Studies in Chemistry of the 8-Hetero Bicyclo[3.2.1]Octan-3-ones

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In Partial Fulfillment of the Requirements

For the Degree of Master of Science

In the Department of Chemistry

University of Saskatchewan

Saskatoon

By

Laura Sikorska

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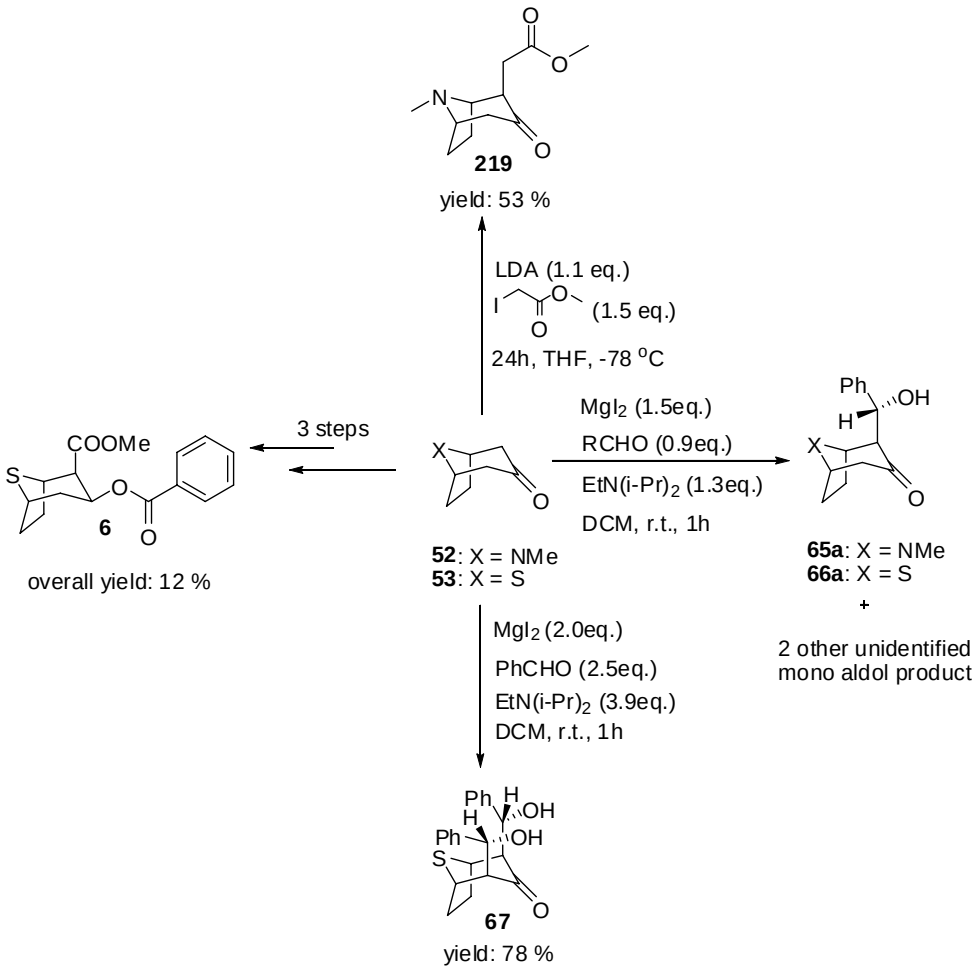
ABSTRACT

New processes that leads to formation of new carbon-carbon bond (the Michael reaction, the Mannich reaction and alkylation reaction) or carbon-heteroatom bond (α-halogenation, α-hydroxylation and α-amination) on bridged bicyclic ketones such as tropinone and TBON were investigated, utilizing LDA in the deprotonation step. All reactions, in which new carbon-heteroatom bond is formed, were not successful either due to low selectivity and/or yields. In case of new carbon-carbon bond forming processes, careful choice of electrophile (electrophile having the ester group in α-position to leaving group), allows for alkylation of tropinone with moderate yield and good selectivity.

Application of new conditions to the aldol reaction of TBON and tropinone (e.g. MgI_2 catalyzed aldol reaction), gave new aldol products that were not detected from the lithium enolate chemistry of these ketones. Modification of reaction conditions in case of MgI_2 catalyzed aldol reaction provides, in a 'one pot' process, bis-aldol product from TBON in good yield and high selectivity, as a single diastereoisomer.

Finally, TBON is used as a suitable scaffold for the synthesis of thiacocaine. The first known synthesis of racemic thiacocaine is presented, *via* deprotonation of TBON with LDA, as a key step.


219
yield: 53 %
LDA (1.1 eq.)
(1.5 eq.)
24h, THF, -78 °C
3 steps
COOMe
6
overall yield: 12 %
MgI2 (1.5eq.)
RCHO (0.9eq.)
EtN(i-Pr)2 (1.3eq.)
DCM, r.t., 1h
52: X = NMe
53: X = S
65a: X = NMe
66a: X = S
+
2 other unidentified
mono aldol product
MgI2 (2.0eq.)
PhCHO (2.5eq.)
EtN(i-Pr)2 (3.9eq.)
DCM, r.t., 1h
67
yield: 78 %

ACKNOWLEDGMENTS

I would like to thank my supervisor Dr Marek Majewski for giving me a chance to be his student and also for his enormous patience and understanding over all these years.

I would like to thank my committee members, Dr J. Balsevich, Dr M. Gravel and Dr D. E. Ward for all help and advices.

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Finally, the greatest thanks go to Dr Kay Akinnusi and Dr Henio Gruza for keeping me ‘alive’ through all those years. Thanks a lot guys!

DEDECATION

For my parents – without you it will never happen!

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Ac	acetyl (ethanoyl)
Ac_2O	acetic anhydride
AcOH	acetic acid
aq	aqueous
ap	apparent (NMR)
Bn	benzyl
Boc	*t*-butoxycarbonyl
Bu	butyl
Bz	benzoyl
^{13}C NMR	carbon-13 nuclear magnetic resonance
CI	chemical ionization
conv.	Conversion
12-crown-4	1,4,7,10-teraoxacyclododecane
C_s	point group of chiral molecules that contain only symmetry plane (σ)
DAM	dansylaminomethylmaleic acid
DCC	1,3-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DEAD	diethyl azodicarboxylate
DIBAL	diisobutylaluminium hydride
DMAP	4-(*N*,*N*-dimethylamino)pyridine

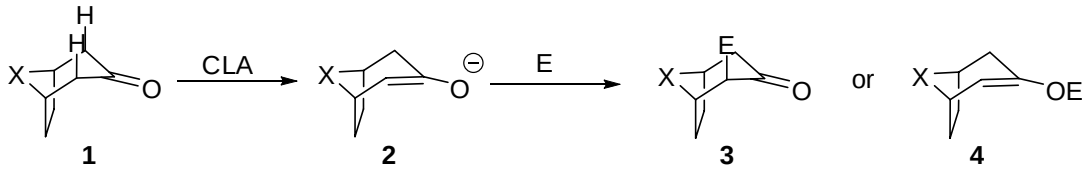
DMF	dimethylformamide
DMPU	1,3-dimethylterahydropyrimidin-2(1*H*)-one (N, N'-dimethylpropyleneurea)
DMSO	dimethyl sulphoxide
dr	diastereomers ratio
DRIFT	diffuse reflectance Fourier transform infrared
ee	enantiomeric excess; for a mixture of two enantiomers *R* and *S*, *ee*=|([*R*]-[*S*])|/([*R*]+[*S*]) x 100%
EI	electron impact ionization
Eq.	equivalent(s)
Et	ethyl
Et_2O	diethyl ether
Et_3N	triethylamine
EtOAc	ethyl acetate
$Eu(fod)_3$	tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato) europium (III)
FCC	flash column chromatography
FID	free induction decay (in NMR spectroscopy)
FTIR	Fourier transform infra red
^{1}H NMR	proton nuclear magnetic resonance
h	hour(s)
HMQC	heteronuclear multiple quantum coherence (1 bond J_{CH} correlation with inverse detection)
HRMS	high resolution mass spectroscopy
i-Pr	isopropyl
IR	infrared
LDA	lithium diisopropylamide

LRMS	low resolution mass spectroscopy
m-CPBA	3-chloroperoxybenzoic acid
Me	methyl
MeCN	acetonitrile
MeLi	methyllithium
MeOH	methanol
MHz	megahertz; 10^6 Hertz
min	minute(s)
MOM	methoxymethyl
MOMCl	methoxymethyl chloride
MS	mass spectrometry
NA	not applicable
NBS	N-bromosuccinimide
n-BuLi	*n*-butyllithium
NfF	nonafluorobutanesulfonate fluoride
NMR	nuclear magnetic resonance
NR	no reaction
OTBDMS	*tert*-butyldimethylsilyloxy
OTf	trifluoromethanesulfonyloxy
O/N	overnight reaction
Ph	phenyl
PTLC	preparative thin layer chromatography
p-TsOH	*p*-toluenesulfonic acid (4-methylbenzenesulfonic acid)
rt	room temperature; ca. 22-24 ˚C
sat.	saturated; as in a saturated aqueous solution

s	second(s)
TBAF	tetra-*n*-butylammonium fluoride
TBDMS or TBS	*t*-butyldimethylsilyl
TBDMSCl or TBSCl	*t*-butyldimethylsilyl chloride
TBON	8-thiabicyclo[3.2.1]-octan-3-one
t-Bu	*tert*-butyl (1,1-dimethylethyl)
t-BuLi	*tert*-butyllithium
Tf	trifluromethanesulphonyl
TFA	trifluoroacetic acid
TFAE	2, 2, 2 –trifluoro-1-(9-anthryl)ethanol
TFPAA	trifluoroperacetic acid
THF	tetrahydrofuran (oxolane)
TIPS	triisopropylsilyl
TIPSOTf	triisopropylsilyl trifluoromethanesulfonate
TLC	thin-layer chromatography
TMS	trimethylsilyl or tetramethylsilane
TMSCl	trimethylsilyl chloride(chlorotrimethylsilane)
TMSTf	trimethylsilyl trifluoromethanesulfonate
TsCl	4-methylbenzenesulfonyl chloride (toluenesulphonyl chloride)
v/v	volume relative to volume measure

CHAPTER 1
CHEMISTRY OF BICYCLO[3.2.1]OCTAN-3-ONES – INTRODUCTION

Bicyclic bridged systems, where the bridging atom is carbon, nitrogen, oxygen or sulfur, such as tropinone or its sulfur analog (TBON), belong to the group of prochiral ketones that possess conformationally locked structures. The rigid structures of these compounds allow for fewer conformations which in turn allows for better facial discrimination when exposed to reactions in a chiral environment. The preference for removal of the α-axial proton from cyclic ketones by bases was rationalized by stereoelectronic effects.[1, 2, 3] Additionally, a carefully chosen chiral lithium amide can selectively remove one of the two axial enantiotopic protons in the process called enantioselective deprotonation (**Scheme 1**). The enolates thus formed can be trapped with different electrophiles affording enantiomerically enriched products. The intrinsic characteristic of the electrophiles employed determines regioselectivity of the reaction. When soft electrophiles such as aldehydes are used, the reaction occurs preferentially on the enolate carbon while hard electrophiles react at the oxygen center (e.g. TMSCl).

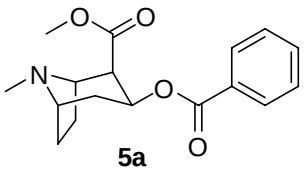


Scheme 1

Although in many cases the products obtained from these bicyclic ketones possess high optical purity, there is no straightforward correlation between the structure of the ketone, the structure of the lithium amide, and selectivity. A major obstacle in the development of a

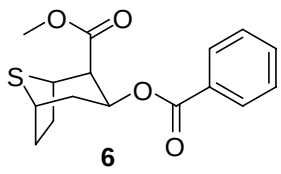
universal protocol for the synthesis of enantiomerically pure products *via* enantioselective deprotonation reactions has to do with the poor understanding of the transition states involved in these processes. Consequently, the choice of chiral lithium amides and developing reaction conditions for every new substrate still relies on guesswork and every reaction must be researched experimentally.

In recent years, asymmetric transformations of bicyclo[3.2.1]octan-3-ones mediated by chiral lithium amides have attracted more attention as the products obtained in these reactions could be made in high optical purity. Consequently, many different reaction types were investigated, thoroughly and are well documented, while some remain unknown (e.g. alkylation reaction). Also, most of the products could be utilized in syntheses of many natural products such as tropane alkaloids (e.g. cocaine) and their analogues (e.g. thiacocaine).



5a

(R)-cocaine



6

(R)-thiacocaine

Figure 1-1. Structures of natural cocaine and its sulfur analog

It is worth to emphasize that tropinone, TBON and the corresponding oxygen analog of tropinone could also provide useful starting materials for the preparation of substituted cycloheptenones. Additionally, in case of TBON the presence of the sulfur atom in the bridge offers potential for more diverse chemistry due to the ability of dialkylsulfur compounds to exist in three oxidation states (sulfides, sulfoxides and sulfones)

Keeping in mind the usefulness of the reactions of enolates of bicyclo[3.2.1]octan-3-ones, their chemistry is discussed in the following sections. The sections are divided by the type of the electrophile and in some cases by the use of the products in the synthesis of biologically active compounds. Also, a few miscellaneous transformations of bicyclo[3.2.1]octan-3-ones are described. By discussing the known chemistry of these compounds, attention can be drawn to the limitations as well as to the aspects that have not been investigated. It is my view that collating

the results of the chemistry of this class of compounds might allow for a trend to be identified, ideally leading to a general rule that could help to determine how to match chiral bases with new substrates.

1 Enolate Chemistry of Bicyclo[3.2.1]octan-3-ones

1.1 Reactions at the Oxygen Center

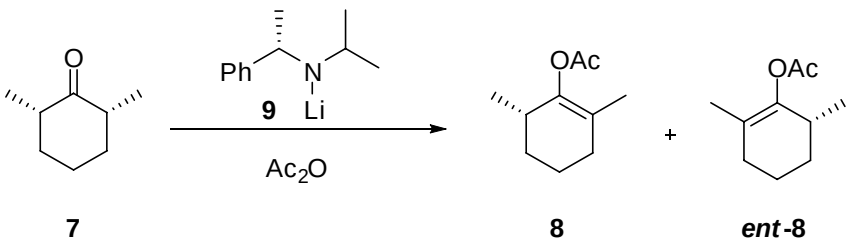
Ketones having C_s symmetry can be converted into chiral products by treatment with chiral bases and trapping the enolate either with acid anhydrides or chlorides or silicon electrophiles (TMSCl). In these cases, the electrophiles (hard) react at the oxygen center of the enolate, affording oxygen substituted products exclusively (**Scheme 1**).

1.1.1 Silyl Enol Ethers

Treatment of bicyclo[3.2.1]octan-3-ones with silicon electrophiles in the presence of chiral lithium amides led to the formation of non racemic silyl enol ethers. In a typical experiment, the ketone was transformed into the non racemic enol silane by one of two protocols: the amide base and TMSCl were premixed prior to the addition of ketone (internal quench protocol) or the base had been allowed to react with the ketone before TMSCl was introduced (external quench method).[4]

To obtain high *ee* values in chiral lithium amide mediated deprotonation, it is often necessary to trap the lithium enolate as the silyl enol ether using the internal quench protocol; however similar results can be obtained under the external quench protocol in the presence of additives such as lithium chloride or lithium bromide.

The pioneering work on the influence of lithium salts on enantioselective deprotonation of ketones was carried out in our group on *cis*-3,5-dimethylcyclohexanone (**Scheme 2**).[5] In this study, addition of lithium bromide resulted in the formation of acetates **8** and ***ent*-8** with higher conversion and enantioselectivity than reactions ran without the additive salt (67 % yield and 64 % *ee*, comparing to 40 % and 41 % *ee*, respectively).

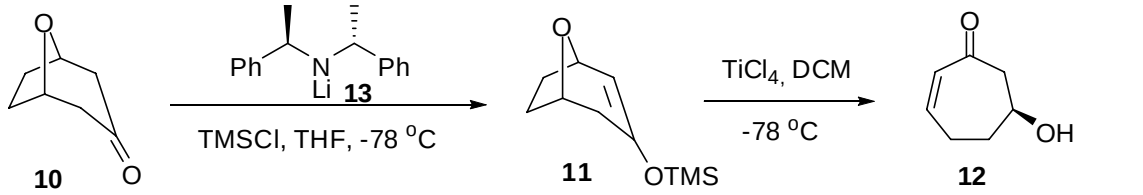


LiBr: y = 67 %, *ee* = 64 %

\- y = 40 %, *ee* = 41 %

Scheme 2

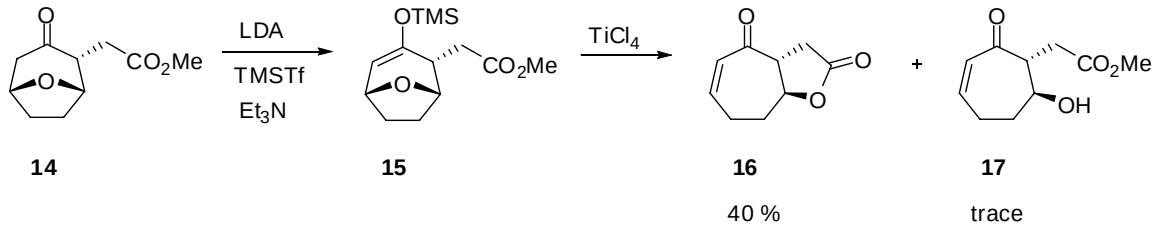
Simpkins *et al.*[6] investigated the conversion of 8-oxabicyclo[3.2.1]octan-3-one into its silyl enol ether (**Scheme 3**). When the internal quench conditions were applied silyl enol ether **11** was prepared with 82 % *ee* while external quench conditions without the addition of lithium chloride gave ca 33 % *ee*. However, in the presence of lithium chloride, the enantioselectivity significantly changed. Interestingly, only 0.1 equivalent of lithium chloride was needed for the enantioselectivity to reach the maximum (84 %). Addition of more lithium chloride (0.4-1.5 eq.) did not appear to make any significant difference. A subsequent exposure of enol silane **11** to $TiCl_4$ resulted in opening of the bicyclic system to give the chiral enantioenriched hydroxycycloheptenone in 76 % yield.[7]



Scheme 3

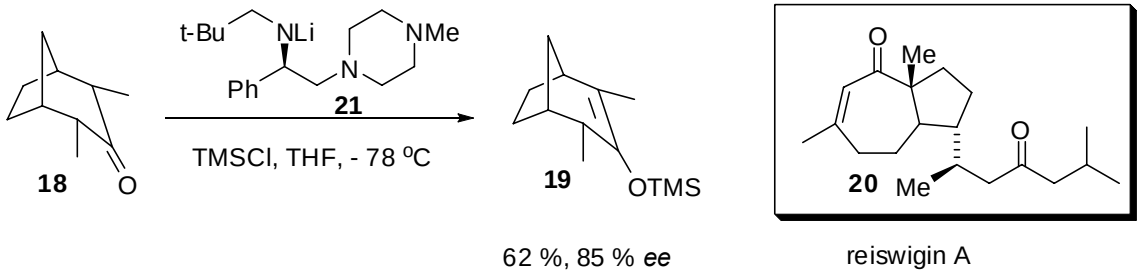
In order to obtain polysubstituted cycloheptenones, silyl enol ether **15** (derived from 8-oxabicyclo[3.2.1]octan-3-one) was treated with titanium (IV) chloride(**Scheme 4**). The reaction furnished a mixture of compounds **16** and **17** (although with low yield), and showed that silyl

enol ethers from the oxygen analog of tropinone can be potential starting materials for a variety of cycloheptenones.[8]



Scheme 4

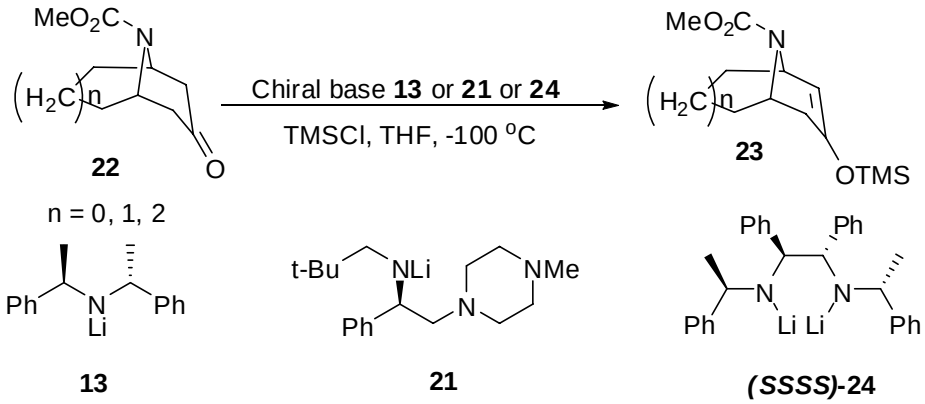
As part of a project aimed at the synthesis of reiswigin A, MaGee *et al.* studied the enantioselective deprotonation of 2,4-dimethylbicyclo[3.2.1]octan-3-one (**Scheme 5**).[9] In that study, a few chiral lithium amides were used and the reaction was performed according to either internal or external quench protocols. Generally, in cases involving the same lithium amide, the internal quench protocol resulted in higher *ee* values. However, it should be noted that reactions carried out according to the external quench protocol were done without any additives. The highest enantioselectivity was obtained with chiral lithium amide **21**, when the internal quench protocol was applied.



Scheme 5

In order to prepare enantiomerically enriched building blocks for alkaloid synthesis, enantioselective deprotonation of a range of carbamates (protected azabicyclic ketones) was extensively studied (**Scheme 6**).[10,11] Irrespective of the ring size, silyl enol ethers having up to 90 % *ee* were obtained under internal quench conditions. The best results were achieved when chiral

lithium amide **21** was utilized in the process. In those cases, silyl enol ethers **23** were obtained in yields as high as 94 % with 93 % *ee* (where $n = 1$ and R = CO_2Me).



Scheme 6

Some of the silyl enol ethers were used as key intermediates in syntheses of a number of natural products such as (+)-pinidine hydrochloride, (+)-monomorine I or (-)-indolizidine 223AB (**Figure 1-2.**). [12,13]

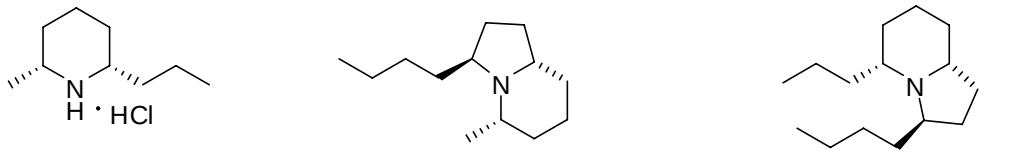
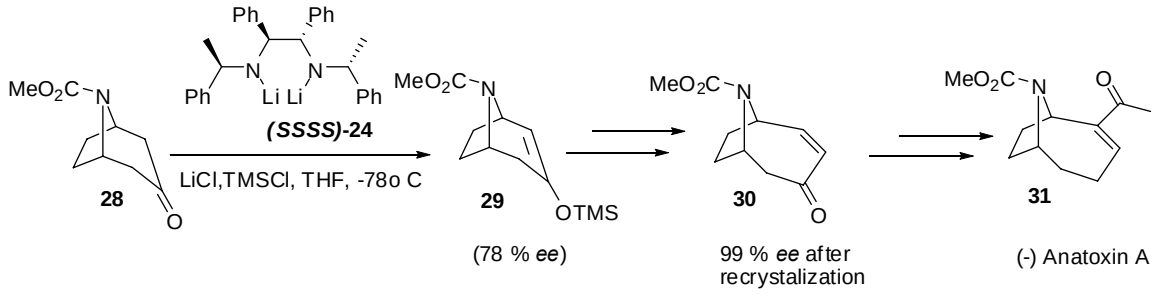


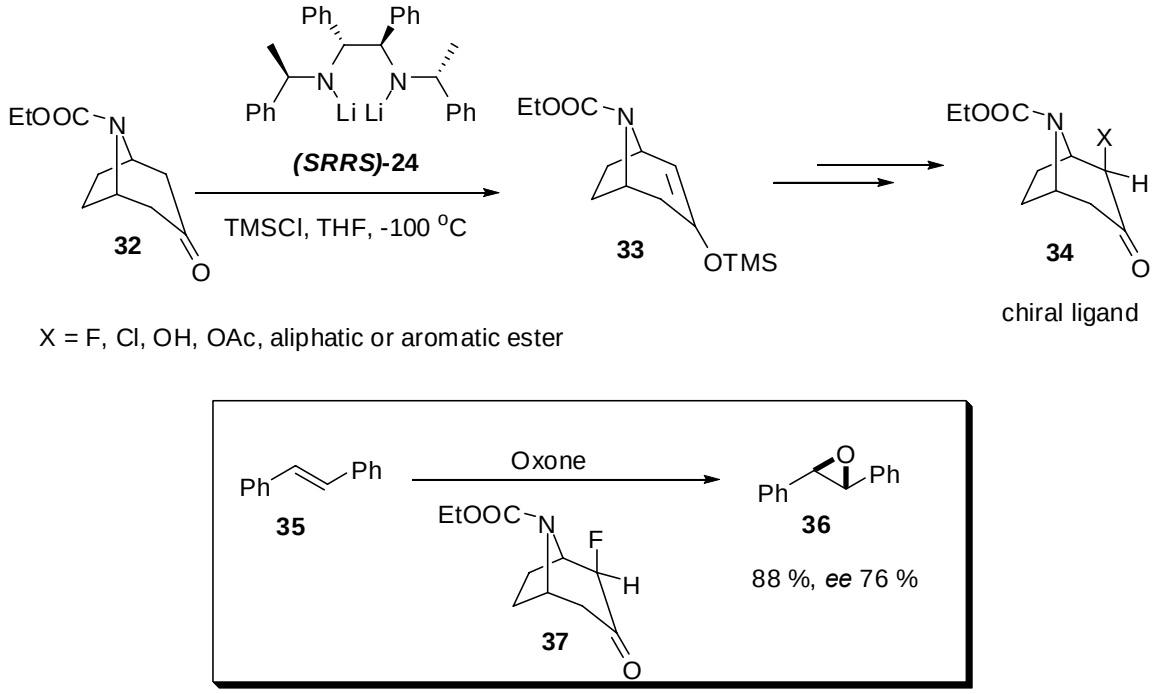
Figure 1-2. Examples of natural products obtained from **22**

Independently, Simpkins *et al.*[14] studied enantioselective deprotonation of tropinone analog **28** (**Scheme 7**). Surprisingly, in the presence of the chiral lithium amide **13** and lithium chloride, low enantiomeric excesses of the product were obtained (15-20 %). Changing the base to dilithiated ***(SSSS)*-24** resulted in a significant improvement in enantioselectivity (*ee* 78 %, yield 84 %). The results illustrate that there are no general rules to allow prediction of the best match between the chiral base and the substrate. The silyl enol ether made in this study was then utilized in the synthesis of (-) anatoxin A - an antagonist of the acetocholine receptor.



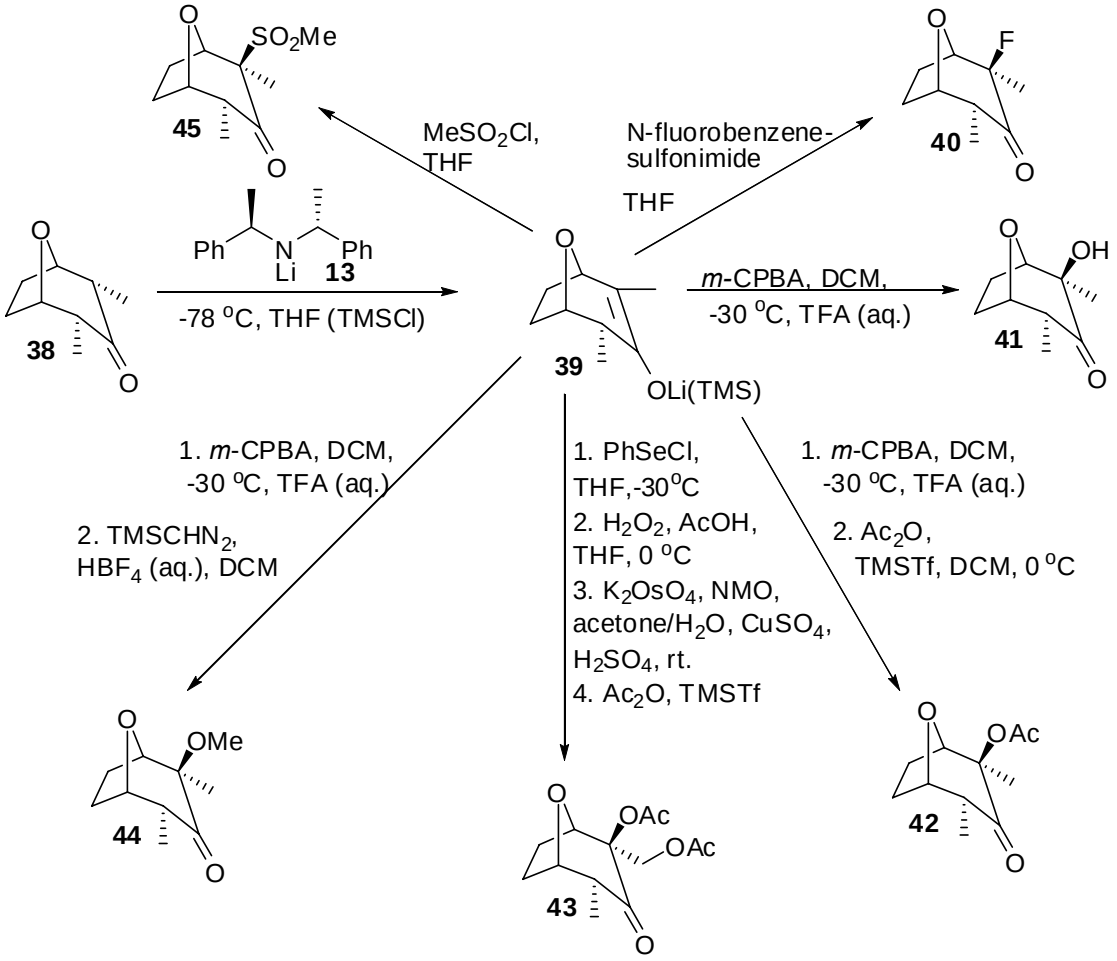
Scheme 7

Different *N*-carbethoxytropinone derivatives have found use as chiral ligands in enantioselective epoxidation of alkenes (**Scheme 8**). [15,16,17,18] In order to obtain these chiral ligands, an enantioselective deprotonation reaction was employed. In all cases, the starting point involved making the silyl enol ether 33 that was then fluorinated, chlorinated, hydroxylated, acylated or esterified. The chiral ligands obtained from these reactions were then utilized in epoxidation reaction that led to formation of different epoxides with up to 98 % *ee* (*ee* was calculated from formula: 100 x epoxide *ee* / ketone *ee,* due to 75-80 % optical purity of used catalysts).



