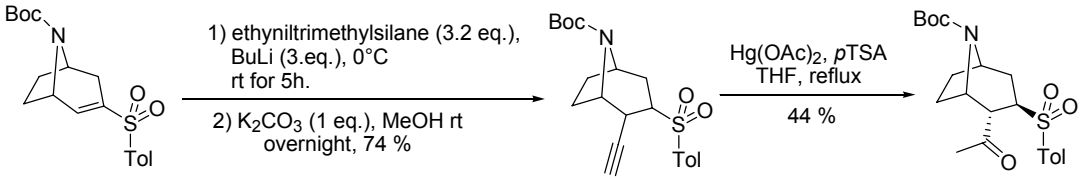


82 **85**

Scheme 38

Nucleophilic addition of nitroethane onto the sulfone **82** using the Bäckvall's conditions did not take place. In refluxing nitroethane, however, some product was obtained but the reaction was not reproducible.

Conjugate addition with the protected acetylene should yield after hydrolysis to the desired methyl ketone. Addition to the vinylsulfone, followed by desilylation, afforded the desired adduct **83** with 74 % yield. The hydrolysis with $Hg(OAc)_2$ was more difficult then expected and **84** was isolated as one diastereoisomer in 44 % yield (scheme 37).



82 **83** **84**

Scheme 37

Ethyl vinyl ether was then used as masked methylketone. Formation of the lithium derivative and addition onto **83** led, after treatment with methanolic hydrochloric acid, to the desired adduct **85** (scheme 38).

Comparison of the two ^{1}H-NMR spectra of **84** and **85** showed that they were not identical. The coupling constants and NOe analysis allowed determination of the relative stereochemistry for the two different isomers. In **84**, the relatively high coupling constant between H_1 and H_2 (J = 11 Hz) indicate that the two protons are *trans*

and both axial. Irradiation of H_1 shows NOe effect with the axial protons on the bridge: the main ring possess a chair conformation. The coupling constant in **85** between H_1 and H_2 is only 5 Hz, and H_1 posses also a coupling constant with H_3 of 12 Hz: this means that the H_1 is in axial conformation and H_1 and H_2 are *cys*. Irradiation of H_1 gives NOe effect with the protons on the bride to confirm also in this case that the main ring posses a chair conformation.

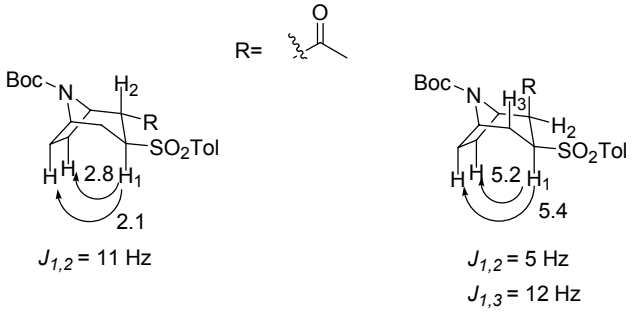
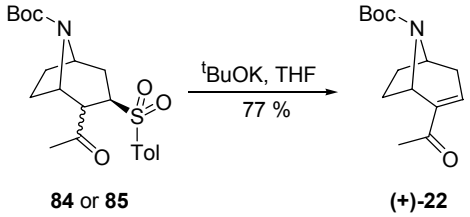


Figure 4

Treatment with *t*-BuOK of **84** or **85**, gave **22** with good yield (scheme 42).



Scheme 39

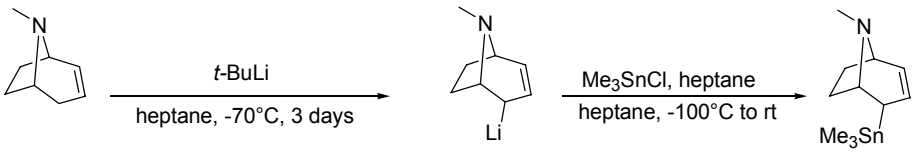
Also in this case as for all the previous steps described, the reaction of elimination ran on the enantiomers of **84** and **85** gave the intermediate (-)-**22** with comparable yield.

This represents a formal synthesis of (+)- and (-)-ferruginine since subsequent transformation into (+)- and (-)-feruginine has been already described by Rapoport.[13]

V.III. Isomerisaton via an allylic anion

The yield limiting step of the synthesis is the resolution of the vinyl sulfoxide. Further study to isomerise the double bond was run in order to improve the total yield.

The deprotonation of tropene with *t*-BuLi followed by trapping with trimethyltin chloride has been reported (scheme 43).[59]



Scheme 40

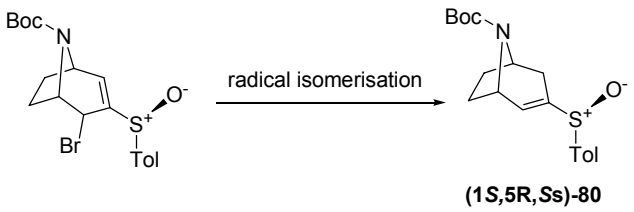
Based on this result, the possibility of isomerisation of the double bond in **79** *via* an allylic anion was investigated.

The reaction of deprotonation was run using LDA or *t*-BuLi running the reaction at different temperature and concentration. In every case the reaction did not gave the result hoped, only degradation of the starting material was observed.

V.IV.Isomerisation via allylic radical

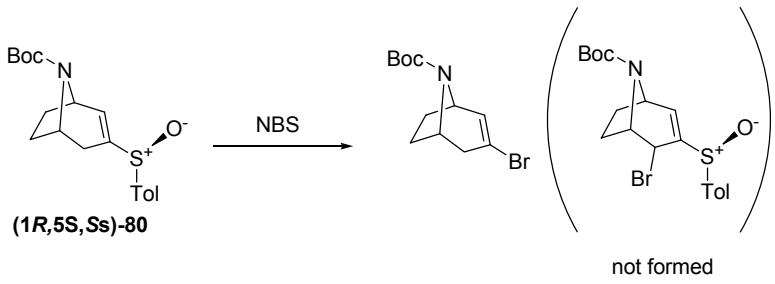
Another possibility to isomerise the double bond is to generate an allylic radical: subsequent reduction should be controlled by the chiral sulfoxide generating preferentially one of the two possible diastereoisomers.

First, it was tried to make an allylic bromination followed by a radical reduction of the allylic bromide.



Scheme 41

Synthesis of a vinyl bromide with NBS was attempted. The vinyl sulfoxide was consumed, but the desired brominated sulfoxide was not observed. ^{1}H-NMR analysis showed the lost of the sulfoxide and generation of the vinyl bromide **73** (scheme 46).

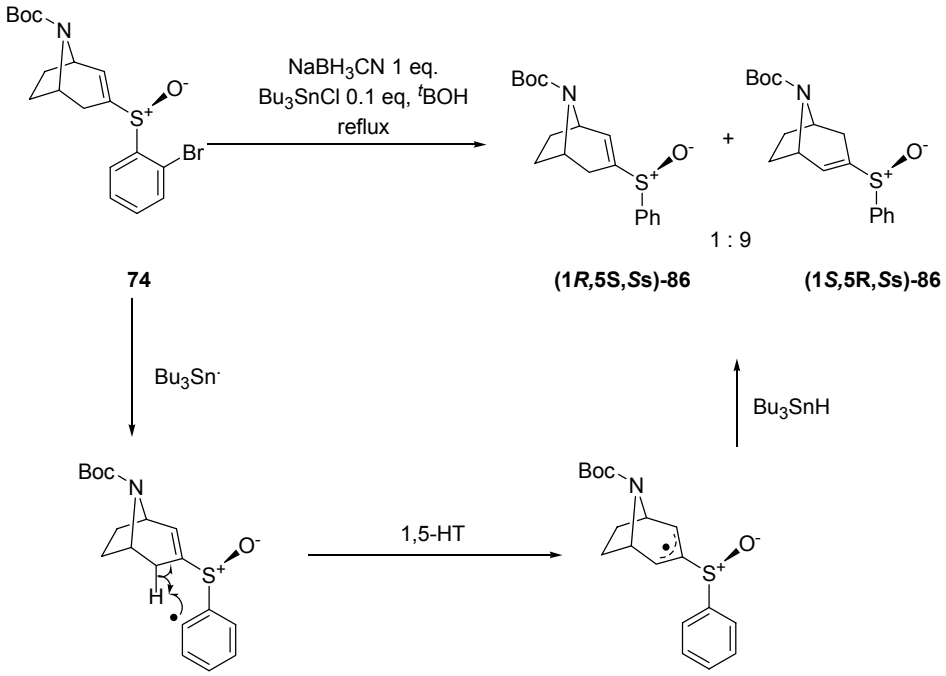


Scheme 42

Another way to generate an allylic radical is to abstract the proton in allylic position. This should be possible using the *o*-bromophenyl sulfoxide: generation of the aryl radical should afford the allylic radical after 1,5-hydrogen transfer. Subsequent reduction is expected to be stereoselective due to the chirality of the sulfoxide

The reaction was carried out in refluxing *t*-BuOH. AIBN was used as radical initiator using Bu_3SnCl in catalytic quantity and $NaBH_3CN$ in stoichiometric quantity.[60]

The tributhylstannyl radical abstracts the bromine atom. The aryl radical abstracts an hydrogen at the allylic position. Subsequent abstraction of hydride from the tin hydride formed *in situ* should give the desired compound (scheme 47).



Scheme 43

In a preliminary experiment run with the diastereomerically pure **74** two different diastereoisomers in a ratio of 9:1 were isolated with 50% overall yield. Comparing the ^{1}H-NMR spectra of these derivatives to the one of the *p*-tolyl analogues **79**, the major diastereoisomer results from the isomerisation. This means that 1,5 hydrogen abstraction is taking place and the sulfoxide is directing the subsequent reduction.

The reaction was repeated using stoichiometric quantity of Bu_3SnD as reducing agent. Due to purification problems this study is still under investigation.

VI. Conclusions

Desymmetrisation of the tropane skeleton to get tropene, using the cascade 1,5-hydrogen abstraction β-fragmentation of the sulfoxide, was successful although the enantiomeric excess was not high. It was not possible to evaluate whether the *endo* derivative could give a better selectivity, since the synthesis of the *endo* derivative was not successful.

The natural ferruginine and its enantiomer were synthesised from the achiral tropinone.

Synthesis of the vinyl sulfoxide led to an easy separation of the two different diastereoisomers that could be used after oxidation in a conjugate addition to introduce the methyl ketone function.

Finally, preliminary experiments have demonstrated that the *o*-bromo phenyl vinyl sulfoxide can be used to generate an allylic radical. Reduction of the radical seems to proceed selectively due to the presence of the chiral sulfoxide, affording the isomerised vinyl derivative without lost of the chiral auxiliary.

Further experiments using Bu_3SnD are currently under investigation to highlith whether the 1,5-hydrogen abstraction is really taking place.

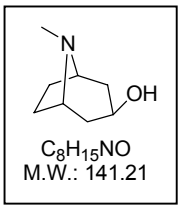
VII. Outlook

Further experiments on the isomerisation of the double bond of the vinylsulfoxide have to be run, first to see whether the also the second diastereoisomer will give the same selectivity affording the same diastereoisomer. This would open e new field of research since this can have a wide application in synthesis. Moreover to the best of our knowledge this is the first time that an allylic radical lead to the isomerisation of the vinyl sulfoxide without β-fragmentation of the sulfoxide

VIII. Experimental Section

General Techniques. C_6H_6, CH_2Cl_2, THF were dried and purified through activated alumina columns prior to use. MeOH was used without previous distillation, elimination of the excess of water was performed adding activated molecular sieves 4 Å. Other reagents were obtained from commercial sources and used as received. Filtration and flash column chromatography (FC): *SdS* silica gel (0.063-0.200 mm); EtOAc, Et_2O, CH_2Cl_2 and hexane as eluents. Thin-layer chromatography (TLC): *Macherey-Nagel SIL G-25 UV$_{254}$* , or *Merks*, *Silica gel 60 F$_{254}$* pre-coated TLC plates; detection either with UV or by dipping in a solution of $KMnO_4$ (3 g), K_2CO_3 (20 g), 5% NaOH (3 mL) in H_2O (300 mL), and subsequent heating. mp: not corrected. NMR spectroscopy: chemical shifts δ in ppm relative to $CHCl_3$ for ^1H (δ = 7.26 ppm) and $CDCl_3$ for ^{13}C (δ = 77.0 ppm), for room temperature spectra, or to DMSO for ^1H (δ= 2.50 ppm) and $(CD_3)_2SO$ for ^{13}C (δ= 39.52 ppm), for high temperature spectra.

Pseudotropine[61,62]

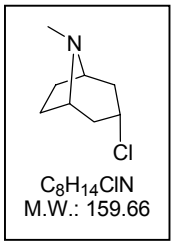


It was made by epimerization of commercial isomer - tropine as following: To a solution of tropine (5 g, 35 mmol) in benzene (10 ml) was added dropwise a solution of MeAl(O*i*-Pr)$_2$ (1 M benzene solution, 40 ml, 40 mmol), which was prepared by addition of calculated amount of absolute *i*-PrOH to a freshly prepared 1 M benzene solution of Me_3Al. After complete addition of MeAl(O^{i}Pr)$_2$ the mixture was stirred until no more gas evolution was observed (30 min). To the resulting mixture, *i*-PrOH (10 ml) followed by acetone (1 ml) were accurately added. Epimerization was completed after heating for 30 h at reflux. The reaction was monitored by ^1H NMR. After then the reaction solution had been cooled and quenched with strong aqueous solution of NaOH, pseudotropine was extracted with CH_2Cl_2 several times. Combined extracts were dried over K_2CO_3 and evaporated that furnished a white solid of pseudotropine (4.9 g, 98 %).

^{1}H-NMR (360 MHz, $CDCl_3$): 3.81 (tt, *J* = 10.4, 6.1 Hz, 1H), 3.10 (m, 2H), 2.87 (br. s, 1H, OH), 2.24 (s, 3H), 1.93 (m, 2H), 1.77-1.71 (m, 2H), 1.57 (td, *J* = 10.4, 2.5, 2H), 1.47 (m, 2H).

^{13}C-NMR (90 MHz, $CDCl_3$): 63.58, 60.37, 39.61, 38.62, 26.80.

3-*endo*-Chlorotropane



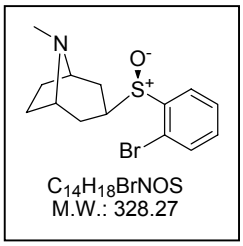
$C_8H_{14}ClN$
M.W.: 159.66

It was prepared in 74% yield (after bulb to bulb distillation), from pseudotropine by treatment with $SOCl_2$ as was described.[63]

^{1}H-NMR (360 MHz, $CDCl_3$): 4.28 (t, *J* = 6.1,1H), 3.07 (m, 2H), 2.33-2.26 (m, 2H), 2.20 (s, 3H), 2.18 (m, 2H), 1.97 (m, 4H).

^{13}C-NMR (90 MHz, $CDCl_3$): 60.25, 53.28, 40.45, 40.06, 25.36.

(*R*)-*exo*-3-(2-Bromo-benzenesulfinyl)-8-methyl-8-aza-bicyclo[3.2.1]octane 67



$C_{14}H_{18}BrNOS$
M.W.: 328.27

A solution of chlorotropane (4.2 g, 26.3 mmol) in THF (3 ml) was added to activated Mg turnings (1.0 g, 41.67 mmol) in THF (20 ml). **Note:** during the reaction with Mg a precipitate formation occurred. After completion of the addition the mixture was stirred for 4 h at 60 °C, after it was cooled to room temperature and added to a solution of sulfinate **68** (4.2 g, 11.6 mmol) in 10 ml of a mixture of benzene/THF (1: 1) at -10-0 °C. The solution was stirred at rt for 1 h, then treated with a saturated solution of NH_4Cl (10 ml), and extracted with ether (30 ml × 3). Organic layer was washed with brine, dried over Na_2SO_4 and evaporated. The title sulfoxide was formed as single diastereomer and isolated by FC in EtOAc/hexane/Et_3N, 1:4:1 on basic Al_2O_3, then dried in vacuum that afford colourless crystals of 3.5 g (93%). M.p. 103.5-104.5 °C (hexane); R_f = 0.29 (EtOAc/hexane/Et_3N, 1:4:1), $[\alpha]_D^{25}$ + 292° (c = 1, acetone).

^{1}H-NMR (360 MHz, $CDCl_3$): 7.76 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.55-7.49 (m, 2H), 7.33 (td, *J* = 7.7, 1.6 Hz, 1H), 3.29 (m, 1H), 3.21 (m, 2H), 2.33 (s, 3H), 2.25 (td, *J* = 12.9, 2.7 Hz, 1H), 2.10 (td, *J* = 12.5, 2.7 HZ, 1H), 2.00 (m, 2H), 1.64-1.61 (m, 1H), 1.57-1.51 (m, 1H), 1.42-1.35 (m, 1H), 0.92-0.88 (m, 1H).

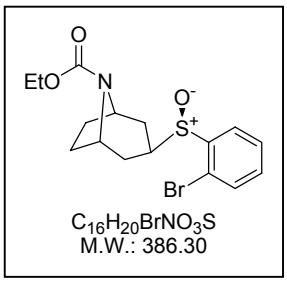
^{13}C-NMR (90 MHz, $CDCl_3$): 141.60, 132.97, 132.12, 128.00, 127.69, 119.29, 59.84, 59.65, 52.53, 37.8, 29.49, 27.15, 26.86, 24.49.

IR (KBr): 3075, 2960, 2843, 2793, 1656, 1448, 1350, 1057, 1014, 767.

ESI-MS (THF): $[M+2]^+$ 330; $[M]^+$ 328.

Elemental Analysis ($C_{14}H_{18}BrNOS$, MW: 328.27): calculated C 51.22%, H 5.52%, Found C 51.29%, H 5.45%

Ethyl (*R*)-*exo*-3-[(2-bromophenyl)sulfinyl]-8-azabicyclo[3.2.1]octane-8-carboxylate. **69**



Compound **69** (0.349 g, 1.06 mmol) and Et_3N (0.138 ml, 1.0 mmol) in benzene (4 ml) were treated with a solution of ethylchloroformate (0.576 g, 0.51 ml; 5.3 mmol) with good stirring. Then the mixture was heated for 1 h at 50 °C, TLC - control hexane/EtOAc, 2:1 on Al_2O_3. To destroy an excess of chloroformate the mixture was stirred with a saturated solution of $NaHCO_3$ for several hours. Organic phase was separated and sulfoxide was purified by filtration through a short Al_2O_3 column in hexane/EtOAc, 2:1, evaporation and drying in vacuum afford white crystals of **69**, yield: 0.408 g (99%). M.p. 107.5-108.5 °C (hexane). R_f = 0.43 (EtOAc/Hexane, 1:4); $[\alpha]_D^{25}$ + 321^0 (c = 1, acetone).