Scheme 8

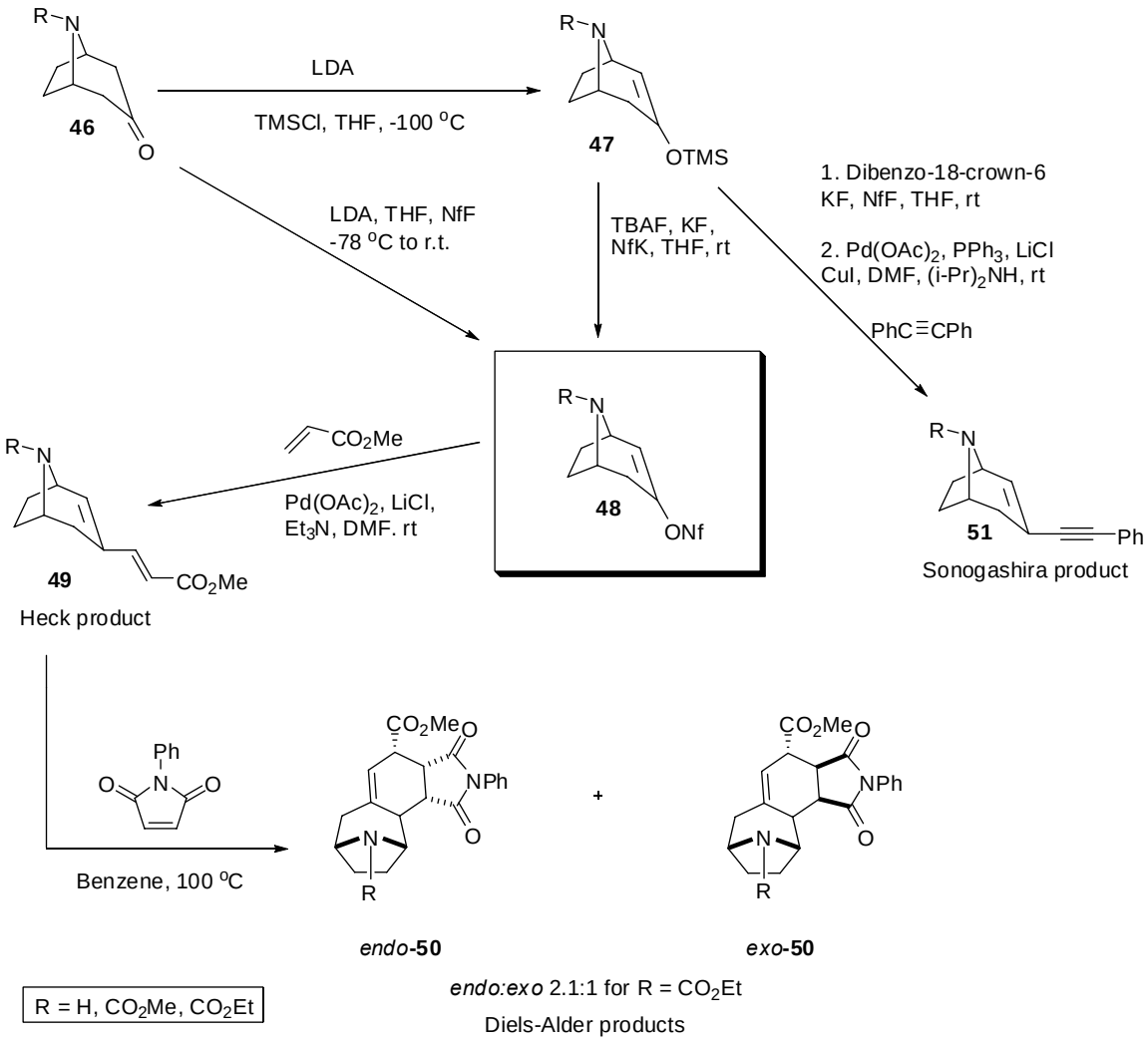
Different derivatives including fluorinated, acylated or hydroxylated compounds were prepared from 2,4-dimethyl-8-oxabicyclo[3.2.1]octan-3-one *via* its silyl enol ether (**Scheme 9**).[19] These products, obtained in high optical purity (90-98 % *ee*), were utilized in asymmetric epoxidation of alkenes. Interestingly, all the derivatives synthesized (**40**-**45**) gave racemic epoxides when used as chiral ligands apart from the fluorinated ketone **40** (98 % *ee*) that catalyzed epoxidation of (*E*)-stilbene with 68 % *ee*.



Scheme 9

Silyl enol ethers[20]derived from tropinone **46** (and its derivatives) were converted into nonaflate (nonafluorobutanesulfonate) derivatives **48** (nonaflates were also obtained directly

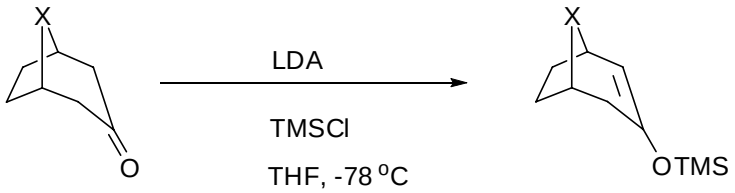
from tropinone derivatives). These opened up the opportunity to explore other types of reaction such as Diels-Alder, Heck and Sonogashira reactions (**Scheme 10**).



Scheme 10

Tropinone and TBON silyl enol ethers as useful intermediates (e.g. oxidation or ring opening) were of interest to the Majewski group and were extensively studied.[21, 22, 23, 24]

As a test run, reactions where LDA was utilized as the base were performed (**Scheme 11**). Tropinone silyl enol ether was obtained in 88 % yield, while the yield of TBON product was as high as 96 %.



52: X = NMe

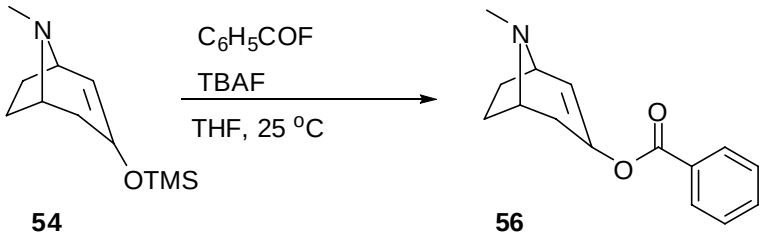
53: X = S

54: X = NMe

55: X = S

Scheme 11

The tropinone silyl enol was then reacted with benzoyl fluoride in the presence of trace (0.05 eq.) tetra-*n*-butylammonium fluoride, to furnish benzoate **56** in almost quantitative yield.[25]

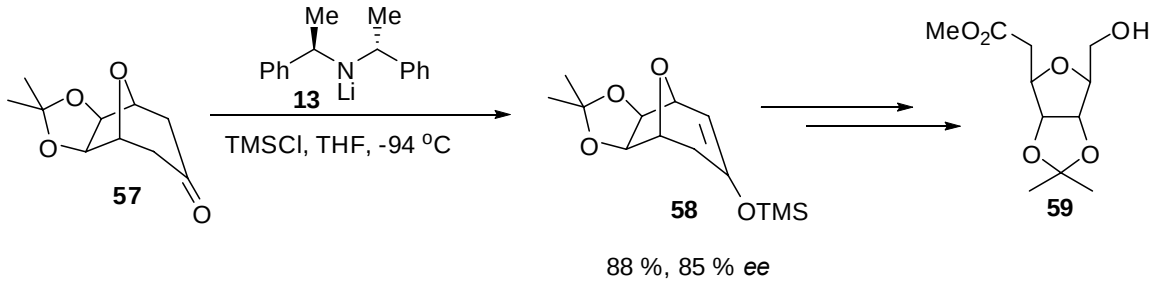


54 **56**

Scheme 12

Silyl enol ether of 8-oxabicyclo[3.2.1]octan-3-one **58** was shown to be an excellent starting material for the synthesis of tetrahydrofuran ester **59**, a known precursor for *C*-nucleosides such as showdomycin (**Scheme 13**).[26, 27] In order to prepare the key intermediate **59**, extensive studies were conducted to access the optically active silyl enol ether **58**. From the study, it was shown that the reaction depended on temperature as the value of *ee* decreased from 85 % (the highest obtained value) at -94°C to 43 % at 0°C. Moreover, the use of an internal quench protocol was necessary to obtaining high enantioselectivity. Interestingly, when the silyl enol ether **58** was prepared according to the external quench protocol, the *ee* obtained was low (27 %) despite the addition of additives such as free amine or lithium chloride. This study underlines the difficulties and limitations of enantioselective deprotonation. It is often not clear

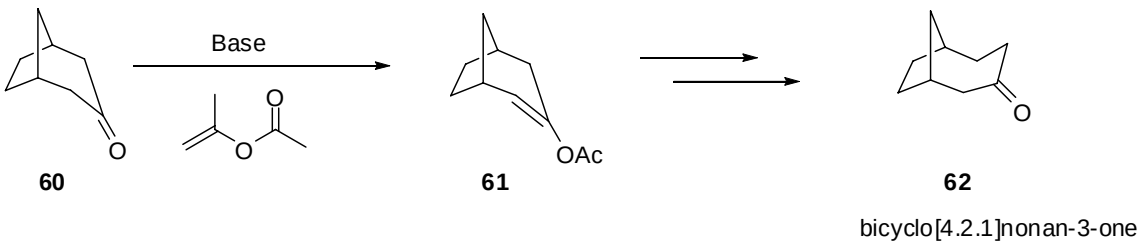
how to match the substrate with the chiral base and what additives will have a significant influence on conversion and *ee*.



Scheme 13

1.1.2 O-Acylation

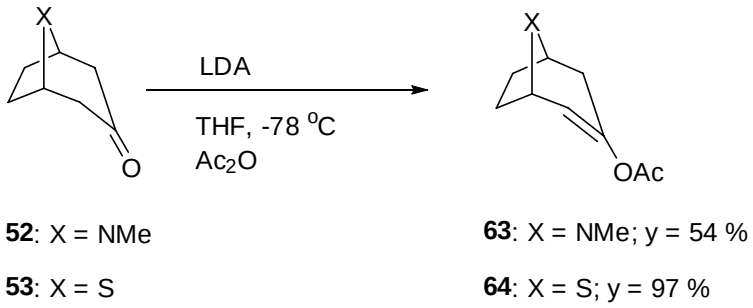
O-Acylation of bicyclo[3.2.1]octan-3-one **60** was a key step in the synthesis of bicyclo[4.2.1]nonan-3-one **62**.[28] Bicyclo[3.2.1]oct-2-en-3-yl acetate **61** was afforded in 93 % yield by the reaction of ketone **60** with isopropenyl acetate in the presence of a base (**Scheme 14**).



Scheme 14

Although this reaction was not carried out with a chiral base, it highlights an example of an O-acylation of a bridged ketone. Employing a chiral base should allow easy access to both stereoisomers of **62**.

Acylation of tropinone or TBON in the presence of LDA using acetic anhydride as the electrophile gave compound **63** in moderate 54 % yield and **64** in 97 % yield.[22, 23, 29]

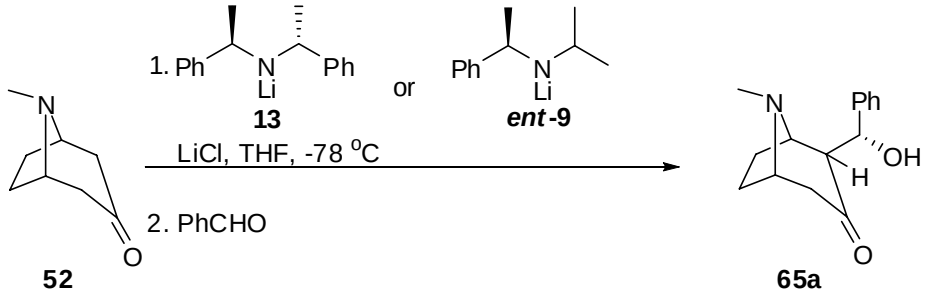


Scheme 15

1.2 Reactions at the Carbon Center

1.2.1 Aldol Reaction

The influence of lithium chloride on aldol reaction of tropinone with benzaldehyde was investigated independently by our group[30,31] and by Simpkins (**Scheme 16**).[6, 32] The results obtained in both cases showed essentially the same trend although there are small differences in absolute *ee* values (~ 2-10 %). In the absence of lithium chloride, the product (*exo-anti*) was obtained in low enantiomeric excess (22-35 %) while addition of lithium chloride significantly increased enantioselectivity. The best results were obtained when one equivalent of lithium chloride was used (88 % *ee* in case of chiral lithium amide **13** and 68 % *ee* for chiral lithium amide ***ent*-9**).

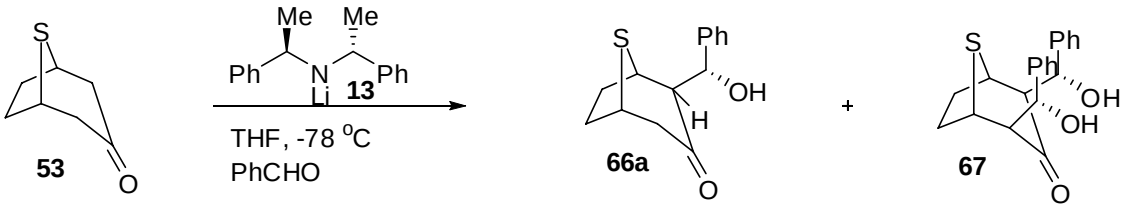


Scheme 16

Additionally, studies performed by our group showed that aldol product **65a** can be obtained with higher enantioselectivity when an alternative method of introducing lithium chloride to the reaction mixture is employed. Generation of both chiral lithium amide **13** and lithium chloride *via* addition of two equivalents of butyllithium to the hydrochloride salt of the appropriate amine increases *ee* of the product from 88 % to 95 %. This method has practical advantages as most chiral amines are difficult to purify. They are often hygroscopic and readily absorb carbon dioxide from air. Similarly, lithium chloride is difficult to dry and readily absorbs moisture from air.

The effect of different inorganic salts on the aldol reaction of tropinone lithium enolate generated with chiral lithium amide **13** was investigated.[30] It was shown that Lewis acids such as titanium tetrachloride and tin tetrachloride kills the reaction while lithium bromide, lithium fluoride, potassium chloride, sodium chloride, sodium bromide or magnesium bromide did not improve the enantioselectivity of the aldol reaction. Adduct **65a** was obtained with essentially the same enantiomeric excess as that obtained in the absence of any salts. Similar results were obtained by our group when base ***ent*-9** was used in the presence of lithium perchlorate and lithium iodide.[32] However, in contrast to the results obtained with chiral base **13**, lithium bromide was found to behave in a similar fashion to lithium chloride when chiral lithium amide ***ent*-9** was used. Enantioselectivity of aldol product **65a** improved from 24 % (no additives) to 69 % in the presence of one equivalent of lithium bromide.

The influence of lithium chloride on the aldol reaction of TBON was also studied (**Scheme 17**).[33] The results obtained were consistent with the tropinone study. When the aldol reaction was carried out according to the usual external quench protocol the *ee* of the obtained product was very low (16 %) even though the yield was 80 %. On the other side, introduction of LiCl (0.6 eq.) into the reaction mixture gave the same adduct **66a** with 84 % *ee* in 71 % yield. Increasing the amount of lithium salt to 1.0 eq. lowered the *ee* of the product to 76 %. Interestingly performing the same reaction under internal quench protocol (*via* making silyl enol ether) resulted in product **66a** with 86 % *ee*.



Scheme 17

Screening different chiral lithium amides with TBON in aldol reaction in the presence of 1.0 eq. of lithium chloride showed that lithium amide **68** is the best match for TBON (**Figure 1-3.**).[22, 34, 35] Lithium amide **68** gave 82 % yield of adduct in 95 % *ee* while the other amides screened varied from 45-74 % ee.

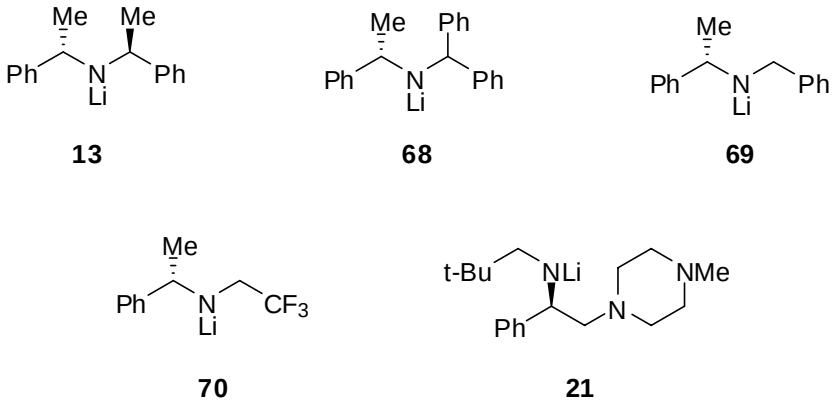
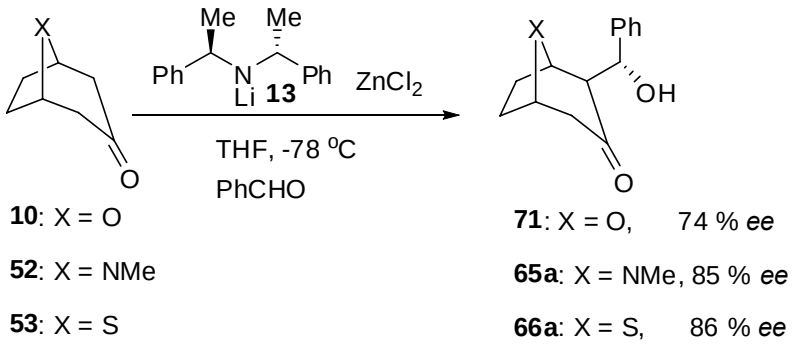


Figure 1-3. Examples of chiral lithium amides in aldol reaction of TBON

The influence of concentration of chiral lithium amide **68** on enantioselectivity of product obtained was investigated. The more concentrated the amide, the lower the yield and enantioselectivity of the product observed (46 % *ee* for 0.12M, while concentration 0.035M gave 71 % *ee*). This could be as a result of less discrimination by the base due to the increase in the rate of the reaction as well as an increase in the bis-aldol adduct that was isolated (2-23 %). This side product was identified as the *exo, exo, anti, anti*-2,4-bis-aldol.

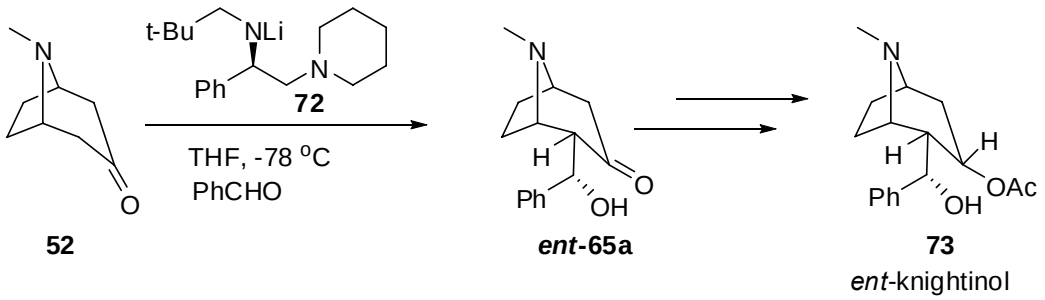
One other inorganic salt additive that was shown to have a significant influence on enantioselectivity of deprotonation of bridged ketones is zinc chloride.[32, 33] Studies on the aldol

reactions of tropinone, TBON and O analogue of tropinone were performed in the presence of zinc chloride and chiral lithium amide **13** (**Scheme 18**). As reported for lithium chloride, enantioselectivity of the reaction increased with the amount of zinc chloride added. The best *ee* values in the case of tropinone was achieved using 0.5 equivalent of $ZnCl_2$ (85 %), for TBON it was 0.4 equivalent (86 %) while the O analogue gave the best result in presence of 0.1 equivalent of the salt (74 %). No explanation was offered for the randomness in the equivalent of zinc chloride that gave the best results for each substrate. It is safe to speculate that the various heteroatoms interacting with zinc might play a part in the selectivity. It is also interesting to note that the enantioselectivity of the reaction tailed off dramatically as the amount of zinc chloride increased (1.0 equivalent of lithium chloride gave the highest *ee* value).



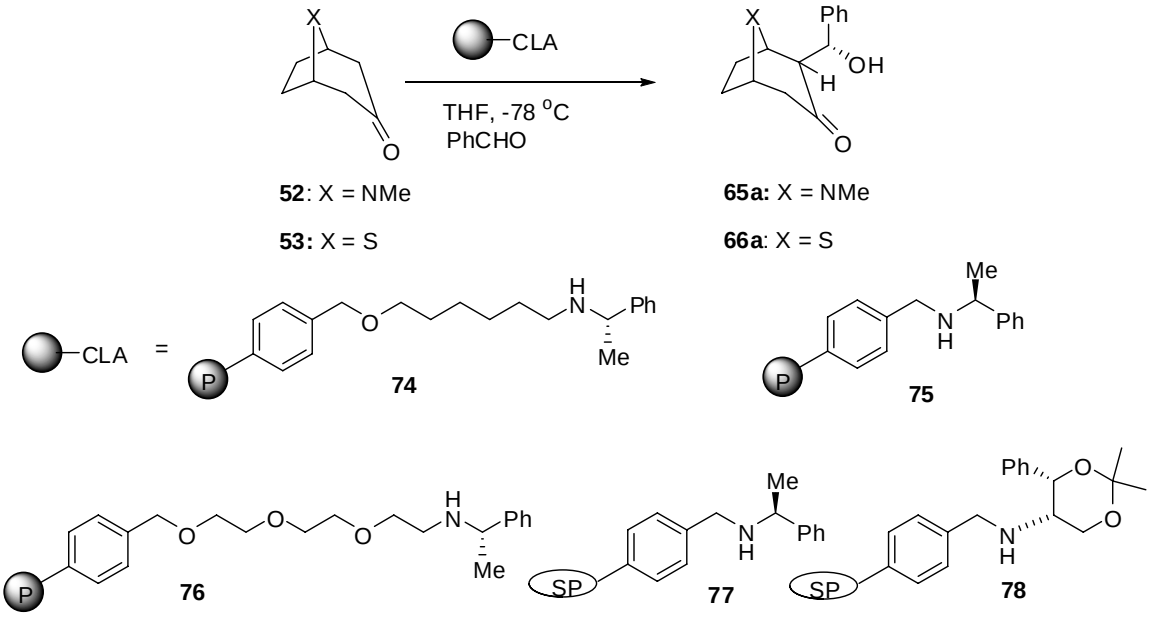
Scheme 18

Enantioselective aldol reaction of tropinone with benzaldehyde utilizing chiral amide **72** under external quench protocol was studied in our group (**Scheme 19**). [30] Surprisingly, addition of lithium chloride did not have any noticeable influence on the enantioselectivity of this reaction. The enantiomeric excess of the aldol product (*ent*-**65**) with, or without, lithium chloride remained constant at 90 %. This result suggests that lithium chloride is not a prerequisite for high enantioselectivity in ketone deprotonations with chiral amides generated from diamines. Adduct *ent*-**65** was later converted into alkaloid *ent*-knightinol **73**.



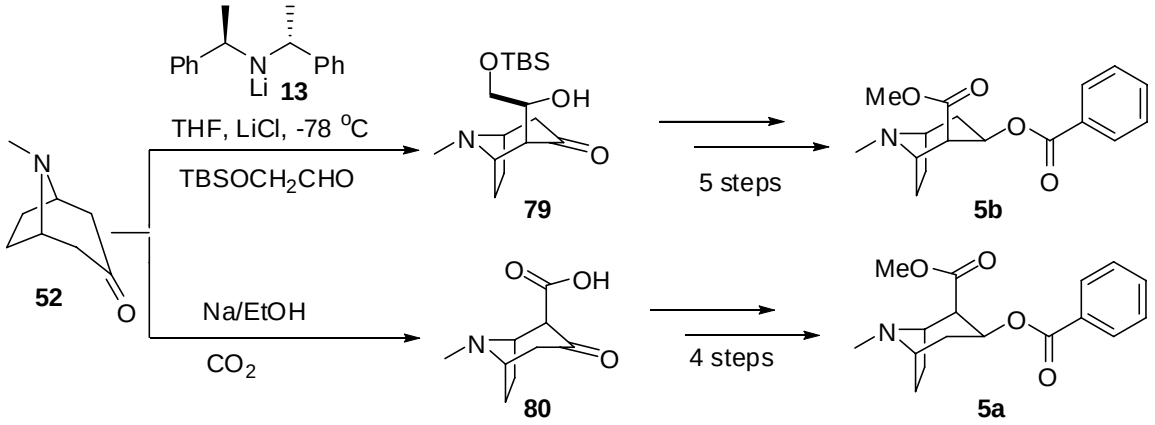
Scheme 19

The use of chiral lithium amide on solid support (Merrifield resin or a soluble analogue) in enantioselective aldol reaction of tropinone and TBON was also studied (**Scheme 20**).[36,37] In the enantioselective deprotonation carried out with the use of amides on solid support, addition of lithium chloride was reported to be necessary as it prevents the formation of a gel (heterogenous system), allowing for the efficient formation of the lithium amides from its amines. Additionally, the reaction is concentration dependent with respect to the amide. Lower concentration of amide (0.026M) gave tropinone aldol in 75 % *ee* while an increase in concentration (0.075M) decreases the *ee* to 30 %. Lastly when amines on insoluble polymer were used addition of another equivalent of butyllitium before addition of electrophile was beneficial. This operation probably prevents the internal proton return,[38] and increases the yields substantially. Unfortunately, all the chiral amides investigated gave products in low to moderate yields (38-77 %) and *ee* (10-75 %). The lithium chloride additive has very little influence on both the yield and enantioselectivity of the reaction (few per cent). The best results for both ketones were obtained with amide **77**. Aldol **66a** was obtained in the presence of 1.0 eq. of LiCl in 72 % yield with 44 % *ee* while 2.0 equivalents of LiCl was needed to form aldol **65a** from ketone **52** in 77 % yield with 75 % *ee*.



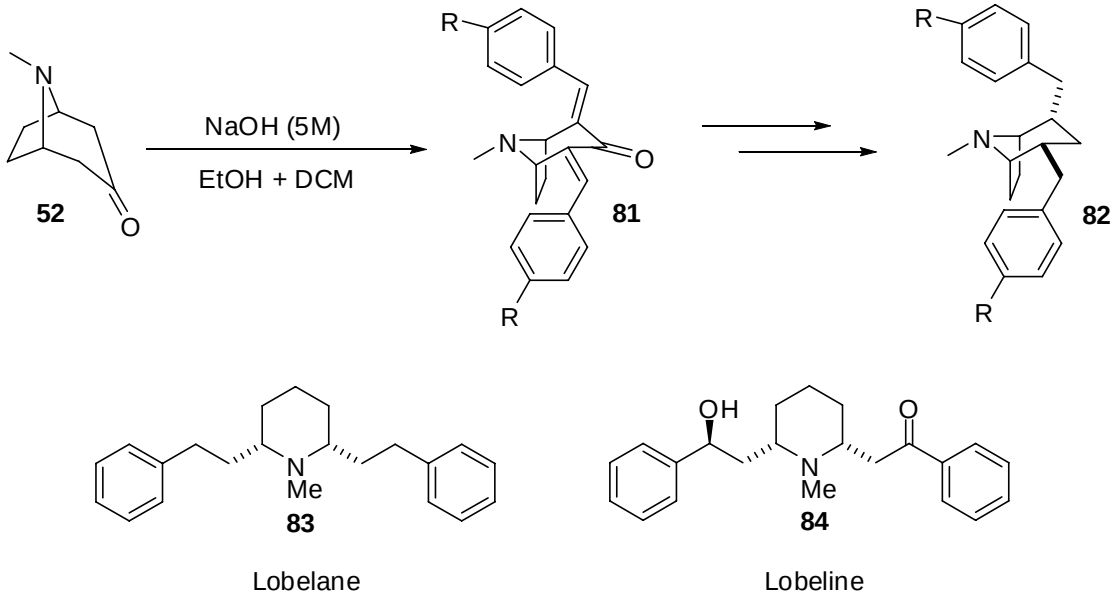
Scheme 20

The aldol reaction of tropinone mediated by chiral lithium amide **13** with TBS protected aldehyde was the key step in synthesis of unnatural cocaine **5b** (**Scheme 21**).[39] Adduct **79** was obtained as single diastereoisomer in 75 % yield and 90-92 % *ee* and was converted to **5b** in 5 steps. The natural cocaine **5a** was synthesized *via* making sodium tropinone enolate and quenching it with carbon dioxide. The acid **80** was then transformed in 4 steps into compound **5a**.[40]



Scheme 21

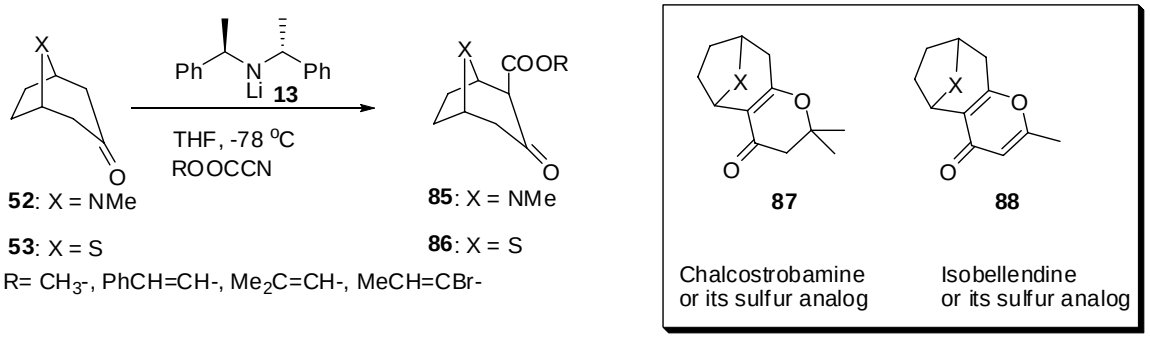
A series of tropane compounds such as lobelane and lobeline have been synthesized (Scheme 22). The first step in the synthesis involves the aldol reaction of tropinone with different aromatic aldehydes mediated by NaOH as the key step in the sequence. [41, 42]



Scheme 22

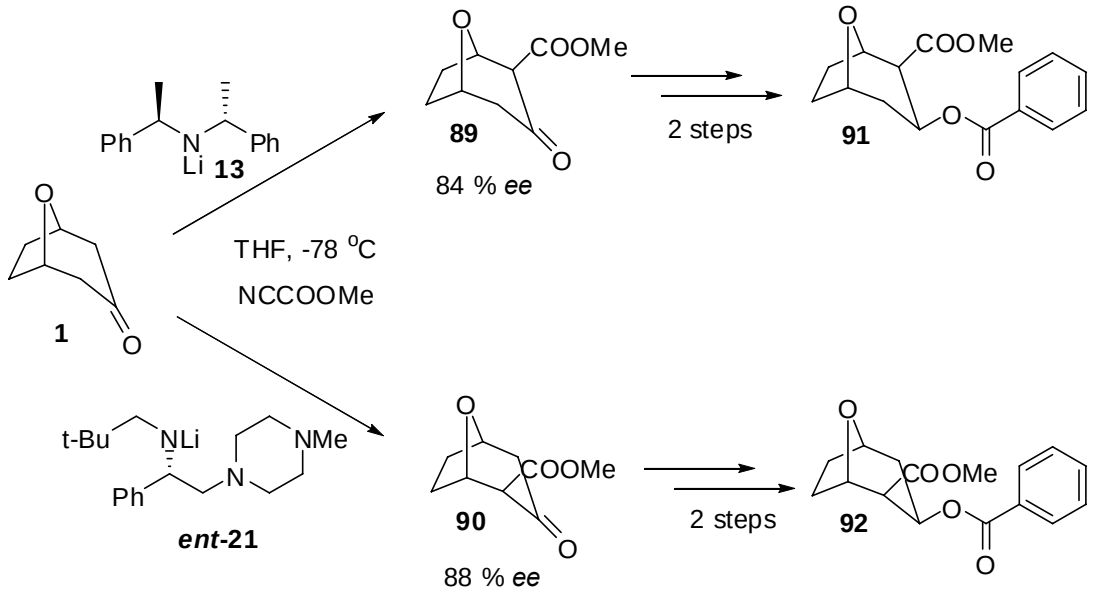
1.2.2 C-Acylation

Carbomethoxylation of tropinone and TBON using Mander's reagent was successfully carried out in our group (**Scheme 23**). [21, 22,34] This process allowed for easy access into tropane alkaloids and it sulfur analogues *via* the use of various acyl cyanides.



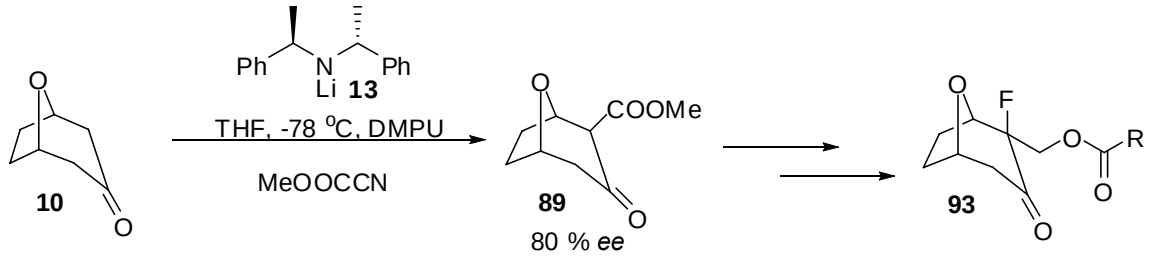
Scheme 23

Carbomethoxylation of 8-oxabicyclo[3.2.1]octan-3-one using chiral lithium amides **13** and ***ent*-21** was also employed as the key step in the syntheses of oxacocaines **91** and **92** in 84 % and 88 % *ee* respectively (**Scheme 24**).[43]



Scheme 24

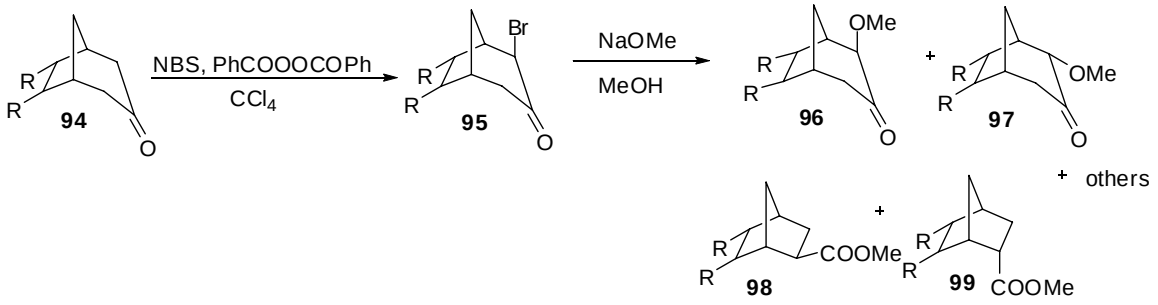
A series of 2-fluoro-8-oxabicyclo[3.2.1]octan-3-ones were prepared from 8-oxabicyclo[3.2.1]octan-3-one and were used as catalysts for alkene epoxidation with Oxone (**Scheme 25**). The first step in the synthesis of a number of these catalysts was the acylation reaction using Mander's reagent.[44]



Scheme 25

1.2.3 α-Bromination

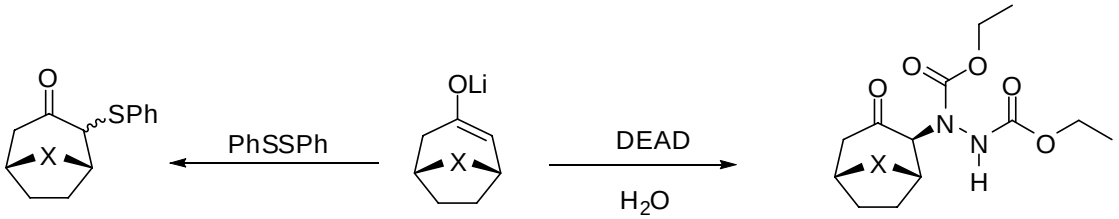
Bicyclo[3.2.1]octan-3-one was easily prepared from reacting it with bromine in acetic acid (**Scheme 26**). In this reaction, a mixture of axial, equatorial and dibromo compounds were isolated. Changing the source of bromine to NBS and employing benzoyl peroxide in carbon tetrachloride gave exclusively product **97**. Compound **97** was later used in a Favorskii rearrangement reaction.[45,46]



Scheme 26

1.2.4 Other Reactions

Different heteroatoms such as nitrogen and sulfur[23 24] were attached to the α–carbon of both tropinone and TBON with good yields and *ee* (**Scheme 27**). Those compounds have the potential for further use as chiral ligands.



100: X = N; y = 75 %

101: X = S quantitative yield

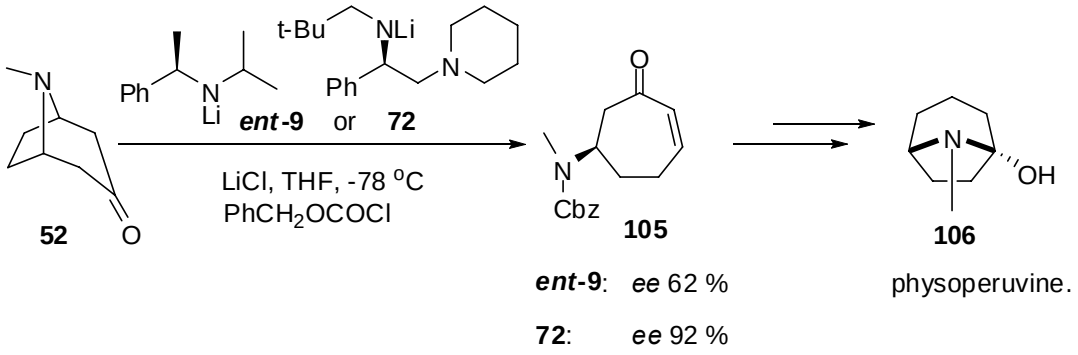
102: X = NMe

103: X = S

104: X = N; y = 94 %

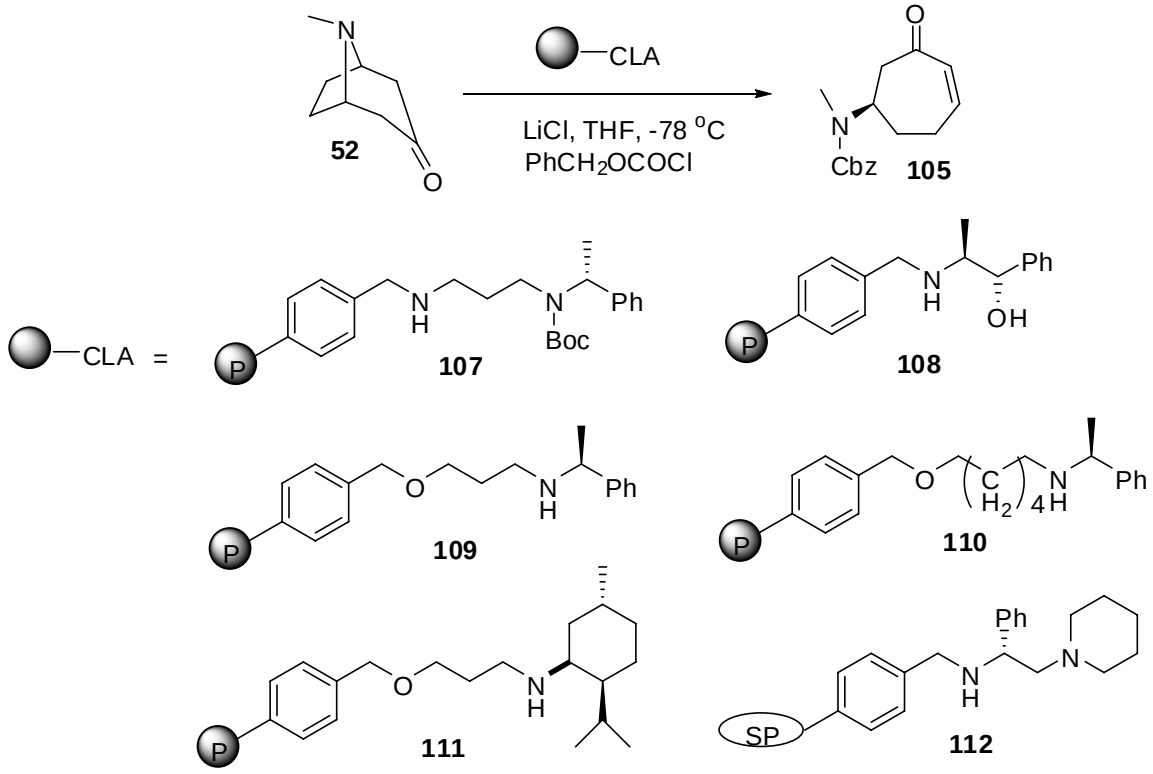
Scheme 27

Treatment of enantiomerically enriched lithium enolates of tropinone with benzyl chloroformate in the presence of 0.5 eq. of lithium chloride generates enone **105** (**Scheme 28**).[29, 47,48] The reaction presumably proceeds *via* *N*-acylation followed by elimination (with concomitant ring opening). The enone **105** obtained was then converted to physoperuvine.



Scheme 28

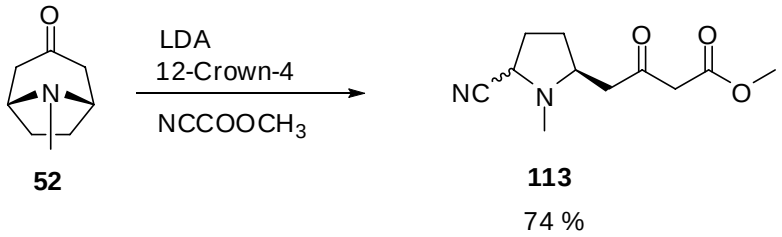
A repeat of the above reaction using chiral amines on solid support gave a much poorer result (*ee* 2-59 %). The best result was obtained when lithium amide 75 was used (37 % yield and 59 % *ee*). Interestingly, in the case of lithium amides 107 and 111, absence of lithium chloride give the major product as levorotatory enantiomer while the addition of LiCl gave the dextrarotatory enantiomer as the major isomer (**Scheme 29**).



P= insoluble polymer support, SP = soluble polymer support

Scheme 29

A different type of ring opening of tropinone was achieved *via* the treatment of the lithium enolate with methyl cyanoformate in the presence of crown ether (**Scheme 30**).[29] 2,5-Substituted pyrrolidine was obtained in 74 % yield. Employing a chiral base in this process should afford non racemic 2,5-substituted pyrrolidine.

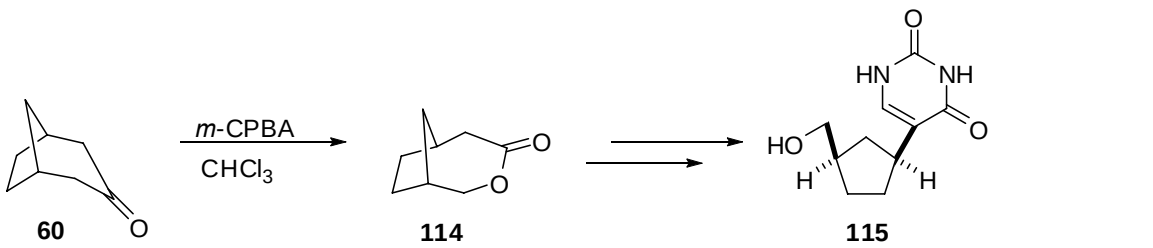


Scheme 30

2 Other Transformations of Bicyclo[3.2.1]octan-3ones

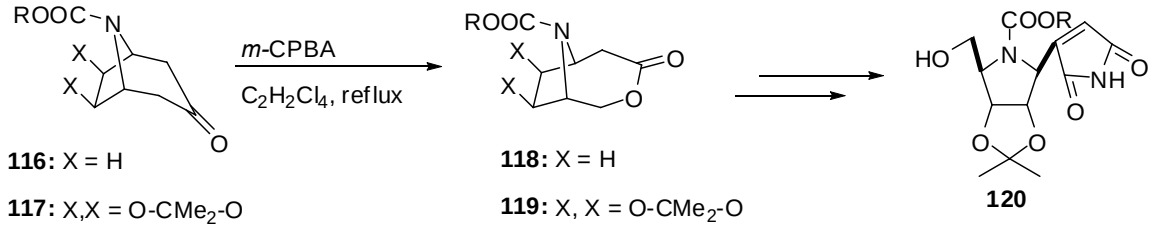
2.1 Oxygen Insertion Reactions

Oxygen insertion reactions (Baeyer-Villiger oxidations) converts bridged bicyclic ketones into bridged bicyclic lactones that were key intermediates in the stereoselective synthesis of many natural products like alkaloids, steroids, carbohydrates, prostaglandins and terpenoids (**Scheme 31**). For example bicyclo[3.2.1]octan-3-one **60** was converted to lactone **114** (81 %) which was further transformed to a carbocyclic analogue of 2', 3'-dideoxypseudouridine.[49]



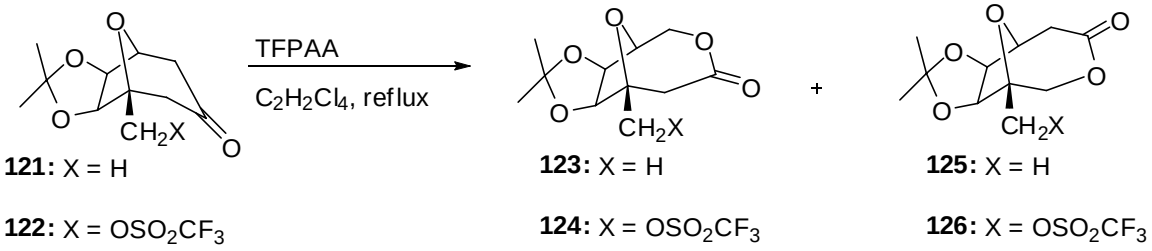
Scheme 31

Under harsh conditions (*m*-CPBA/tetrachloroethane/reflux), *N*-carbomethoxy-8-azabicyclooctan-3-ones **116** and **117** were oxidized to lactones **118** (75 %) and **119** (60 %).[50] Finally, lactones **119** were converted into nitrogen analogues of showdomycin, a *C*-nucleoside antibiotic (**Scheme 32**).



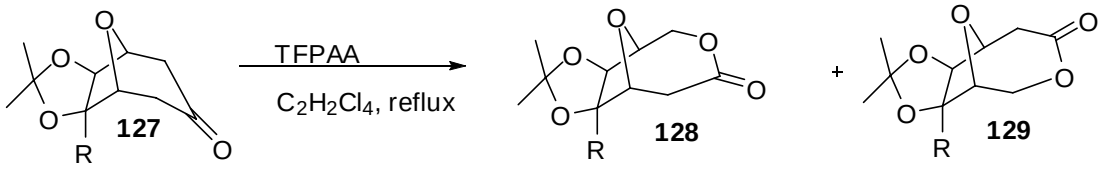
Scheme 32

Regioselectivity in oxygen insertion reactions depends on the combination of electronic and steric effects.[51] For example in the trifluoroperacetic acid (TFPAA) mediated oxidations of γ-substituted 8-oxabicyclo[3.2.1]octan-3-ones 121 and 122 (80-100 %), two regioisomers of each compounds were obtained (**Scheme 33**). An increase in electron withdrawing ability of the group X (OSO_2CF_3) at the γ- position resulted in 86:14 ratio of two products 124:126. When X was changed into H ratio of both products 123:125 changed into 47:53.



Scheme 33

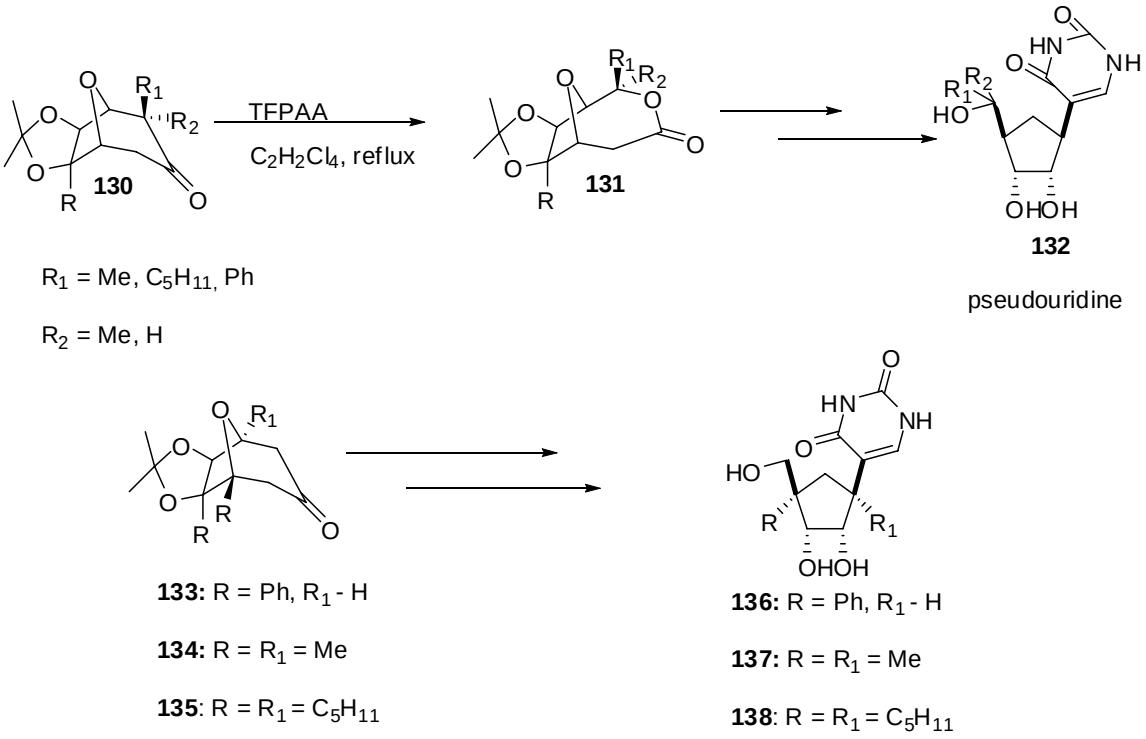
Interestingly, steric effects do not have a significant influence on the regioselectivity of the Baeyer-Villiger oxidation (**Scheme 34**). A bulky R group (*t*-butyl) inhibits the reaction but generally the ratio of diastereoisomers does not differ irrespective of the size of the R group.



R = CH3	33	:	67
R = Ph	39	:	61
R = CH2OCOPh	40	:	60
R = *t*-Bu		0	

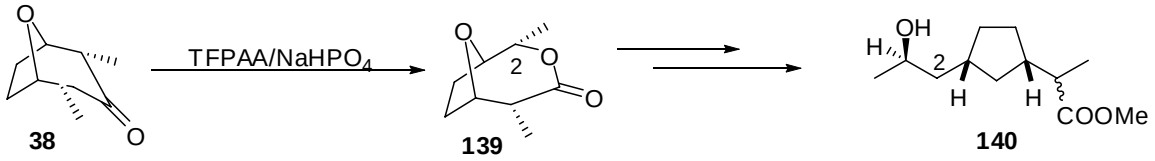
Scheme 34

Ketone **130** was regioselectively oxidized with TFPAA in DCM to lactones **131** (80 %) that was easily transformed to different pseudouridines. Oxidation of ketones **133-135** provided the first stereocontroled entry to 1', 4'-dialkylated pyrimidine *C*-nucleasides **136-138** (**Scheme 35**).[52]



Scheme 35

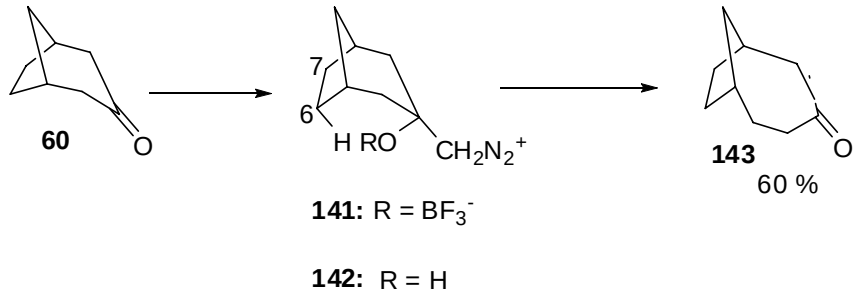
Finally, lactone **139** was utilized to synthesize methyl nonactate and methyl-8-epinonactate **140**.[53]



Scheme 36

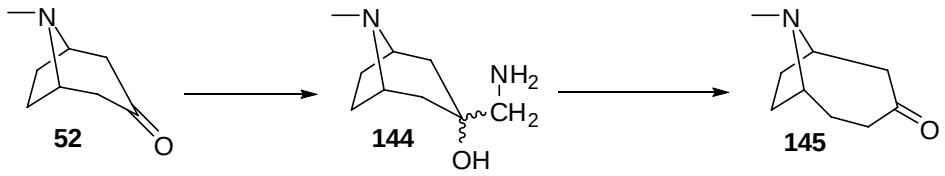
2.2 One Carbon Ring Extension

Boron trfluoride etherate catalyst was needed to facilitate the reaction of bicyclo[3.2.1]octan-3-one **60** with DAM (**Scheme 37**)[54]. The lack of reactivity of **60** towards DAM was explained *via* repulsive interaction between O atom and the two *endo* hydrogens attached to C6 and C7 in the transition state for rearrangement of intermediate **141.** However after successful expansion of intermediate **142** to product **143** by Hartman,[55] the lack of reactivity in case of **60** towards DAM was explained again as difficulty in formation of **141**.



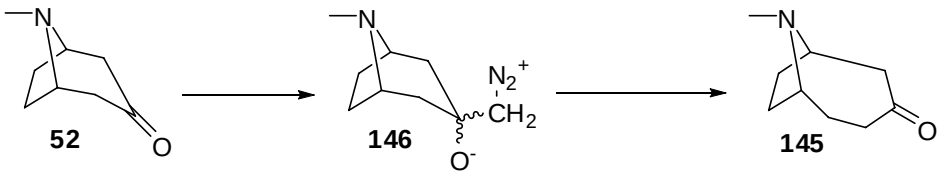
Scheme 37

Cope *et al.*[56] have expanded tropinone ring **52** *via* making 3-aminomethyl-hydroxy derivative **144** that was treated with nitrous acid in acetic acid giving rise to homotropinone **145** in 75 % yield (**Scheme 38**).



Scheme 38

Similarly employing diazomethane easy access to compound **145** from tropinone can be obtained.[57]

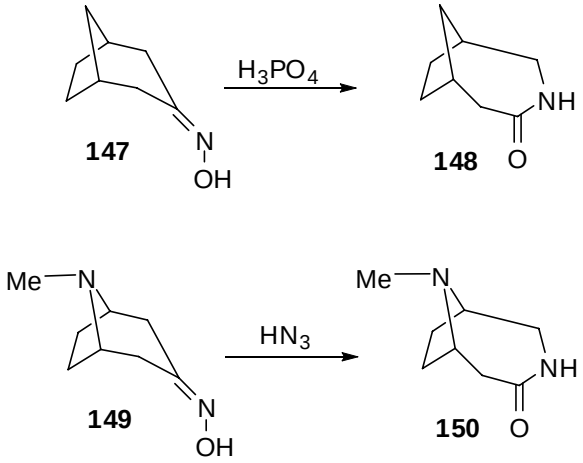


Scheme 39

2.3 Nitrogen Insertion Reaction

Nitrogen insertion reaction of bridged bicyclic ketones leads to bridged bicyclic lactams. The major issues in this reaction have to do with the regioselectivity of the nitrogen insertion, the reactivity of substrates and the competition between nitrogen insertion and cleavage processes.

For example bicyclo[3.2.1]octan-3-one oxime **147** rearranges with polyphosphoric acid to lactam **148** in 75 % yield.[58] On the other hand tropinone oxime **149** undergoes Schmit rearrangement with hydrazoic acid to lactam **150** in 90 % yields (**Scheme 40**).



Scheme 40

In a parallel syntheses of pyrrolizidine alkaloid hemiloline **153** by Glass *et al*.[59] and Wilson *et al*., 8-oxabicyclo[3.2.1]hept-6-en-3-one oxime **151** was tosylated and a rearrangement reaction in ether/potassium hydroxide or potassium carbonate/aqueous tetrahydrofuran afforded the lactam

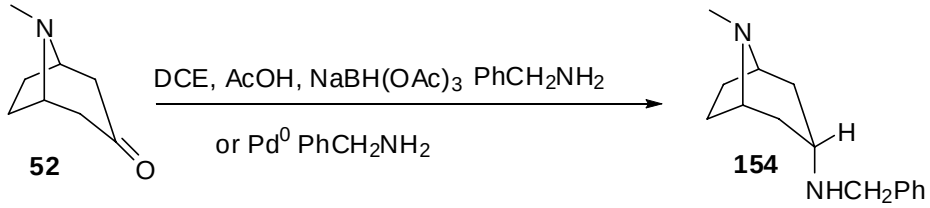
152 in 68 % and 92 % yield, respectively (**Scheme 41**). Lithium aluminum hydride reduction of **152,** followed by bromine mediated transannular cyclization of the resultant amine, and a hydride removal of halogen afforded hemiloline **153.**

E

Scheme 41

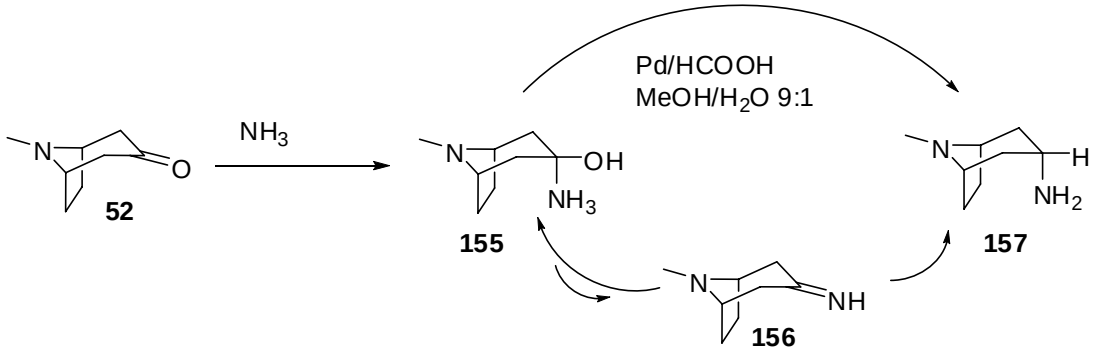
2.4 Reductive Amination

Reductive amination of tropinone was achieved *via* two different methods. The classical approach[53,60,61] gave amine **154** in yields as high as quantitative.