^{1}H-NMR (500.13 MHz, T=338 K): 7.70 (dd, *J* = 6.44, 1.67 Hz, 1H), 7.68 (dd, *J* = 6.46, 1.67 Hz, 1H), 7.57 (dd, *J* = 3.82, 1.08 Hz, 1H), 7.55 (dd, *J* = 3.81, 1.07 Hz, 1H), 7.52 (tt, *J* = 2.27, 1.28 Hz, 2H), 7.37 (tt, *J* = 7.64, 1.75 Hz, 2H), 4.45 (m, 1H), 4.39-4.34 (m, 2H), 4.3 (m, 1H), 4.11 (m, 4H), 3.40 (m, 2H), 2.19 (td, *J* = 12.8, 3.0 Hz, 1H), 2.13 (td, *J* = 12.7, 2.9 Hz, 1H), 2.04-1.86 (m, 8H), 1.64 (m, 2H), 1.47 (m, 2H), 1.23 (dt, *J* = 7.1, 3.9 Hz, 6H), 1.04 (m, 1H), 0.94 (m, 1H).

^{13}C-NMR (125.76 MHz, T=338 K): 153.47,153.41, 140.62, 140.25, 133.23, 133.15, 132.61, 128.25, 127.75, 127.52, 119.11, 118.87, 61.35, 52.84, 52.81, 52.77, 51.94, 51.26, 32.31, 32.04, 28.71, 28.37, 27.85, 27.5, 26.66, 26.16, 14.90, 14.87.

IR (KBr): 3078, 2974 , 2935, 1691, 1423, 1323, 1190, 1109, 1105.

ESI-MS (THF): $[M+2]^+$ 388, $[M]^+$ 386.

Elemental Analysis ($C_{16}H_{20}BrNO_3S$, MW. 386.30): calculated C 49.75%, H 5.22, Found: C 49.61%, H 5.11%

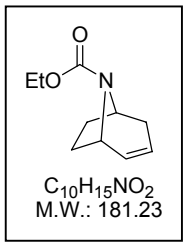
Enantiomeric purity >99.9%, HPLC Chiracel OD-H column; hexane/*i*-PrOH, 9:1, rate of flow 0.6 ml/min t_R (*R*-isomer) = 45.1 min, t_R (*S*-isomer) = 53.1 min.

Representative procedure: radical fragmentation reaction.

Sulfoxide (1.0 mmol), pyridine (1 M solution in benzene, 0.2 ml, 0.2 mmol) in toluene (7 ml) were stirred at room temperature. To this mixture a solution of Bu_3SnH (727 mg, 2.5 mmol) in toluene (20 ml) and a solution of di-*tert*-butylperoxyoxalate (468 mg, 2.0 mmol) in benzene (20 ml) were added simultaneously in individual syringes by

syringe pump over 2.5 h with stirring. After complete addition the reaction mixture was stirred for 20 min, then concentrated under reduced pressure at 30 °C. Residue was dissolved in ether and treated with 1 M solution of NaOH for 4 h to remove tin containing species.[64]

Ethyl 8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate 70



It was obtained as viscous oil after purification by FC in hexane/EtOAc, 4:1 (88 mg, 49%). R_f = 0.41 (Hexane/EtOAc, 5:1). $[\alpha]_D^{25}$ $+3.7^0$ (c = 3, $CHCl_3$)

^{1}H-NMR (360 MHz, $CDCl_3$): 5.97 (br.s, 1H), 5.50 (br.d, *J* = 9.5 Hz; 1H), 4.34 (br.m, 2H), 4.12 (m, 2H), 2.75 (br.t, *J* = 16.8 Hz; 1H), 2.15 (br.m, 1H), 1.92 (m, 2H), 1.79 (dd, *J* = 16.8, 4.0 Hz, 1H), 1.69 (m, 1H), 1.24 (t, *J* = 7.0 Hz, 3H).

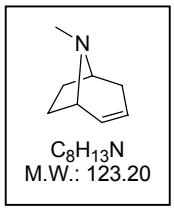
^{13}C-NMR (90 MHz, $CDCl_3$): 154.3, 132.7, 132.3, 124.0, 123.6, 60.7, 53.1 52.24, 35.03, 34.79, 34.34, 34.15, 30.24, 29.38, 14.62.

IR (neat): 3034, 2978, 2908, 1703, 1419, 1317, 1186, 1105, 1020, 879.

GC-MS (EI, 70 eV): M^+ 181.1 (95%), $[M\text{-}Et]^+$ 152.1 (98%), $[M\text{-}COEt]^+$ 124.0 (70%), 108.0 (72), 93.1 (54), 80.0 (100), 67.1 (30), 53.1 (30).

Elemental Analysis ($C_{10}H_{15}NO_2$, MW: 181.23): calculated C, 66.27% H 8.34%, Found: C 66.24%, H 8.24%

(+)-Tropidine 43[65]



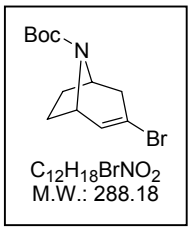
To estimate of an enantiomeric purity of the olefine, it was transformed to tropidine as following: A solution of **70** (60 mg, 0.33 mmol) in THF (5 ml) was treated with $LiAlH_4$ (120 mg, 3.3 mmol). The reaction mixture was heated at reflux for 5 h, then quenched carefully with NaOH (10%) by dropwise. The resulting clear THF solution was separated from a solid on the bottom of the flask. The solid was washed several times with CH_2Cl_2, then combined dried extracts were evaporated to furnish pure tropine in quantitative yield (39.8 mg, 98%). GC on chiral phase (58^0 C): t_R (-)-tropidine = 43.06 min; t_R (+)-tropidine = 44.89 min; e.e. 56%. $[\alpha]_D^{25}$ +24.5° (c = 2, $CHCl_3$) (lit: (-)-tropine $[\alpha]_D^{21}$ –47° (c = 1, $CHCl_3$) and NMR)[66].

^{1}H-NMR (360 MHz, $CDCl_3$): 5.76-5.72 (m, 1H), 5.54-5.51 (br d, *J* = 9.5 Hz, 1H), 3.18 (m, 2H), 2.50 (br d, *J* = 17.5 Hz, 1H), 2.36 (s, 3H); 2.13 (m, 1H), 2.01 (septet, *J* = 5.7 Hz, 1H),

1.83 (ddd, *J* = 11.3, 9.3, 2.3 Hz, 1H), 1.64 (m, 1H), 1.55 (m, 1H).

GC-MS (EI, 70 eV): M^+ 123.1(54%), $[M\text{-}CH_3]^+$ 108.1 (48), $[M\text{-}NCH_3]^+$ 94.0 (100), 82.1 (45), 67.1 (35), 57.1 (35), 42.1 (50).

3-Bromo-8-aza-bicyclo[3.2.1]oct-2-ene-8-carboxylic acid tert-butyl ester 73[52,53]**:**



$C_{12}H_{18}BrNO_2$
M.W.: 288.18

Preparation of the hydrazone: a solution of hydrazine monohydrate (46 ml, 946 mmol) in MeOH (125 ml) and molecular sieves 4 Å in powder (25 g) was stirred for 30 min, a solution of **75** was added under N_2 (10.6 g, 47.0 mmol) in MeOH (63 ml). The solution was stirred at rt for 3 h, then it was filtered on Celite and the solvent evaporated, the excess of hydrazine is removed under high vacuum. The oily solid is then used without further purification.

Preparation of the geminal dibromide: A suspension of $CuBr_2$ (63.1 g, 283 mmol) in MeOH (130 ml) and NEt_3 (19 ml, 136 mmol) is stirred for 15 min, then a solution in MeOH (65 ml) of the prepared hydrazone is added dropwise at 0 °C. When the addition is finished the ice bath is removed and the reaction stirred for 2 h. The mixture is the poured into a 3% solution of NH_4OH and CH_2Cl_2. The aqueous phase is extracted with CH_2Cl_2. The combined organic phases are washed with NH_4OH (3% solution), water and brine. After drying on $MgSO_4$ and evaporation of the solvent an orange oil is obtained. After filtration on SiO_2 (Hex/EtOAc, 9:1) a colourless oil is obtained.

Preparation of the vinylbromide: A solution of the mixture in benzene (110 ml) of DBU (11 ml, 73.6 mmol), of the vinylbromide and of the geminal dibromide is refluxed under nitrogen overnight. When the mixture is came back to rt a saturated aqueous solution of NH_4Cl is added, the aqueous layer is extracted with Et_2O. The combined organic layers are washed with brine dried on $MgSO_4$. The solvent is evaporated to give yellowish oil. FC (Hex/EtOAc, 9:1) affords a white solid (10.1 g, 35.1 mmol, 74% yield for the 3 steps). Mp. 53-55 °C.

^{1}H-NMR (500.13 MHz, DMSO, T=338 K): 6.42 (dt, *J* = 5.45, 1.49 Hz, 1H), 4.27 (t, *J* = 5.7 Hz, 1H), 4.22-4.18 (m, 1H), 3.00-2.93 (m, 1H), 2.26-2.20 (d, *J* = 17.3, 1 H), 2.13 (q, *J* = 10.6, 1H), 1.93-1.80 (m, 2H), 1.74-1.66 (m, 1 H), 1.40 (s, 9H).

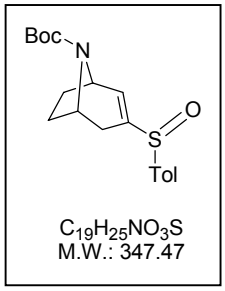
^{13}C-NMR (125.8 MHz, DMSO, T=338 K): 152.7, 134.1, 119.1, 78.7, 54.3, 52.8, 43.1, 33.3, 28.7, 27.7.

EI-MS m/z(%): 289 (1), 287 (1), 233 (25), 231 (25), 189 (5), 187 (5), 160 (11), 158 (11), 108 (38), 91 (10), 57 (100).

EI-MSHR: calculated 287.052090, found 287.052090

IR (KBr pill):2978, 2926, 2876, 2833, 1686, 1628, 1412, 1364, 1353, 1321, 1314, 1162, 1105, 1006, 972, 886, 751, 709.

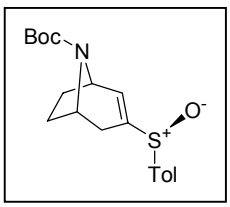
***tert*-Butyl 3-[(4-methylphenyl)sulfinyl]bicyclo[3.2.1]oct-2-ene-8-carboxylate 80:**



$C_{19}H_{25}NO_3S$
M.W.: 347.47

The Grignard reagent is prepared starting from a solution of **73** (7.6 g, 26.3 mmol) in THF (40 ml), Mg (960 mg, 39.5 mmol) and MeI (0.2 ml) to activate the Mg. When the solution of the Grignard is cold down at room temperature a suspension is form. The suspension is then transferred via canula at 0-4 °C to a solution of (-)-(1*R*)-Menthyl (*S*)-*p*-toluenesulfinate **81** (11.6 g, 39.4 mmol), in of benzene (100 ml). The flask containing the Grignard is rinsed with THF (2 x 10 ml) in order to transfer the entire compound. When the addition is finished the ice bath is removed and the reaction is stirred at room temperature for 20 h. Then Et_2O (80 ml) and a saturated solution of NH_4Cl (100 ml) are added to the reaction mixture. The water layer is washed with Et_2O (3 x 50 ml), the combined organic layers are then washed with brine and dried on $MgSO_4$. Evaporation of the solvent affords a yellowish solid containing a 1:1 mixture of the two diasteroisomers. On this mixture a FC (hexane/EtOAc, 1:2) is carried out to remove the impurities. FC using Lobar apparatus (hexane/EtOAc, 1:1.7) afford the two pure diasteromeric sulfoxides: R_f = 0.57 (EtOAc: hexane 3:1) (2.46 g, 7.07 mmol). Mp. 122-124 °C) and R_f = 0.48 (EtOAc: hexane 3:1) (2.44 g, 7.02 mmol). Mp 114-115 °C (54% yield).

(1*R*,5*S*,*S*s)-**80** (R_f = 0.57)



^{1}H-NMR (400.13 MHz, DMSO, T=333 K): 7.45-7.43 (m, 2H), 7.36-7.35 (m, 2H), 6.89-6.86 (dm, *J* = 5.2 Hz, 1H), 2.40-2.33 (m+ s, 1+ 3H), 2.10-2.00 (m, 1H), 1.99-1.85 (m, 2 H), 1.63 (d, *J* = 17 Hz, 1H), 1.41-1.29, (m, 1H), 1.32 (s, 9H).

^{13}C-NMR (125.8 MHz, DMSO, T=333 K): 152.8, 141.1, 140.9, 139.4, 134.6, 129.5, 124.3, 78.7, 69.0, 53.2, 51.2, 33.2, 29.3, 29.2, 28.5, 27.6, 20.5.

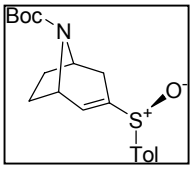
EI-MS m/z(%): 347 (8), 291 (29), 274 (9), 246 (16), 230 (40), 208 (52), 202 (33), 152 (88), 140 (39), 124 (20), 123 (22), 108 (100), 106 (22), 92 (22), 91 (51), 81 (24), 79 (20), 57 (94), 41 (46).

EI-MSHR: calculated 347.155516, found 347.155460

IR (KBr pill): 3048, 2973, 2915, 2841, 1697, 1594, 1379, 1325, 1176, 1102, 1043, 1012, 807, 625, 527, 507, 436.

$[\alpha]_D^{20}$=+127.6 ° ($CHCl_3$, c = 1.12)

(1*S*,5*R*,*S*s)-**80** (R_f = 0.48)



^{1}H-NMR (400.13 MHz, DMSO, T=343 K): 7.42-7.40 (m, 2H), 7.35-7.30 (m, 2H), 6.96 (dt, *J* = 5.1, 1.7 Hz, 1H), 4.51-4.40 (m, 1H), 4.25-4.19 (m, 1H), 2.36 (s, 3H), 2.23 (dm, *J* = 17 Hz, 1H), 2.16- 2.05 (m, 1H), 1.99-1.85 (m, 3 H), 1.49-1.37 (m, 1H), 1.28 (s, 9H).

^{13}C-NMR (125.8 MHz, DMSO, T=343 K): 152.6, 141.4, 140.4, 139.2, 136.8, 129.2, 123.8, 78.5, 52.8, 51.3, 32.9, 28.4, 27.4, 27.3, 20.2

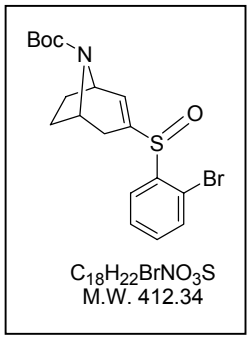
EI-MS m/z(%): 347 (6), 291 (16), 274 (6), 246 (12), 230 (24), 208 (34), 202 (19), 152 (80), 140 (21), 124 (9), 123 (9), 109 (90), 91 (19), 80 (17), 57 (100), 41 (14).

EI-MSHR: calculated 347.155516, found 347.155430

IR (KBr pill): 3047, 2971, 2927, 1686, 1591, 1415, 1365, 1326, 1172, 1113, 1081, 1047, 1008, 890, 813, 624, 511.

$[\alpha]_D^{20}$= -65.5 ° ($CHCl_3$, c = 1.115)

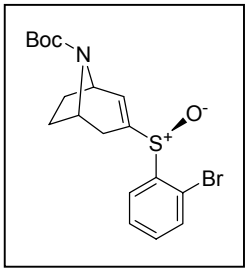
***tert*-Butyl 3-[(3-bromophenyl)sulfinyl]bicyclo[3.2.1]oct-2-ene-8-carboxylate 74:**



The Grignard reagent is prepared starting from a solution of **73** (2.6 g, 9 mmol) in THF (14 ml), Mg (330 mg, 13.5 mmol) and MeI (0.1 ml) to activate the Mg. When the solution of the Grignard is cold down at room temperature a suspension is form. The suspension is then transferred via canula at 0-4°C to a solution of (-)-(1*R*)-menthyl (*S*)-*o*-bromobenzenesulfinate **68** (1.6 g, 13 mmol) in benzene (35 ml). The flask containing the Grignard is rinsed with THF (2 x 10 ml) in order to transfer the entire compound. When the addition is finished the ice bath is removed and the reaction is stirred at rt for 20 h. Then Et_2O (10

ml) and a saturated solution of NH_4Cl (5 ml) are added to the reaction mixture. The water layer is washed with Et_2O (3 x 5 ml), the combined organic layers are then washed with brine and dried on $MgSO_4$. Evaporation of the solvent afforded a yellowish solid containing a 1:1 mixture of the two diasteroisomers. On this mixture a FC (hexane/TBME, 1:2) is carried out to remove the impurities. FC using Lobar apparatus (hexane/TBME, 1:2) afforded the two pure diastereomeric sulfoxides: R_f = 0.5 (hexane/TBME, 1:2) (940 mg, 2.28 mmol) and R_f = 0.35 (TBME/hexane, 2:1) (960 mg, 2.33 mmol) (51% yield).

(1*R*,5*S*,*S*s)-**74** (R_f = 0.5)



^{1}H-NMR (500.13 MHz, DMSO, T=343 K): 7.80-7.73 (m, 1H), 7.70-7.62 (m, 2H), 7.53-7.44 (m, 1H), 7.01 (dm, *J* = 5.16 Hz, 1H), 4.45-4.39 (m, 1H), 4.25-4.18 (m, 1H), 2.20-2.07 (m, 2H), 1.98-1.90 (m, 2H), 1.48 (dt, *J* = 12.9, 7.8 Hz, 1H), 1.43-1.36 (m, 1 H), 1.24 (s, 9H).

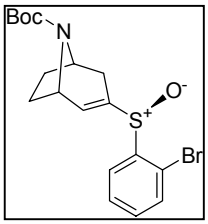
^{13}C-NMR (125.8 MHz, DMSO, T=343 K): 152.7, 140.8, 140.1, 137.9, 132.9, 132.4, 127.9, 126.3,118.9, 78.5, 53.1, 51.5, 32.9, 28.4, 27.4, 26.5

EI-MS m/z(%): 413 (1), 411 (1), 357 (6), 355 (6), 340 (3), 338 (3), 312 (5), 310 (5), 296 (12), 294 (12), 208 (45), 152 (75), 108 (78), 91 (35), 80 (20), 57 (100).

EI-MSHR: calculated 411.050377, found 411.05026

IR (KBr pill): 2974, 2938, 2877, 1680, 1379, 1321, 1170, 1014, 752.

(1*S*,5*R*,*S*s)-**74** (R_f = 0.35)



^{1}H-NMR (400.13 MHz, DMSO, T=343 K): 7.75-7.68 (m, 2H), 7.67-7.61 (m, 1H), 7.52-7.47 (m, 1H), 7.02 (dt, *J* = 5.16, 1.56 Hz, 1H), 4.51-4.45 (m, 1H), 4.25-4.19 (m, 1H), 2.56 (dm, *J* = 16.8 Hz, 1H), 2.12- 2.01 (m, 1H), 1.96-1.85 (m, 2 H), 1.58 (d, J = 17.0 Hz, 1H), 1.34 (s, 9H).

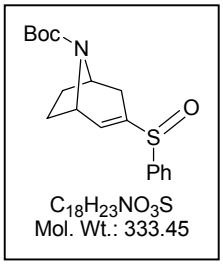
^{13}C-NMR (125.8 MHz, DMSO, T=343 K): 152.7, 141.8, 139.2, 138.1, 132.9, 132.6, 128.4, 126.3, 119.4, 78.7, 53.2, 51.2, 32.9, 28.9, 28.7, 27.7, 27.6

EI-MS m/z(%): 413 (3), 411 (3), 357 (13), 355 (13), 340 (4), 338 (4), 312 (8), 310 (8), 296 (20), 294 (20), 208 (54), 152 (78), 108 (80), 91 (32), 80 (30), 57 (100).

EI-MSHR: calculated 411.050377, found 411.05060

IR (KBr pill): 3083, 2971, 2940, 2911, 1683, 1405, 1325, 1162, 1107, 1062, 1011, 739.

***tert*-Butyl 3-[benzenesulfinyl]bicyclo[3.2.1]oct-2-ene-8-carboxylate 86**



$C_{18}H_{23}NO_3S$
Mol. Wt.: 333.45

To a solution of (1*R*,5S,Ss)-**74** (206 mg, 0.5 mmol) in *t*-BuOH (50 ml) is added Bu_3SnCl (7 μl, 0.025 mmol) and $NaBH_3CN$ (63 mg, 1.0 mmol) and AIBN (8 mg, 0.05 mmol). The reaction is stirred at reflux for 4 h, then other AIBN (8 mg, 0.05 mmol) is added and let react for other 4 h at reflux. When the reaction is cooled down, evaporation of the solvent and FC afforded two fractions. The first one is a 1:1 mixture of the two diastereoisomers (17 mg) and the second one is the pure (1*S*,5*R*,Ss)-**86** (67 mg 0.25 mmol, 50% yield).

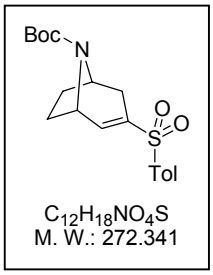
(1*S*,5*R*,Ss)-**86**

^{1}H-NMR (400.13 MHz, DMSO, T=343 K): 7.60-7.45 (m, 5H), 7.02 (dm, *J* = 5.01 Hz, 1H), 4.47-4.39 (m 1H), 4.25-4.17 (m 1H), 2.26-2.05 (m, 2 H), 2.00-1.85 (m, 2 H), 1.50-1.35 (m, 2H), 1.26 (s, 9H).

(1*R*,5*S*,Ss)-**86**

^{1}H-NMR (400.13 MHz, DMSO, T=343 K): (characteristic signals: 6.91 (dm, *J* = 5.26 Hz, 1H).

***tert*-Butyl 3-[(4-methylphenyl)sulfonyl]bicyclo[3.2.1]oct-2-ene-8-carboxylate (-)-82**



$C_{12}H_{18}NO_4S$
M. W.: 272.341

To a solution of (1*S*,5*R*,*S*s)-**80** (1.12 g, 3.22 mmol) in MeOH (40 ml) is added at 0° C a buffered water solution (20 ml, pH=5) of Oxone® (1.98 g, 3.22 mmol). After the addition the cooling bath is removed and the reaction stirred for 3 h. To the reaction mixture water and CH_2Cl_2 (20 ml) are added; the aqueous phase is extract with CH_2Cl_2. The combined organic layers are washed with brine and dried on $MgSO_4$. FC (hexane/AcOEt, 2:1) afford of a white solid (1.09 g, 3.0 mmol, 93 % yield). Mp: 113-114 °C. $[\alpha]^{20}_D$: -51.9° ($CHCl_3$, c = 1).

^{1}H-NMR (400.13 MHz, DMSO, T=343 K): 7.69-7.63 (m, 2H), 7.46-7.40 (m, 2H), 7.20 (dt, *J* = 5.3, 1.7 Hz, 1H), 4.49 (t, *J* = 5.2 Hz, 1H), 4.25 (dd, *J* = 7.2, 4.9 Hz, 1H), 2.57 (dm, *J* = 17.2 Hz, 1H), 2.41 (s, 3H), 2.16- 2.04 (m, 1H), 1.99 (d, *J* = 17.2 Hz, 1 H), 1.99-1.85 (m, 2 H), 1.48-1.38 (m, 1H), 1.28 (s, 9H).

^{13}C-NMR (125.8 MHz, DMSO, T=343 K): 152.8, 143.8, 141.6, 137.2, 135.5, 129.4, 127.0, 78.8, 52.6, 51.0, 32.6, 31.0, 28.6, 27.4, 20.5

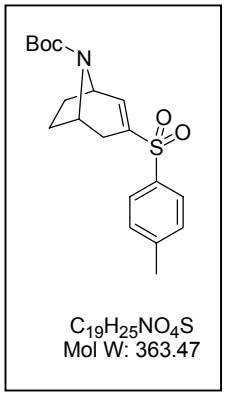
EI-MS m/z(%): 363 (3), 308 (12), 307 (50), 263 (36), 247 (14), 234 (12), 199 (13), 198 (13), 139 (24), 108 (100), 91 (50), 80 (25), 79 (50), 57 (95), 52 (12), 41 (43).

EI-MSHR: calculated 363.150430, found 363.150700

IR (KBr pill): 3091, 3056, 3004, 2970, 2952, 2877, 1932, 1698, 1627, 1595, 1463, 1393, 1371, 1354, 1325, 1312, 1165, 1147, 1106, 1093, 1028, 946, 817, 665, 611..

$[\alpha]_D^{20}$= -51.9 ° ($CHCl_3$, c = 1.00)

***tert*-Butyl 3-[(4-methylphenyl)sulfonyl]bicyclo[3.2.1]oct-2-ene-8-carboxylate (+)-82**



To a solution of (1*R*,5*S*,*S*s)-**80** (920 g, 2.65 mmol) in MeOH (30 ml) is added at 0° C a buffered water solution (15 ml, pH=5) of Oxone® (1.63 g, 2.65 mmol). After the addition the cooling bath is removed and the reaction stirred for 3 h. To the reaction mixture water and CH_2Cl_2 (20 ml) are added; the aqueous phase is extracted with CH_2Cl_2. The combined organic layers are washed with brine and dried on $MgSO_4$. FC (Hhexane/AcOEt, 2:1) afforded a white solid (870 g, 2.4 mmol; 90% yield). $[\alpha]^{20}_D$: +42.9° ($CHCl_3$, c = 1)

^{1}H-NMR (400.13 MHz, DMSO, T=343 K): 7.69-7.63 (m, 2H), 7.46-7.40 (m, 2H), 7.20 (dt, *J* = 5.3, 1.7 Hz, 1H), 4.49 (t, *J* = 5.2 Hz, 1H), 4.25 (dd, *J* = 7.2, 4.9 Hz, 1H), 2.57 (dm, *J* = 17.2 Hz, 1H), 2.41 (s, 3H), 2.16- 2.04 (m, 1H), 1.99 (d, *J* = 17.2 Hz, 1 H), 1.99-1.85 (m, 2 H), 1.48-1.38 (m, 1H), 1.28 (s, 9H).

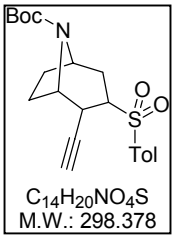
^{13}C-NMR (125.8 MHz, DMSO, T=343 K): 152.8, 143.8, 141.6, 137.2, 135.5, 129.4, 127.0, 78.8, 52.6, 51.0, 32.6, 31.0, 28.6, 27.4, 20.5

EI-MS m/z(%):363 (7), 307 (33), 263 (23), 247 (14), 109 (13), 108 (100), 91 (15), 80 (12), 79 (23), 57 (75), 41 (11)

EI-MSHR: calculated 363.150430, found 363.150910

IR (KBr pill): 3085, 3051, 3003, 2969, 2948, 2873, 1928, 1697, 1626, 1595, 1459, 1391, 1371, 1353, 1324, 1314, 1163, 1147, 1103, 1090, 1027, 946, 818, 664, 609.

***tert*-Butyl 2-ethynyl-3-[(4-methylphenyl)sulfonyl]-8-azabicyclo[3.2.1]octane-8-carboxylate 83a**



$C_{14}H_{20}NO_4S$
M.W.: 298.378

To a solution of ethynyl trimethylsilane (930 µl, 6.7 mmol) in THF (19 ml) *n*-BuLi (4.6 ml, 6.4 mmol) is added at 0 °C. The reaction mixture is stirred for 30 min. Then it is added via canula at 0 °C to a solution in toluene (45 ml) of **(+)-82** (780 mg, 2.14 mmol). When the addition is finished the bath is removed and the reaction is allowed to react for 5 h at room temperature. A saturated solution of NH_4Cl and ether are added. The two phases separated and the aqueous layer is washed with Et_2O. The combined organic layers are washed with brine and dried on $MgSO_4$. After the evaporation of the solvent the residue is dissolved in MeOH (11 ml) and of K_2CO_3 (300 mg, 2.17 mmol) are added. The reaction mixture is stirred for 16 h. Then water and Et_2O are added. The aqueous phase is then washed with Et_2O and the combined organic layers are washed with brine. Evaporation of the solvent and purification via FC (cyclohexane/EtOAc, 2:1) affords a white solid (600 mg, 1.55 mmol, 73 % yield) (mp 148-150 °C).

^{1}H-NMR (400.13 MHz, DMSO, T=343 K): 7.83-7.79 (m, 2H), 7.46-7.41 (m, 2H), 4.40-4.35 (m, 1H), 4.35-4.30 (m, 1H), 3.58 (d,t, *J* = 12.7, 4.8 Hz, 1 H), 2.84-2.80 (m, 1H), 2.77-2.73 (m, 1H), 2.43 (s, 3H), 1.98 (td, *J* = 12.7, 2.8 Hz, 1H), 1.86-1.65 (m, 3H), 1.51-1.40 (m, 1H), 1.40 (s, 9H).

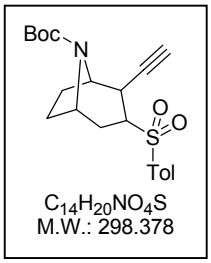
^{13}C-NMR (100.61 MHz, DMSO, T=343 K): 151.6, 143.9, 134.9, 129.0, 128.4, 79.5, 78.1, 74.9, 57.1, 56.9, 51.2, 32.5, 27.8, 27.6, 26.7, 26.5, 20.5.

EI-MS *m/z* (%):316 (40), 235 (7), 234 (40), 179 (20), 178 (72), 135 (27), 134 (84), 132 (19), 117 (15), 106 (17), 91 (50), 68 (23), 65 (12), 57 (100).

IR (KBr pill): 3272, 2985, 2932, 2874, 1684, 1421, 1318, 1288, 1147, 1110, 1086, 875, 817, 679.

Elemental Analysis ($C_{14}H_{20}NO_4S$, MW.298.34): Calculated C 64.75%, H 6.99%, N 3.60%, Found: C 64.75%, H 6.98%, N 3.68%.

***tert*-Butyl 2-ethynyl-3-[(4-methylphenyl)sulfonyl]-8-azabicyclo[3.2.1]octane-8-carboxylate 83b**



To a solution of ethynyl trimethylsilane (1.0 ml, 7.2 mmol) in THF (20 ml) of is added at 0 °C *n*-BuLi (5 ml, 6.9 mmol). The reaction mixture is stirred for 30 min. Then it is added via canula at 0 °C to a solution of (-)-**82** (840 mg, 2.3 mmol) in toluene (46 ml). When the addition is finished the bath is removed and the reaction is allowed to react for 5 h at rt. A saturated solution of NH_4Cl and ether are added. The two phases are separated and the aqueous layer is washed with Et_2O. The combined organic layers are washed with brine and dried on $MgSO_4$. After the evaporation of the solvent the residue is dissolved in MeOH (12 ml) and 320 mg of K_2CO_3 (2.3 mmol) are added. The reaction mixture is stirred for 16 h. Then water and Et_2O are added. The aqueous phase is then washed with Et_2O and the combined organic layers are washed with brine. Evaporation of the solvent and purification via FC (cyclohexane/EtOAc, 2:1) afforded (650 mg, 1.66 mmol, 72 % yield) of a white solid (mp 148-149 °C).

^{1}H-NMR (400.13 MHz, DMSO, T=343 K): 7.83-7.79 (m, 2H), 7.46-7.41 (m, 2H), 4.40-4.35 (m, 1H), 4.35-4.30 (m, 1H), 3.58 (dt, *J* = 12.7, 4.8 Hz, 1 H), 2.84-2.80 (m, 1H), 2.77-2.73 (m, 1H), 2.43 (s, 3H), 1.98 (td, *J* = 12.7, 2.8 Hz, 1H), 1.86-1.65 (m, 3H), 1.51-1.40 (m, 1H), 1.40 (s, 9H).

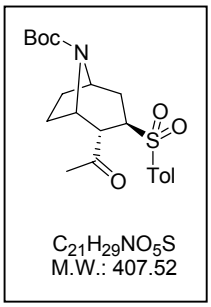
^{13}C-NMR (100.61 MHz, DMSO, T=343 K): 151.6, 143.9, 134.9, 129.0, 128.4, 79.5, 78.1, 74.9, 57.1, 56.9, 51.2, 32.5, 27.8, 27.6, 26.7, 26.5, 20.5

EI-MS m/z(%): 389 (2), 316 (10), 235 (20), 234 (75), 179 (43), 178 (92), 135 (59), 134 (100), 132 (51), 117 (51), 106 (46), 91 (90), 67 (54), 65 (54), 57 (90).

IR (KBr pill): 3271, 2985, 2932, 2874, 1681, 1419, 1317, 1288, 1146, 1109, 1086, 875, 817, 678.

Elemental Analysis ($C_{14}H_{20}NO_4S$, MW.298.34):: Calculated C 64.75%, H 6.99%, N 3.60%, Found: C 64.75%, H 6.98%, N 3.68%.

***tert*-Butyl 2-acetyl-3-(phenylsulfonyl)-8-azabicyclo[3.2.1]octane-8-carboxylate (+)-84**



A solution of **83a** (890 mg, 2.28 mmol), $Hg(OAc)_2$ (220 mg, 0.68 mmol) and of *p*-toluensulfonic acid (440 mg, 2.3 mmol) in THF (70 ml) is refluxed for 1.5 h. When the reaction mixture is cooled a room temperature the solvent is reduced to 1/7 of the volume and filtrated over silica gel eluting with Et_2O. Evaporation of the solvent affords a yellow residue that is dissolved in Et_2O (5 ml) and (+)-**84** is let crystallize at 4 °C. After a first filtration the mother liquid is evaporated and a second crop can be obtained repeating the crystallization. At the end of (+)-**84** (418 mg, 1.02 mmol, 45% yield) is obtained as white solid. Mp. 142-143 °C. $[\alpha]^{20}_D$: +78.0° ($CHCl_3$, c = 1.00).

^{1}H-NMR (400.13 MHz, DMSO, T=343 K): 7.69-7.64 (m, 2H), 7.48-7.43 (m, 2H), 4.23 (dd, *J* = 6.8, 3.3 Hz, 1H), 4.15-4.09 (m, 1H), 4.03 (td, *J* = 11.6, 6.44Hz, 1H), 3.25 (dd, *J* = 11.3, 3.24 Hz, 1 H), 2.42 (s, 3H), 2.22 (s, 3H), 1.92-1.54 (m, 6 H), 1.39 (s, 9H).

^{13}C-NMR (100.61 MHz, DMSO, T=343 K): 203.9, 151.8, 144.3, 133.9, 129.4, 128.1, 79.1, 55.9, 53.3, 52.1, 48.9, 29.2, 28.5, 27.6, 26.3, 22.4, 20.5

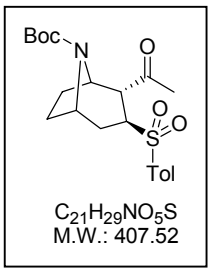
nOe difference spectra (400.13 MHz, T=343 K): 3.29-3.22 (C*H*$COCH_3$) → 7.69-7.64 (3.41 %), 4.26-4.21 (8.93%), 4.08-3.99 (1.72%), 2.24-2.19 (6.19), 1.90-1.79 (1.23%); 4.09-3.99 (C*H*SO2Ar) →. 7.69-7.64 (3.78 %), 3.31-3.23 (1.77%), 1.91-1.80 (0.57%), 1.80-1.71 (2.80%), 1.71-1.63 (3.13%), 1.63-1.54 (2.10%).

EI-MS m/z(%): 407 (0.2), 389 (0.3), 253 (20), 252 (56), 195 (51), 180 (17), 153 (64), 152 (100), 139 (55), 136 (36), 135 (32), 122 (28), 108 (46), 91 (35), 68 (81), 57 (89).

HR-MS (ESI-POS, [M+Na$^+$], sample dissolved in MeOH/H2O/Hfo (74+25+1)): found 430.1669 calculated 430.1664

IR (KBr pill): 2966, 2932, 2890, 1711, 1688, 1595, 1457, 1388, 1368, 1331, 1314, 1302, 1172, 1130, 1106, 1083, 827, 820, 770,743, 647.

***tert*-Butyl 2-acetyl-3-(phenylsulfonyl)-8-azabicyclo[3.2.1]octane-8-carboxylate (-)-84**



$C_{21}H_{29}NO_5S$
M.W.: 407.52

A solution of **83b** (530 mg, 1.36 mmol), $Hg(OAc)_2$ (130 mg, 0.4 mmol) and *p*-toluensulfonic acid (280 mg, 1.47 mmol) in THF (40 ml) is refluxed for 1.5 h. When the reaction mixture is cooled a room temperature the solvent is reduced to 1/7 of the volume and filtrated over silica gel eluting with Et_2O. Evaporation of the solvent afforded a yellow residue that is dissolved in Et_2O (5 ml) and (-)**-84** is let crystallize at 4 °C. After a first filtration the mother liquid is evaporated and a second crop can be obtained repeating the crystallization. At the end (-)**-84** (244 mg, 0.60 mmol, 44% yield) is obtained as white solid. Mp 141-142°C. $[\alpha]^{20}_D$: -74.2° ($CHCl_3$, c=1.01).

^{1}H-NMR (400.13 MHz, DMSO, T=343 K): 7.69-7.64 (m, 2H), 7.48-7.43 (m, 2H), 4.23 (dd, *J* = 6.85, 3.3, 1H), 4.15-4.09 (m, 1H), 4.03 (td, *J* =11.6, 6.44 Hz, 1H), 3.25 (dd, *J* = 11.3, 3.24 Hz, 1 H), 2.42 (s, 3H), 2.22 (s, 3H), 1.92-1.54 (m, 6 H), 1.39 (s, 9H).

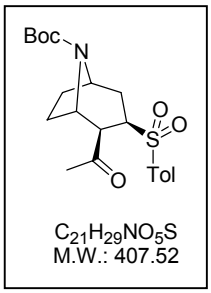
^{13}C-NMR (100.61 MHz, DMSO, T=343 K): 203.9, 151.8, 144.3, 133.9, 129.4, 128.1, 79.1, 55.9, 53.3, 52.1, 48.9, 29.2, 28.5, 27.6, 26.3, 22.4, 20.5

EI-MS m/z(%): 407 (0.2), 389 (0.3), 253 (17), 252 (56), 195 (39), 153 (70), 152 (100), 139 (54), 135 (36), 122 (22), 108 (35), 91 (27), 68 (92), 57 (88).

HR-MS (ESI-POS, [M+Na$^+$], sample dissolved in MeOH/H2O/Hfo (74+25+1)): found 430.1646 calculated 430.1664

IR (KBr pill): 2966, 2932, 2886, 1710, 1687, 1595, 1457, 1388, 1369, 1331, 1314, 1302, 1172, 1130, 1106, 1083, 827, 820, 770,743, 647.