Scheme 42

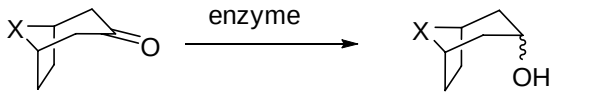
Palladium catalyzed reductive amination was equally carried out to afford the 3-*endo*-tropanamine as in the case of 7-azaindolylcarboxy-*endo*-tropanamide-new antitussive drug presently in phase II clinical trials.[62,63] The proposed reaction mechanism is shown on **Scheme 43**.



Scheme 43

2.5 Reduction

Tropine and TBON were also reduced enzymatically to afford alcohols.[64,65]



52: X= NMe

53: X = S

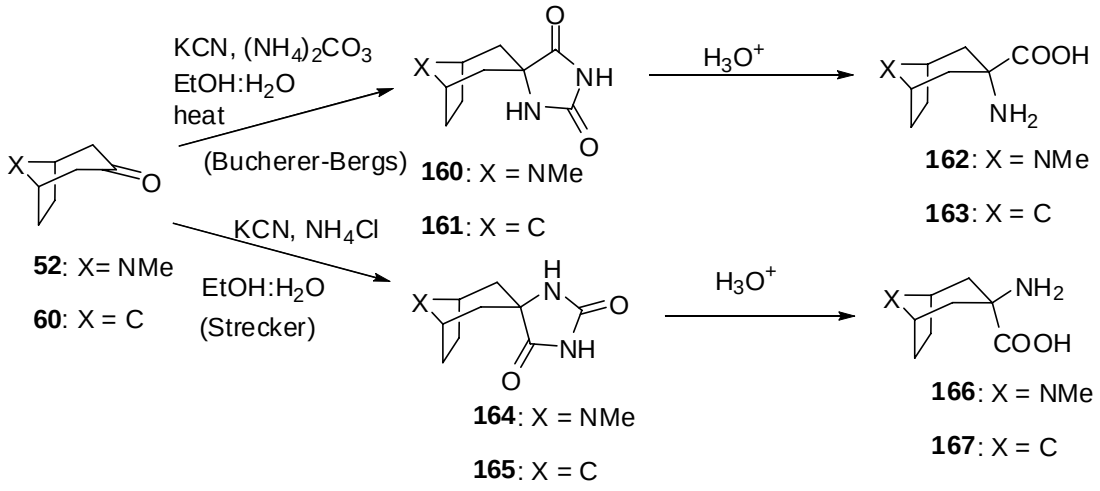
158: X = NMe

159: X = S

Scheme 44

2.6 Bucherer-Bergs and Strecker Reactions

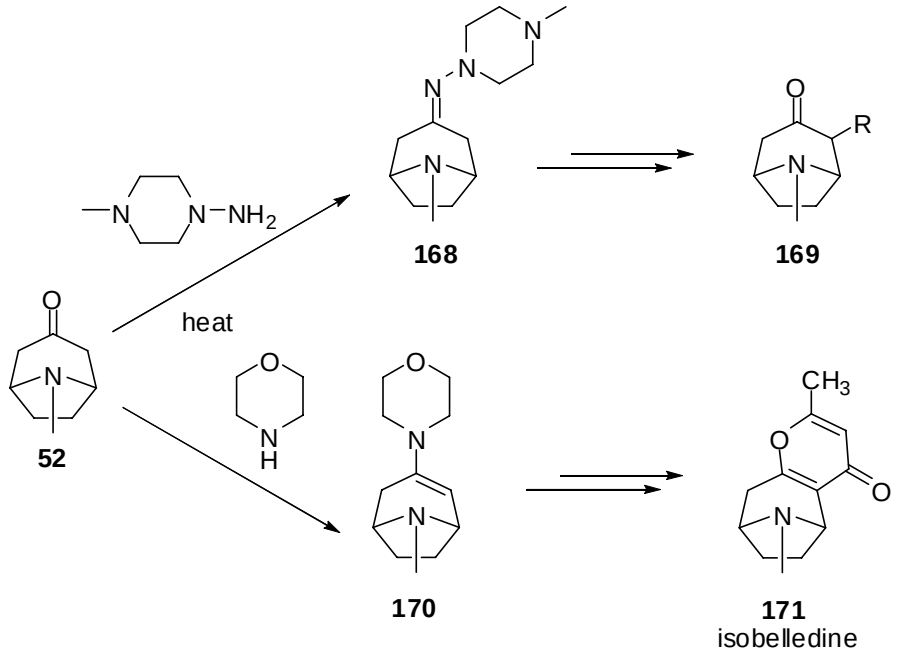
Bicyclic ketones were shown to undergo Bucherer-Bergs or Strecker reactions selectively.[66] Hydrolysis of the intermediates obtained allows access to bicyclic amino acids.[67]



Scheme 45

2.7 Hydrazones and Enamines

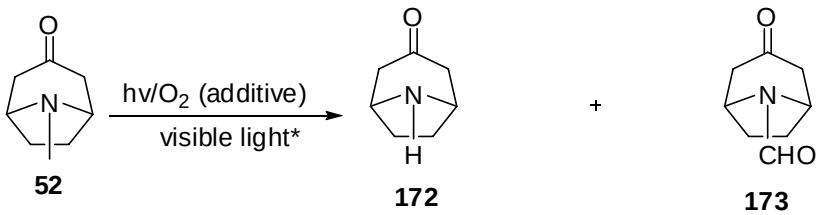
Lazny[68,69] employed the hydrazone of tropinone from 1-amino-4-methylpiperazine in order to indirectly alkylate tropinone **52** (**Scheme 46**). A similar approach using the enamine from morpholine and tropinone was employed in the synthesis of isobellendine.[70]



Scheme 46

2.8 Other Reactions

Photooxydation of tropinone in the presence of $LiClO_4$ leads to nor-tropinone while the same reaction without salt gave both nor- and formyl tropinone (**Scheme 47**).[71]

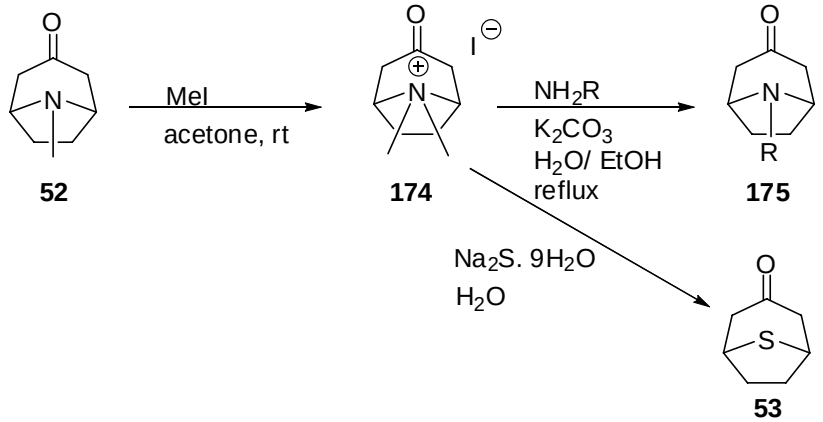


additive:		
0.25 $LiClO_4$	100 %	-
-	35 %	65 %

* irradiation with a 500 W high-pressure Hg lamp through a U.V. cut-off glass filter ($\lambda \geq 420$ nm)

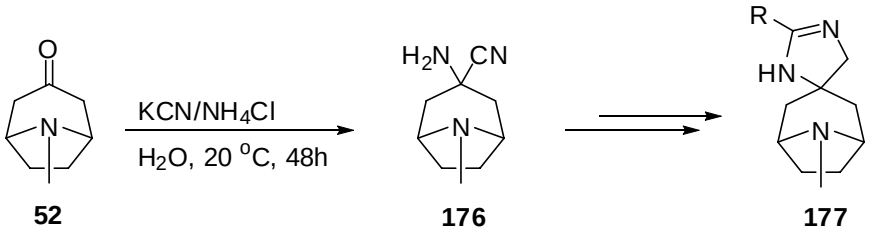
Scheme 47

A different approach to making nortropinone derivatives involves preparation of *N*-methyl tropinone iodide [72] which is also an intermediate in the preparation of TBON from tropinone (**Scheme 48**).[60]



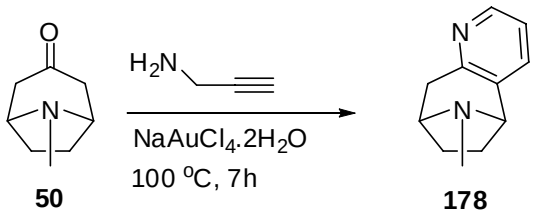
Scheme 48

A series of 2'-aryl-3-azabicyclospiro-4'(5')imidazolines were synthesized from tropinone. The first step in the synthesis involves the preparation of tropinone amino cyanide (**Scheme 49**).[73]



Scheme 49

Various pyridines were synthesized in the reaction of carbonyl compounds with propargylamine (**Scheme 50**). Among them was also pyridine derivative from tropinone.[74]



Scheme 50

3 Conclusions

Bridged bicyclic ketones are interesting compounds from the point of view of their synthetic usefulness as potential starting materials for many natural products. Their unique rigid structures make them also ideal candidates in enantioselective deprotonation processes. The interest in using these compounds in different enantioselective reactions have increased within the last decade due to the fact that generally useful products of high optical purity could be obtained (*ee* usually over 90 %). Despite the many reactions that have been carried out in this area, a lot is still left to be understood in terms of the types of reactions investigated to date and the ability to predict the best match between chiral bases and substrates. For example, the C-

alkylation of this class of compounds with alkyl electrophiles has not been well studied as evident in the lack of examples in the literature.

CHAPTER 2
RESULT AND DISCUSION

1 Introduction

Previous studies on enantioselective deprotonation of tropinone and TBON were described in the preceding section. My research goals were as follows:
(i) to extend the enantioselective deprotonation methodology previously developed for tropinone and TBON to unknown areas (such as alkylation and use of other electrophiles),
(ii) to explore different conditions for conducting the established reactions (e.g. aldol reaction promoted by magnesium iodide) and finally,
(iii) to apply this knowledge in synthesis of natural products and analogs (thiacocaine).

2 α-Derivatives of Tropinone and TBON

2.1 Introduction

The synthesis of new natural products from tropinone and TBON is directly connected to the chemistry of both bicyclic bridged ketones. Although some properties of these compounds under various reactions had been investigated, some questions remained unanswered.

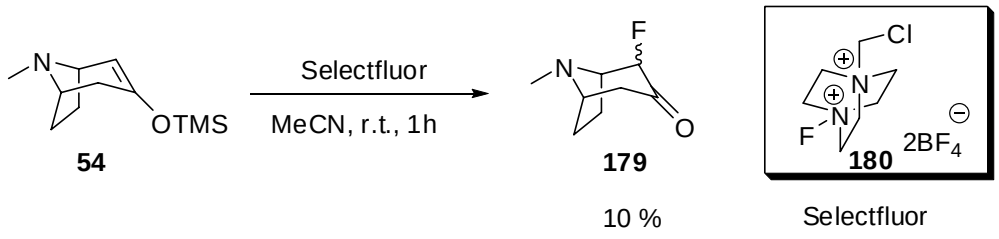
For example a very useful reaction – alkylation (the first step in the synthesis of alkaloid-KD)[29] remained problematic. All previous attempts to alkylate tropinone failed for reasons unknown while TBON seemed to undergo alkylation but in unreasonably low yield.[25] Moreover, some common reactions such as halogenation, the Michael reaction, and the Mannich reaction were never investigated in the context of enantioselective deprotonation. The potential usefulness of products of these reactions as chiral ligands could open up a new area as well as present a new set of problems that might be associated with the introduction of hetereoatoms such as oxygen,

nitrogen or halides at the α-position to the ketone. The chemistry mentioned above is described in the following section of this thesis.

2.2 Connecting a Heteroatom-Based Functional Group at the α-Position of Tropinone

2.2.1 α-Halogenation

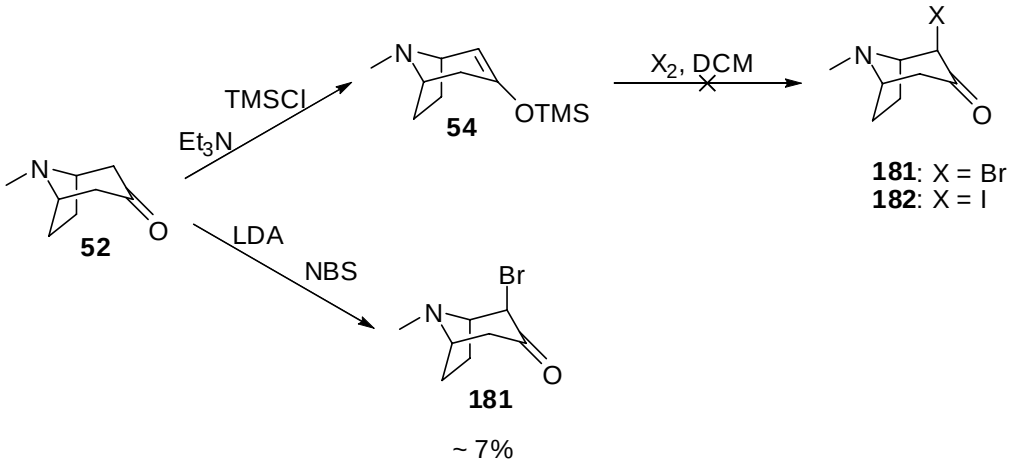
Introduction of a halide at the α–position of the ketone should be, in principle, the easiest method for accessing compounds that could be used as chiral ligands. The initial attempts to prepare halogenated derivatives of tropinone were carried out under non chiral conditions (using LDA in the generation of tropinone enolate) so as to determine the intrinsic propensity of the ketone to this type of substitution. My first attempt towards halogenation of tropinone was fluorination, simply because this process had already been known to work with *N*-ethoxycarbonyl tropinone (**Scheme 51**).[16] Unfortunately, for reasons unknown, all attempts to carry out fluorination on tropinone according to the reported protocol (starting from TMS-ether of the ketone and using Selectfluor as the electrophile) gave products as a mixture of two diastereoisomers in 1:1 ratio with consistently low yields (~ 10 %). Modification of the reaction protocol involving increase in reagent amounts, reaction time, and concentration did not improve the yield.



Scheme 51

Other attempts to halogenate tropinone such as iodination or bromination were even less successful than fluorination (**Scheme 52**). In the case of iodination using I_2, decomposition of the starting material was observed. In the reaction with Br_2, only the starting materials were

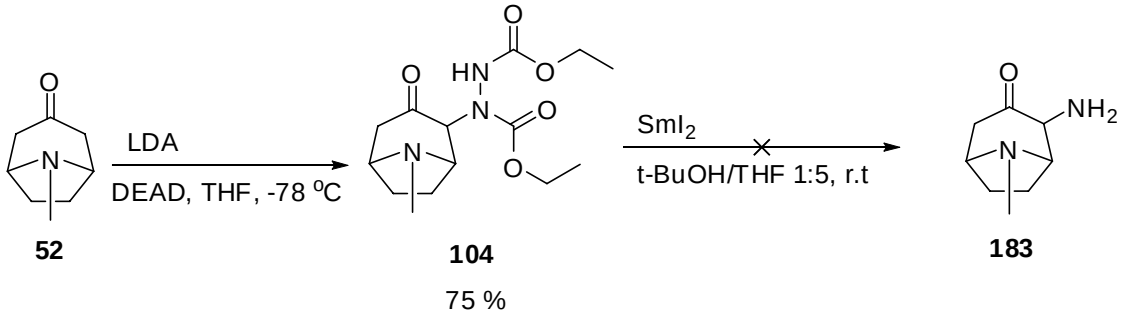
recovered (in the case of tropinone 70 % recovery) however the same reaction *via* generation of the corresponding lithium enolate followed by the addition of NBS as the source of the electrophilic bromine gave the desired compound although in only ~ 7 % yield. Attempts to improve the yield did not meet with any success.



Scheme 52

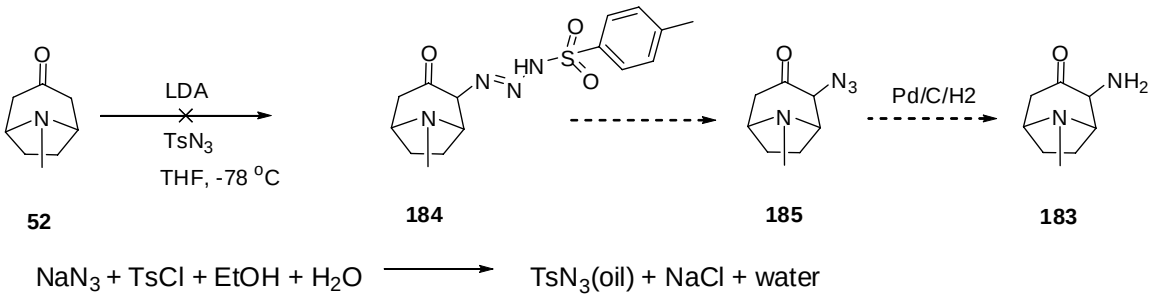
2.2.2 α-Amination

The α-amination reaction especially in the case of tropinone could open a new window of possibilities affording new chiral ligands. The first approach to introduce nitrogen to the tropinone ring was *via* an already established reaction using DEAD (**Scheme 53**).[24] Unfortunately, attempts to transform this adduct to a useful product by reductive cleavage of the N-N bond using SmI_2 failed. ^1H NMR analysis of the crude reaction mixture showed traces of the product but all attempts to optimize the process failed.



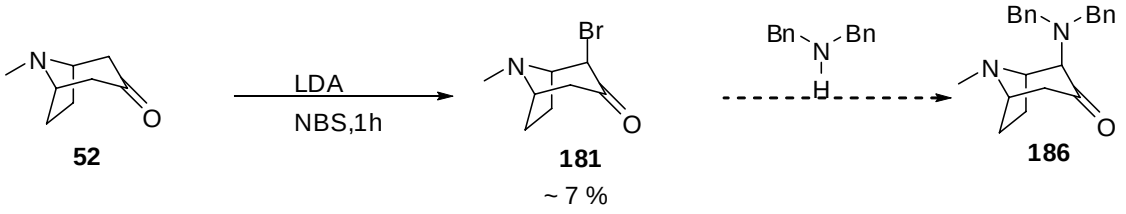
Scheme 53

Another approach in which TsN_3 was utilized as the nitrogen source in α-amination of tropinone wasn't successful either (**Scheme 54**). Even though that TsN_3 was prepared (by a known procedure),[75] although in low 32 % yield, attempts to obtain the corresponding tropinone azide failed (only starting materials were recovered).



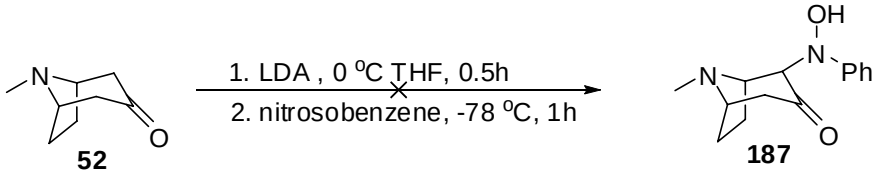
Scheme 54

The next approach that involved dibenzylamine, that was easily prepared in good yield (97 %) *via* reductive amination of benzaldehyde with benzylamine in presence of sodium triacetoxyborohydride,[76] was also not effective (**Scheme 55**). An attempt to use this amine in reaction with brominated tropinone gave no trace of the product. Since the brominated tropinone was obtained in a very low yield, this approach was abandoned.



Scheme 55

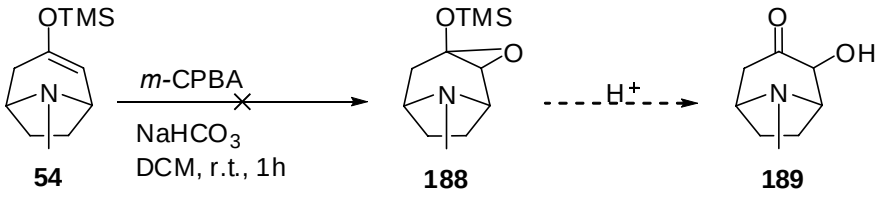
The last attempt towards α-aminaton of tropinone involved using nitrosobenzene as the nitrogen source (**Scheme 56**).[77] Although the reaction mixture showed trace amount of the product by ^{1}H NMR, attempts to isolate this product failed, giving only the starting material in 72 % recovered yield.



Scheme 56

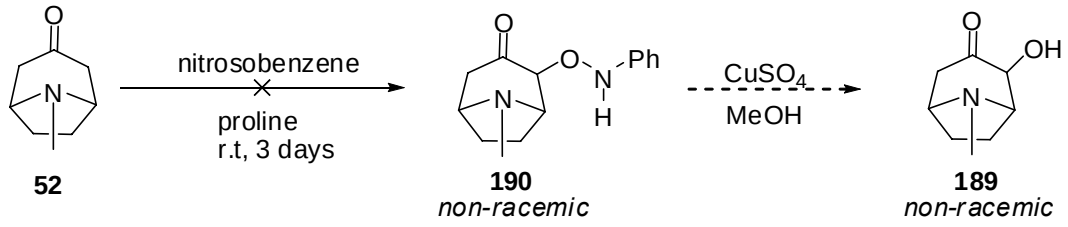
2.2.3 α-Hydroxylation

Introducing the hydroxyl group at the α-position of tropinone ring could also be used in the synthesis of potential new chiral ligands. The main problem associated with this chemistry involves the high tendency of the nitrogen in the ring towards oxidation during the course of the hydroxylation. The first attempt to synthesize α-hydroxy tropinone was done by treating the TMS enol ether of tropinone with *m*-CPBA in order to obtain the corresponding epoxide that on hydrolysis of the silyl group should afford the desired product (**Scheme 57**). This two-step reaction was done in a "one pot protocol" with no success. Attempt to do it stepwise equally failed.



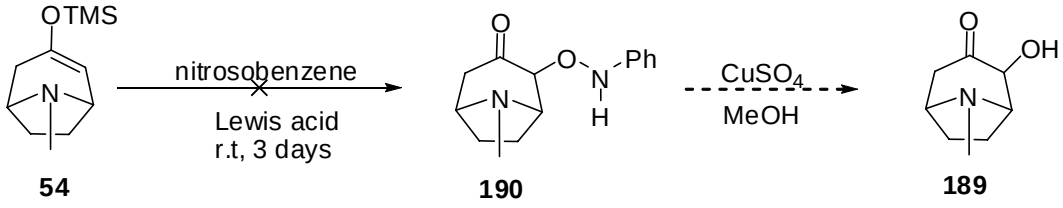
Scheme 57

Applying another known protocol[78] involving the use of organocatalysis (proline) and nitrosobenzene as the oxygen source also gave no reaction (**Scheme 58**). The starting materials were recovered.



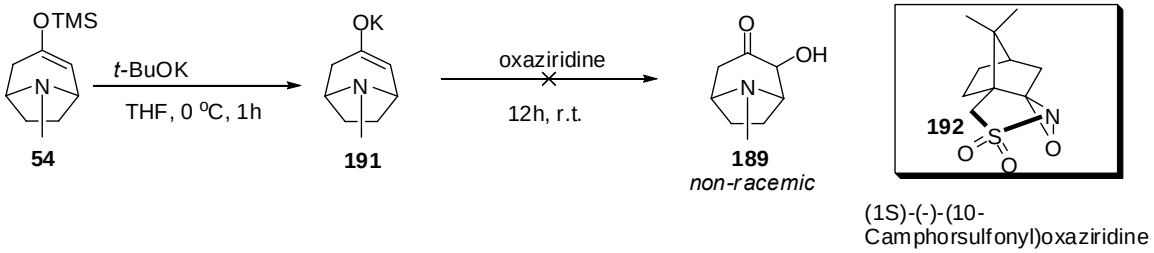
Scheme 58

Attempts to perform this reaction by employing the silyl enol ether of tropinone and various Lewis acids ($FeCl_3$ and $TiCl_3$),[79] under various reaction conditions equally did not give the product (**Scheme 59**).



Scheme 59

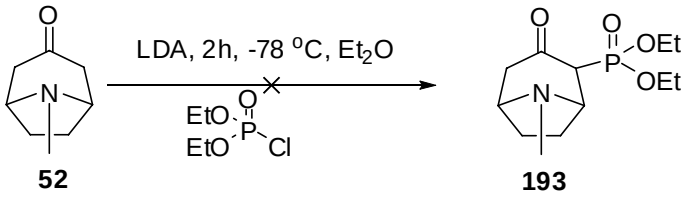
The last protocol that was applied involved generation of the potassium enolate (from its TMS enol ether) followed by treatment with an oxaziridine (**Scheme 60**).[80] Less than 50 % of the starting material was recovered from the reaction suggesting the oxidation at the nitrogen instead which would give a highly polar *N*-oxide.



Scheme 60

2.2.4 Phosphorous derivative

Phosphorous was the last heteroatom that was approached as a potential substituent on the tropinone ring (**Scheme 61**). Phosphorylation of lithium enolates of cyclic ketones had previously been investigated.[81] Generation of the lithium enolate and attempts to trap the enolate with phosphorus reagents gave no traces of the desired product. The starting material was always recovered in good yields.



Scheme 61

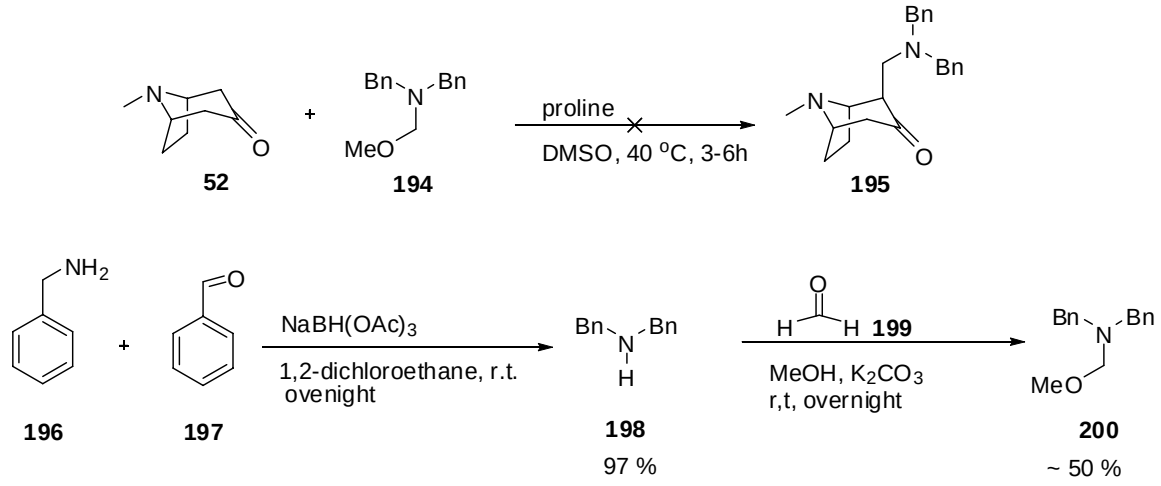
2.3 Summary of Connecting a Heteroatom-Based Functional Group at the α-Position of Tropinone

Although the potential usefulness of tropinone having any heteroatom at the α-position can't be denied, all attempts to prepare these types of compounds were unsuccessful. In case of fluorination and bromination, the desired products were obtained in very low yields (< 10 %) thereby making further transformations to potential chiral ligands difficult to investigate. Equally, attempts to introduce oxygen, nitrogen or phosphorous atoms at the α-position of tropinone also failed. These preliminary studies indicate that the α-functionalization of tropinone is not straightforward. The reasons why tropinone does not behave as other cyclic ketones in these reactions is not well understood. It is worth to emphasize that whole studies on that subject didn't explore all known possibilities from literature to introduce heteroatom at the α-position of ketone.

2.4 Connecting a Carbon-Based Functional Group at the α-Position of Tropinone

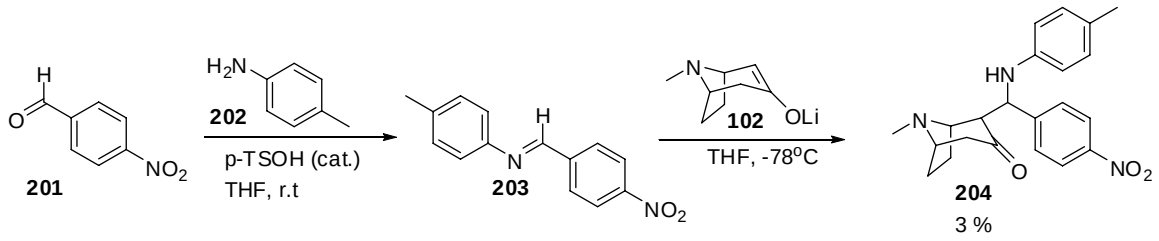
2.4.1 The Mannich Reaction

My attention was next turned to the Mannich reaction as this reaction would in one step introduce nitrogen in the β-position of the tropinone framework (the products potentially might be useful from the point of view of making chiral ligands from tropinone). The first attempt to carry out this reaction was catalyzed by proline using *N*,*N*-dibenzyl-1-methoxymethanamine as the source of nitrogen. However, numerous attempts under this condition failed to give any product (**Scheme 63**).



Scheme 62

When the reaction was carried out as a three component reaction using proline as the catalyst in trifluoroethanol, only proline, the imine resulting from the 4-methylaniline reacting with 4-nitrobenzaldehyde and traces of tropinone were detected (**Scheme 63**). Suspecting that the low reactivity of the formed imine might account for the lack of useful products, the protocol for the whole process was changed. This time, the lithium enolate of tropinone was added to the imine generated *in situ*. Even though the final product in this case was isolated in only 3 % yield (PTLC), it clearly indicates that this reaction is possible to perform on tropinone.

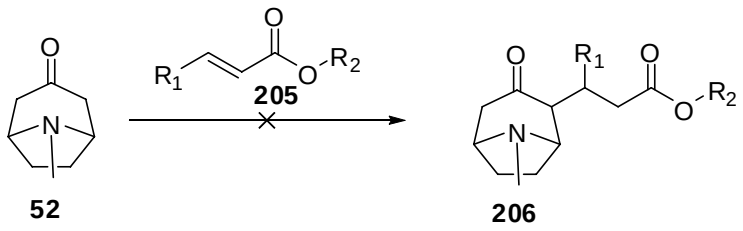


Scheme 63

2.4.2 The Michael reaction

One of the most common reactions in enolate chemistry is the Michael reaction. A search of the literature yielded a single example of this reaction with tropinone and under no

stereocontrol.[82] Unfortunately in this case all attempts to introduce different Michael acceptors (methyl acrylate, methyl cinnamate, *trans*-β-nitrostyrene) at the α-position of tropinone ring failed – in all cases the starting material was recovered with good mass recovery. It is worth to mention that the results obtained did not depend at all on the reaction time (tropinone was recovered back). Similarly, the way in which the reaction was performed seemed to make no difference. Among the reactions carried were those involving the generation of lithium and titanium ($TiCl_4$) enolates. Also, reactions performed organocatalytically using either proline or its derivatives were tested. Finally, an attempt to perform this reaction *via* generation of the enamine (with piperidine) was tried. In all cases, no products were detected by ^{1}H NMR.



Scheme 64

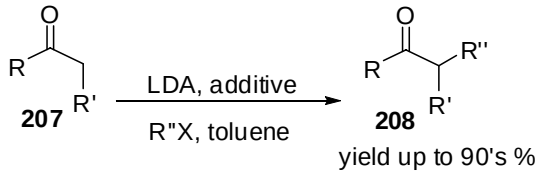
2.4.3 Alkylation Reaction

Alkylation reaction is one of the most common reactions in enolate chemistry. The process is very useful from a synthetic point of view, as it allows for formation of a new C-C bond at the α-position of the ketone. Initial studies within the group indicated that tropinone does not undergo alkylation while TBON although it can be alkylated, gave products with unreasonably low yields.[25, 29] As a part of my project a few methods were investigated in order to find conditions under which tropinone could be alkylated.

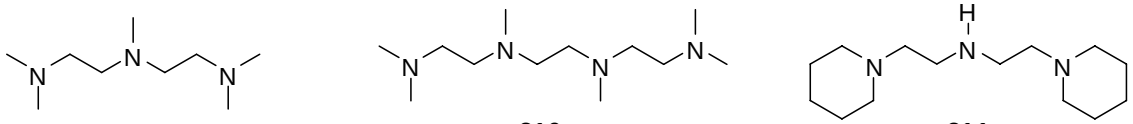
2.4.3.1 Alkylation of Tropinone with Utilization of Koga's Amines

Koga's extensive studies[83, 84, 85] had showed that alkylation of ketones with alkyl halides is a non trivial reaction and, working on model compounds such as cyclohexanone or 1-tetralone,

he had determined that using toluene as the solvent (and not, as often assumed THF), maintaining the temperature between
-45 and -20 ºC, and addition of tridentate or tetradentate achiral amines or HMPA as additives significantly improved the yields of these reactions (up to 90's %).



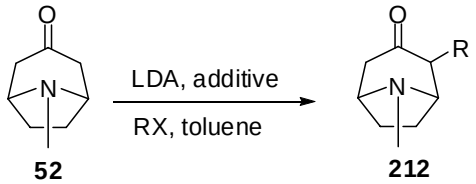
Amines that could serve as additives:



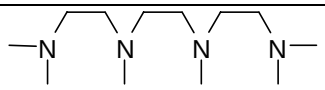
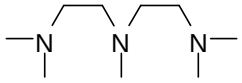
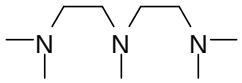
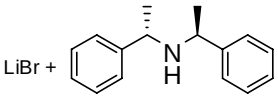
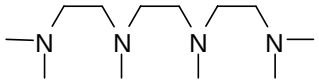
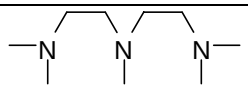
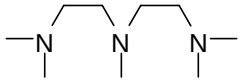
Scheme 65

Following these tips, attempts to alkylate tropinone were carried out (**Table 2-1.**). Unfortunately, in all cases involving bicyclic bridged ketones none of the given 'controls' seemed to have any effect on the reaction. Finally, Koga's original procedure[86] resulted in obtaining the desired product in 10 % yield as a mixture of 2 diastereoisomers in 1:1.5 ratio. For comparison, the same reaction conditions were applied to cyclohexanone and TBON. Surprisingly, under this conditions the cyclohexanone gave alkylated product in only 25 % isolated yield, while TBON did not react at all (starting material was recovered).

Table 2-1. Attempted alkylation of tropinone with utilization of Koga's amines



52 **212**

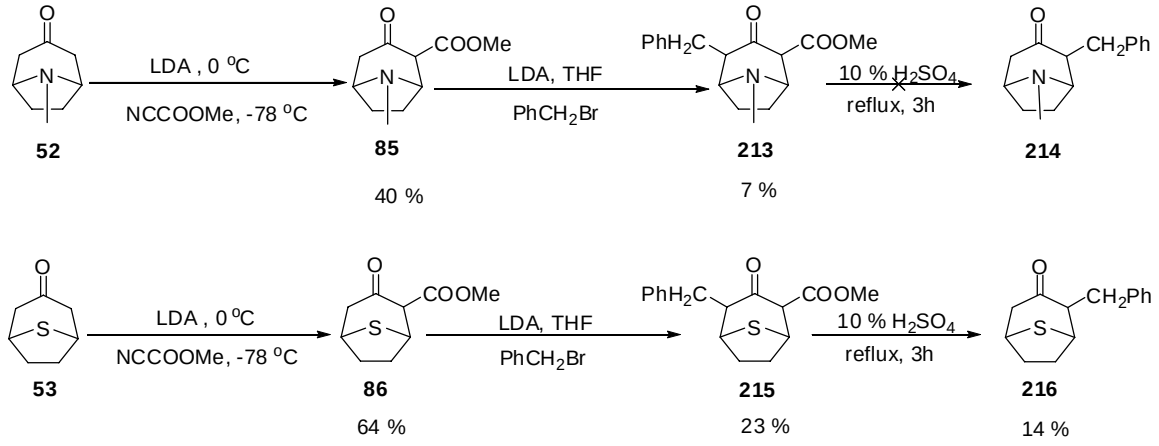
	ELECTROPHILE	***TEMP. [ºC]***	***ADDITIVE***	***ALKYLATION TIME***	***YIELD***
1	*Allyl bromide*	*-78 to -23*		*2h*	-
2	*Allyl bromide*	*-23*		*2h*	-
3	*Allyl bromide*	*RT*		*20h*	-
4	*Allyl bromide*	*-45 to RT*		*16.5h*	-
5	*Benzyl bromide*	*-23*		*40min*	*~10 %**
6	*Benzyl bromide*	*-78 to -23*		*2.5h*	-
7	*Methyl iodide*	*-78 to -23*		*2.5h*	-

Note: **Reaction according to original Koga's procedure*

2.4.3.2 Weiler's Method

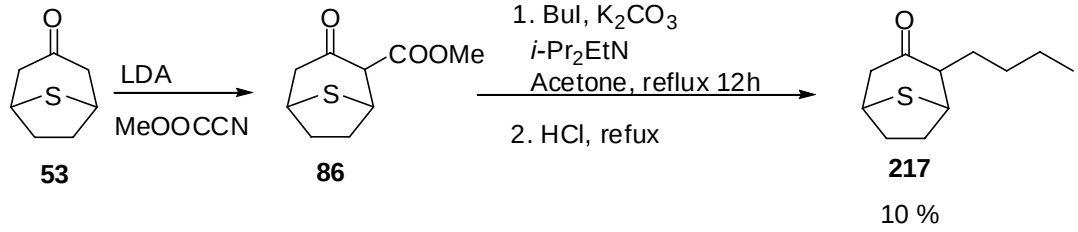
A three step alkylation *via* a β-ketoester derivative (Weiler's method, **Scheme 67**) [87, 88] of tropinone and TBON was the next approach to be considered. Unfortunately, also in this case tropinone did not give the expected result (the synthesis failed during the hydrolysis with

H_2SO_4). Potentially, the problem could be with protonation of the amine moiety in tropinone which could lead to decomposition of this adduct. In the case of TBON the desired product was obtained in only 3 % overall yield after the three steps of synthesis.



Scheme 66

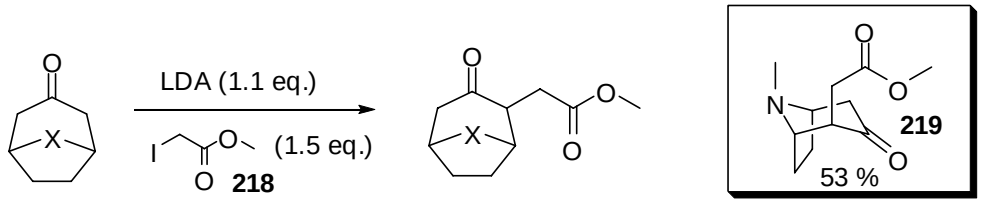
Thus, even though the original Weiler's method worked on TBON, the yield of the alkylated product was extremely low. A search of the literature reveled that it is possible to alkylate β–ketoesters using a mild base preferentially at the C4 rather than C2 position[89] and, more importantly, the whole synthesis should be shorter by one step. Decarboxylation gives the ketone alkylated product. This approach was applied to TBON. As it was indicated in the original procedure BuI was used as the electrophile, unfortunately this method also gave a very low yield although the overall yield in this case was somewhat higher (the final product was a mixture of 2 diastereoismers in a 1:1 ratio and was produced in 10 % overall yield after 2 steps, compared to 3 % in the first case; **Scheme 67**).



Scheme 67

2.4.3.3 Alkylation utilizing electrophiles containing the ester group

Many attempts to alkylate tropinone were carried out to no positive result. Finally, the idea of utilizing electrophiles containing groups that can coordinate to the enolate (e.g. the ester group) was investigated (**Scheme 68**). The reaction was first tested using methyl chloroacetate as the electrophile with no positive result (starting materials were recovered). Fortunately, the use of more reactive electrophile (methyl iodoacetate) resulted in the case of tropinone the desired product as a single diastereoisomer in 53 % yield. Under the same reaction condition, TBON gave alkylated product in 10 % yield as a mixture of diastereoisomers in 1:1.4 ratio (these isomers could be not separated).



52: X = NMe

53: X = S

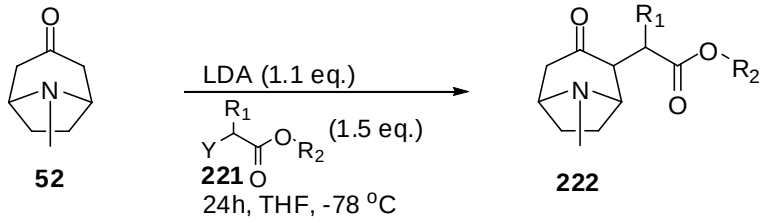
219: X = NMe; y = 53 %

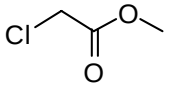
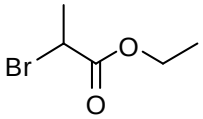
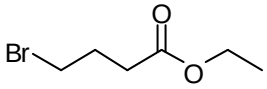
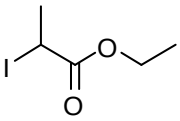
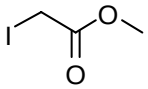
220: X = S; y = 10 % (mixture of diastereoisomers 1:1.4 ratio)

Scheme 68

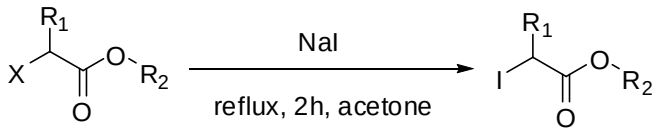
In order to find the appropriate electrophile that would make alkylation of tropinone possible a few other compounds were tested. As mentioned before methyl chloroacetate did not give any product, so my next attention was focused on more reactive electrophiles like bromides and iodides. All the electrophiles tested in this mini study are summarized in **Table 2-2.**

Table 2-2. Mini study on choice of electrophile in alkylation reaction of tropinone



	TIME	*SOLVENT*	*ELECTROPHILE*	*YIELD*
1	*24h*	*THF*		-
3	*24h*	*THF*		-
4	*24h*	*THF*		*trace*
5	*24h*	*THF*		*trace*
6	*24h*	*THF*		*53 %*

Synthesis of methyl iodoacetate was easily achieved in one-step process (starting from methyl chloroacetate) in which the desired compound was obtained in 83 % yield (**Scheme 69**). Similar process for obtaining ethyl 2-iodopropionate from the bromoester resulted in 72 % yield of desired product.



223: X = Cl, R_1 = H, R_2 = Me

224: X = Br, R_1 = Me, R_2 = Et

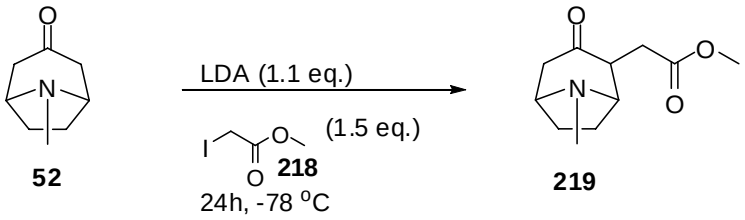
218: R_1 = H, R_2 = Me; y = 80 %

225: R_1 = Me, R_2 = Et ; y = 72 %

Scheme 69

Another aspect of the study involved an investigation of the effect of different solvents on the results of the alkylation of tropinone. As the standard electrophile methyl iodoacetate was used in these experiments. Interestingly, the solvent of choice was found to be THF, while toluene proved to be less effective in this reaction. This result was totally different from Koga's postulate that toluene is the best solvent for alkylation reactions.[89]

Table 2-3. Study on the effect of solvents on alkylation reaction of tropinone

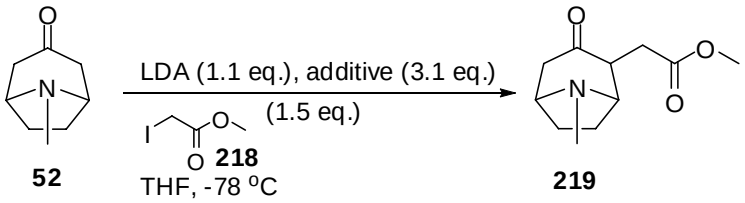


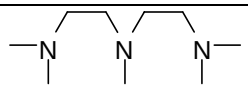
	TIME	*SOLVENT*	*YIELD*
1	*24h*	*THF*	*53 %*
2	*24h*	*Et_2O*	*32 %*
3	*24h*	*Toluene*	*~ 8 %*
4	*24h*	*Benzene*	*~ 7 %*

Finally, the effects of same additives on the alkylation results were tested. A somewhat higher yield was obtained when the reaction was carried out for 24h, but longer reaction times significantly decreased the yield of the product (**Table 2-4.**, entries 5,6,7). It is also worth to

emphasize that addition of Koga's tridentate amine decreased the yield of alkylation from 53 % to 13 %.

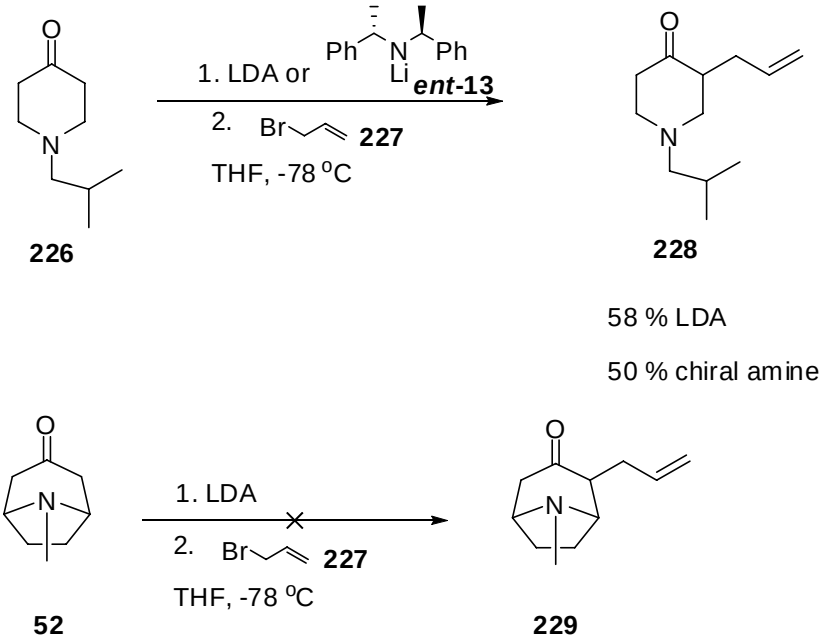
Table 2-4. Study on influence of time and additives on alkylation of tropinone



	TIME	***ADDITIVES***	***YIELD***
1	*2h*	-	*SM*
2	*4h*	-	*trace*
3	*6h*	-	*34 %*
4	*8h*	-	*36 %*
5	*24h*	-	*53 %*
6	*28h*	-	*14 %*
7	*3d*	-	*22 %*
8	*24h*		*13 %*
9	*24h*	*LiBr*	*SM*
10	*24h*	*DIA (1.1eq.)*	*9 %*
11	*24h*	*DIA (2.2q.)*	*~8 %*

Considering all of the above it seems that the coordination of the electrophile to the tropinone enolate *via* the lithium metal is important for reactivity in this reaction as well as is the issue of aggregation. Although Koga's tridentate amine method addresses the issue of aggregation, the amine will also affect (at least to a certain extent) the coordination of the electropihile to the lithium enolate and this might account for the lower yields.

Finally, two other questions needed to be addressed; does the presence of a heteroatom in the ketone ring influences the alkylation? Is the ring size important (7-member bridged ring in case of tropinone)? In order to be able to investigate these questions, both tropinone and 1-(2-methylpropyl)-4-piperidone (chosen as a model ketone because of its similarity to tropinone), were subjected to the same general alkylation protocol (**Scheme 70**).



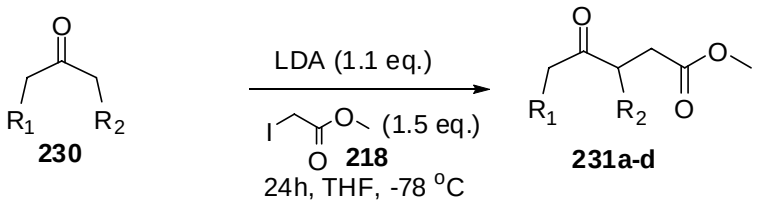
Scheme 70

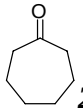
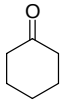
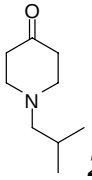
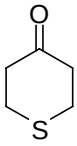
As anticipated, tropinone gave no reaction but on the contrary 1-(2-methylpropyl)-4-piperidone underwent alkylation, albeit in modest yield, after deprotonation with either LDA or the chiral lithium amide. This outcome might suggest that the presence of nitrogen does not significantly affect the alkylation itself and it is not the reason why tropinone does not undergo this reaction under standard protocol.

In order to finish the study of 1-(2-methylpropyl)-4-piperidone, attempts to measure the enantioselectivity were carried out. Unfortunately, all attempts to measure the *ee* of the product with chiral shift reagents (TFAE and europium tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorate]) failed. Also, an effort to make the Mosher's ester from the alcohol (reduced ketone) was not successful as well as determination of *ee* using acylated product and TFAE.

The last part of research on alkylation of tropinone was to submit 1-(2-methylpropyl)-4-piperidone along with few different ketones (cyclohexanone, cycloheptanone, thiopyranone) to alkylation with methyl iododoacetate. In all cases products were obtained with yields between 30-49 %. The results are pretty close to what was previously obtained for tropinone itself (53 %) and actually are difficult to interpretate as all ketones, including cyclohexanone (49 %), gave alkylated products in low yields. These results seem to suggest that the reasons for low efficiency of these reactions could be connected to the reaction conditions and/or the electrophile.

Table 2-5. Investigation on influence of heteroatom and size of the ring of ketone on alkylation reaction.



	KETONE	***YIELD***
1	 ***231a***	*30 %*
2	 ***231b***	*49 %*
3	 ***231c***	*40 %*
4	 ***231d***	*3 %*

2.5 Summary of Connecting a Carbon-Based Group at the α-Position of Tropinone

Attempts to connect a carbon-based group to the α-position of tropinone were not successful. In all cases, none of investigated reactions (the Mannich reaction or the Michael reaction) worked fine. Although the Mannich reaction gave product when the lithium enolate was employed, the yield of the reaction is very low. The fact that there was reaction and product could be isolated give promise that the reaction can be carried out if proper conditions and reactants were found.

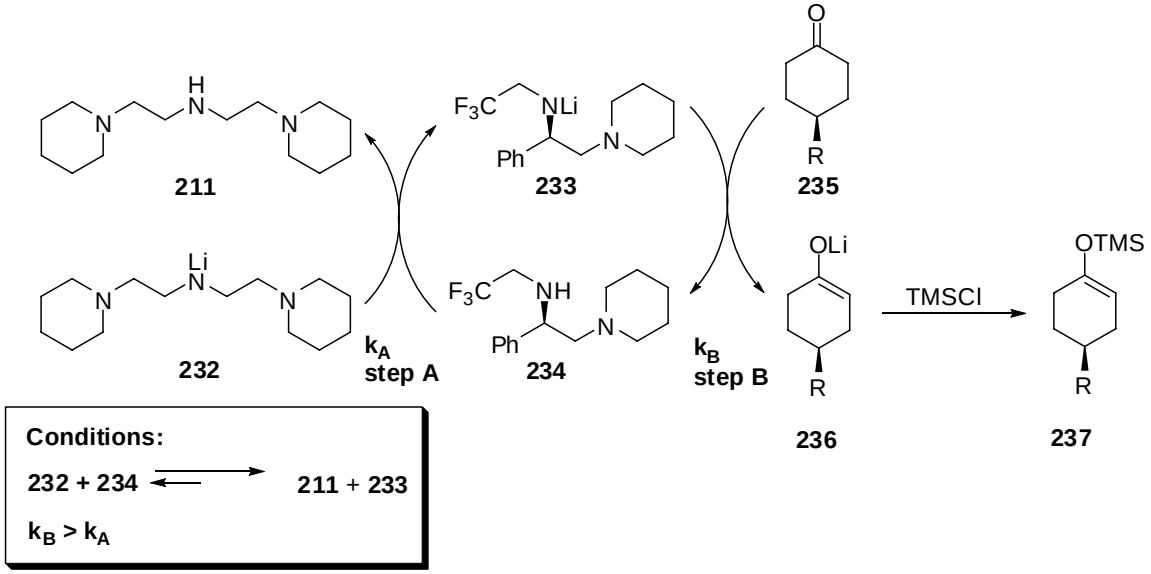
The extensive study on alkylation reaction of bridged bicyclic ketones tropinone and TBON showed that these compounds are not easy to alkylate. Alkylation procedure proposed by Koga gave desired alkylated tropinone in very low yields (ca. 9 %) while the same conditions when applied to TBON resulted in recovery of starting materials. The use of Weiler's method (three-step process) in case of tropinone gave no product at all while alkylated TBON was obtained in very low overall yields. The use of electrophiles containing an ester group resulted in alkylated products in moderate 53 % yield for tropinone while TBON gave desired products in only 10 % yield. This result indicates that it is possible to alkylate tropinone but under specialized conditions or with electrophiles having heteroatoms that can coordinate to the metal center on the enolate.

3 Synthesis of Tridentate Achiral Amine as an Additive

3.1 Introduction

The previous study on the alkylation of tropinone and TBON, described above, created a great opportunity for better understanding of the conditions in which this particular reaction and in general enantioselective deprotonation of ketones should be performed. For example, all Koga's work strongly suggests that to obtain high yields in deprotonation reactions (e.g. alkylation and aldol reactions), presence of different additives is very important.[83, 84, 85, 89] Among several employed additives (e.g. HMPA or LiBr) that had key influence on alkylation result in case of cyclohexanone or 1-tetralone were different achiral bidentate, tridentate or tetradentate

amines. One of those amines (**211**) that is not commercially available and was first used in the catalytic enantioselective deprotonation of 4-substituted cyclohexanones (process shown on **Scheme 72.**), attracted my attention as the protocol for the synthesis of this compound (**211**) was not published anywhere, according to my knowledge. More importantly, compound **211** was not tested as an additive in the alkylation study reported by Koga. The facts stated above prompted my desire to synthesize compound **211**.



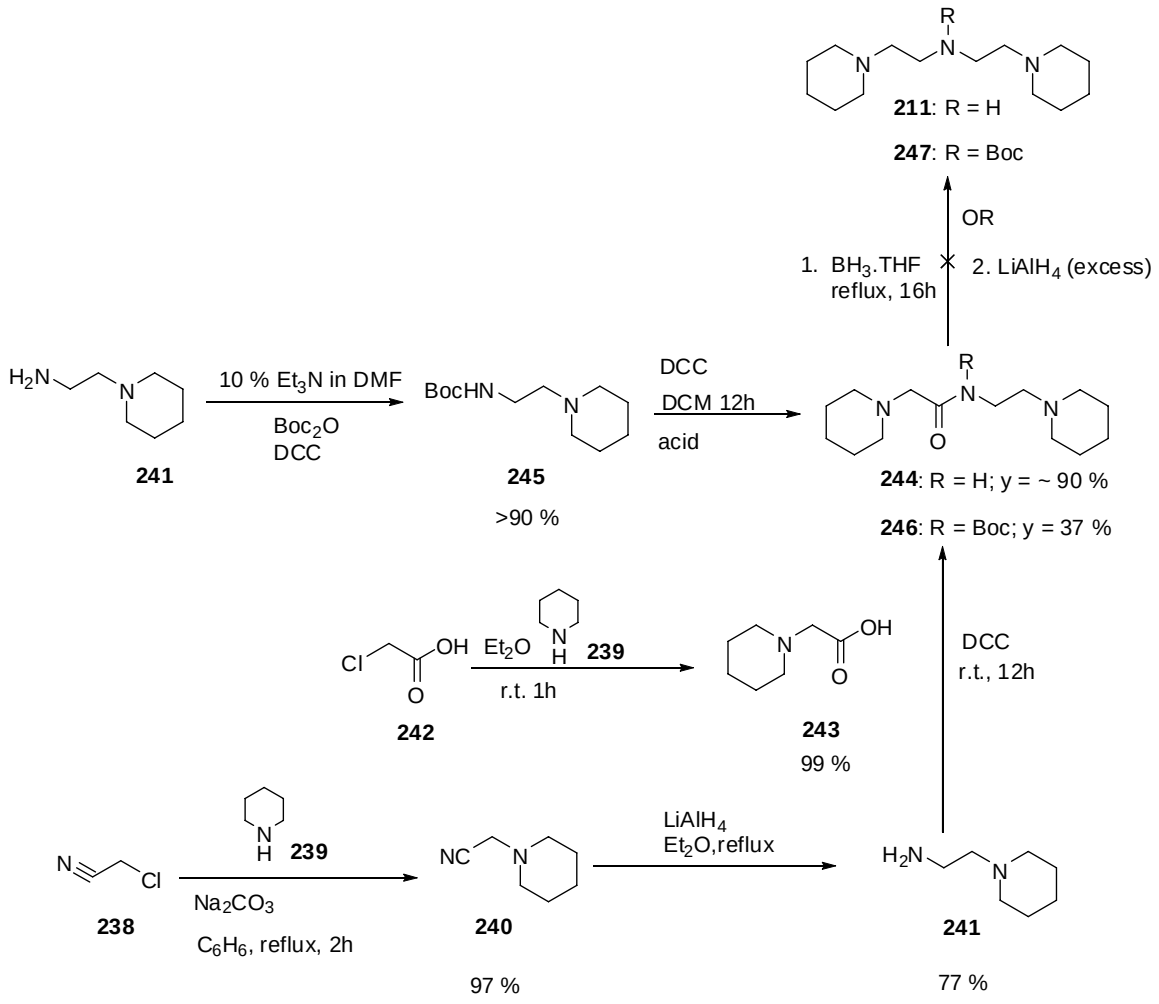
Scheme 71

3.2 Approach *via* Amide Formation

The easiest way to synthesize amine **211** seemed to be simple coupling reaction between acid **243** and amine **241** in the presence of DCC. The amide adduct thus obtained should undergo reduction to give the desired product (**Scheme 72**).

The amine part was obtained according to a known procedure[90] in two-steps in high yields. In the first step, chloroacetonitrile was reacted with piperidine to give nitrile **240** in 97 % yields. Reduction of nitrile **240** using $LiAlH_4$ under reflux gave amine **241** in 77 % yields. The acid moiety was synthesized from the reaction of chloroacetic acid with piperidine in 99 % yield. The DCC mediated coupling of **243** and **241** gave the desired amide in 90 % yield. Attempts to

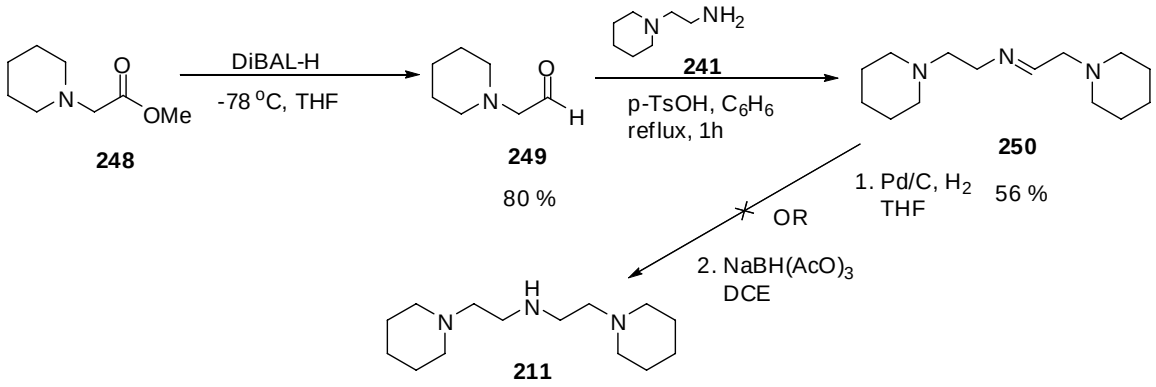
reduce amide **244** to the desired amine with BH_3 and $LiAlH_4$ were unsuccessful. Since nothing was recovered from the reduction reaction, it was suspected that the tridentate amine formed from the reduction probably complexes with aluminum making it difficult to isolate. To potentially avoid this problem, Boc protected amide **246** prepared in 37 % yields was subjected to the same reducing agent. Interestingly, this reaction equally did not give the desired product.