***tert*-Butyl 2-acetyl-3-(phenylsulfonyl)-8-azabicyclo[3.2.1]octane-8-carboxylate (-)-85**



$C_{21}H_{29}NO_5S$
M.W.: 407.52

t-BuLi (1.2 ml,1.5 M in hexane) is added dropwise at –78°C to a solution of ethyl vinyl ether (450 ml, 4.74 mmol) in THF (1.6 ml). The reaction mixture turns yellow and it decolours at 0°C. A solution of (-)**-84** (325 mg, 0.89 mmol) in THF (1.4 ml) is added at –20°C. Then after 4 h a solution of NH_4Cl is added, and the mixture is let coming to room temperature. Water and Et_2O are added, the aqueous phase is extracted with Et_2O and the combined organic layers are washed with brine. Drying over on Mg_2SO_4, evaporation of the solvent and FC (cyclohexane/EtOAc, 7:3) afforded

a colourless oil which is dissolved in MeOH (3.6 ml). To this solution is added HCl 0.5 M (1 ml). After 10 min a white precipitate is formed, but the reaction mixture is stirred for additional 20 min then water and EtOAc are added. After separation the aqueous phase is extracted twice with EtOAc and the combined organic layers are washed with brine, and dried on $MgSO_4$. Evaporation of the solvent afforded a white solid (253 mg, 0.62 mmol, 70% yield). Mp 184-185 °C. $[\alpha]_D^{20}$ = -40.0 (c = 1.01, $CHCl_3$).

^{1}H-NMR (400.13 MHz, DMSO, T=343 K): 7.71-7.65 (m, 2 H), 7.46-7.39 (m, 2H), 4.51 (d, *J* = 6.72 Hz, 1H), 4.25-4.31 (m, 1H), 3.59 (dt, *J* = 12.6, 5.26 Hz, 1H), 3.23 (dd, *J* = 4.82, 1.77 Hz, 1H), 2.43 (s, 3H), 2.36 (td, *J* = 12.5, 2.57 Hz, 2H), 2.18 (s, 3H), 2.05-1.89 (m, 1H), 1.87-1.72 (m, 2H), 1.66-1.58 (m, 1H), 1.51-1.39 (m, 1H), 1.34 (s, 9H).

^{13}C-NMR (100.61 MHz, DMSO, T=343 K): 203.5, 150.8, 143.6, 136.6, 129.1, 127.8, 78.3, 59.4, 53.5, 51.3, 29.2, 27.6, 27.4, 26.5, 20.6

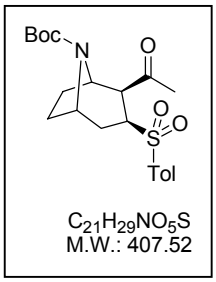
nOe difference spectra (400.13 MHz, T=343 K): 3.65-3.57 (C*H*COCH$_3$) → 3.27-3.23 (8.73%), 1.89-1.74 (3.12%), 1.69-1.61 (5.40%), 1.54-1.43 (5.27%).

EI-MS m/z(%): 334 (5), 252 (5), 195 (8), 152 (100), 139 (11), 108 (34), 91 (60), 68 (40), 57 (98), 43 (46), 41 (47).

IR (KBr pill): 2975, 2932, 2984,1709, 1685, 1409, 1173, 1105, 677

HR-MS (ESI-POS, [M+Na$^+$], sample dissolved in H_2O/ACN 1:1): found 430.1669 calculated 430.1664

***tert*-Butyl 2-acetyl-3-(phenylsulfonyl)-8-azabicyclo[3.2.1]octane-8-carboxylate (+)-85**



$C_{21}H_{29}NO_5S$
M.W.: 407.52

t-BuLi (1.1 ml, 1.5M in hexane) is added dropwise, at –78°C to a solution of ethyl vinyl ether (425 ml, 4.42 mmol) in THF (1.5 ml). The reaction mixture turns yellow and it decolours at 0°C. A solution of (+)-**84** (300 mg, 0.83 mmol) in THF (1.3 ml) is added at –20 °C. Then after 4 h a solution of NH_4Cl is added, and the mixture is let coming to room temperature. Water and Et_2O are added, the aqueous phase is extracted with Et_2O and the combined organic layers are washed with brine. Drying over Mg_2SO_4, evaporation of the solvent and FC (cyclohexane/EtOAc, 7:3) afforded a colourless oil which is dissolved in MeOH (3.6 ml). To this solution is added HCl 0.5M (1 ml). After 10 min a white precipitate is formed, but the reaction mixture is stirred for additional 20 min then water and EtOAc are added. After separation the aqueous phase is extracted twice with EtOAc and the combined organic layers are washed with

brine, and dried on $MgSO_4$. Evaporation of the solvent affords a white solid (236 mg, 0.58 mmol, 70% yield). Mp. 187-188 °C. $[\alpha]_D^{20}$ = +47.3° (c=1.005, $CHCl_3$).

^{1}H-NMR (400.13 MHz, DMSO, T=343 K): 7.71-7.65 (m, 2 H), 7.46-7.39 (m, 2H), 4.51 (d, *J* = 6.72 Hz, 1H), 4.31-4.25 (m, 1H), 3.59 (dt, *J* = 12.6, 5.26 Hz, 1H), 3.23 (dd, *J* = 4.82, 1.77 Hz, 1H), 2.43 (s, 3H), 2.36 (td, *J* = 12.5, 2.57 Hz), 2.18 (s, 3H), 2.05-1.89 (m, 1H), 1.87-1.72 (m, 2H), 1.66-1.58 (m, 1H), 1.51-1.39 (m, 1H), 1.34 (s, 9H).

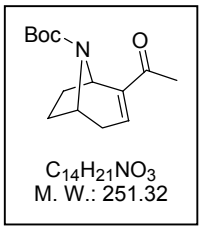
^{13}C-NMR (100.61 MHz, DMSO, T=343 K): 203.5, 150.8, 143.6, 136.6, 129.1, 127.8, 78.3, 59.4, 53.5, 51.3, 29.2, 27.6, 27.4, 26.5, 20.6

EI-MS m/z(%):334 (9), 252 (10), 195 (18), 152 (100), 139 (29), 108 (63), 91 (61), 68 (48), 57 (94), 43 (19), 41 (55).

IR (KBr pill): 2975, 2928, 2984,1709, 1685, 1410, 1174, 1105, 677

HR-MS (ESI-POS, [M+Na$^+$], sample dissolved in H_2O/ACN 1:1): found 430.1651 calculated 430.1664

(-)-N-Boc-norferruginine (-)-22

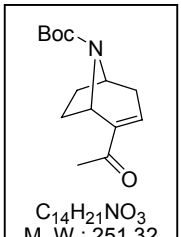


$C_{14}H_{21}NO_3$
M. W.: 251.32

A mixture of (-)-**85** (194 mg, 0.48 mmol), 53 mg (0.48 mmol) of *t*-BuOK in THF (5.5 ml) is stirred under nitrogen for 1 h, during which the solution become yellow and white salt precipitate. Water and Et_2O are added, the two phases are separated and the aqueous one is washed with ether and dried on $MgSO_4$. Evaporation of the solvent affords yellowish oil. FC (cyclohexane/EtOAc, 7:3) affords a white solid (92 mg, 0.37 mmol, 77 % yield). Mp 63-64 °C. $[\alpha]^{20}_D$: -125.2° ($CHCl_3$, c = 1.03), lit. $[\alpha]^{24}_D$: -126.8° ($CHCl_3$, c = 1.00)[13]

^{1}H-NMR (300 MHz, $CDCl_3$): 6.70-6.60 (m, 1H), 4.91 (d, *J* = 6.0 Hz, 1H), 4.39-4.30 (m, 1H), 2.93 (bd, *J* = 19.0 Hz, 1H), 2.26 (s, 3H), 2.23-1.97 (m, 3H), 1.84-1.73 (m, 1H), 1.64-1.45 (m, 1H), 1.42 (s, 9H).

(+)-N-Boc-norferruginine (+)-22



$C_{14}H_{21}NO_3$
M. W.: 251.32

A mixture of (+)-**85** (205 mg, 0.50 mmol), of *t*-BuOK (57 mg, 0.50 mmol) in THF (7 ml) is stirred under nitrogen for one hour, during which the solution become yellow and white salt precipitate. Water and Et_2O are added, the two phases are separated and the aqueous one is washed

with ether and dried on $MgSO_4$. Evaporation of the solvent affords yellowish oil. FC (cyclohexane/EtOAc 7:3) affords a white solid (100 mg, 0.40 mmol, 79% yield) (mp 65-66°C). $[\alpha]^{20}_D$: +113.7° ($CHCl_3$, c=1.00), lit. $[\alpha]^{24}_D$: +129.1° ($CHCl_3$, c = 1.00).[13]

^{1}H-NMR (300 MHz, $CDCl_3$): 6.70-6.60 (m, 1H), 4.91 (d, *J* = 6.0 Hz, 1H), 4.39-4.30 (m, 1H), 2.93 (bd, *J* = 19.0 Hz, 1H), 2.26 (s, 3H), 2.23-1.97 (m, 3H), 1.84-1.73 (m, 1H), 1.64-1.45 (m, 1H), 1.42 (s, 9H).

IX. References

(1) Willstaetter, R. *Justus Liebigs Annalen der Chemie* **1901**, *317*, 204-265.
(2) Robinson, R. *Journal of the Chemical Society, Abstracts* **1917**, *III*, 762-768.
(3) Ralph, I.; Bick, C.; Gillard, J. W.; Leow, H.-M. *Aust. J. Chem.* **1979**, *32*, 2523-2536.
(4) Ralph, I.; Bick, C.; Gillard, J. W.; Leow, H.-M. *Aust. J. Chem.* **1979**, *32*, 2537-2543.
(5) Swanson, K. L.; Albuquerque, E. X. In *Handbook of Experimental Pharmacology*; Springer-Verlag ed.: Berlin, Heidelberg, 1992; Vol. 102, pp 620-621.
(6) Schwarz, S.; Kampchen, T.; Tilotta, M. C.; Gundisch, D.; Seitz, G. *Pharmazie* **2003**, *58*, 295-299.
(7) Gohlke, H.; Schwarz, S.; Gundisch, D.; Tilotta, M. C.; Weber, A.; Wegge, T.; Seitz, G. *Journal of Medicinal Chemistry* **2003**, *46*, 2031-2048.
(8) Gohlke, H.; Guendisch, D.; Schwarz, S.; Seitz, G.; Tilotta, M. C.; Wegge, T. *Journal of Medicinal Chemistry* **2002**, *45*, 1064-1072.
(9) Nicolotti, O.; Pellegrini-Calace, M.; Carrieri, A.; Altomare, C.; Centeno, N. B.; Sanz, F.; Carotti, A. *Journal of Computer-Aided Molecular Design* **2001**, *15*, 859-872.
(10) Gundisch, D.; Kampchen, T.; Schwarz, S.; Seitz, G.; Siegl, J.; Wegge, T. *Bioorganic & Medicinal Chemistry* **2001**, *10*, 1-9.
(11) Gundisch, D.; Harms, K.; Schwarz, S.; Seitz, G.; Stubbs, M. T.; Wegge, T. *Bioorganic & Medicinal Chemistry* **2001**, *9*, 2683-2691.
(12) Rigby, J. H.; Pigge, F. C. *Journal of Organic Chemistry* **1995**, *60*, 7392-7393.
(13) Hernandez, A. S.; Thaler, A.; Castells, J.; Rapoport, H. *Journal of Organic Chemistry* **1996**, *61*, 314-323.
(14) Davies, H. M. L.; Matasi, J. J.; Hodges, L. M.; Huby, N. J. S.; Thornley, C.; Kong, N.; Houser, J. H. *Journal of Organic Chemistry* **1997**, *62*, 1095-1105.
(15) Gauthier, I.; Royer, J.; Husson, H.-P. *Journal of Organic Chemistry* **1997**, *62*, 6704-6705.
(16) Katoh, T.; Kakiya, K.; Nakai, T.; Nakamura, S.; Nishide, K.; Node, M. *Tetrahedron: Asymmetry* **2002**, *13*, 2351-2358.
(17) Aggarwal, V. K.; Astle, C. J.; Rogers-Evans, M. *Org. Lett.* **2004**, *6*, 1469-1471.
(18) Allin, S. M.; Shuttleworth, S. J.; Page, P. C. B. *Organosulfur Chemistry* **1998**, *2*, 97-155.
(19) Baird, C. P.; Rayner, C. M. *Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry* **1998**, 1973-2003.
(20) Rayner, C. M. *Contemporary Organic Synthesis* **1996**, *3*, 499-533.
(21) Rayner, C. M. *Contemporary Organic Synthesis* **1995**, *2*, 409-440.
(22) Rayner, C. M. *Contemporary Organic Synthesis* **1994**, *1*, 191-203.
(23) Pitchen, P.; Kagan, H. B. *Tetrahedron Letters* **1984**, *25*, 1049-1052.
(24) Pitchen, P.; Dunach, E.; Deshmukh, M. N.; Kagan, H. B. *Journal of the American Chemical Society* **1984**, *106*, 8188-8193.
(25) Kagan, H. B.; Rebiere, F. *Synlett* **1990**, 643-650.
(26) Zhao, S. H.; Samuel, O.; Kagan, H. B. *Tetrahedron* **1987**, *43*, 5135-5144.
(27) Zhao, S. H.; Samuel, O.; Kagan, H. B. *Comptes Rendus De L Academie Des Sciences Serie Ii* **1987**, *304*, 273-274.
(28) Dunach, E.; Kagan, H. B. *Nouveau Journal de Chimie* **1985**, *9*, 1-3.
(29) Bortolini, O.; Difuria, F.; Licini, G.; Modena, G.; Rossi, M. *Tetrahedron Letters* **1986**, *27*, 6257-6260.

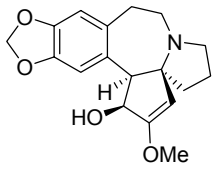
(30) Difuria, F.; Modena, G.; Seraglia, R. *Synthesis-Stuttgart* **1984**, 325-326.
(31) Bolm, C.; Bienewald, F. *Angewandte Chemie, International Edition in English* **1996**, *34*, 2640-2642.
(32) Andersen, K. K. *Tetrahedron Letters* **1962**, 93-95.
(33) Phillips, H. *Journal of the Chemical Society, Abstracts* **1925**, *127*, 2552-2587.
(34) Herbrandson, H. F.; Dickerson, R. T. *Journal of the American Chemical Society* **1959**, *81*, 4102-4106.
(35) Mioskowski, C.; Solladie, G. *Tetrahedron* **1980**, *36*, 227-236.
(36) Lockard, J. P.; Schroeck, C. W.; Johnson, C. R. *Synthesis-Stuttgart* **1973**, 485-486.
(37) Solladie, G.; Greck, C.; Demailly, G.; Solladiecavallo, A. *Tetrahedron Letters* **1982**, *23*, 5047-5050.
(38) Solladie, G.; Demailly, G.; Greck, C. *Tetrahedron Letters* **1985**, *26*, 435-438.
(39) Carreno, M. C.; Ruano, J. L. G.; Martin, A. M.; Pedregal, C.; Rodriguez, J. H.; Rubio, A.; Sanchez, J.; Solladie, G. *Journal of Organic Chemistry* **1990**, *55*, 2120-2128.
(40) Solladie, G.; Frechou, C.; Demailly, G.; Greck, C. *Journal of Organic Chemistry* **1986**, *51*, 1912-1914.
(41) Schmitz, F. J.; Kraus, K. W.; Ciereszk.Ls; Sifford, D. H.; Weinheim.Aj *Tetrahedron Letters* **1966**, 97.
(42) Cimino, G.; Destefano, S.; Guerriero, A.; Minale, L. *Tetrahedron Letters* **1975**, 1417-1420.
(43) Shono, T.; Matsumura, Y.; Yamane, S. *Tetrahedron Letters* **1981**, *22*, 3269-3272.
(44) Rothberg, I.; Shubiak, P. *Tetrahedron Letters* **1975**, 769-772.
(45) Iwata, C.; Maezaki, N.; Kurumada, T.; Fukuyama, H.; Sugiyama, K.; Imanishi, T. *J. Chem. Soc.-Chem. Commun.* **1991**, 1408-1409.
(46) Imanishi, T.; Kurumada, T.; Maezaki, N.; Sugiyama, K.; Iwata, C. *J. Chem. Soc.-Chem. Commun.* **1991**, 1409-1411.
(47) Maignan, C.; Raphael, R. A. *Tetrahedron* **1983**, *39*, 3245-3249.
(48) Arai, Y.; Kuwayama, S.; Takeuchi, Y.; Koizumi, T. *Tetrahedron Letters* **1985**, *26*, 6205-6208.
(49) Buezo, N. D.; De la Rosa, J. C.; Priego, J.; Alonso, I.; Carretero, J. C. *Chemistry--A European Journal* **2001**, *7*, 3890-3900.
(50) Delouvrie, B.; Fensterbank, L.; Lacote, E.; Malacria, M. *Journal of the American Chemical Society* **1999**, *121*, 11395-11401.
(51) Kuznetsov, N.; Renaud, P., Unpubblished results.
(52) Takeda, T.; Sasaki, R.; Yamauchi, S.; Fujiwara, T. *Tetrahedron* **1997**, *53*, 557-566.
(53) Marchand, A. P.; Aavula, B. R.; Bott, S. G. *Tetrahedron* **1998**, *54*, 5105-5118.
(54) Imboden, C.; Villar, F.; Renaud, P. *Org. Lett.* **1999**, *1*, 873-875.
(55) Addie, M. S.; Taylor, R. J. K. *ARKIVOC [online computer file]* **2000**, *1*, 660-666.
(56) Shapiro, R. H. *Org. React.* **1976**, *23*, 405-507.
(57) Cusack, N. J.; Reese, C. B.; Risius, A. C.; Roozpeikar, B. *Tetrahedron* **1976**, *32*, 2157-2162.
(58) Jonsson, S. Y.; Loefstroem, C. M. G.; Baeckvall, J.-E. *Journal of Organic Chemistry* **2000**, *65*, 8454-8457.
(59) Brown, S. J.; Gao, X.; Kowalchuk, M. G.; Spence, R. E. v. H.; Stephan, D. W.; Swabey, J. *Canadian Journal of Chemistry* **2002**, *80*, 1618-1624.
(60) Stork, G.; Sher, P. M. *Journal of the American Chemical Society* **1986**, *108*, 303-304.
(61) Casy, A. F.; Jeffery, W. K. *Canadian Journal of Chemistry* **1972**, *50*, 803-809.
(62) House, H. O.; Muller, H. C.; Pitt, C. G.; Wickham, P. P. *Journal of Organic Chemistry* **1963**, *28*, 2407-2416.

(63) Bottini, A. T.; Grob, C. A.; Schumacher, E.; Zergenyi, J. *Helvetica Chimica Acta* **1966**, *49*, 2516-2524.
(64) Renaud, P.; Lacote, E.; Quaranta, L. *Tetrahedron Letters* **1998**, *39*, 2123-2126.
(65) Honrubia, M. A.; Rodriguez, J.; Dominguez, R.; Lozoya, E.; Manaut, F.; Seijas, J. A.; Villaverde, M. C.; Calleja, J. M.; Cadavid, M. I.; et al. *Chemical & Pharmaceutical Bulletin* **1997**, *45*, 842-848.
(66) Lin, R.; Castells, J.; Rapoport, H. *Journal of Organic Chemistry* **1998**, *63*, 4069-4078.