Scheme 72

3.3 Approach *via* Enamine Formation

The problems encountered with the reduction of the amides **244** and **246** in the previous section prompted a change in the route to synthesizing amine **211**. Enamine **250** prepared form the condensation of aldehyde **249** with amine **241** in 56 % yields (crude product) was subjected to reduction using both Pd on carbon and $NaBH(AcO)_3$ (**Scheme 73**). Unfortunately both reductions equally did not give any meaningful result.



Scheme 73

3.4 Summary of Synthesis of Tridentate Achiral Amine Additive

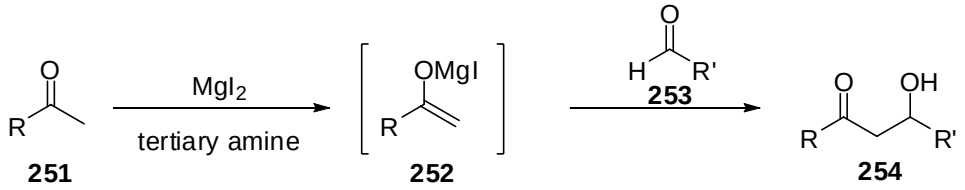
The synthesis of tridentate amine **211** was not successful. Although the intermediates were prepared in good yields, the reason why the reduction of amide **244** (**246**) or enamine **250** did not yield any meaningful result is not fully understood.

4 Direct Aldol Reaction Catalyzed by MgI_2

4.1 Introduction

Direct, stereoselective coupling between aromatic or non-aromatic aldehydes and a wide variety of ketones, giving rise to a range of β-hydroxy ketones or esters can be promoted by

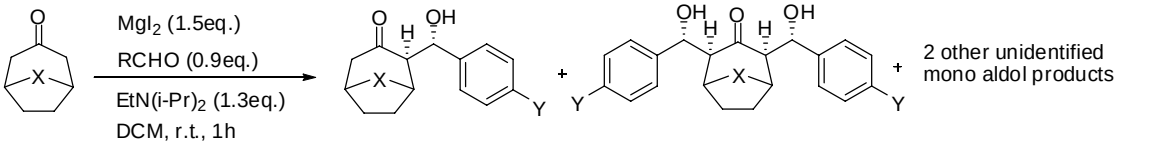
magnesium iodide (Lewis acid) in the presence of tertiary or secondary amines (**Scheme 74**).[91, 92, 93] The reaction proceeds with medium-to-excellent yields (60-98 %) and *anti* aldol products are usually obtained as the major aldol adducts. When unsymmetrical ketones are employed in this magnesium iodide mediated direct aldol reaction, addition always occurs at the less hindered side. As shown in **Scheme 74**, the key step in the reaction is the formation of magnesium enolate, followed by addition to the aldehyde.



Scheme 74

Although a wide range of ketones have been investigated, the ketones used were generally simple ones with very limited synthetic usefulness. With this in mind, I chose to apply the protocol to a more complicated system as a means of testing the generality of the protocol as well as possibly to obtain new aldol diastereoisomers of tropinone and TBON not accessible *via* the lithium enolate chemistry developed within our group.

4.2 Aldol Reaction



52: X = NMe

53: X = S

65a: X = NMe, Y = H
255a: X = NMe, Y = NO_2

253: X = NMe, Y = H
256: X = NMe, Y = NO_2

65b + **65c**: X = NMe, Y = H
255b + **255c**: X = NMe, Y = NO_2

66a: X = S, Y = H
257a: X = S, Y = NO_2

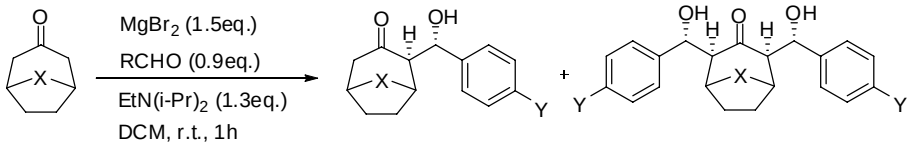
67: X = S, Y = H
258: X = S, Y = NO_2

66b+ **66c**: X = S, Y = H
257b + **257c**: X = S, Y = NO_2

Scheme 75

The magnesium catalyzed aldol reaction of tropinone and TBON with benzaldehyde or p-nitrobenzaldehyde was first performed according to the published protocol[91, 92, 93] using $MgBr_2$ instead of MgI_2. As shown in **Table 2-6.**, the results obtained were not very promising.

Table 2-6. Direct aldol reaction of tropinone and TBON with aromatic aldehydes catalyzed by $MgBr_2$



52: X = NMe

53: X = S

65a: X = NMe, Y = H
255a: X = NMe, Y = NO_2

253: X = NMe, Y = H
256: X = NMe, Y = NO_2

66a: X = S, Y = H
257a: X = S, Y = NO_2

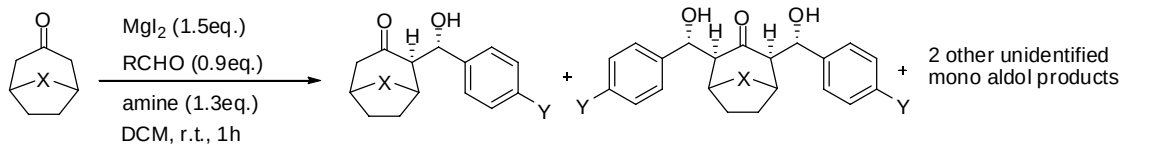
67: X = S, Y = H
258: X = S, Y = NO_2

	KETONE	***ALDEHYDE***	***TIME***	***CONV.***	***RESULT***
1	*TBON*	*B*	*1h*	*63 %*	***67:66a** (1.2:2)*
2	*TBON*	*B*	*2h*	*<2 %*	*Trace of product***
3	*TBON*	*N*	*0.5h*	*<5 %*	*Trace of product*
4	*TBON*	*N*	*1h*	*-*	*SM*
5	*TBON*	*N*	*2h*	*<2 %*	*Trace of product*
6	*TBON*	*N*	*5h*	*-*	*SM*
7	*TBON*	*N*	*O/N*	*-*	*SM***
8	*Tropinone*	*B*	*1h*	*-*	*Trace of product*
9	*Tropinone*	*N*	*0.5h*	*<10%*	***256:255a** (1:2)*
10	*Tropinone*	*N*	*1h*	*-*	*Trace of product*
11	*Tropinone*	*N*	*2h*	*80 %*	***256:255a** (1:1.3)***
12	*Tropinone*	*N*	*O/N*	*-*	*SM***

Note: *all concentrations of reaction 0.6M (according to ketone), B-Benzaldehyde, N-p-Nitrobenzaldehyde, O/N –overnight reaction,** concentration of reaction 0.24M*

When magnesium iodide etherate (obtained by refluxing an excess of magnesium turnings (1.1eq.) with iodine (1eq.) in dry ether for 3 to 4 h) was employed, the results changed dramatically to give aldol products in good yields. To optimize the reaction with respect to yield and diastereoselectivity, a few modifications to the published protocol were carried out. The first variable that I looked at was the effect of the base on the reaction. Et_3N (cheap and commercially available) and piperidine (second best result reported in the original paper) were compared with $EtN(i\text{-}Pr)_2$ under the same reaction conditions.

Table 2-7. Study on choice of amine in aldol reaction of tropinone and TBON with aromatic aldehydes catalyzed by MgI_2



52: X = NMe

53: X = S

253: X = NMe, Y = H
256: X = NMe, Y = NO_2

65b + **65c**: X = NMe, Y = H
255b + **255c**: X = NMe, Y = NO_2

67: X = S, Y = H
258: X = S, Y = NO_2

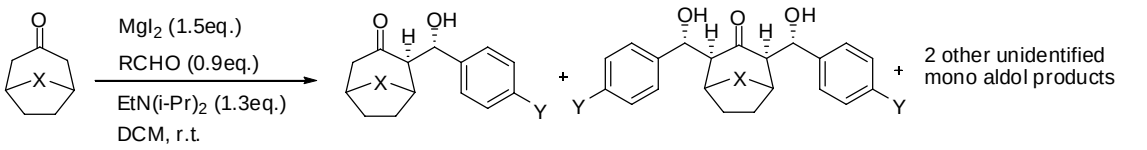
66b+ **66c**: X = S, Y = H
257b + **257c**: X = S, Y = NO_2

	ALD.	***KETONE***	***AMINE***	***CONV.***	***RESULT***
1	*N*	*TBON*	*Et_3N*	*>95 %*	***258*:*257a*:*257b*:*257c*** *(1:1.3:2.8:10.2)*
2	*N*	*Tropinone*	*Et_3N*	*>95 %*	***256*:*255a*:*255c*** *(2:1:5.3)*
3	*N*	*TBON*	*Piperidine*	*-*	*SM*
4	*B*	*TBON*	*Piperidine*	*28 %*	***67*:*66a*** *(1:3)*
5	*N*	*Tropinone*	*Piperidine*	*>80 %*	***256*:*255a*:*255b*:*255c*** *(1:1.3:1:3)*
6	*B*	*Tropinone*	*Piperidine*	*62 %*	***253*:*65a*:*65b*** *(1:1:2.6)*
7	*N*	*Tropinone*	*EtN(i-Pr)$_2$*	*70 %*	***256*:*255a*:*255b*:*255c*** *(1:4.2:4.6:17.5)*
8	*B*	*Tropinone*	*EtN(i-Pr)$_2$*	*70 %*	***253*:*65a*:*65b*:*65c*** *(1:1.6:2:7.8)*
9	*N*	*TBON*	*EtN(i-Pr)$_2$*	*75 %*	***258*:*257a*:*257b*** *(1:3.6:15.7)*
10	*B*	*TBON*	*EtN(i-Pr)$_2$*	*50 %*	***67*:*66a*:*66b*** *(1:4:2.1)*

Note: *B-Benzaldehyde, N-p-Nitrobenzaldehyde*

The effect of the reaction time on conversion and selectivity on the aldol reaction was investigated next (**Table 2-8.**). The best results in terms of selectivity and conversion were obtained for reactions performed in 0.5h. As was anticipated, benzaldehyde gave better selectivity with lower conversion when compared with *p*-nitrobenzaldehyde.

Table 2-8. Study on effect of time of aldol reaction of tropinone and TBON with aromatic aldehydes catalyzed by MgI_2



52: X = NMe

53: X = S

65a: X = NMe, Y = H
255a: X = NMe, Y = NO_2

253: X = NMe, Y = H
256: X = NMe, Y = NO_2

65b + **65c**: X = NMe, Y = H
255b + **255c**: X = NMe, Y = NO_2

66a: X = S, Y = H
257a: X = S, Y = NO_2

67: X = S, Y = H
258: X = S, Y = NO_2

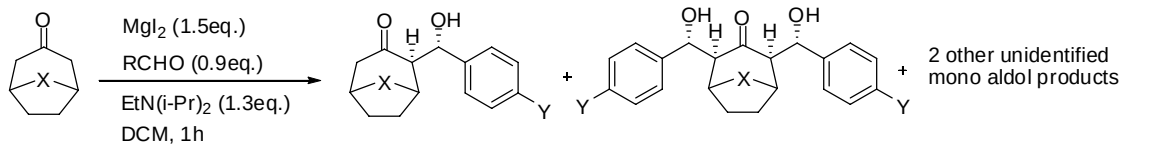
66b+ **66c**: X = S, Y = H
257b + **257c**: X = S, Y = NO_2

	ALD.	***KETONE***	***TIME***	***CONV.***	***RESULT***
1	*N*	*tropinone*	*15min*	*>90 %*	***256:255a:255b:255c*** *(1:1.6:4.3:18.3)*
2	*N*	*tropinone*	*0.5*	*>90 %*	***256:255a:255b:255c*** *(1:1.2:4.6:19.1)*
3	*N*	*tropinone*	*1*	*70 %*	***256:255a:255b:255c*** *(1:4.2:4.6:17.5)*
4	*B*	*tropinone*	*15min*	*68 %*	*4products*
5	*B*	*tropinone*	*0.5*	*78 %*	*6 products*
6	*B*	*tropinone*	*1*	*70 %*	***253:65a:65b:65c*** *(1:1.6:2:7.8)*
7	*N*	*TBON*	*15min*	*75 %*	***258:257a:257b:257c*** *(1:3.3:5.3:7.2)*
8	*N*	*TBON*	*0.5*	*>95 %*	***258:257a:257b:257c*** *(1:2.1:2.1:18.5)*
9	*N*	*TBON*	*1*	*75 %*	***258:257a:257b*** *(1:3.6:15.)*
10	*B*	*TBON*	*15min*	*80 %*	***67:68a:68b*** *(1:7:1.6)*
11	*B*	*TBON*	*0.5*	*>60 %*	***67:66a:66b*** *(1:6.7:2.1)*
12	*B*	*TBON*	*1*	*<50 %*	***67:66a:66b*** *(1:4:2.1)*

Note: *B-Benzaldehyde, N-p-Nitrobenzaldehyde*

The next variable that was investigated was the temperature of the reaction. The results of this study are shown in **Table 2-9.** Reactions that proceeded at -10 ºC gave a smaller number of products (2-3), but selectivity did not improve. Warming up the reaction mixture to 0 ºC slightly improved the selectivity however those results were still worse in terms of selectivity than those obtained at rt.

Table 2-9. Study on effect of temperature on aldol reaction of tropinone and TBON with aromatic aldehydes catalyzed by MgI_2



52: X = NMe

53: X = S

65a: X = NMe, Y = H
255a: X = NMe, Y = NO_2

253: X = NMe, Y = H
256: X = NMe, Y = NO_2

65b + **65c**: X = NMe, Y = H
255b + **255c**: X = NMe, Y = NO_2

66a: X = S, Y = H
257a: X = S, Y = NO_2

67: X = S, Y = H
258: X = S, Y = NO_2

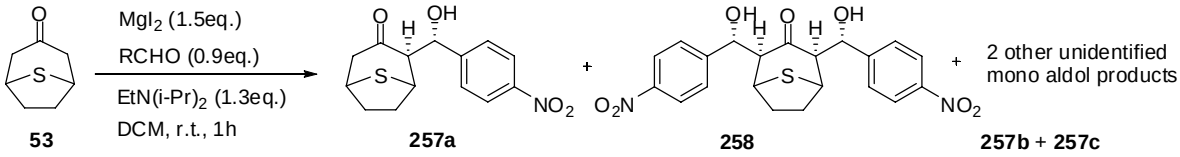
66b+ **66c**: X = S, Y = H
257b + **257c**: X = S, Y = NO_2

	ALD.	***KETONE***	***TIME***	***TEMP [C°]***	***CONV.***	***RESULT***
1	*N*	*tropinone*	*1h*	*R.T*	*70 %*	***256*:*255a*:*255b*:*255c*** *(1:4.2:4.6:17.5)*
2	*N*	*tropinone*	*1h*	*0*	*80 %*	***256*:*255a*:*255b*** *(1:2.6:5.6)*
3	*N*	*tropinone*	*2h*	*0*	*>95 %*	***256*:*255a*:*255b*** *(1:2.3:10.3)*
4	*N*	*tropinone*	*1h*	*-10*	*60 %*	***256*:*255a*:*255b*:*255c*** *(1:1.6:4:2)*
5	*B*	*tropinone*	*1h*	*R.T.*	*70 %*	***253*:*65a*:*65b*:*65c*** *(1:1.6:2:7.8)*
6	*B*	*tropinone*	*1h*	*-10*	*30 %*	***253*:*65a*:*65b*:*65c*** *(1:4.5:1.7:2.8)*
7	*N*	*TBON*	*1h*	*R.T*	*75 %*	***258*:*257a*:*257b*** *(1:3.6:15.7)*
8	*N*	*TBON*	*1h*	*0*	*~20 %*	*4products*
9	*N*	*TBON*	*2h*	*0*	*~50 %*	*4products*
10	*N*	*TBON*	*1h*	*-10*	*71 %*	***258*:*257a*:*257b*:*257c*** *(1:5:10:2.4)*
11	*B*	*TBON*	*1h*	*R.T.*	*50 %*	***67*:*66a*:*66b*** *(1:4:2.1)*
12	*B*	*TBON*	*1h*	*-10*	*72 %*	***67*:*66a*** *(1:3.2)*

Note: *B-Benzaldehyde, N-p-Nitrobenzaldehyde*

The last variable that was looked at was the concentration (calculated based on TBON). As anticipated, the higher the concentration, the better the selectivity and higher the conversion (**Table 2-10.** entry 1 and 4).

Table 2-10. Study on effect of concentration on aldol reaction of TBON with *p*-nitrobenzaldehyde catalyzed by MgI_2



53 **257a** **258** **257b** + **257c**

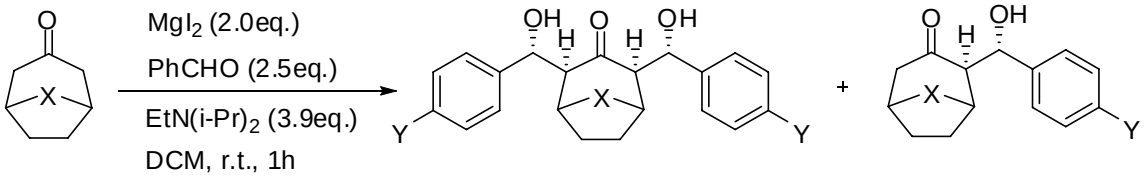
Note:

	ALD.	*KETONE*	*CONC. [M]*	*CONV.*	*RESULT*
1	*N*	*TBON*	*0.4*	*>98 %*	***258*:*257a*:*257b*** *(1:4:11.3)*
2	*N*	*TBON*	*0.2*	*>85 %*	***258*:*257a*:*257b*** *(1:5.4:2.6)*
3	*N*	*TBON*	*0.1*	*75 %*	***258*:*257a*:*257b*** *(1:4.8:1.4)*

N-p-Nitrobenzaldehyde

4.3 The Bis-Aldol Reaction

In the course of optimizing the MgI_2 catalyzed aldol reactions of tropinone and TBON, one of the products detected in variable amounts was always the bis-aldol adduct. This bis-aldol product has previously been obtained *via* the titanium enolate prepared by transmetalation of the lithium enolate of TBON with $TiCl_4$.[22] Since this aldol adduct was obtained in varying amounts in the MgI_2 catalyzed direct aldol reaction described in the previous section, it was decided to optimize the reaction conditions to obtain exclusively the bis-aldol.



52: X = NMe

53: X = S

253: X = NMe, Y = H
256: X = NMe, Y = NO_2

67: X = S, Y = H
258: X = S, Y = NO_2

major product

65a: X = NMe, Y = H
255a: X = NMe, Y = NO_2

66a: X = S, Y = H
257a: X = S, Y = NO_2

minor product
exo-anti

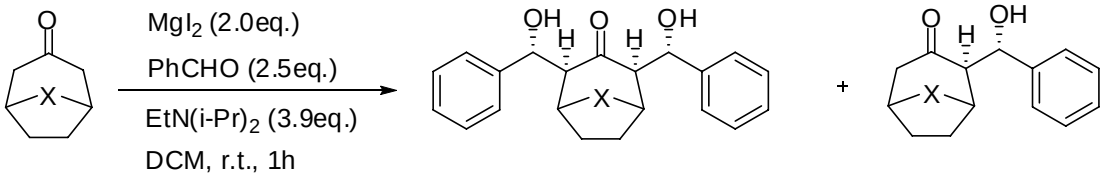
253: y = 44 % (mixture of isomers)

67: y = 78 % (single diastereoisomer)

Scheme 76

After a few modifications of the reaction conditions described in section 2.4.2., with respect to stiochiometry of the reagents, the bis-aldol adduct was obtained as the main product from the reaction with moderate selectivity, especially in the case of TBON. The summary of the results are combined in **Table 2-11**.

Table 2-11. Optimization of the MgI_2 catalyzed aldol reaction of tropinone and TBON with benzaldehyde towards obtaining the bis-aldol product



52: X = NMe
53: X = S

253: X = NMe
67: X = S

65a: X = NMe
66a: X = S

	ALDEHYDE	***KETONE***	***AMINE***	***MgI_2***	***RESULT***
1	*B (2.5eq.)*	*Tropinone*	*3.9 eq.*	*2.0 eq.*	***253*:*65a*** *(~3:1)*
2	*B (2.5eq).*	*TBON*	*3.9 eq.*	*2.0 eq.*	***67*:*66a*** *(~4.5:1)*

Note: *B-Benzaldehyde, N-p-Nitrobenzaldehyde*

The reaction was mainly carried out with benzaldehyde as the more reactive *p*-nitrobenzaldehyde was less selective and the products were very difficult to isolate due to their high instability to acidic medium. In the case of TBON, the bis-aldol adduct *exo*, *exo*, *anti*, *anti* product[22] was isolated in 78 % *via* column chromatography (DCM:MeOH 98:2). Although the reaction of tropinone with benzaldehyde under the same conditions as TBON gave a moderate ratio of bis:mono aldol adduct with a 100 % conversion, only a mixture of diastereoisomers in 44 % combined isolated yield was obtained due to the instability of the aldol adducts to the isolation process. A considerable amount of retro aldol products were always obtained during purification. For example deactivation of silica gel with Et_3N gave exclusively retro aldol products, column chromatography using neutral Al_2O_3 gave mainly decomposition and attempts to protect the products from the aldol reaction prior to purification with TBSCl or MOMCl resulted in recovery of starting materials. The stability of the aldol adduct from tropinone was checked by mixing it

with a slurry of silica gel, the result indicated a considerable amount of retro aldol products within minutes and complete within 24 h as detected by ^{1}H NMR.

4.4 Summary of Aldol Reaction Catalyzed by MgI_2

Magnesium catalyzed direct aldol reaction of TBON and tropinone was successful. As anticipated, two different diastereoisomers of the mono addition aldol products were detected in greater ratios when compared to the *exo-anti* aldol adduct obtained from lithium enolate chemistry. Unfortunately, the inability to isolate this adducts without retroaldolization and isomerization prevented me from determing their structures. However based on the fact that *E*-enolates should preferentially give *anti* aldol adducts (Zimmerman-Traxler closed transition state) I would expect that one of the unidentified mono aldol products should be *endo-anti* diastereoisomer. Also, it is known that electrophile favors attack from *exo* side of brigded bicyclic ketone which would lead in my case to the formation of *exo-syn* adduct. Based on this facts, the two new adducts formed would be the *endo-anti* and the *exo-syn* adducts.

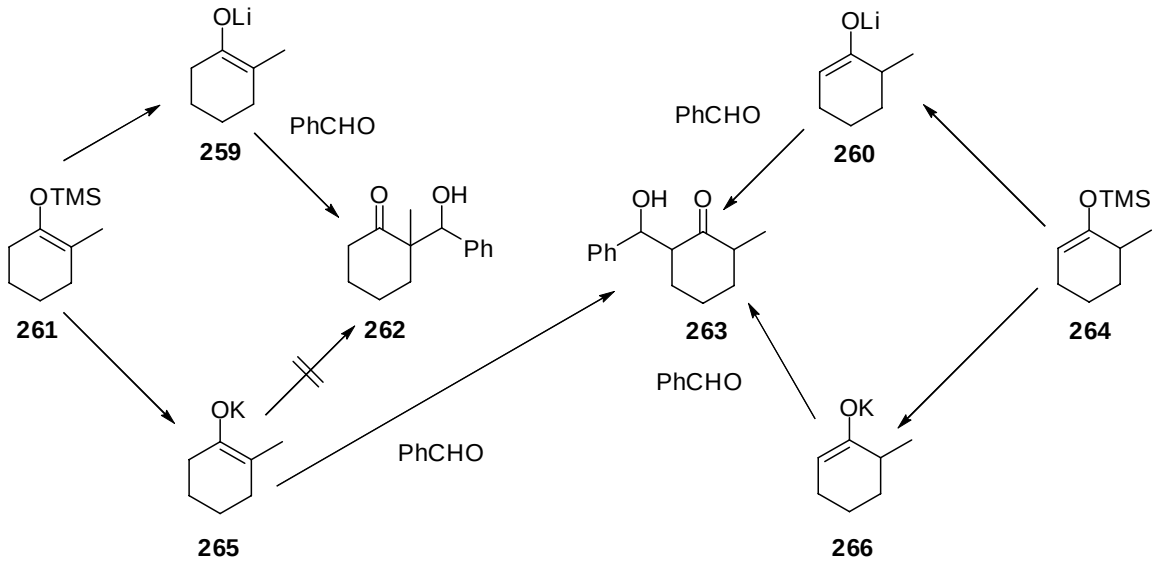
Manipulations of the reaction conditions in terms of stiochiometry led to either the mono addition or the bis addition aldol as the main product from the reaction. The simplicity of this protocol when compared to the titanium chemistry[22] makes this a more attractive method for obtaining the bis-aldol products, exclusively. This protocol should also find use in the preparation of other bis-aldol adducts when different ketones are employed.

5 Aldol Reaction of Potassium and Sodium Enolates

5.1 Introduction

In the mid 90's Duhamel and coworkers[94,95] reported a methodology involving the cleavage of oxygen-silicon bond of silyl enol ethers with alkali alkoxides, to form enolates that where then utilized in regiospecific alkylation, aldol condensations and Michael addition reactions. It was reported that the enolate counter ion has a great influence on the site of reaction in unsymmetric ketones (derivatives of cyclohexanone and cycloheptanone) in aldol reactions. In

the case of lithium enolates, more substituted enolates gives more substituted aldol product while less substituted one leads to less substituted aldol adducts. Potassium enolates gave a totally different reaction profile. Irrespective of the substitution on the ketone moiety, the result from the aldol reaction is always the same; the less substituted adduct was always obtained (**Scheme 77**).



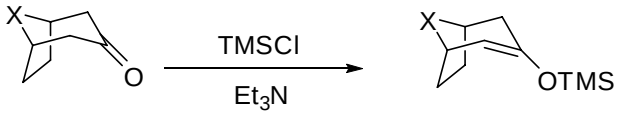
Scheme 77

In the light of this discovery I decided to investigate the aldol condensations of different enolates of tropinone and its sulfur analogue with simple aldehydes. The goal was to find out if different counter ions on the enolate would affect the diastereoselectivity of the aldol reaction, preferably to give a single isomer and hopefully a different one to what was previously obtained from the lithium enolate chemistry.

5.2 Aldol Reaction

The reaction was first tested on cyclohexanone potassium enolate (obtained from the corresponding TMS enol ether). In this case, the desired products were obtained in 60 % yield (assigned by ^{1}H NMR) in 1.5:1 ratio of *anti* to *syn* diastereoisomer.

Similarly, tropinone and TBON enolates were prepared from their respective TMS enol ethers obtained according to a known procedure[24] in 93 % isolated yield and >95 % purity by ^{1}H NMR in case of tropinone and in a slightly higher 96 % yield for TBON (**Scheme 78**). Treatment of those TMS-enolates with *t*-BuOK or NaOEt gave the respective potassium or sodium enolates that were than treated with an aldehyde to give the expected aldol adducts.

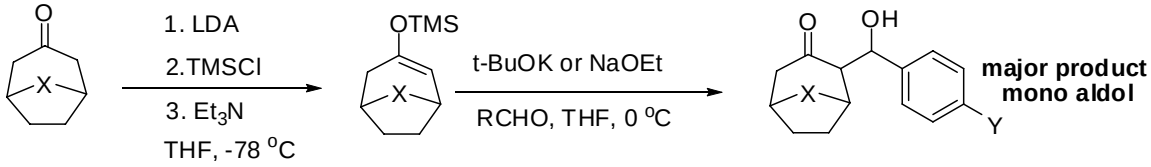


52: X = NMe
53: X = S

54: X = NMe; y = 93%
55: X = S; y = 96%

Scheme 78

Unfortunately, the aldol reactions of potassium and sodium enolates of TBON and tropinone did not give any useful results. Firstly, the reaction was not selective and secondly, it proceeded with very low yields and rather low conversions (measured by ^{1}H NMR using the aldehyde which was the limiting reagent as an internal standard). In the case of the potassium enolate of TBON, for some reasons unknown, the reaction gave only a trace amount of product with the starting materials recovered in good amounts. The sodium enolates gave small amount of products when benzaldehyde was used. The major product from both enolates was usually mono aldol product – either *exo-anti* adduct, or the other unidentified mono aldol product (**Tables 2-12.** and **2-13.**).



52: X = NMe
53: X = S

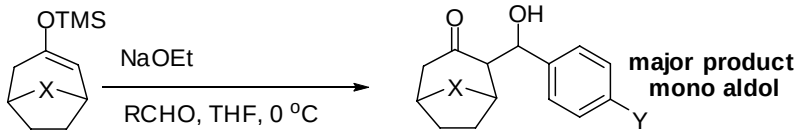
54: X = NMe
55: X = S

65: X = NMe, Y = H
255: X = NMe, Y = NO_2

66: X = S, Y = H
257: X = S, Y = NO_2

Scheme 79

Table 2-12. Aldol reaction of sodium enolates of tropinone and TBON



54: X = NMe

55: X = S

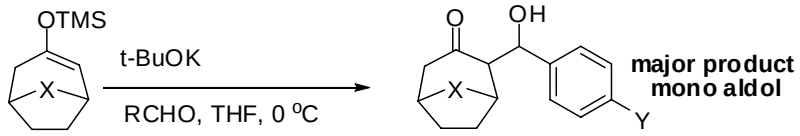
65: X = NMe, Y = H
255: X = NMe, Y = NO_2

66: X = S, Y = H
257: X = S, Y = NO_2

	KETONE	***ALD.***	***TEMP. [°C]***	***CONV.***	***YIELD (exo-anti)***	***RESULT***
1	*Tropinone*	*N*	*-78*	*80 %*	*-*	***256:255a:255b:255c*** *(1:1:1:1)*
2	*Tropinone*	*B*	*-78*	*10 %*	*5 %*	*2 products*
3	*TBON*	*N*	*-78*	*-*	*-*	*SM*
4	*TBON*	*B*	*-78*	*30 %*	*3 %*	***67:66a:66b*** *(1:1.3:2.3)*

Note: *B-Benzaldehyde, N-p-Nitrobenzaldehyde*

Table 2-13. Aldol reactions of potassium enolates of tropinone and TBON



54: X = NMe

55: X = S

65: X = NMe, Y = H
255: X = NMe, Y = NO_2

66: X = S, Y = H
257: X = S, Y = NO_2

	KETONE	***ALD.***	***TEMP. [°C]***	***CONV.***	***YIELD (exo-anti)***	***RESULT***
1	*Tropinone*	*N*	*-78*	*85 %*	*12 %*	***256:255a:255b*** *(1:5:1)*
2	*Tropinone*	*B*	*-78*	*30 %*	*11 %*	***253:65a:65b*** *(1:1:3)*
3	*TBON*	*N*	*-78*	-	-	*SM*
4	*TBON*	*B*	*-78*	-	-	*SM*

Note: *B-Benzaldehyde, N-p-Nitrobenzaldehyde*

As in the case of magnesium catalyzed aldol reaction, isolation and purification of the products from this reaction were difficult due to retroaldolization and isomerization that occurs in any acidic medium (silica gel and chloroform-*d*). Additionally, attempts to neutralize the silica gel with base resulted in faster isomerization.