A study toward the synthesis of *Cephalotaxus* alkaloids

I. Cephalotaxine: natural occurrence and properties.

Cephalotaxine is a representative Cephalotaxus alkaloid, which was for the first time isolated in a pure form in 1963 from *Cephalotaxus fortunei* and *C. harringtonia* var. *drupacea* by Paudler.[1]



(-)-1

A first attempt to determine the structure was run by Paudler. Two different structures were suggested, one of which was confirmed to be the right by X-ray analysis. The absolute configuration of the natural product was disclosed later since the derivative on which the structure was elucidated was found to be racemic.[2-5]

Cephalotaxine was isolated together with other alkaloids. Although cephalotaxine does not show any interesting biological activity, some of the related compounds were found to have antileukemia activity. In particular the compounds that shows anticancer activity are the harringtonines: harringtonine **2**, isoharringtonine **4**, homoharringtonine **5** and deoxyharringtonine **3**, which differ from cephalotaxine by the ester derivative (Figure 1).[6,7]

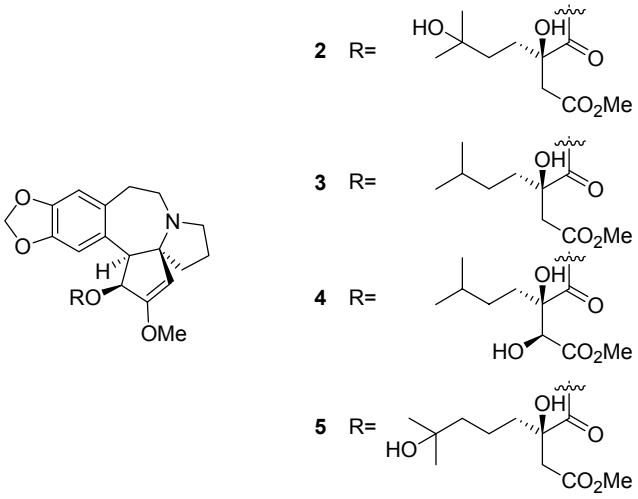


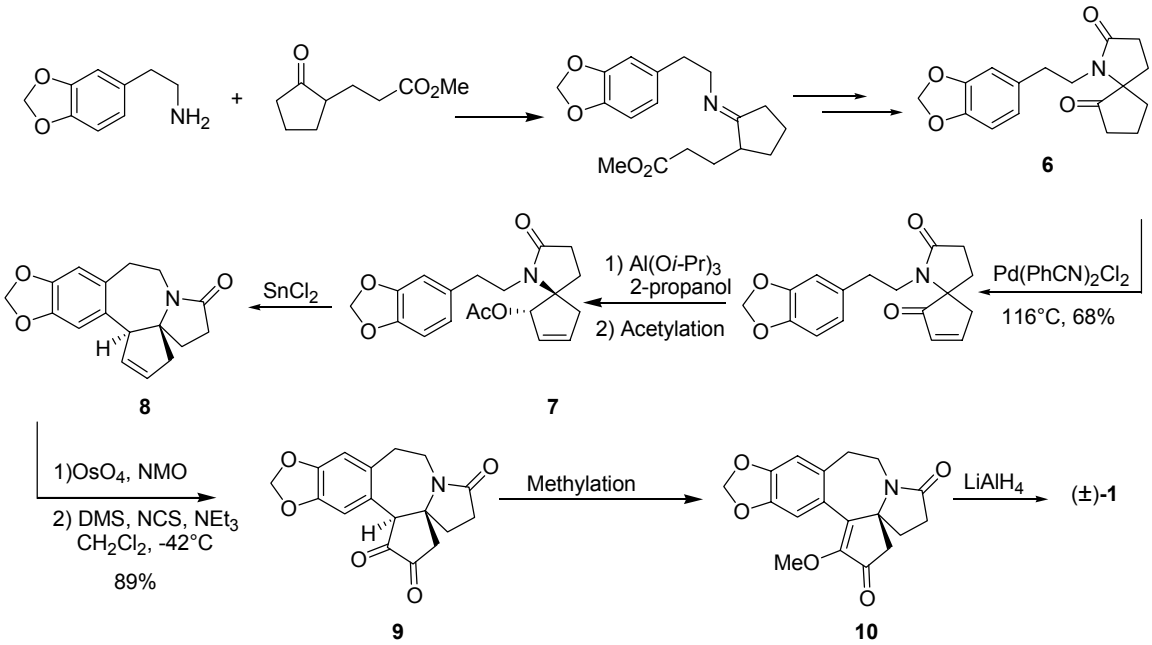
Figure 1

The potential anticancer activity of these molecules induces the research of a good synthesis for cephalotaxine, since the transformation into the different cephalotaxus alkaloids is easily achieved

II. Cephalotaxine: synthesis

For the time being, only four asymmetric total syntheses leading to the optically pure **1** are reported. The first total synthesis was reported by Weinreb in 1972, followed by several others.[8]

Kuehne and co-workers reported the synthesis of the racemic cephalotaxine.[9] They synthesised the intermediate **6**, which then was oxidised to the α,β-unsaturated keton upon treatment with Pd(II) salts. Reduction using the Meerwein-Pandorff-Verlay method (Al(O*i*-Pr)$_3$ and 2-propanol) and acylation afforded **7**. Intramolecular Friedel-Craft alkylation afforded **8**. Dihydroxilation, oxidation of the two alcohols arose the compound **9**, which was alkylated with trimethylsilyl ether and triflic acid to give the intermediate **10**, which after reduction with $LiAlH_4$ gave racemic cephalotaxine (scheme 1).

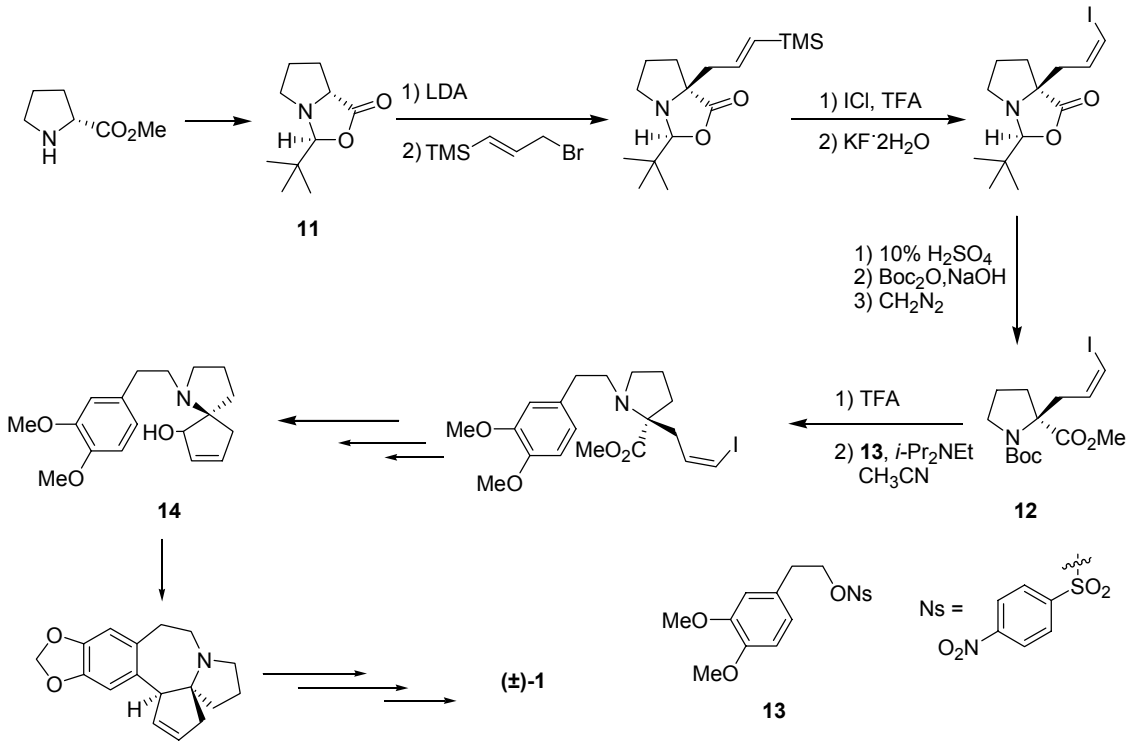


Scheme 1

In 1995 Mori reported the first enantiopure synthesis of cephalotaxine.[10]

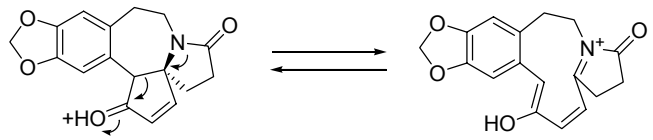
Starting from D-(+)-proline Mori and co-workers prepared compound **11**. Diasteroselective alkylation with trimethylsilyl allylbromide allowed the control of the quaternary centre of the spiro-moiety. Conversion into the vinyliodide and opening of the

lactone ring afforded, after protection with the Boc-group, compound **12**. Alkylation of the nitrogen atom and cyclisation gave compound **14**. Here again intramolecular Friedel-Craft alkylation generated the last ring of cephalotaxine (scheme 2).



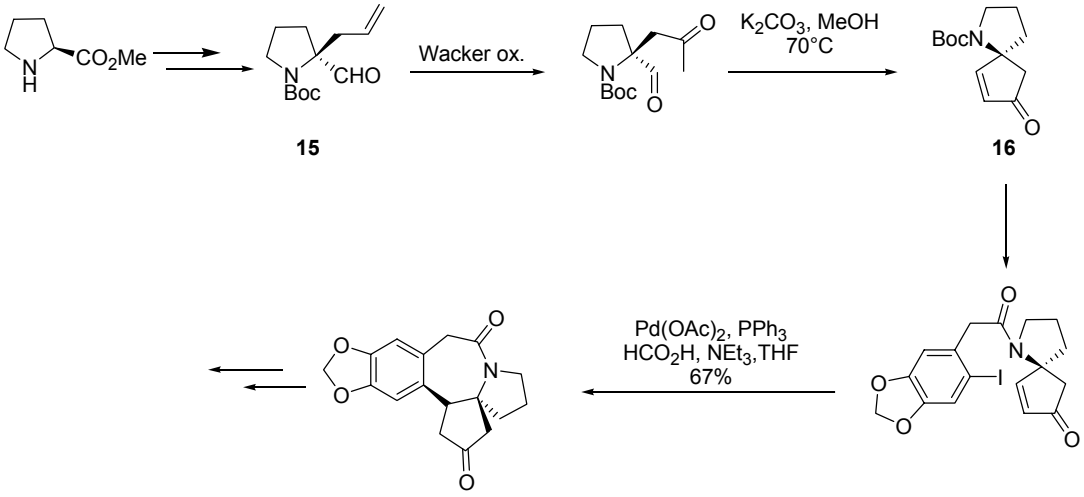
Scheme 2

Following a procedure similar to the one reported by Kuehne, they prepared cephalotaxine. Unfortunately the last methylation occurred with complete racemisation, probably due to an acid-catalysed retro-Mannich reaction. This problem was circumvented using a different reaction condition for the methylation. Final reduction with $NaBH_4$ afforded (-)-cephalotaxine.



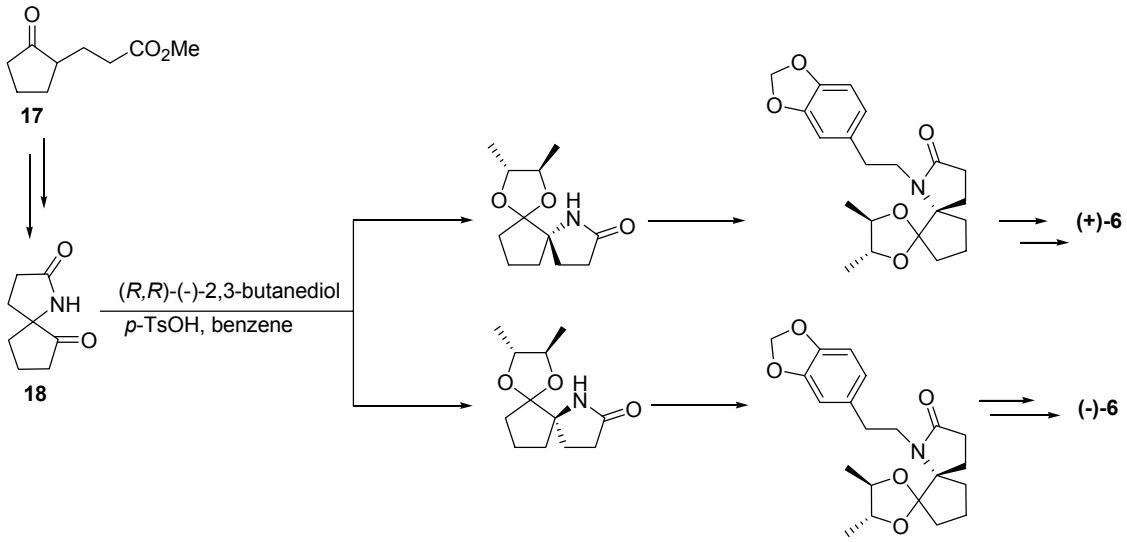
Scheme 3

Ikeda described almost at the same time a formal synthesis of cephalotaxine.[11-15] They synthesised compound **15,** starting from D-(+)-proline, following the same strategy of Mori. After reduction and oxidation to the aldehyde they formed the spiro-cycle using an intramolecular aldolisation (scheme 4).



Scheme 4

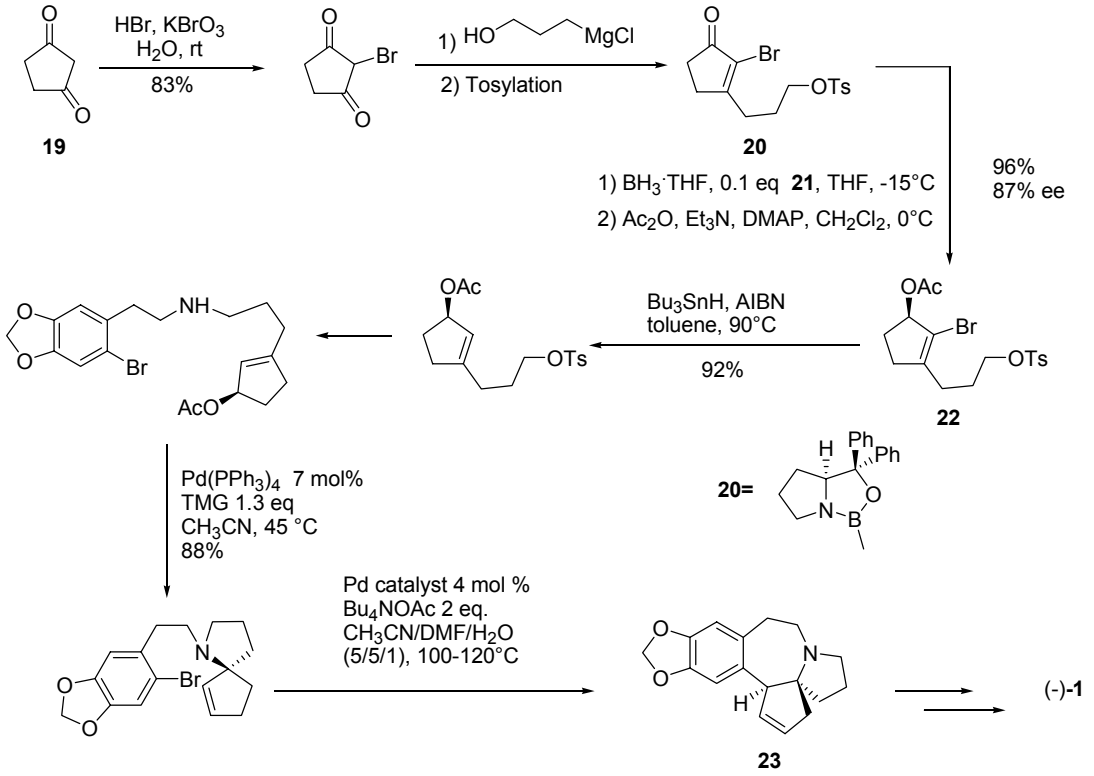
Two years later Nagasaka reported the synthesis and the resolution of the spiro-cycle **17**.[16] They synthesised compound **16** by alkylation of the pyrrolidine enamine of cyclopentanone with methyl acrylate. This one was then converted in the ketolactame **17**. Protection of the ketone with (*R,R*)-(-)-2,3-butanediol gave a mixture of two diastereoisomers which were easily separable by chromatography. Alkylation of the nitrogen and deprotection of the chetal afforded the enantiopure compounds (+)- and (-)-**6**, which were already described by Kuehne (scheme 5).



Scheme 5

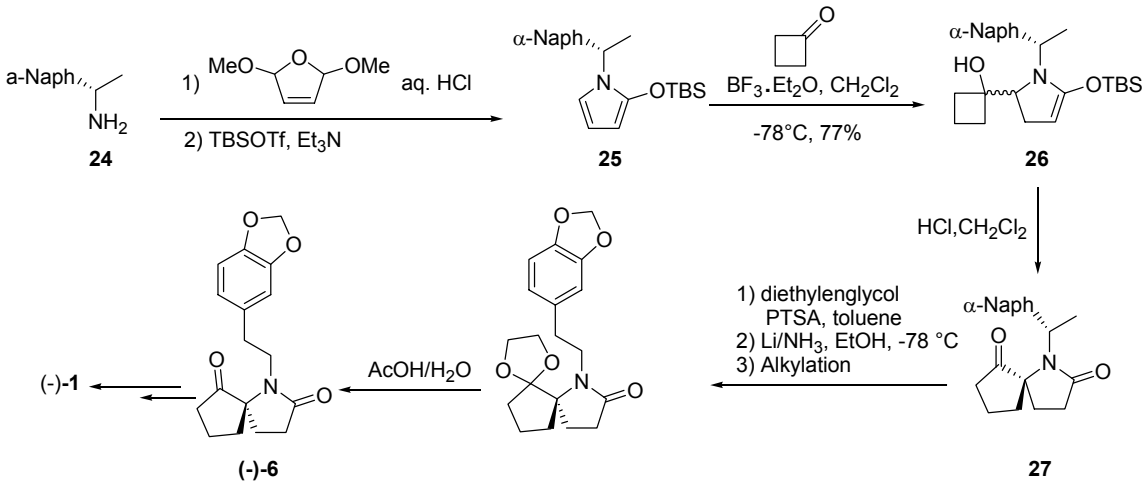
More recently Tietze and co-workers described the enantioselective synthesis of cephalotaxine using two successive Pd-catalysed reactions.[17-22] The spiro-centre was formed via an intramolecular palladium-assisted allylation of an amine from an optically pure allylacetate. Asymmetric reduction with **21** introduced the chirality in

20, which was formed after few steps from the diketone **19**. The reduction of the ketone was performed using BH_3 and an oxazaborolidine as chiral catalyst. In this way the alcohol **22** was obtained with 87% ee. Heck cyclisation gave the intermediate **23** already described by Mori (scheme 6).



Scheme 6

In the 2004 Royer and co-worker published a stereoselective synthesis of the intermediate (-)-**6**.[23] They synthesised compound **26** starting from the chiral amine **24** and the dimethoxydihydrofuran. This compound was used in a Mukaiyama type aldol reaction with the cyclobutenone to afford **25** with low diastereomeric excess. Acid treatment induced a semi-pinacol type rearrangement to afford the spiro-cycle **27** with good diastereomeric ratio (90:10). The two diastereoisomers were found to be easily separable. Protection of the ketone, deprotection of the nitrogen, alkylation and deprotection of the acetal afforded the intermediate (-)-**6**.