5.3 Summary of Aldol Reactions of Potassium and Sodium Enolates

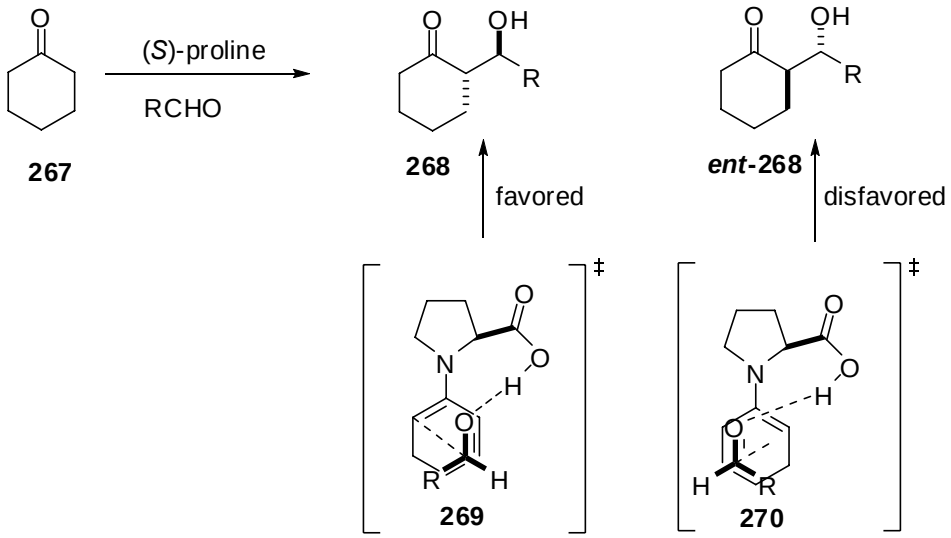
Aldol reactions of both potassium and sodium enolates were not successful. The major aldol adduct obtained from the reactions in cases when the reaction worked, was either *exo-anti* product or other unidentified mono aldol adduct. Generally, the conversions of the reactions

were low and the products difficult to purify. Similarly like in case of MgI_2 catalyzed aldol reaction, the other diastereoisomers of the aldol adducts that were detected in the ^1H NMR of the crude reaction mixture were not possible to isolate and characterize due to retro-aldol.

6 Proline Catalyzed Aldol Reaction

6.1 Introduction

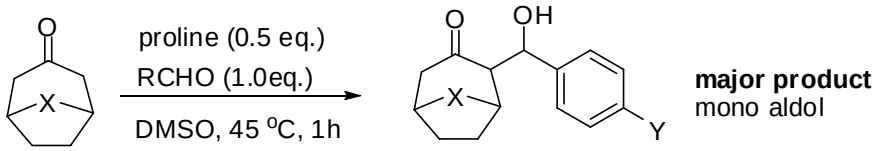
During the past 18 years, many different proline catalyzed enantioselective reactions have been developed.[96, 97, 98] Among these reactions, the aldol reaction occupies a special place as the mechanism of this particular reaction has been thoroughly studied.[99,100] These studies strongly suggest that only one proline molecule is involved in the enantioselective-determining step with the amine functional group activating the carbonyl donor by the formation of an enamine. This allows the carboxylic acid moiety to form a hydrogen bond to the aldehyde or ketone acceptor (**Scheme 80**).



Scheme 80

One major limitation to this process is the limited ketone derivatives used for the study. With this in mind investigation of the proline catalyzed aldol reaction of more complex ketones

such as tropinone and its sulfur analogue was investigated (**Scheme 81**) as a way of extending the scope of the reaction.



52: X = NMe

53: X = S

65: X = NMe, Y = H
255: X = NMe, Y = NO_2

66: X = S, Y = H
257: X = S, Y = NO_2

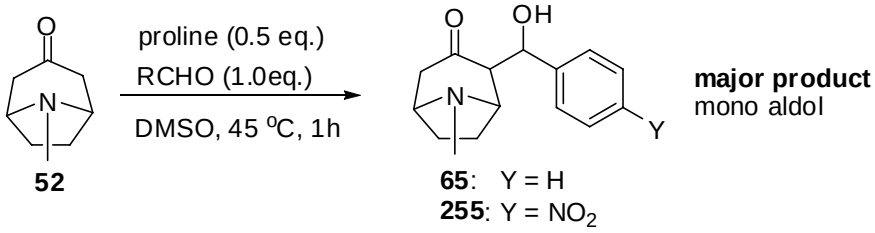
Scheme 81

6.2 Aldol Reaction

The results of the proline catalyzed reaction (**Table 2-14** and **2-15**) were similar to what was observed in case of potassium and sodium enolate chemistry. First of all the reaction was not selective and in most cases in which the conversion was high enough (>50 %) 4 products in an almost equal ratios were obtained. In cases when the four products were obtained in different ratios, the main product was usually the *exo-anti* isomer (the same as the one obtained from the lithium enolate chemistry) or sometimes the other mono aldol product. Not surprisingly, for both tropinone and TBON – the conversions were always higher when using p-nitrobenzaldehyde and this aldehyde was chosen to optimize the reaction conditions. Attempts to optimize the conditions for yield and selectivity by adding additives (water, PPTS etc.) gave no appreciable improvement. It is also worth mentioning that the reaction performed poorly when DMF was employed as the solvent.

Attempts to subject the mixture of diastereoisomers obtained from the reaction to isomerization using either DMAP or imidazole as reported by Ward *et al.* [101,102] with the hope of obtaining one of the isomers as the main product were not successful. The ratio of the diastereoisomers remained constant suggesting that the mixture obtained from the reaction was thermodynamically stable.

Table 2-14 . L (-) Proline catalyzed aldol reaction of tropinone



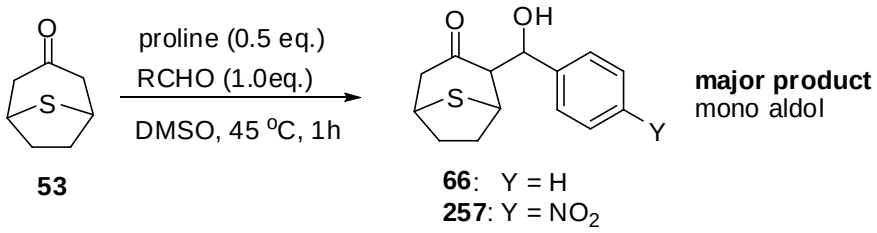
52

65: Y = H
255: Y = NO_2

	ALD.	***ADDITIVE***	***SOLVENT***	***TEMP. [°C]***	***TIME***	***CONV.***	***RESULT***
1	*N*	*-*	*DMSO (40 % proline)*	*RT*	*1.2h*	*55 %*	*4 products*
2	*N*	*H_2O (300 % mol)*	*DMSO*	*45*	*1.2h*	*-*	*SM*
3	*N*	*-*	*DMF*	*RT*	*1h*	*10 %*	*2 products*
4	*N*	*-*	*DMF*	*45*	*1h*	*60 %*	*4 products*
5	*N*	*-*	*DMSO*	*45*	*15min*	*>95 %*	*4 products*
6	*N*	*-*	*DMF*	*RT*	*3d*	*<20 %*	*4 products*
7	*B*	*-*	*DMSO*	*RT*	*2d*	*<20 %*	*2 products*
8	*B*	*H_2O*	*DMSO*	*RT*	*2d*	*<20 %*	*2 products*
9	*B*	*PPTS*	*DMSO*	*RT*	*10d*	*-*	*SM*
10	*B*	*AcOH*	*DMSO*	*RT*	*10d*		*SM*
11	*B*		*DMF*	*RT*	*2d*	*<20 %*	*2 products*
12	*B*	*H_2O*	*DMF*	*RT*	*2d*	*<20 %*	*2 products*
13	*B*	*PPTS*	*DMF*	*RT*	*10d*	*-*	*SM*
14	*B*	*AcOH*	*DMF*	*RT*	*10d*	*-*	*SM*
15	*C*	*-*	*DMF*	*RT*	*8d*	*-*	*SM*
16	*C*	*-*	*DMSO*	*RT*	*8d*	*-*	*SM*
17	*T*	*-*	*DMF*	*RT*	*8d*	*-*	*SM*
18	*T*	*-*	*DMSO*	*RT*	*8d*	*-*	*SM*

Note: *B-benzaldehyde, N-p-nitrobenzaldehyde, C-cyclohexylaldehyde, T-tertbutylaldehyde;*

Table 2-15. L (-) Proline catalyzed aldol reaction of TBON



53

66: Y = H
257: Y = NO_2

	ALD.	***ADD.***	***SOLV.***	***TEMP. [°C]***	***TIME***	***CONV.***	***RESULT***
1	*N*	*-*	*DMSO*	*45*	*1.2h*	*-*	***258:257a:257b:257c*** *(1:1.7:1:0.7)*
2	*N*	*-*	*DMSO*	*RT*	*1.2h*	*73 %*	***258:257a:257b:257c*** *(1:1.9:1:2)*
3	*N*	*-*	*DMSO*	*45*	*2h*	*40 %*	***258:257a:257b:257c*** *(1:2:1:1)*
4	*N*	*-*	*DMSO*	*45*	*3h*	*40 %*	***258:257a:257b:257c*** *(1:1.5:0.8:4.5)*
5	*N*	*-*	*DMF*	*RT*	*1h*	*20 %*	*3 products*
6	*N*	*-*	*DMF*	*45*	*1h*	*70 %*	*4 products*
7	*B*	*-*	*DMSO*	*RT*	*2d*	*-*	*2 products*
8	*B*	*H_2O*	*DMSO*	*RT*	*2d*	*-*	*2 products*
9	*B*	*PPTS*	*DMSO*	*RT*	*10d*	*-*	*SM*
10	*B*	*AcOH*	*DMSO*	*RT*	*10d*	*-*	*SM*
11	*B*	*-*	*DMF*	*RT*	*2d*	*-*	*2 products*
12	*B*	*H_2O*	*DMF*	*RT*	*2d*	*-*	*2 products*
13	*B*	*PPTS*	*DMF*	*RT*	*10d*	*-*	*SM*
14	*B*	*AcOH*	*DMF*	*RT*	*10d*	*-*	*SM*

Note: *B- benzaldehyde, N-p-nitrobenzaldehyde*

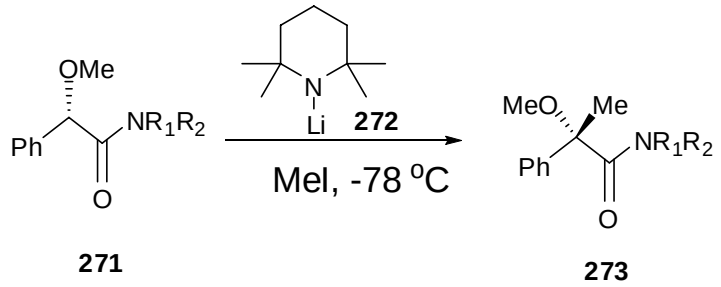
6.3 Summary of Proline Catalyzed Aldol Reaction

The proline catalyzed aldol reactions of tropinone and TBON were also not successful. The reactions proceeded with low conversions and were none selective (usually 4 products were obtained). In cases when the ratio of products was slightly different, the mono aldol adduct was obtained as the main product.

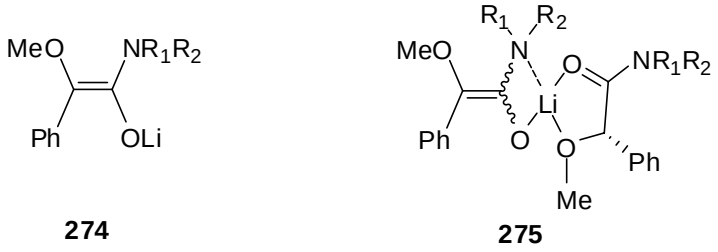
7 Chirality Transfer

7.1 Introduction

It had been reported that during alkylation of chiral amides derived from (*S*)-O-methyl mandelic acid and achiral amines, which proceed *via* the enolate intermediate, asymmetric induction had occured (**Scheme 82**).[103] This fact could be explained by formation of mixed aggregates consisting of an achiral enolate with chiral not deprotonated starting material giving rise to products with good enantioselectivity. Combining this information with the fact that tropinone has been shown not to undergo alkylation under standard alkylating conditions; I envisaged that mixing enantiomerically pure enolates of tropinone and racemic enolates of another ketone that is known to undergo alkylation reaction should furnish non racemic alkylated products. To obtain the non-racemic alkylated products, there must be formation of mixed aggregates between the enantiomerically pure tropinone enolates and the racemic enolates of the employed ketone. This concept was put to test in two different reactions as described in the following section.



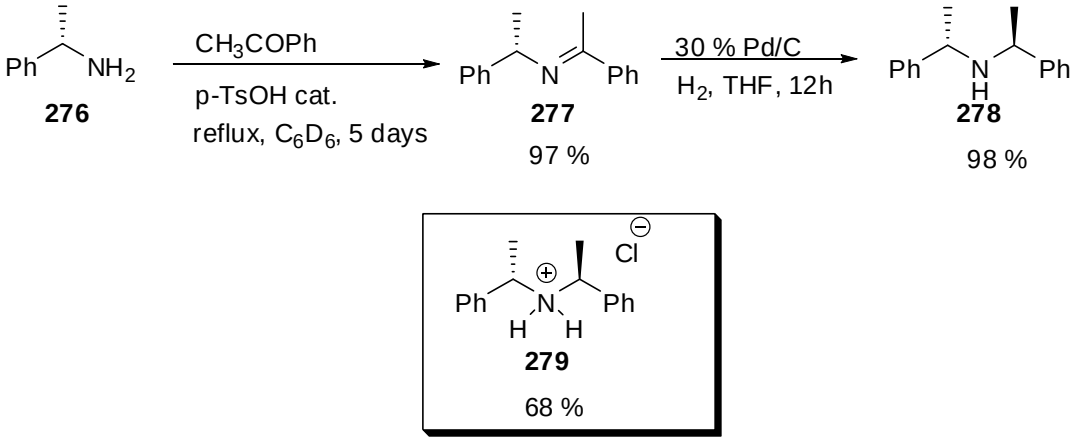
ACHIRAL ENOLATE **MIXED AGREGGATE**



Scheme 82

7.2 Preparation of the Chiral Amine

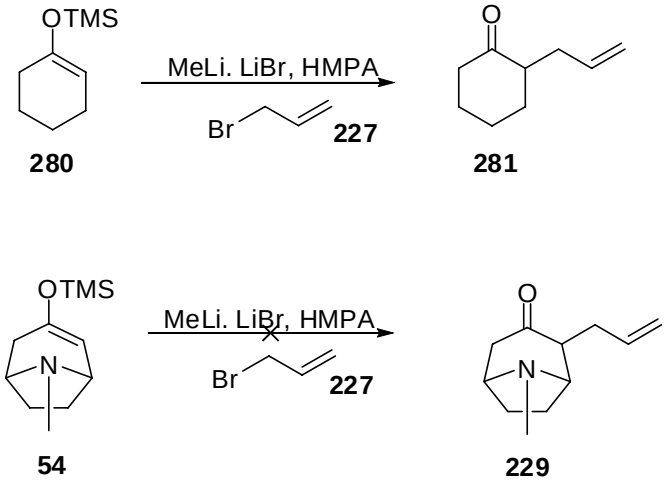
The choice of chiral amine used for generation of the enantiomerically enriched tropinone enolate was based on the fact that it had been used before in our laboratory and can be obtained by simple synthetic method[29]. In the first step of the synthesis, (S)-α-methyl benzylamine was refluxed with acetophenone in the presence of p-TsOH to give enamine **277** in 97 % yield. Reduction of the enamine using Pd on carbon gave the crude product in 98 %. Purification by crystallization as the hydrochloride salt gave the product in 68 % (**Scheme 83**).



Scheme 83

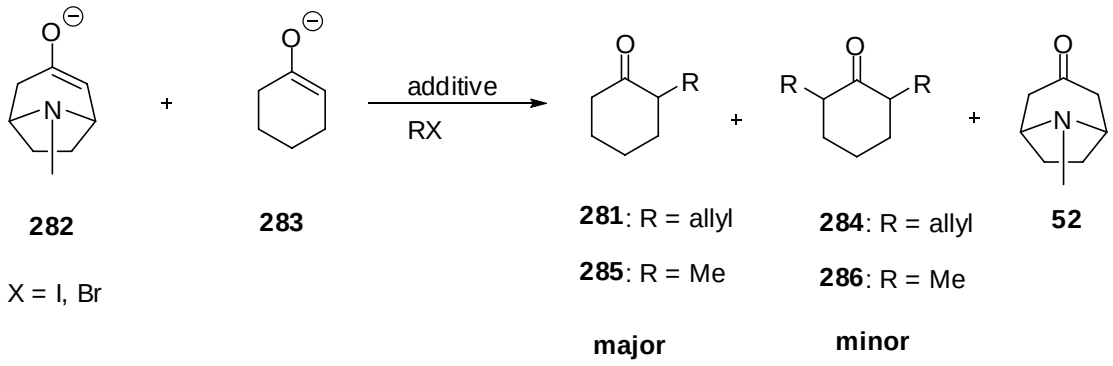
7.3 Chirality Transfer Reaction

Racemic cyclohexanone enolate was chosen as the standard enolate to test the concept explained in the previous section and to confirm that the substrate undergoes alkylation under standard conditions; the lithium enolate was alkylated with allyl bromide as an electrophile. Simultaneously, racemic tropinone lithium enolate was also subjected to a similar alkylating conditions as a control experiment to once again establish its inability to react under this protocol. As expected, in the case of tropinone, no product was detected while 2-allyl cylohexanone was obtained in quantitative yield as a mixture of 2 diastereoisomers in a 1:1 ratio (**Scheme 84**).



Scheme 84

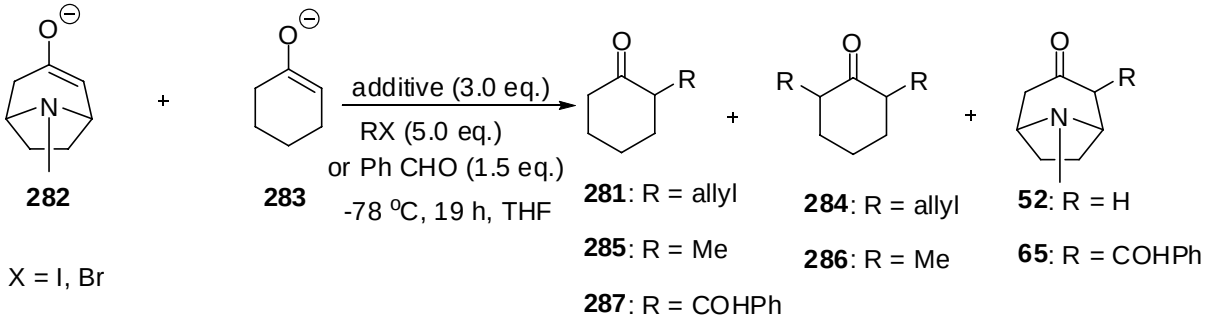
The first approach to this concept described in the previous section involved generating the enolates separately. Two equivalents of methyl lithium (1:1 with respect to tropinone silyl enol ether and cyclohexanone) were added to the separate mixtures of the silyl enol ether at 0 ºC, followed by addition of different additive at different temperatures. The enolates were then mixed together and allowed to stir for 0.5h before the addition of the alkyl halide. The second approach that was investigated involved the generation of both enolates from their silyl enol ethers together in the same flask.



Scheme 85

When methyl iodide was employed as the electrophile, ^{1}H NMR of the crude reaction mixture after workup shows traces of methylated product however attempts to purification the desired compound were not successful presumably due to the small amount and lower boiling point of the product. Switching the electrophile to allyl bromide and employing HMPA as additive, gave a better result. The alkylated cyclohexanone obtained from the reaction was isolated albeit in low yields (**Table 2-16.**). The reactions in which the enolates were generated separately in the presence of HMPA prior to mixing gave a much higher yield of product than when they were generated together (**Table 2-16**).

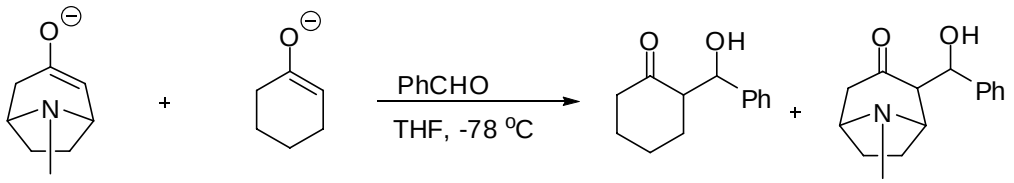
Table 2-16. Chirality transfer reactions



	SOLVENT	*TEMP. [ºC]*	*ADDITIVE*	*TIME*	*ELECTR.*	*YIELD*
1	*THF*	*-78*	*LiBr (1.0eq.)*	*2h*	*MeI*	-
2	*THF*	*-78*	*HMPA*	*50min*	*MeI*	*1.5 %*
3	*THF*	*-78*	*3N*	*50min*	*MeI*	*Trace*
4	*THF*	*-78*	*4N*	*50min*	*MeI*	*Trace*
5	*THF*	*-23*	*4N*	*1h*	*Allyl bromide*	-
6	*Et_2O*	*-23*	*3N*	*1h*	*Allyl bromide*	*Trace*
7	*Et_2O*	*-23*	*4N*	*1h*	*Allyl bromide*	*Trace*
8	*Toluene*	*-23*	*LiBr (1.0eq.)*	*1h*	*MeI*	-
9	*Toluene*	*-23*	*HMPA*	*1h*	*MeI*	-
10	*Toluene*	*-23*	*3N*	*1h*	*MeI*	-
11	*Toluene*	*-23*	*4N*	*1h*	*MeI*	-
12	*Toluene*	*-23*	*4N*	*1h*	*Allyl bromide*	-
13	*Toluene*	*-23*	*4N*	*3h*	*Allyl bromide*	-
14	*Toluene*	*-23*	*4N*	*21h*	*Allyl bromide*	*5 %*
15	*Toluene*	*-23*	*HMPA*	*1h*	*Allyl bromide*	*18 %[1]*
16	*Toluene*	*-23*	*HMPA*	*19h*	*Allyl bromide*	*26 %[1]*
17	*THF*	*-78*	-	*5min*	*Benzaldehyde*	*60 %[1]*

Note: *[1]Enolates generated separately; 3N = N,N,N`,N`, N``, N"-pentamethyldiethylenetriamine; 4N = 1,1,4,7,10,10-hexamethlyltriethylenetetraamine*

The poor yields from the alkylation reaction prompted the use of a more reactive electrophile to investigate if active enolates were present in solution (**Scheme 86**). Unfortunately, the aldol products obtained from cyclohexanone (1:1.2 ratio of diastereoisomers, 60 % yield) showed no chirality transfer as indicated by the optical rotation ([α] $^{22}_{D}$ = 0.1 (1.2 $CHCl_3$). The *ee* was not determined as attempts to use different chiral shift reagents or make derivatives of the obtained aldol failed.



282 **283** **287** **65**

Scheme 86

7.4 Summary of Chirality Transfer Reaction

The concept of chirality transfer as proposed in the opening section of this study could not be extended to the reactions carried out. Although the products from the reaction were obtained in poor to moderate yields, the inability to improve the *ee* of the products indicated that the either the enolates are not forming a mixed aggregates or the aggregates formed are not reactive under the reaction conditions employed.

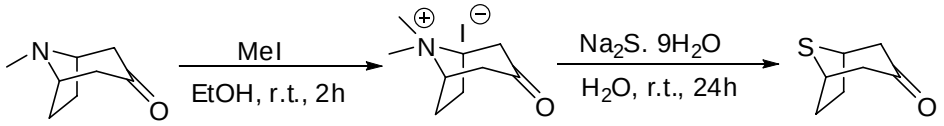
8 Synthesis of Thiacocaine

8.1 Introduction

8-Thiabicyclo[3.2.1.]octan-3-one (TBON) can be viewed as a potential scaffold for construction of sulfur analogs of tropane alkaloids. Previous work within the group has provided a comprehensive strategy for the stereoselective synthesis of tropane alkaloids based on enantioselective deprotonation of tropinone using appropriate chiral lithium amides as the key

step. Using this strategy, a number of tropane alkaloids were achieved including unnatural cocaine.[39,29] Compound like this, as a potent central nervous system stimulant and major drug of abuse, have attracted considerable attention in development of its antagonists and partial antagonists that could help in the treatment of its abuse.[104,105]Surprisingly, even though that cocaine was synthesized as early as 1898 (R. M. Willstätter),[106] attention has not been drawn to its sulfur analog as a potential compound that could possess similar biological activity without the addictive properties. This prompted my choosing of thiacocaine as a synthetic target.

8.2 Preparation of Starting Materials



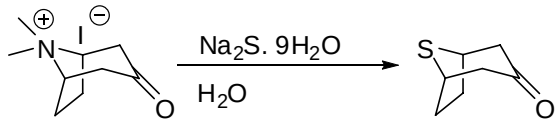
52 **288** **53**

>90 % ~ 60 %

Scheme 87

Sulfur analog of tropinone was prepared from tropinone according to known procedure[76] (**Scheme 87**). In the first step of the synthesis, *N*-methyl tropinone iodide was obtained in >90 % yields (reported 91 %). Incidentally, the next step that leads to the final product was not that straightforward. When the reaction was carried out according to the reported protocol, the product was always obtained in around 26 % yield (reported 55 %). Working towards optimization of the reaction conditions, it was discovered that both time and especially temperature of reaction plays a key role in the amount and purity of the product obtained. After extensive optimization, the best, reproducible results were obtained when the reaction was carried out over 24h at room temperature (61 %). The results of the optimization study are combined in **Table 2-17**.

Table 2-17. Optimization of conditions for obtaining TBON



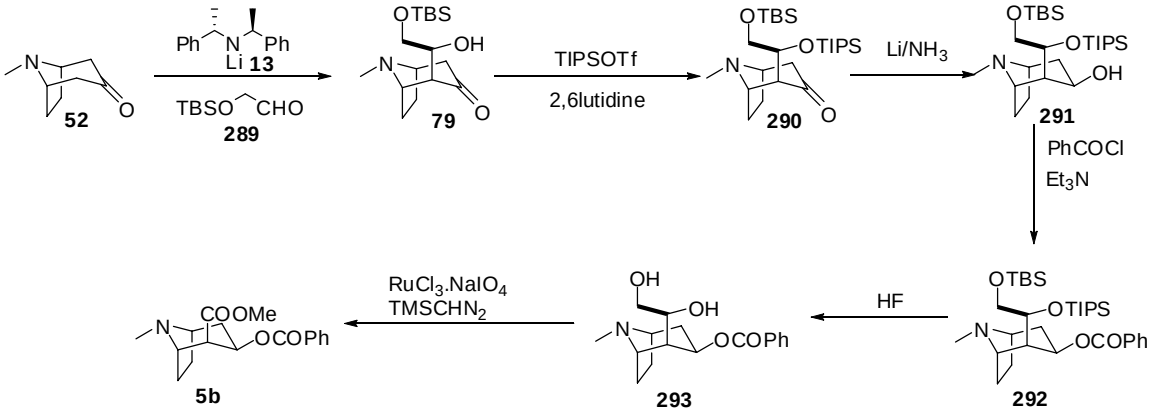
288 **53**

	TIME	*TEMPERATURE*	*YIELD*
1	*0.5h*	*80 ºC*	*29 %*
2	*1h*	*80 ºC*	*34 %*
3	*2h*	*80 ºC*	*26 %**
4	*5h*	*80 ºC*	*14 %*
5	*12h*	*80 ºC*	*7 %*
6	*24h*	*RT*	*61 %*
7	*48h*	*RT*	*48 %*

Note: **conditions according to original procedure*

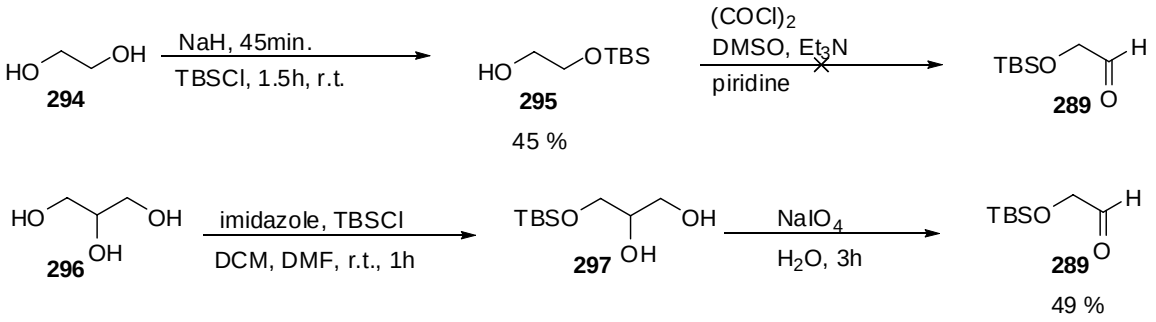
8.3 The First Approach to Thiacocaine

The first attempted synthesis of thiacocaine was *via* an identical sequence of reactions already reported for the synthesis of unnatural cocaine (**Scheme 88**).[39]



Scheme 88

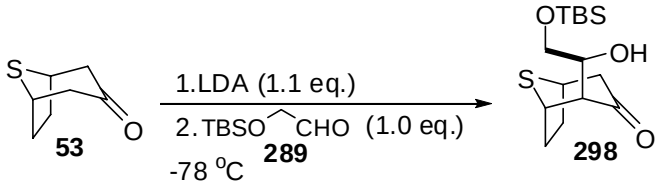
In this approach, the synthesis of the aldehyde coupling partner was found not to be straightforward presumably due to the reactivity of the substrate. Attempts to oxidize the mono protected ethylene glycol gave a mixture of unknown products (**Scheme 89**). Ultimately, the selective TBS protection of glycerol followed by periodate cleavage afforded the desired aldehyde unit, but in low yield. The aldehyde **288** was found not to be stable to storage and purification (column chromatography) so it had to be prepared prior to use in the crude form.