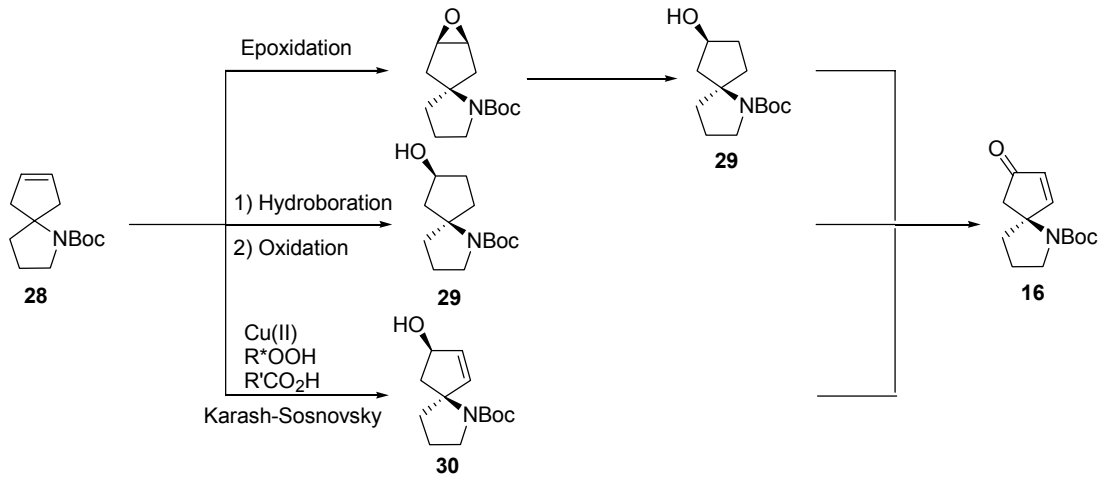
Scheme 7

III. Objective of the work

The key compound of the synthesis of cephalotaxine reported by Ikeda and co-workers is the spiro-compound **26**. In order to have a formal synthesis of cephalotaxine this compound was chosen as target for this project.

Bubnov reported recently an easy synthesis of the achiral spiro-cycle **28** (scheme 20).[24,25] This compound is interesting since the double bond can be used to introduce different functionalities. Selective functionalisation of the double bond will introduce two new asymmetric centres, desymmetrising **28**.

In order to synthesise **26** is necessary to hydroxilate the double bond. This can be achieved in different ways such as epoxidation followed by selective ring opening, leading to **29**; asymmetric Karasch-Sovnosky reaction,[26-29] leading to the allylic alcohol **30**; asymmetric hydroboration, leading to **29**. One pot oxidation of **29** with AIBX should give the desired compound (scheme 8).[30-32]



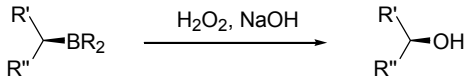
Scheme 8

Based on the to the results obtained by Hodgson on a similar substrate, we focused our attention on the asymmetric hydroboration, (scheme).

Asymmetric hydroboration can be carried out both in stoichiometric way using chiral boranes and in catalytic way using chiral catalyst. We decide so to investigate for first chiral boranes and subsequently to investigate the catalytic hydroboration.

IV. Asymmetric Hydroboration

The discovery of hydroboration in 1956[33] resulted in a very important tool in organic synthesis. It allows the introduction of many different functionalities from an alkene with the control of the stereochemistry.[34,35] This is due to the fact that substitution of the boron atom occurs with completely retention of configuration at the carbon. For instance it is possible to have besides hydroxylation, halogenation, amination, carbonylation.



Scheme 9

Chiral organoboranes has been largely developed and used in synthesis, but at the same time other hydroborating agent has been developed using catalytic systems, formed by a metal and chiral phosphines.

IV.I.Chiral organoboranes

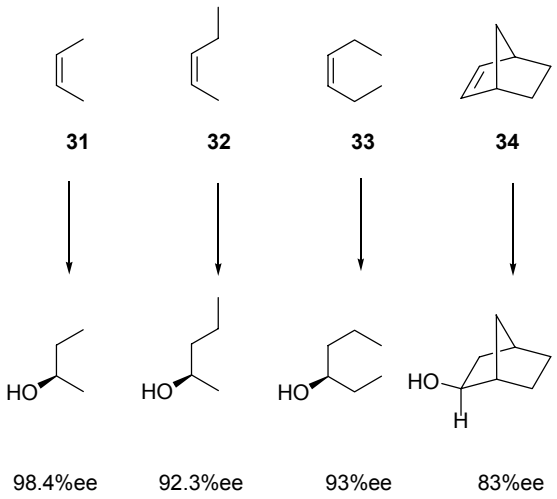
IV.I.I. Diisopinocampheylborane: preparation and structure

Hydroboration of naturally occurring optically active alkenes leads to the formation of intermediates that can be used as asymmetric hydroborating agents. In particularly Brown, in 1961, described the first synthesis of a chiral hydroborating agent, diisopinocampheylborane (Ipc_2BH).[36]

Preparation of the Ipc_2BH is carried out by simple hydroboration of α-pinene with $BH_3{\cdot}DMS$.[37,38] Reaction of a 15% excess solution of α-pinene with borane at 0°C for three days leads to the quantitative formation of Ipc_2BH. Equilibration of the species presents in solution allows the incorporation of the major enantiomer of α-pinene into the borane, which precipitates as a solid of high optical purity.

IV.II.Diisopinocampheylborane: reactivity

Hydroboration of *cis* olefins proceeds rapidly to the trialkylborane. The organoboranes do not undergo racemisation over a period of 48 hours at room temperature.[39] Oxidation with hydrogen peroxide affords the corresponding alcohols with very good enantioselectivities. For example using the 100% ee Ipc_2BH hydroboration of the olefins **31-34** gives the corresponding alcohols with ee up to 90%. Only in the case of the borneol the ee is poorer but still is good (scheme 12).[38]



Scheme 10

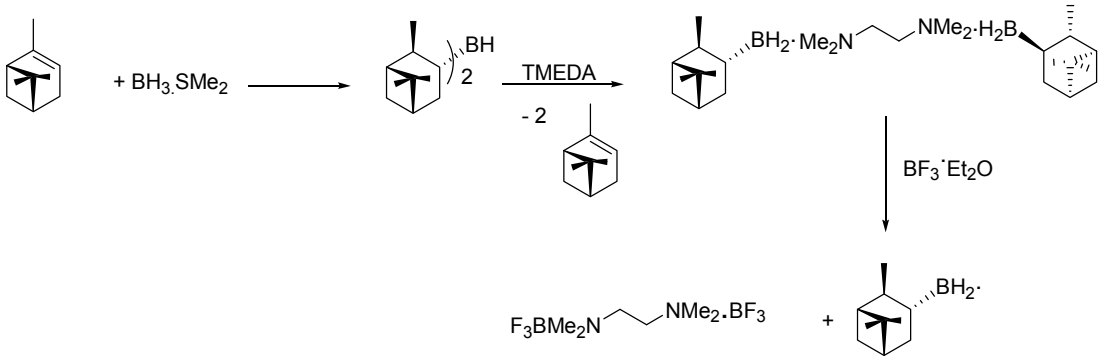
Noteworthy is the tendency of solution in THF of Ipc_2BH to undergo β-hydride elimination leading to the starting α-pinene and to $IpcBH_2$, which reacts faster of the Ipc_3BH giving product of opposite configuration, thus reducing the optical purity of the final product.[40] This difficulty has been partially solved by carrying out the reaction in diglyme a solvent in which the dissociation is slow. For example the hydroboration in THF of *cis*-2-butene affords (R)-2-butanol in 78% ee, while in diglyme gives 87% ee.[39]

IV.III. Monoisopinocampheylborane: preparation

When Ipc_2BH has been applied for the more hindered olefins such as trisubstituted or *trans* olefins the selectivity dropped down drastically.[39] Ipc_2BH is too bulky to react with these types of olefins[40]

$IpcBH_2$ cannot be formed by direct hydroboration of α-pinene since this does not stop at the first stage. When TMEDA is added to a solution of Ipc_2BH the crystalline $(IpcBH_2)_2$·TMDA complex is formed. Treatment of this complex with

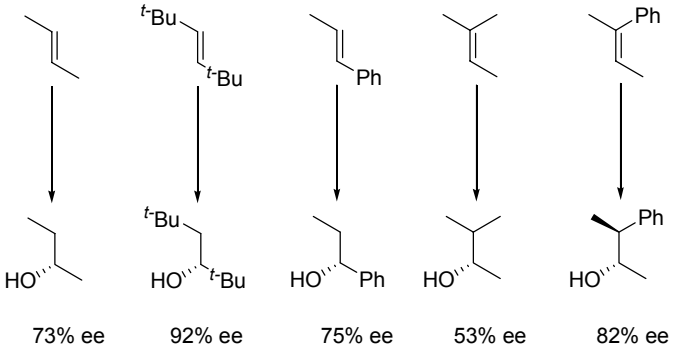
$BF_3{\cdot}Et_2O$ forms a $TMDA{\cdot}BF_3$ complex, which precipitates as a white solid, leaving in solution the desired $IpcBH_2$ (scheme 11).[41]



Scheme 11

IV.III.I. Monoisopinocampheylborane: reactivity

$IpcBH_2$ appeared to be an excellent reagent in the case of bulky olefins, like *trans*-alkenes or trisubstituted ones.



Scheme 12

As we can see the results obtained in the case of Ipc_2BH and $IpcBH_2$ are completely complementary: in the case of *cis* alkenes the Ipc_2BH gives very good enantioselectivities, while the $IpcBH_2$ gives poor ee. This is reversed in the case of trisubstituted olefins or *trans*-ones[42].

IV.IV.Catalytic Asymmetric Hydroboration

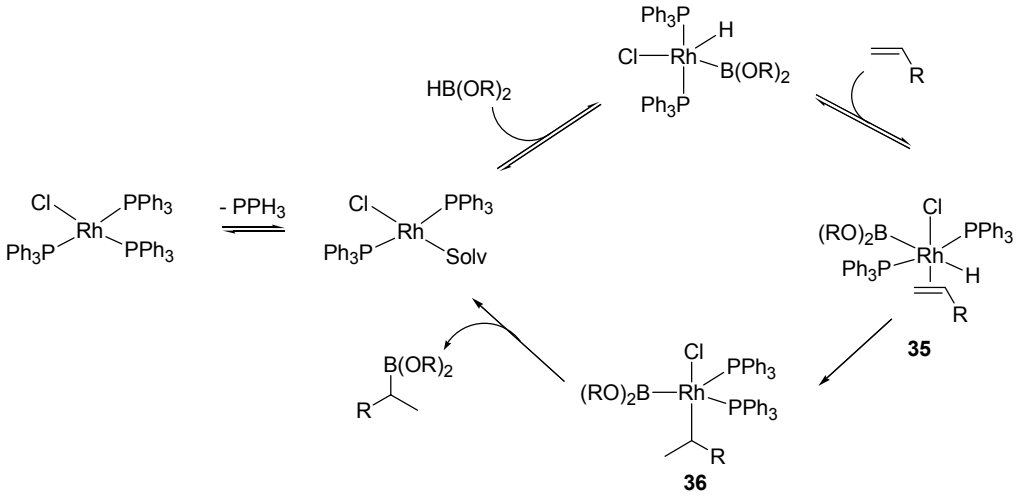
Although the good efficiency of chiral boranes in hydroboration, a large quantity of product deriving from the chiral auxiliary (i.e. α-pinene) induced to search for different hydroborating systems.

In 1985 Mannig and Noth reported the first application of catalytic hydroboration using catecholborane (catBH) and wilkinson's catalyst.[43]

The use of catBH, as hydroborating agent, had been already described by Brown and co-workers and actually the reactivity of catBH is much reduced in comparison with other boranes.[44-46] The reduced reactivity offers the advantage of making the hydroboration tolerant towards the presence of several functional groups such as alkyl and aryl aldehydes, nitro groups, sulfones, disulfides, thiols, primary amides, ether, sulfides and alcohols.[47] Noteworthy is that the chemoselectivity, regioselectivity and diastereoselectivity of catBH in the catalytic version are different than when the reaction it is not catalysed.[43,48-51]

IV.IV.I.Mechanism

In the case of the Wilkinson's catalyst the reaction begins with the dissociation of one phosphine from the rhodium followed by oxidative addition of the catBH (scheme **31**). The product formed has been isolated by Kono[52], while Westcott[53] isolated the corresponding complex where the phosphine was P*i*-Pr$_3$ and determined its structure by X-ray crystallography. Then complexation of the olefin generates the six-coordinated intermediate **37** with the hydride and the boryl ligands *trans*.[54] Insertion of the olefin into the metal-hydride bond gives **38**, which affords after reductive elimination the desired compound and regenerate the catalyst.



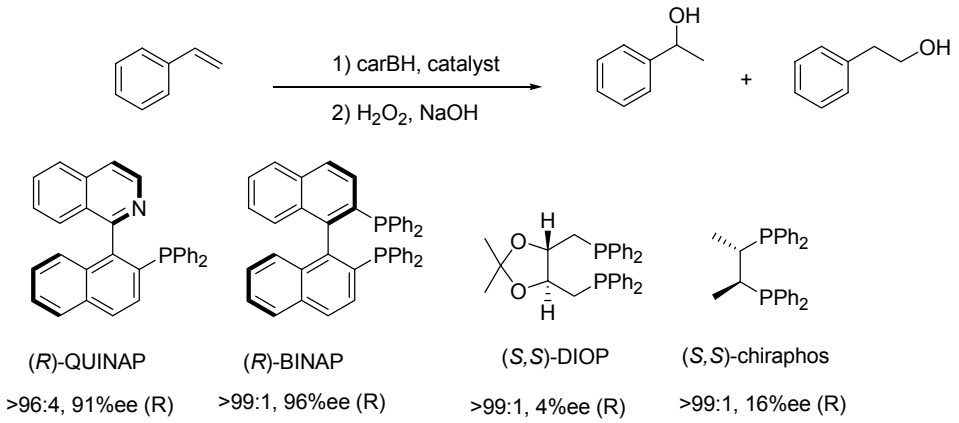
Scheme 13

IV.IV.II. Chiral phosphines

Once that it has been proved the efficiency of the rhodium catalysed hydroboration with the Wilkinson's catalyst it immediately appeared the opportunity to adopt this reaction in an asymmetric way using chiral phosphines.

The reaction was extensively studied with styrene. Different conditions have been used in order to study the effect of the solvent, temperature and the ligand, of course.

For instance hydroboration with catBH and the rhodium catalyst generated from



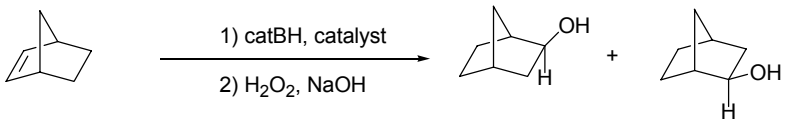
Scheme 14

[Rh(COD)]BF_4 and (*R*)-BINAP in DME at –78°C gave the highest yield of the alcohol of up to 96% ee. Normally DME is the solvent of choice for reaction at low temperature, because in other solvents catBH is not soluble at low temperature.

The selectivity is dependent on the temperature: the lower the temperature, the higher the ee.

Other phosphine have been tested like for instance (*S*,*S*)-DIOP, (*S*,*S*)-chiraphos, (S)-QUINAP, but all of them, with the exception of (*S*)-QUINAP, resulted to be less effective then (*R*)-BINAP.

Hydroboration of norbornene is also reported in an asymmetric way. In this case (*S*,*S*)-BDPP resulted to be the best enantioselective ligands (table 2).



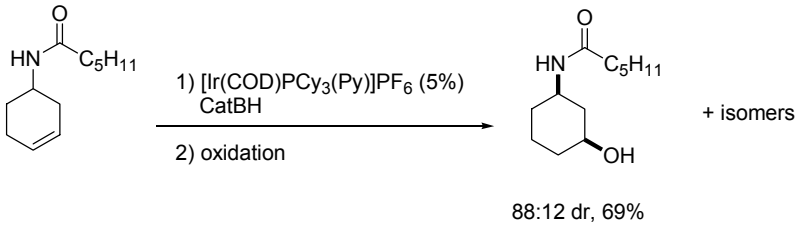
Scheme 15

Entry	Catalyst (mol%)	Solvent	Temp (°C)	Time (h)	Yield (%)	ee% (config.)	Ref.
3	½[RhCl(C_2H_4)$_2$] (1) /(*S,S*)-DIOP (1)	PhMe	-5	3 days	81	59 (1*S*)	[55]58
4	½[RhCl(C_2H_4)$_2$] (1) /(*S,S*)-chiraphos (1)	PhMe	-5	3 days	76	10 (1*S*)	[55]58
5	(S,S)-BDPP	THF	-25	-	-	80 (1*R*)	
6	[Rh(cod)$_2$]BF_4 (1)/ (*R*)-BINAP (1)	THF	25	1	61	15 (1*S*)	[48]48

Table 2. Hydroboration of norbornene

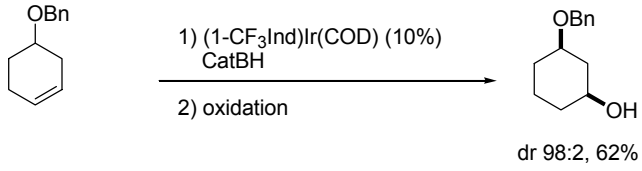
Although rhodium is the most studied, other metals are reported to be efficient in catalysing the hydroboration of double bonds. For instance iridium is the second more widely used catalyst after rhodium.[56,57]

Crabtree's catalyst, [Ir(COD)PCy_3(Py)]PF_6, has been reported by Evans and Fu to be highly effective for direct hydroboration of allylic and homoallylic amides (scheme 16).[58]



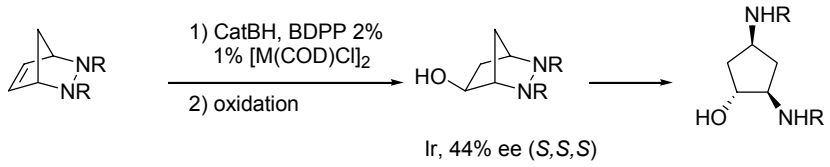
Scheme 16

Later on Sowa jr. reported that indenyl iridium complexes, [Ir(COD)Ind(CF_3)], result to be much more effective giving up to 98% of the 1,3-*cis* isomer.[59]



Scheme 17

Bonin, Micouin and co-workers disclosed that hydroboration of olefin using catBH and iridium catalyst, generated from [Ir(COD)Cl]$_2$ and a chiral phosphine gave the corresponding alcohol with acceptable an enantioselectivity.[60]



Scheme 18

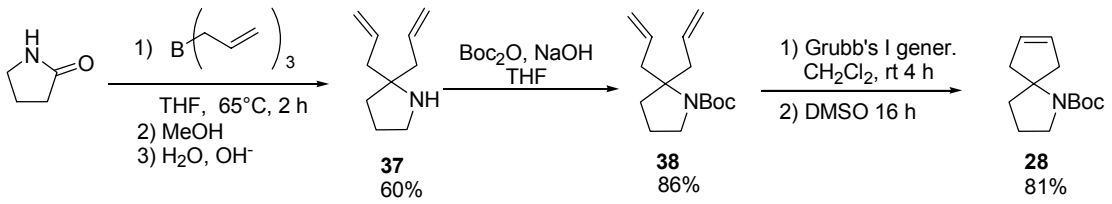
In particular they reported the hydroboration with iridium resulted to be complementary to the one of rhodium, since it gives the opposite selectivity (cfr. scheme **18** with scheme **7** in chapter 1).

catBH is not the only hydroborating agent reported in literature for asymmetric hydroborations, for instance pinacolborane is also reported to be efficient (scheme).

V. Results and Discussion

V.I. Preparation of the substrate

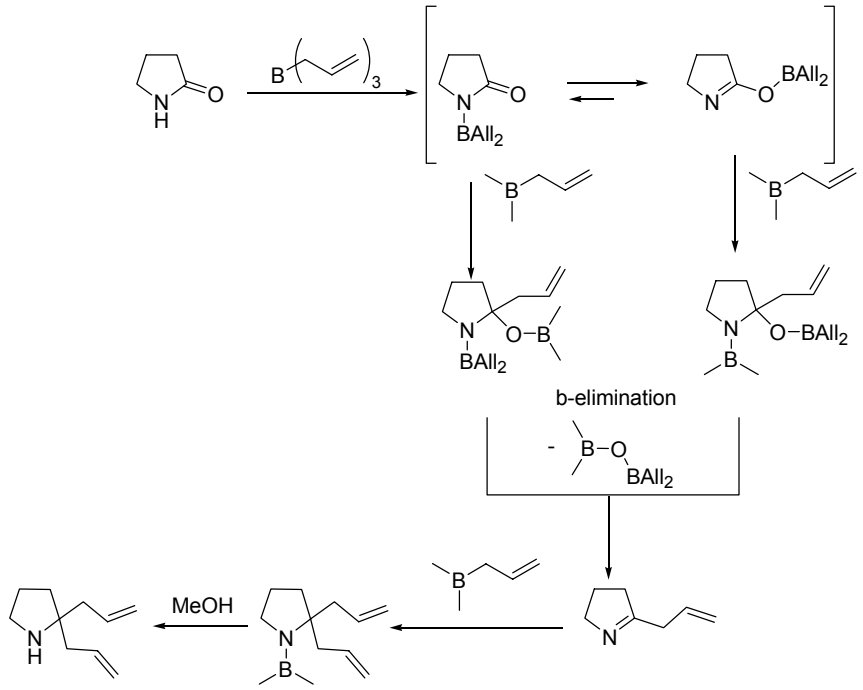
In order to investigate the asymmetric hydroboration for the synthesis of **16** we synthesised the spiro-cycle **28**. This is easily formed following a procedure described by Bubnov.[24,61] Double allylation of the 2-pirrolidinone with triallylborane affords the bisallyl-derivative **39**.



Scheme 19

The possible mechanism of the reaction is described in the scheme **20**.

Protection of the nitrogen with Boc-group and metathesis with the Grubb's catalyst yield the desired spiro compound with good yield. The simplicity of this



Scheme 20

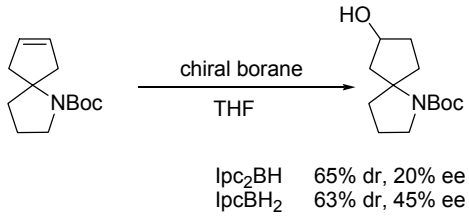
procedure allows us to prepare the spiro-compound in gram quantities (up to 100 mmol).

VI. Results and discussion

During this study on hydroboration of **28** all the enantiomeric excess and diastereomeric ratio were determined via chiral GC. The hydroboration afforded two different diasteroisomers one of which was strongly major, the retention times of each enantiomers in GC were 136 and 140 min. The latest retention time is referred to the one enantiomer that normally was in excess. The enantiomers of the minor diastereoisomer had a retention time of 93 and 95 min. The two enantiomers of the major diastereoisomer were difficult to separate, although it was anyway possible to measure the ee.

Preliminary experiments of hydroboration with $IpcBH_2$ and Ipc_2BH were run on **28**.

Due to the normal reactivity of these boranes we can expect that the second will give the better enantioselectivity, instead this was not the case and $IpcBH_2$ was the one that gave the better selectivity (table 3). These results were comparable with the one



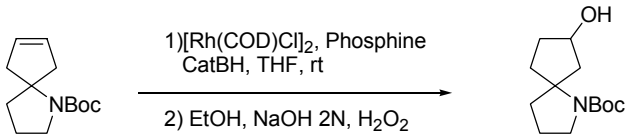
Scheme 21

reported by Hodgons.

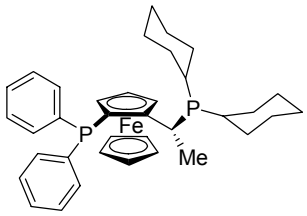
entry	chiral borane	dr	ee (%)	conversion (%)
1	Ipc_2BH	82:18	20	
2	$IpcBH_2$	82:18	45	

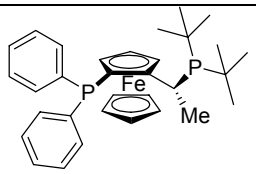
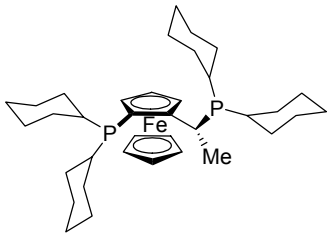
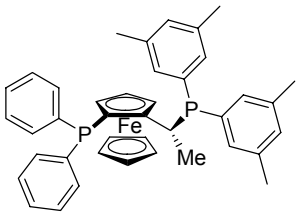
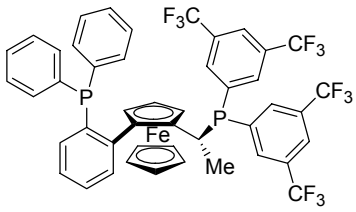
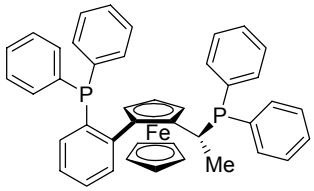
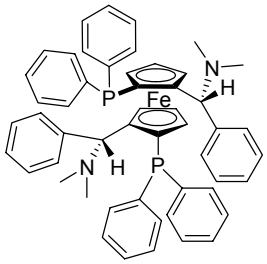
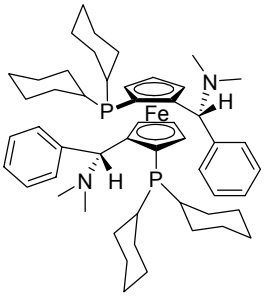
Table 3. Hydroboration with chiral boranes

We started then to investigate the catalytic version. We chose as source of the metal $[Rh(COD)Cl]_2$, and we started to screen different phosphines. The alkene and the catechol were added at –78°C to a 1M solution in THF of the catalyst. Then the reaction mixture was warm up to room temperature and let react overnight. byphenyl was added to the reaction mixture, before the work up, as an internal standard to measure the conversion.



Scheme 22

Entry	Phosphine	Eq.	e.e. (%) Dia. 1	e.e (%) dia. 2[a]	*trans*:*cis*[b]	Conv. (%)
1	(S,S)-BDPP	1	38.8	47.6	93:7	-
2	(+)-BINAP	1	3.36*	33.5*	91:9	-
4	(-)-DIOP	1	42.9	22.2	94:6	-
5		1	2.0	4.6	82:18	-

Entry	Phosphine	Eq.	e.e. (%) Dia. 1	e.e (%) dia. 2[a]	*trans*:*cis*[b]	Conv. (%)
6		1	1.6	10.6	86:14	-
7		1	2.1	1.5	70:30	-
8		1	1.3	1.9	43:57	-
9		1	10.4	5.4	94:6	96.2
10		1	14.5	30.3	97:3	98
11		1	n.d	37.8	n.d	90
12		1	0.7	0.6	51:49	85

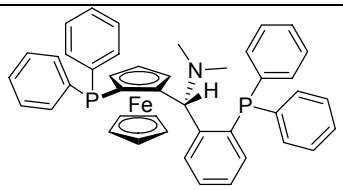
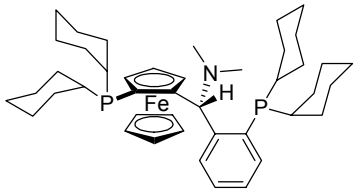
Entry	Phosphine	Eq.	e.e. (%) Dia. 1	e.e (%) dia. 2[a]	*trans*:*cis*[b]	Conv. (%)
13		1	n.d	21.6	n.d	74
14		1	2.6	6.3	40:60	88

Table 4. Screening of different phosphines.a) the major enantiomer is the one with higer retention time (140 min); b) in comparison with Hodgson work, but not proof *) in this case the enantiomer is the opposite one.

The results obtained with the various phosphines are summarised in table 4. Two diastereoisomers are obtained; unfortunately the structure of the major isomer could not be determined. In comparison with Hodgson's work, we can suppose that the relative configuration of the major diastereoisomer is *trans*.

In some cases (entry 11 and 13) the minor isomer was detected but it was impossible to integrate due to the few quantity. In the case of some of the ferrocenyl-based phosphines (entry 5, 6, 9, 10, 11,13) the diastereoselectivity was good, although the major diastereoisomer was racemic with the exception of entry 10, 11 and 13: in this case the phosphines gave a low enantioselectivity. The best result was obtained with (*S*,*S*)-BDPP (entry 1), while (*R*)-BINAP (entry 2) gave a good enantioselectivity but the major enantiomer was the opposite one.

Following test were then run using (S,S)-BDPP, since was the one that gave the best enantioselectivity.

The effect of the solvent was investigated in more details, in order to see whether the solvent influence the reactivity and the enantioselection.

Entry	Phosphine	Eq.	Solvent	Temperature	e.e (%)	*trans*:*cis*[b]	Conv. (%)
1	(*S*,*S*)-BDPP	1	THF	r.t.	47.6	94:6	n.d
2	(*S*,*S*)-BDPP	1	DCM	r.t.	3	71:29	98
3	(*S*,*S*)-BDPP	1	PhH	r.t.	39.2	98:2	86
4	(*S*,*S*)-BDPP	1	Tol	r.t.	7.8	96:4	94
5	(*S*,*S*)-BDPP	1	DME	r.t.	20.4	95:5	98

Table 5. Effect of temperature and of the solvent, b) in comparison with Hodgson work, but not proof

There is a strong effect of the solvent. In THF (entry 1) the reaction gave good selectivity, while DME (entry 5) or toluene (entry 4) gave only low selectivity. The selectivity obtained with benzene (entry3) was comparable to the one of THF (table 5).

Finally we look for the effect of the temperature. Surprisingly we found out that differently from what has been reported till now, for hydroboration of alkenes, increasing the temperature give better results than at lower temperature (table 6).

Entry	Phosphine	Eq.	Solvent	Temperature	e.e (%)	*trans*:*cis*[b]	Conv. (%)
1	(S,S)-BDPP	1	THF	80	19.9	n.d	n.d.
2	(S,S)-BDPP	2	THF	r.t, then 50	57.6	99:1	n.d.*
3	(S,S)-BDPP	1	THF	r.t.	47.6	93:7	n.d.*
4	(S,S)-BDPP	1	THF	0 °C	35	87:13	92
5	(S,S)-BDPP	1	THF	-50	9.1	n.d.	n.d.

Table 6. Effect of temperature and of the solvent; *) not measured: no internal standard was introduced. b) in comparison with Hodgson work, but not proof

In particular at –50°C (entry 5) the reaction gave poor ee, while at room temperature (entry 3) gave a better ee.

On the other hand when the reaction is run at 80°C selectivity is not good anymore.

When 2 equivalents of phosphine (entry 2) were used the reaction at room temperature did not proceed, but it was necessary to warm it at 50 °C. In this case the reaction gave the best result.

It was already described that an excess of phosphine can increase the enantioselectivity, because during the reaction the phosphine can be oxidised, thus the catalyst is not more effective. The phosphine in excess replaces the phosphinoxide.

On the other hand it is difficult to rationalise, why the decrease of the temperature decrease the ee. Further experiments at this stage have to be carried out.

Noteworthy is that this kind of reaction are not reproducible. In fact the

experiment run at room temperature was difficult for the time being to reproduce.

VII. Conclusions

Based on the results shown here we can say that **28** can be desymmetrised using asymmetric hydroboration, although further studies has to be run in order optimise the enantioselectivity. It has been shown that a decrement of temperature do not improve the enantioselectivity, but on the contrary it decreases. There is also to highlight that this procedure for the moment often does not gives reproducible results. Further studies has to be run in order to solve this problem.

VIII. Outlook

As future development ring opening of epoxides with lewis acid or chiral base and the Karasch-Sosnovsky reaction has to be also studied in order to see whether this can be used efficiently in the desymmetrisation of **28.**

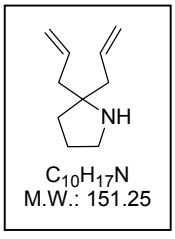
IX. Experimental Part

General Techniques. C_6H_6, CH_2Cl_2, Toluene, THF were dried through activated alumina columns prior to use. DME was distilled from CaH_2, MeOH was used without previous distillation, elimination of the excess of water was performed adding activated molecular sieves 4 Å. Other reagents were obtained from commercial sources and used as received. Filtration and flash column chromatography (FC): *SdS* silica gel (0.063-0.200 mm); TMBE, Et_2O, CH_2Cl_2 and cyclohexane as eluents. Thin-layer chromatography (TLC): *Merks*, *Silica gel 60 F_{254}* pre-coated TLC plates; detection either with UV or by dipping in a solution of $KMnO_4$ (3 g), K_2CO_3 (20 g), 5% NaOH (3 mL) in H_2O (300 mL), and subsequent heating. Chiral GC was performed using as chiral support Heptakies (2,3-*O*-dimethyl-6-tert-butyldimethylsilyl-)β-cyclodextrin, the column was heated at a constant temperature of 125°C. mp: not corrected. NMR spectroscopy: chemical shifts δ in ppm relative to $CHCl_3$ for ^1H (δ = 7.26 ppm) and $CDCl_3$ for ^{13}C (δ = 77.0 ppm).

Preparation of the triallylborane:

A flask is charged with Al (22.5 g, 834 mmol), $HgCl_2$ (150mg, 0.55 mol), and Et_2O. Allylbromide is added dropwise paying attention that the temperature does not raise more than 35-40 °C. When the addition is finished the reaction mixture is stirred at 40°C for 3 h. Then tributylborate (69 g, 81 ml) is added drop wise at a temperature between 55 and 60 °C. When the addition is finished the reaction mixture is stirred at 60 °C for 6 h. When the mixture is cooled down, a prior distillation to remove the Et_2O is carried out under N_2 at atmospheric pressure. The triallylborane is then distilled at 17 torr at a temperature of 70 °C. A second distillation of the product it then carried out to obtain 20.3 g (152 mmol, 51% yield) of the pure organoborane.

2,2-diallylpyrrolidine 37:

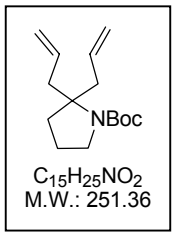


Triallylborane (20.3 g, 152 mmol) is added dropwise to a stirring solution of 2-pyrrolidinone (9.7g, 114 mmol) in THF (38 ml). The mixture is refluxed for 1.5 h, and then 19 ml of MeOH is added at room temperature. After refluxing for 1 h a 5 M NaOH solution is added and

the mixture is vigorously stirred until complete deboronation (no green coloration of the flame) of the organic layer (normally after 30 min). The organic layer was separated and the aqueous one extracted with Et_2O. The combined organic layers were dried over K_2CO_3 and concentrated. Distillation afforded 9.2 g of a colourless liquid ($bp_{13\ torr}$ 86-88).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm)**:** 5.81 (dt, *J* = 16.4, 7.35 Hz, 2H); 5.14-4.97 (m, 4H), 2.91 (t, *J* = 6.9 Hz, 2 H), 2.16 (dd, *J* = 7.5, 1.1 Hz, 4H), 1.81-1.50 (m, 5H).

***N*-(tert-butoxycarbonyl)-2,2-diallylpyrrolidine 38:**

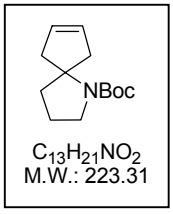


$C_{15}H_{25}NO_2$
M.W.: 251.36

To a stirred solution of **37** (3.2 g, 21 mmol) in THF (32 ml) is added a 1M water solution of NaOH (21 ml) and Boc_2O (4.6 g, 21 mmol). The reaction is stirred overnight at rt. Then Et_2O is added (20 ml) and the organic phase is separated. The aqueous layer is extracted with Et_2O and the combined organic layers washed with brine, dried on $MgSO_4$. Evaporation of the solvent afforded a colourless liquid that has been purified by FC (TBME/cyclohexane, 1:11) affording 4.5 g (18 mmol, 86% yield) of a colourless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm)**:** 5.80-5.63 (m, 2H), 5.09 (d, *J*= 16.01 Hz, 4H), 3.39 (dt, *J* = 13.4, 6.78 Hz, 2 H), 2.85 (dd, *J* = 13.4 6.8 Hz, 1H), 2.69 (dd, *J* = 13.5, 6.31 Hz, 1H), 2.37-2.19 (m, 2H), 1.94-1.77 (m, 2H), 1.75-1.58 (m, 2H), 1.52-1.39 (m, 9H).

***tert*-butyl 1-azaspiro[4.4]non-7-ene-1-carboxylate 28:**



$C_{13}H_{21}NO_2$
M.W.: 223.31

First generation Grubb's catalyst (148 mg, 0.18 mmol) was dissolved in CH_2Cl_2 (36 ml) and **38** (4.53 g, 18 mmol) was added at rt. The reaction mixture was stirred until disappearance of the staring material (normally 6 h): the progress of the reaction was followed *via* GC. Then DMSO (3.6 ml) was added in order to facilitate the removal of the catalyst decomposition products. The mixture was stirred for 18 h and the solvent evaporated under reduced pressure. FC (cyclohexane/TBME, 13:1) afforded 3.3 g (14.7 mmol, 81% yield) of a colourless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm)**:** 5.61 (s, 2H), 3.41 (t, *J* = 6.4 Hz, 2 H), 3.00 (bd, *J* = 15.2 Hz, 2H), 2.14 (d, *J* = 14.5 Hz, 2H), 1.89 (t, *J* = 6.7 Hz, 2H), 1.75 (quint, 6*J* = Hz, 2H), 1.41 (s, 9H).

Hydroboration with Ipc_2BH:

Preparation of Ipc_2BH: Ipc_2BH was prepared as described by Brown *via* direct hydroboration of α-pinene with BH_3·DMS in THF.[38] (+)-α-pinene (7.9 ml, 50 mmol) is added dropwise at 0°C to a solution of BH_3·DMS (2.53 ml, 25 mmol) in THF. When the addition is finished the flask is stored at 0°C for 20 h (-)-Ipc_2BH is crystallised, the solvent is removed via canula and the solid is washed twice with Et_2O. The solid is then dried under vacuum obtaining 3.72 g (53% yield) of the borane.

*Hydroboration of **28**:* To a suspension in THF (2 ml) of Ipc_2BH (578 mg, 2 mmol) is added at –30 °C **28** (448 mg, 2 mmol). The reaction mixture stirred for 16 h at this temperature, then was warmed at 0°C and reacted for other 24 h during which it reached rt. Dissolution of the borane confirmed the end of the reaction.

Oxidative work up is made adding at 0 °C 2 ml of EtOH, 2 ml of NaOH 2 M and 2 ml of H_2O_2 33%, then the reaction is stirred at reflux for 2 h. When the reaction is cooled at room temperature it was poured in a mixture of Et_2O, H_2O, biphenyl is added as external standard for the measure of the conversion; the organic phase was separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine and then dried over $MgSO_4$. A sample of this solution was then analysed via chiral GC to determine the ee.

Hydroboration with $IpcBH_2$:

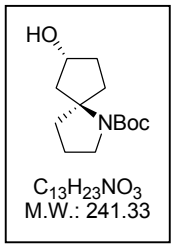
Preparation of $IpcBH_2$: BF_3·Et_2O (590 µl, 4.7 mmol) is added to a suspension in Et_2O (4 ml) of $IpcBH_2$·TMEDA (1 g, 2.4 mmol). The reaction is stirred for 2 h and then was filtrated and washed with Et_2O (2 x 4 ml) afforded a solution of the borane about 0.4 M.

*Hydroboration of **28**:*

A 0.4 M solution of $IpcBH_2$ (2.7 ml, 1.08) is added at –25 °C to a solution of **28** (238 mg, 1.06 mmol) in THF (2.2 ml). The reaction mixture was stirred for 24 h and then H_2O (1.6 ml) and $NaBO_3$·$4H_2O$ (490 mg, 3.18 mmol) were added. Then the reaction mixture was stirred for 5 h at room temperature. Biphenyl is added as internal standard for the measure of the conversion, the two phases were separated and the water layer was extracted with Et_2O. The combined organic layers were washed with brine and dried

over $MgSO_4$. A sample of this solution was then analysed via chiral GC to determine the ee.

Hydroboration with Wilkinson's catalyst:



$C_{13}H_{23}NO_3$
M.W.: 241.33

catBH (350 µl, 3.3 mmol) was added at –78° to a solution of the Wilkinson's catalyst (28 mg, 0.03 mmol) and the alkene (671 mg, 3.0 mmol) in THF (6 ml). Oxidative work up is made adding at 0 °C 6 ml of EtOH, 6 ml of NaOH 2 M and 6 ml of H_2O_2 33%. The reaction mixture is then stirred for 6 h at rt. The reaction mixture is then poured in H_2O and the two phases are separated. The aqueous layer is extracted with Et_2O and the combined organic layers are washed with brine. A sample of this solution was then analysed via chiral GC to measure the ratio of the racemic mixture. Evaporation of the solvent and FC (cyclohexane/TBME, 1:1) afforded 455 mg (1.88 mmol, 63% yield) of the major diastereoisomer (R_f = 0.26), the minor one (R_f = 0.48) is obtained as an oil in 92 mg (0.38 mmol, 12% yield).

(R_f = 0.48)

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm)**:** 4.25-4.10 (m, 1H), 3.55-3.39 (m, 1H), 3.35-3.21 (m, 1H), 2.38 (td, *J* = 15.68, 6.76 Hz, 1H), 2.29 (dd, *J* = 15.04, 2.81 Hz, 1H), 1.95-1.81 (m, 3H), 1.81-1.68 (m, 3H), 1-55-1.35 (m, 11H)

^{13}C-NMR (125 MHz, $CDCl_3$) δ (ppm)**:**. 154.0, 79.8, 72.8, 68.5, 47.9, 47.3, 43.2, 35.5, 34.6, 28.5, 23.2.

EI-MS m/z(%): 241 (20), 141 (22), 112 (51), 96 (56), 83 (100), 57 (94). 41 (61).

EI-MSHR: calculated 241.16751, found 241.16751

IR (KBr pill): 3407, 2965, 2874, 1663, 1395, 1159.

(R_f = 0.26)

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm)**:** 4.63-4.37 ((m, 1H), 3.47-3.23 (m, 2H), 2.73-2.45 (m, 1), 2.33-2.07 (m, 2H), 2.07-1.85 (m, 2H), 1.80-1.37 (m, 15 H).

^{13}C-NMR (125 MHz, $CDCl_3$) δ (ppm)**:** 153.6, 78.9, 73.2, 68.2, 47.8, 45.9, 45.4, 44.1, 35.6, 35.2, 28.7, 22,7.

EI-MS m/z(%): 241 (13), 141 (18), 112 (35), 96 (46), 83 (100), 57 (96). 41 (56).

EI-MSHR: calculated 241.16751, found 241.16748

IR (KBr pill): 3435, 2965, 2936, 2874, 1650, 1408

General procedure for the catalytic hydroboration with chiral phosphines:

To a solution in the desired solvent of $[Rh(COD)Cl]_2$ (0.01 mol) and the chiral phosphine (0.02 mol) is added the alkene (1 mmol). The solution is then cooled at –78 °C, and then catBH (1.2 mmol) is added. The reaction mixture is then stirred at the desired temperature until disappearance of the starting material in TLC. Oxidative work up is made adding at 0 °C 2 ml of EtOH, 2 ml of NaOH 2 M and 2 ml of H_2O_2 33%. The reaction mixture is then stirred for 6 h at room temperature. The reaction mixture is poured in H_2O and Et_2O and Biphenyl is added as internal standard for the measure of the conversion, and the two phases are separated. The aqueous layer is extracted with Et_2O and the combined organic layers are washed with brine. A sample of this solution was then analysed via chiral GC to determine the ee.

X. References

(1) Paudler, W. W.; Kerley, G. I.; McKay, J. *Journal of Organic Chemistry* **1963**, *28*, 2194-2197.
(2) Abraham, D. J.; Rosenstein, R. D.; McGandy, E. L. *Tetrahedron Letters* **1969**, 5085-5086.
(3) Powell, R. G.; Weisleder, D.; Smith, C. R., Jr.; Wolff, I. A. *Tetrahedron Letters* **1969**, 4081-4084.
(4) Arora, S. K.; Bates, R. B.; Grady, R. A.; Powell, R. G. *Journal of Organic Chemistry* **1974**, *39*, 1269-1271.
(5) Arora, S. K.; Bates, R. B.; Grady, R. A.; Germain, G.; Declercq, P.; Powell, R. G. *Journal of organic chemistry* **1976**, *41*, 551-554.
(6) Lin, X.; Kavash, R. W.; Mariano, P. S. *Journal of Organic Chemistry* **1996**, *61*, 7335-7347.
(7) Burkholder, T. P.; Fuchs, P. L. *Journal of the American Chemical Society* **1990**, *112*, 9601-9613.
(8) Auerbach, J.; Weinreb, S. M. *Journal of the American Chemical Society* **1972**, *94*, 7172-7173.
(9) Kuehne, M. E.; Bornmann, W. G.; Parsons, W. H.; Spitzer, T. D.; Blount, J. F.; Zubieta, J. *Journal of Organic Chemistry* **1988**, *53*, 3439-3450.
(10) Isono, N.; Mori, M. *Journal of Organic Chemistry* **1995**, *60*, 115-119.
(11) Ikeda, M.; Okano, M.; Kosaka, K.; Kido, M.; Ishibashi, H. *Chemical & Pharmaceutical Bulletin* **1993**, *41*, 276-281.
(12) Ikeda, M.; Matsubayashi, K.-I.; Imoto, T.; Kitao, K.; Ishibashi, H.; Sato, T. *Heterocycles* **1994**, *38*, 1237-1240.
(13) Ikeda, M.; Hirose, K.-i.; El Bialy, S. A. A.; Sato, T.; Yakura, T.; Bayomi, S. M. M. *Chemical & Pharmaceutical Bulletin* **1998**, *46*, 1084-1089.
(14) Ikeda, M.; El Bialy, S. A. A.; Hirose, K.-I.; Kotake, M.; Sato, T.; Bayomi, S. M. M.; Shehata, I. A.; Abdelal, A. M.; Gad, L. M.; Yakura, T. *Chemical & Pharmaceutical Bulletin* **1999**, *47*, 983-987.
(15) El Bialy, S. A. A.; Ismail, M. A.; Gad, L. M.; Abdelal, A. M. M. *Medicinal Chemistry Research* **2002**, *11*, 293-300.
(16) Nagasaka, T.; Sato, H.; Saeki, S.-I. *Tetrahedron: Asymmetry* **1997**, *8*, 191-194.
(17) Tietze, L. F.; Schirok, H. *Angewandte Chemie, International Edition in English* **1997**, *36*, 1124-1125.
(18) Tietze, L. F.; Schirok, H. *Journal of the American Chemical Society* **1999**, *121*, 10264-10269.
(19) Tietze, L. F.; Schirok, H.; Wohrmann, M.; Schrader, K. *European Journal of Organic Chemistry* **2000**, 2433-2444.
(20) Tietze, L. F.; Schirok, H.; Wohrmann, M. *Chemistry--A European Journal* **2000**, *6*, 510-518.
(21) Tietze, L. F.; Modi, A. *Medicinal research reviews* **2000**, *20*, 304-322.
(22) Tietze, L. F.; Schirok, H.; Wohrmann, M. *Chemistry* **2000**, *6*, 510-518.
(23) Planas, L.; Perard-Viret, J.; Royer, J. *Journal of organic chemistry* **2004**, *69*, 3087-3092.
(24) Bubnov, Y. N.; Pastukhov, F. V.; Yampolsky, I. V.; Ignatenko, A. V. *European*

Journal of Organic Chemistry **2000**, 1503-1505.
(25) Wrackmeyer, B.; Tok, O. L.; Bubnov, Y. N. *Appl. Organomet. Chem.* **2004**, *18*, 43-50.
(26) Kharasch, M. S.; Sosnovsky, G. *Journal of the American Chemical Society* **1958**, *80*, 756.
(27) Denney, D. B.; Denney, D. G.; Feig, G. *Tetrahedron Letters* **1959**, 19-23.
(28) Kharasch, M. S.; Sosnovsky, G.; Yang, N. C. *Journal of the American Chemical Society* **1959**, *81*, 5819-5824.
(29) Kharasch, M. S.; Fono, A. *Journal of Organic Chemistry* **1959**, *24*, 72-78.
(30) Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y. L. *Journal of the American Chemical Society* **2002**, *124*, 2245-2258.
(31) Nicolaou, K. C.; Zhong, Y. L.; Baran, P. S. *Journal of the American Chemical Society* **2000**, *122*, 7596-7597.
(32) Tohma, H.; Kita, Y. *Advanced Synthesis & Catalysis* **2004**, *346*, 111-124.
(33) Brown, H. C.; Rao, B. C. S. *Journal of the American Chemical Society* **1956**, *78*, 2582-2588.
(34) Brown, H. C. *Organic Syntheses via Boranes*, 1975.
(35) Brown, H. C. *Hydroboration. With Supplement Nobel Lecture, December 8, 1979*, 1980.
(36) Brown, H. C.; Zweifel, G. *Journal of the American Chemical Society* **1961**, *83*, 486-487.
(37) Brown, H. C.; Yoon, N. M. *Israel Journal of Chemistry* **1977**, *15*, 12-16.
(38) Brown, H. C.; Singaram, B. *Journal of Organic Chemistry* **1984**, *49*, 945-947.
(39) Brown, H. C.; Ayyangar, N. R.; Zweifel, G. *Journal of the American Chemical Society* **1964**, *86*, 397-403.
(40) Brown, H. C.; Ayyangar, N. R.; Zweifel, G. *Journal of the American Chemical Society* **1964**, *86*, 1071-1076.
(41) Brown, H. C.; Schwier, J. R.; Singaram, B. *Journal of Organic Chemistry* **1978**, *43*, 4395-4397.
(42) Mandal, A. K.; Jadhav, P. K.; Brown, H. C. *Journal of Organic Chemistry* **1980**, *45*, 3543-3544.
(43) Maennig, D.; Noeth, H. *Angewandte Chemie* **1985**, *97*, 854-855.
(44) Brown, H. C.; Chandrasekharan, J. *Journal of Organic Chemistry* **1983**, *48*, 5080-5082.
(45) Brown, H. C.; Gupta, S. K. *Journal of the American Chemical Society* **1975**, *97*, 5249-5255.
(46) Brown, H. C.; Gupta, S. K. *Journal of the American Chemical Society* **1971**, *93*, 1816-1818.
(47) Lane, C. F.; Kabalka, G. W. *Tetrahedron* **1976**, *32*, 981-990.
(48) Hayashi, T.; Matsumoto, Y.; Ito, Y. *Tetrahedron: Asymmetry* **1991**, *2*, 601-612.
(49) Zhang, J.; Lou, B.; Guo, G.; Dai, L. *Journal of Organic Chemistry* **1991**, *56*, 1670-1672.
(50) Burgess, K.; Van der Donk, W. A.; Ohlmeyer, M. J. *Tetrahedron: Asymmetry* **1991**, *2*, 613-621.
(51) Burgess, K.; Ohlmeyer, M. J. *Journal of Organic Chemistry* **1991**, *56*, 1027-1036.
(52) Kono, H.; Ito, K.; Nagai, Y. *Chemistry Letters* **1975**, 1095-1096.
(53) Westcott, S. A.; Taylor, N. J.; Marder, T. B.; Baker, R. T.; Jones, N. J.; Calabrese, J. C. *Journal of the Chemical Society, Chemical Communications* **1991**, 304-305.
(54) Widauer, C.; Gruetzmacher, H.; Ziegler, T. *Organometallics* **2000**, *19*, 2097-2107.

(55) Sato, M.; Miyaura, N.; Suzuki, A. *Tetrahedron Letters* **1990**, *31*, 231-234.
(56) Mirabelli, M. G. L.; Sneddon, L. G. *Journal of the American Chemical Society* **1988**, *110*, 449-453.
(57) Knorr, J. R.; Merola, J. S. *Organometallics* **1990**, *9*, 3008-3010.
(58) Evans, D. A.; Fu, G. C. *Journal of the American Chemical Society* **1991**, *113*, 4042-4043.
(59) Brinkman, J. A.; Nguyen, T. T.; Sowa, J. R. *Org. Lett.* **2000**, *2*, 981-983.
(60) Luna, A. P.; Bonin, M.; Micouin, L.; Husson, H. P. *Journal of the American Chemical Society* **2002**, *124*, 12098-12099.
(61) Nieczypor, P.; Mol, J. C.; Bespalova, N. B.; Bubnov, Y. N. *European Journal of Organic Chemistry* **2004**, 812-819.

Riccardo PICCARDI

CURRICULUM VITAE

General Information

Date of birth:	September 7th, 1975
Nationality:	Italian
Institution:	Berne University, Departement für Chemie und Biochemie
Work address:	Freiestrasse 3, CH-3012, Berne - Switzerland
Phone:	+41(0)31 631 4328
Home address:	Tannenweg 20, CH-3012, Berne - Switzerland
Phone:	+41(0)76 560 4392

Education

18th-23rd, September 2004, Ischia, Italy

Attendance of IASOC 2004 - Ischia Advanced School of Organic Chemistry: "Creativity in organic Synthesis, from Target to Function", organised by "*Italian Chemistry Society - Organic chemistry division* and *University "Federico II", Naples*" (the attendance to the school has been supported by a fellowship as "early stage researcher").

16th-20th, September 2001, Champéry, Switzerland

Attendance of the "31ème Séminaire "Hors-Ville d'Automne" and 21st Regio Symposium in Organic and Bioorganic Chemistry", organised by *Convention Intercantonale d'enseignement du 3ème cycle en chimie"*

6th-9th, June 2001, Champéry, Switzerland

Workshop attendance: "Selective Synthesis: new reagents for specific transformations", organised by Chairmen of the European Research Councils Chemistry Committees CERC3

Since May 2001

Ph.D student in the group of Prof. Philippe Renaud at the Departement für Chemie und Biochemie, Universität Bern (Switzerland)

November 1999-February 2001

Diploma work in the group of Dr. Gianna Reginato at the CNR-Centro di Studio sulla Chimica e la Struttura dei Composti Eterociclici e loro Applicazioni c/o Dipartimento di Chimica Organica Ugo Schiff, Università di Firenze (Italy)

September 1994-February 2001

Graduate studies in Chemistry at the University of Florence (Italy).

Degree

February 26th 2001

Laurea in Chemistry (Organic Chemistry), mark 104/110

Research experience

From January 2004

Research activity in the group of Prof. Philippe Renaud. Subject: "*Desymetrisation of prochiral molecules toward the synthesis of alkaloids*"

May 2001-December 2003

Research activity in the group of Prof. Philippe Renaud. Subject: "*Total Synthesis of Ferruginine*"

November 1999-February 2001

Research activity in the group of Dr. Gianna Reginato: Subject: "*Synthesis of new β-aminoacrylate stannylated as useful precursors in the synthesis of β-aminoacids*"

Skills

Problem solving in organic synthesis

Analytical and purifications techniques: Chromatography, GC, HPLC (analytical and preparative)

Spectroscopic techniques: IR, NMR (1D, 2D), MS

Informatics: use and knowledge of Windows® and Macintosh® operative systems; use of word-processing programs; chemistry software (ChemDraw, and Isisdraw); database programs (IsisBase, and EndNote); research bibliography database programs (Beilstein and SciFinder); NMR processing programs (1D, and 2D WinNMR).

Teaching experience

April 2004-July 2004

Supervision of a forth year student from the University Pierre and Marie Curie - Paris VI (France): "Maitrise" diplom

From October 2001

Teaching assistant at the University of Berne (Switzerland)

Language

Italian-mother language

English-fluent
French-good knowledge
German-basic knowledge

Posters

Total Synthesis of (+)-Ferruginine: A possible pathway towards the synthesis of analogues, Fall Meeting of the Swiss Chemical Society, Zurich (Switzerland) October 28th 2004. Abstract: Piccardi, R., Renaud, P. Chimia **2004**, *58*, 530 (nr. 333).

Total Synthesis of (+)-Ferruginine: A possible pathway towards the synthesis of analogues, IASOC 2004, Ischia (Italy) September 18th-23rd 2004. Book of Abstracts n° .This poster has been chosen for an oral presentation

Total Synthesis of (+) and (-)-Ferruginine, Fall Meeting of the Swiss Chemical Society, Lausanne (Switzerland) October 10th 2003. Abstract: Piccardi,R., Renaud,P. Chimia **2003**, *57*, 433 (nr. 209). Poster and short presentation.

Publications

Synthesis of non-racemic β-branched β-(aminoalkyl)-acrylates from naturally occurring amino acids, Reginato, G.; Mordini, A.; Valacchi, M.; R. Piccardi *Tetrahedron: Asymmetry* **2002**, *13*, 595-600.

Total Synthesis of (+) and (-)-Ferruginine, Renaud, P., Piccardi, R. *Manuscript in preparation*

References

Prof. Philippe Renaud, Universität Bern, Departement für Chemie und Biochemie, Freiestrasse 3, CH-3012 Berne, Switzerland
Tel: +41(0)31 6314359, Fax: +41(0)31 6313426
E-Mail: philippe.renaud@ioc.unibe.ch,
http://www.dcb.unibe.ch/groups/renaud/index.html

Dr. Gianna Reginato, ICCOM – CNR, Istituto di Chimica dei Composti Organo Metallici c/o Dipartimento di Chimica Organica,Ugo Schiff, POLO SCIENTIFICO - Università degli Studi di Firenze, Via della Lastruccia, 13-50019 Sesto Fiorentino (Firenze), Italy.
Tel. +39 055 4573558, Fax +39 055 4573580
E-mail: gianna.reginato@unifi.it