Scheme 88

Initial investigation into the synthesis of thiacocaine *via* the sequence in **Scheme 90** was carried out using LDA as the base. The aldol reaction with the freshly prepared aldehyde proceeded uneventfully to afford yields varying from 54-98 %. The wide range in the yield can be attributed to the varying level of purity of the aldehyde. The longer the reaction time for the generation of the enolate (2 h), the higher the yield of product obtained (**Table 2-18.**).

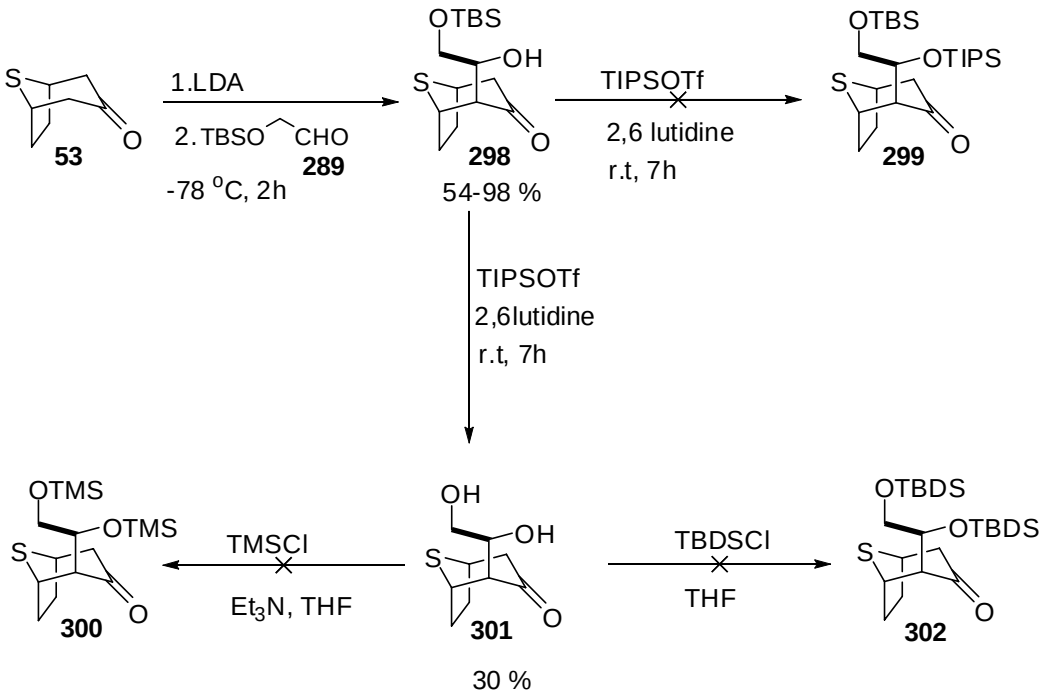
Table 2-18. Optimization of yield for TBS-protected aldol product



	TIME OF ALDOL REACTION	***YIELD***
1	*<1min*	*trace*
2	*5min*	*27 %*
3	*1h*	*35 %*
4	*2h*	*54-98* %*

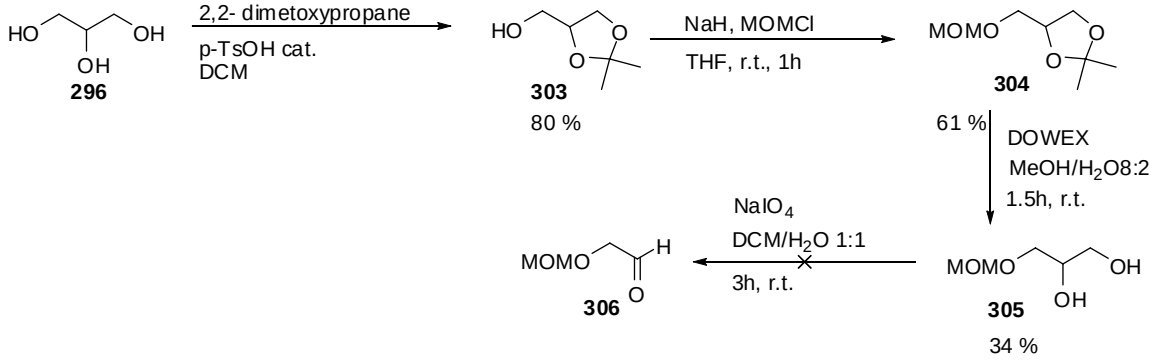
***Note:** * Depends on the purity of TBS-protected aldehyde*

The second step of the synthetic sequence was problematic (**Scheme 90**). Attempts to protect the hydroxyl group using TIPSOTf failed. Interestingly, not only did the protection reaction failed, the TBS group fell off from aldehyde part of compound suggesting that maybe this particular group was too bulky to be used in the process. Additionally, attempts to re-protect the unprotected diol (TMSCl, TBSCl) proved to be difficult and unsuccessful (no reaction).



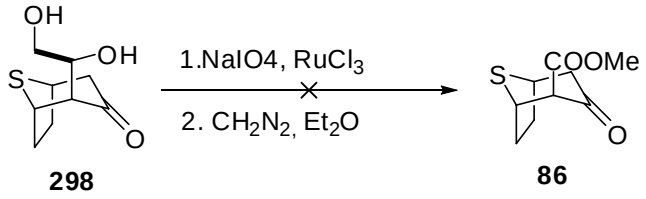
Scheme 90

The problem encountered with the silicon protecting groups necessitated a modification to the protocol. The use of a different, smaller and more robust protecting group for the starting aldehyde should avoid the problem previously encountered. Unfortunately, attempts to make a more stable protected aldehyde (**Scheme 91**) using a less bulky protecting group (MOMCl) failed at the final step for reasons unknown.



Scheme 91

Finally, to be able to determine if this protocol is worth investing time and effort in, the last step in the sequence[39] involving oxidative cleavage was probed with the unprotected diol obtained from the reaction with TIPS triflate (**Scheme 92**). Unfortunately, the reaction failed. Instead of the expected β-ketoester of TBON, an unknown compound was isolated. Additionally, no starting material was observed in the crude reaction mixture.



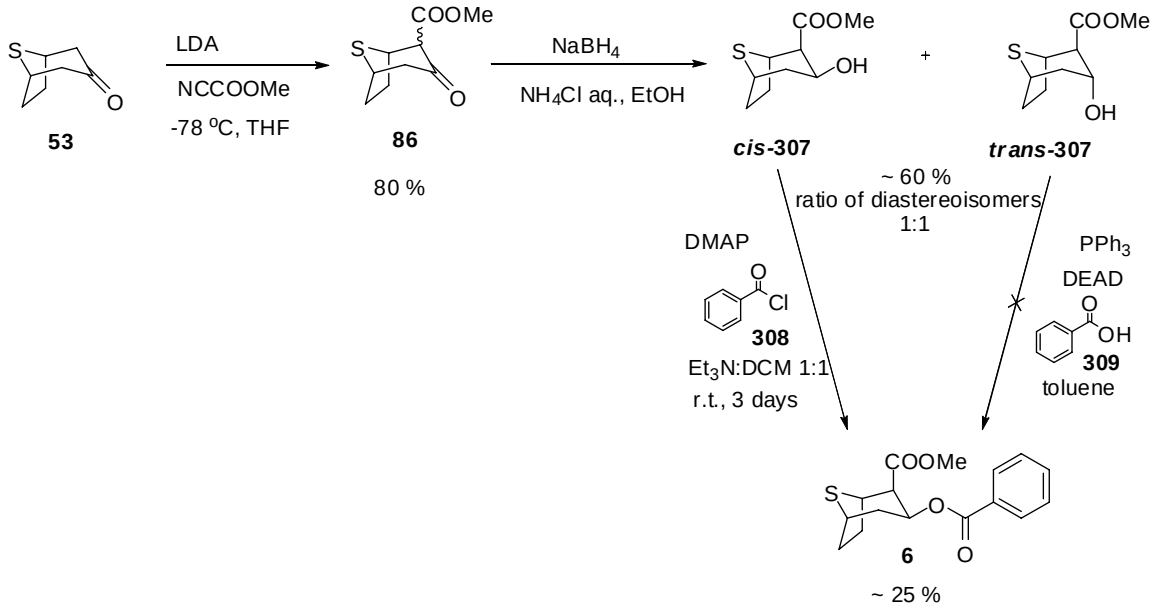
298 **86**

Scheme 92

The results obtained above necessitated a complete change of direction in synthetic strategy towards the preparation of thiacocaine.

8.4 The Second Approach to Thiacocaine

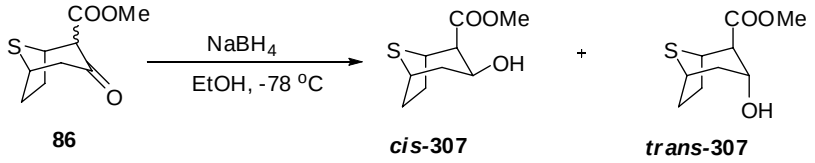
The simplest way to synthesize thiacocaine seemed to be *via* the route involving making the β-ketoester of TBON, followed by selective reduction of the product and finally benzoylation of the obtained alcohol (**Scheme 93**).



Scheme 93

The first step in the synthesis gave the desired product in good yield uneventfully. Unfortunately, the second step involving the reduction of β-ketoester (**86**) was a bit problematic so a closer attention was paid to it. Test reaction conducted over 24 h at -78 ºC gave 2 isomers in a combined isolated yield of 14 % (1:1.5 ratio) plus recovered starting material, indicating that the product might not be very stable to the reaction conditions. When the reduction was carried out in 1h, 30 % isolated combined yield of 4 isomers in similar ratios, with a concomitant recovery of 60 % starting material was obtained. Ultimately, the best result was obtained for reaction conducted over 3h – ca. 50 % combined yield of 2 isomers in 1:1.2 ratio, but in all cases the reaction did not go to completion and significant amount of starting material were always recovered (**Table 2-19.**).

Table 2-19. Mini study on influence of time on reduction of β-ketoester (**86**)



86 ***cis*-307** ***trans*-307**

	TIME	***YIELD***	***RESULT*** **(*cis*-308:*trans*-308)**
1	24h	14 %	1:1.5
2	3h	50 %	1:1.2
3	1h	30 %	~1:1:1*:1*

Note: ** two other possible diastereoisomers that have COOMe group in equatorial position*

Once the optimal time for the reaction was established, the influence of temperature on the reaction conditions was investigated. Reduction was performed simultaneously at -78 ºC, 0 ºC and RT. In all cases ratios of both diastereoisomers was approximately close to 1:1 however the highest yield (ca. 60 %) was obtained at 0 ºC. It is worth to mention that in case of both reactions carried out at 0 ºC and RT, trace amount of a third diastereoisomer was detected (too small amount to isolate and characterize).

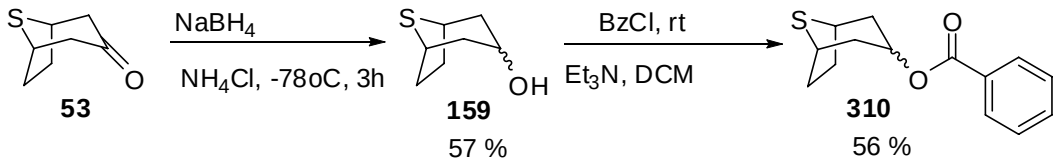
After purification and separation of those two major isomers on column chromatography (hexane:Et_2O 6:4), ^1H NMR analysis showed that one diastereoisomer is the desired product having the ester group in the axial position and hydroxyl group in the equatorial position. In the case of the second isomer, the hydroxyl group is in the axial position (**Scheme 93**).

The esterification of the alcohol mixtures obtained from the reduction reaction was equally problematic. Standard esterification conditions (benzoyl chloride, Et_3N in THF or CH_2Cl_2) gave only trace of desired products in 1:2 ratios (2.4 % yields by PTLC) with recovered starting materials (quantitative mass recovery). Subjecting a mixture of the isomers to esterification under modified reaction conditions (high concentration of starting material and Et_3N as co-solvent, 3 days) gave the product in 25-27 %, however in this case only one

diastereoisomer reacted to give thiacocaine. The second diastereoisomer was recovered back from the reaction mixture. However when both diastereoisomers were refluxed under the same reaction conditions overnight, both of them reacted with a 50 % isolated yields. The unreacted diastereoisomer was then subjected to Mitsunobu reaction to invert the configuration of the hydroxyl group and benzoylate it in a "one pot" process. Unfortunately, no matter the reaction conditions applied (different reaction time, solvents or temperature) only the starting material was recovered.

The low yield obtained from the bezoylation reaction prompted a look at the reaction conditions for the benzoylation. Employing benzoic anhydride (obtained from benzoyl chloride in the presence of Et_3N and H_2O in acetone) gave poorer yields ca. 15 %. Changing DMAP for tetrabutylammonium iodide as well did not give any significant difference (ca. 21 % yield).

The problem encountered with the reduction and esterification of TBON prompted an investigation into the stability of the ring (**Scheme 94**). The reduction reaction of TBON under the same conditions used for the β–ketoester (**86**) gave a 1:1 ratio of isomers in 57 % isolated yield. This result shows that isolation of the hydroxy TBON from the reaction mixture is a little difficult probably due to stability of the product. Although the benzoylation reaction in standard conditions worked, the isolated yield was equally low. In both cases, there was no recovery of any starting materials.



Scheme 94

Finally, attempt to synthesize thiacocaine enantioselectively *via* utilization of chiral lithium amide **13**, was carried out. In this case, the β-ketoester was obtained in 39 % yield. Reduction of the compound resulted in mixture of 2 diastereoisomers (~1:1 ratio) in 20 % yield. For reasons unknown benzoylation of the obtained alcohol failed - starting material was recovered with more than 50 % mass recovery. Attempts to use NaH to generate the alkoxide

followed by trapping with benzoyl chloride; employing benzoyl chloride, terabutylammonium iodide and Et_3N or the benzoyl anhydride as a source of electrophile equally gave no product.

8.5 Summary of Synthesis of Thiacocaine

The synthesis of racemic thiacocaine was achieved in short sequence of reactions although with very low 12 % yield over three steps and with poor stereocontrol. The initial protocol following the method reported for the synthesis of unnatural cocaine *via* enantioselective deprotonation of tropinone[29] was not successful due to problems with protection of one of the intermediates (**297**). Attempts to repeat the protocol developed for the synthesis of thiacocaine in an enantioselective manner did not succeed at the final stage of benzoylation for reasons unknown.

9 Conclusions

All the projects described in the Result and Discussion section above dealt with enolate chemistry of two bicyclic bridged ketones: tropinone (8-methyl-8-azabicyclo[3.2.1.]octan-3-one) and TBON (8-thiabicyclo[3.2.1.]octan-3-one). Although a lot of information was available regarding the properties of these compounds, my research went a long way to demonstrate that some important information is still missing. For example, the reasons why benzoylation of the β-hydroxlyl ester of tropinone occurs smoothly while under the same reaction condition, TBON gave < 10% yield are still unclear. Similarly, the disparity in the yields obtained from the reduction of the β-ketoesters derived from substrates by α-carboalkoxylation is also not well understood. Finally, the reasons why only one isomer of the β-hydroxyl ester of TBON reacted in the esterification process while the other showed no reactivity at ambient temperature remained unknown.

It was also shown that alkylation of tropinone using alkyl halides is possible although in low yield when carried out under Koga's conditions. When electrophiles with atoms that can coordinate to lithium were used, the reaction proceeded to give the expected products in moderate yields.

Finally, the aldol reaction of tropinone and TBON was investigated under different conditions (organocatalysis, potassium and sodium enolates or MgI_2 catalyzed reaction). The major product obtained from these reactions in all cases was either the same *exo-anti* product that had been obtained *via* previously established lithium enolate chemistry or other not identified mono aldol adduct. It was also possible to prepare, in a "one pot process", the bis-aldol adducts from tropinone and TBON in moderate yields and diastereoselectivity.

CHAPTER 3
EXPERIMENTAL

1 General Methods

All solvents were distilled prior to use. Anhydrous solvents were distilled under argon atmosphere as follows: tetrahydrofuran (THF) from benzophenone sodium ketyl; ether from benzophenone sodium ketyl; CH_2Cl_2, $CHCl_3$ and toluene from CaH_2; MeOH from $Mg(OMe)_2$; benzene from sodium metal and stored over 5Å molecular sieves and dimethyl sulfoxide was stored over 5Å molecular sieves for 1 week prior to use. All experiments involving air- and/or moisture-sensitive compounds were conducted in an oven dried round-bottom flask capped with a rubber septum, and attached *via* a needle and connecting tubing to a nitrogen manifold equipped with mercury bubbler (ca. 5 mm positive pressure of nitrogen). Low temperature baths were ice/water (0 °C) CO_2(s)/acetone (-78 °C) and liquid nitrogen/ether (-100 °C). Reaction temperatures refer to that of the bath.

Preparative TLC (PTLC) was carried out on glass plates (20 × 20 cm) precoated (0.25 mm) with silica gel 60 F254. Materials were detected by visualization under an ultraviolet lamp (254 nm) and/or by treating a 1 cm vertical strip removed from the plate with a solution of phosphomolybdic acid (5%) containing a trace of cerium sulfate in aqueous sulfuric acid (5% v/v), followed by charring on a hot plate or ninhydrine solution. Concentration refers to removal of volatiles at water aspirator pressure on a rotary evaporator. Unless otherwise noted, all reported compounds were homogeneous by thin layer chromatography (TLC) and by NMR. Flash column chromatography (FCC) was performed according to Still *et a.l*[107]. with Merck Silica Gel 60 (40-63 μm). Medium pressure chromatography (MPC) was performed as reported by Taber.[108] All mixed solvent eluents are reported as v/v solutions.

High resolution mass spectra (HRMS) and low resolution mass spectra (LRMS) were obtained on a VG 70E double focusing high resolution spectrometer; only partial data are reported. EI ionization was accomplished at 70 eVand CI at 50 eV with ammonia as the reagent

gas; only partial data are reported. IR spectra were recorded on a Fourier transform interferometer using a diffuse reflectance cell (DRIFT); only diagnostic and/or intense peaks are reported. Unless otherwise noted, NMR spectra were measured in $CDCl_3$ solution at 500 MHz. Signals due to the solvent (^{13}C NMR) or residual protonated solvent (^{1}H NMR) served as the internal standard: $CDCl_3$ (7.27 δ H, 77.23 δ C); C_6D_6 (7.16 δ H, 128.39 δ C). The ^{1}H NMR chemical shifts and coupling constants were determined assuming first-order behavior. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), brs (broad singlet), ap (apparent); the list of couplings constants (*J*) corresponds to the order of the multiplicity [1] assignment. Couplings constants (*J*) are reported to the nearest 0.5 Hz. The ^{1}H NMR assignments were made based on chemical shift and multiplicity and were confirmed, where necessary, by homonuclear decoupling and/or NOE experiments. The ^{13}C NMR assignments were made on the basis of chemical shift and multiplicity (as determined by *J*-modulation[109]) and were confirmed, where necessary, by two dimensional $^{1}H/^{13}C$ correlation experiments (HMQC and/or HMBC[110]).

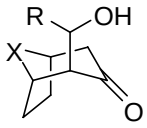
The reference numbers following the compound name (title) indicates that the compound is known and the spectra data obtained is in agreement with the literature.

All other reagents were commercially available and unless otherwise noted, were used as received.

[1] The multiplicity of ^{13}C NMR signals refers to the number of attached H's (i.e., s = C, d = CH, t= CH_2, q = CH_3)

2 General Procedures

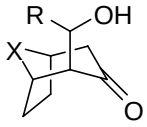
General procedure for proline catalyzed aldol reaction



Modified procedure was adapted from reference [111]

Proline (20 mg, 0.15 mmol) and aldehyde (0.8 mmol) was added to the solution of ketone (0.7 mmol) in dry DMSO (2.0 mL). The reaction was stirred for 1 h at 45 ºC. After cooling down to rt, the reaction was quenched with NH_4Cl and extracted with AcOEt (3 x 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated to afford the crude product as a mixture of 2-4 diastereoisomers. Attempts to purify and isolate the products were unsuccessful due to high instability of the compounds.

General procedure for potassium or sodium enolate aldol reaction

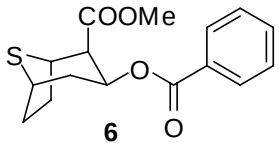


Procedure adapted from reference **94**

Dry t-BuOK or NaOEt (0.93 mmol) was dissolved in dry THF (10 mL) and cooled to 0 ºC. TMS enol ether **54** or **55** (0.93 mmol) in dry THF (1.0 mL) was added dropwise. After stirring for 0.5 h, aldehyde (0.93 mmol) in dry THF (1.0 mL) was slowly added and whole reaction was stirred for another 2.5h at rt. The reaction was quenched with water, extracted with CH_2Cl_2 (4 x 10 mL), dried over $MgSO_4$ and the solvent was evaporated. After purification by column chromatography pure product was afforded.

3 Experimental and Spectra Data of Synthesized Compounds

Methyl-3-(benzoyloxy)-8-thiabicyclo[3.2.1]octane-2-carboxylate



6

The hydroxyl ester *cis*-**308** (32 mg, 0.16 mmol) was dissolved in Et_3N: CH_2Cl_2 1:1 ratio (1.6 mL). DMAP (3.6 mg, 0.03 mmol) was added followed by addition of benzoyl chloride (0.024 mL, 0.24 mmol). The reaction mixture was stirred for 3 days at r.t., diluted with NaOH (2.0 mL, 5%) and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and solvent was evaporated. The crude mixture was purified by column chromatography (Et_2O:hexane 4:6) to furnish viscous oil in 27% yield (13.0 mg).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.04 (d, 2H, *J* = 7.5), 7.56 (t, 1H, *J* = 7.5), 7.44 (t, 2H, *J* = 7.5), 5.31 (ddd, 1H, *J* = 6.0, 6.0, 11.5), 4.00 (m, 1H), 3.74 (br s, 3H), 3.70 (br s, 1H), 3.32 (t, 1H, *J* = 5.0), 2.54 (t, 1H, *J* = 12.5), 2.24-2.13 (m, 5H).

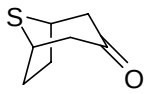
^{13}C NMR (500 MHz, $CDCl_3$) δ: 170.1, 166.1, 133.3, 130.4, 130.0, 128.6, 67.8, 51.8, 50.3, 49.2, 45.8, 36.7, 33.3, 33.1.

IR (**D**RIFT) ν_{max}: 1747, 1714, 1434, 1150, 712 cm^{-1}.

LRMS (EI), *m/z* (relative intensity): 306 ($[M]^+$, 14), 184 (71), 105 (90), 97 (25), 85 (35), 77 (100).

HRMS *m/z* calcd. for $C_{16}H_{18}O_4S$: 306.0926; found: 306.0926.

8-Thiabicyclo[3.2.1]octan-3-one (TBON)[76]



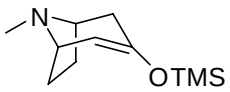
53

Tropinone methiodide **291** (8.34 g, 29.7 mmol) and $Na_2S.9H_2O$ (0.94 g, 3.84 mmol) were dissolved in water (20 mL) and stirred under nitrogen at rt overnight. The solution was extracted with Et_2O (4 x 40 mL), the combined organic layer washed with 0.1M HCl (15 mL), brine and filtered through an $MgSO_4$ / Celite pad. After removing the solvent under vacuum, a light yellowish powder was obtained in 61 % (2.57 g).

mp.: 154-156 ºC, **Lit. mp.**: 155-157 ºC

^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.83 (m, 2H), 2.72 (ap dq, *J* = 17.0, 3.0 Hz, 4H), 2.19-2.17 (m, 2H), 2.05-2.00 (m, 2H).

8-Methyl-3-(trimethylsilyloxy)-8-azabicyclo[3.2.1]oct-2-ene[24]

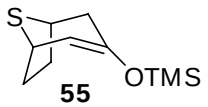


54

A solution of *n*-BuLi in hexane (2.5 M, 1.32 mL, 3.28 mmol) was added dropwise to the solution of DIA (0.46 mL, 3.28 mmol) in THF (5.0 mL) at 0 ºC under nitrogen atmosphere and the mixture was stirred for 0.5h. After cooling to -78 ºC, TMSCl (2.06 mL, 10.8 mmol) was added and the resulting solution was stirred for another 5 mins. A solution of tropinone **52** (417 mg, 3.0 mmol) in dry THF (2.0 mL) was added followed by Et_3N (1.92 mL, 13.72 mmol) after 20 mins at the same temperature. The reaction allowed to warm up to rt, and the solvent was removed. The residue was suspended in hexane and filtered through Celite and $MgSO_4$. Evaporation of the solvent gave the titled compound in 93 % yield (589.0 mg).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.92 (d, 1H, *J* = 5.5), 3.28 (d, 1H, *J* = 5.5), 3.26 (d, 1H, *J* = 5.5), 2.53 (dd, 1H, *J* = 20.0, 9.5), 2.37 (s, 3H), 2.13 (m, 1H), 2.00 (m, 1H), 1.83 (m, 1H), 1.58 (m, 2H), 0.20 (s, 9H).

8-Thiabicyclo[3.2.1]oct-2-en-3-yloxy)trimethylsilane[22]

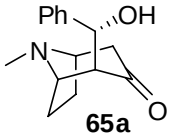


55

A solution of *n*-BuLi in hexane (2.5 M, 1.32 mL, 3.28 mmol) was added dropwise to the solution of DIA (0.46 mL, 3.28 mmol) in THF (5.0 mL) at 0 ºC under nitrogen atmosphere and the mixture was stirred for 0.5h. After cooling to -78 ºC, TMSCl (2.06 mL, 10.8 mmol) was added and the resulting solution was stirred for another 5mins. A solution of TBON **53** (426 mg, 3.0 mmol) in dry THF (2.0 mL) was added followed by Et_3N (1.92 mL, 13.72 mmol) after 20 mins at the same temperature. The reaction was allowed to warm up to rt, and the solvent removed. The residue was suspended in hexane and filtered through Celite and $MgSO_4$. Evaporation of the solvent gave the titled compound in 96% yield (616.0 mg).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.38 (d, 1H, *J* = 7.5), 3.88 (m, 1H), 3.68 (m, 1H), 2.64 (ap d, 1H, *J* = 17.5), 2.35 (ddd, 1H, *J* = 2.0, 8.5, 11.0), 2.23 (m, 1H), 2.10-2.02 (m, 2H), 1.93 (ddd, 1H, *J* = 5.5, 8.0, 13.0), 0.18 (br s, 9H).

2-(Hydroxy(phenyl)methyl)-8-methyl-8-azabicyclo[3.2.1]octan-3-one [24]



65a

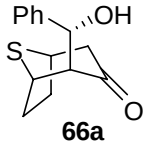
Procedure adapted from reference **94**

Dry t-BuOK (104 mg, 0.93 mmol) was dissolved in dry THF (10 mL) and cooled to 0 ºC. TMS-tropinone **54** (197 mg, 0.93 mmol) in dry THF (1.0 mL) was then added dropwise. After stirring for 0.5 h, benzaldehyde (0.09 mL, 0.93 mmol) was slowly added and the reaction was stirred for another 2.5 h at rt. The reaction was quenched with water, extracted with CH_2Cl_2 (4 x 10 mL), the combined organic layers dried over $MgSO_4$ and the solvent was evaporated. Purification by FCC using hexane:AcOEt 1:1 gave the pure product in 12 % yield (27.0 mg).

Note: The same reaction (same scale) using EtONa instead of t-BuOK gave a 5 % yield (12.4 mg)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.42-7.20 (m, 5H), 5.23 (d, 1H, *J* = 3.0), 3.60 (d, 1H, *J* = 6.5), 3.60-3.45 (m, 1H), 2.86 (ddd, 1H, *J* = 15.5, 5.0, 1.5), 2.47 (s, 3H), 2.45-2.41 (m, 1H), 2.32 (ddd, 1H, *J* = 15.5, 4.0, 1.5), 2.35-2.10 (m, 2H), 1.70-1.50 (m, 2H).

2-(Hydroxy(phenyl)methyl)-8-thiabicyclo[3.2.1]octan-3-one [23]



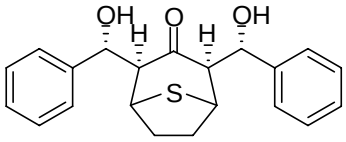
66a

Procedure adapted from reference **94**

NaOEt (63.2 mg, 0.93 mmol) was dissolved in dry THF (10 mL) and cooled to 0 ºC. TMS-TBON **55** (199 mg, 0.93 mmol) in dry THF (1.0 mL) was then added dropwise. After stirring for 0.5 h, benzaldehyde (0.09 mL, 0.93 mmol) was slowly added and the reaction was stirred for another 2.5 h at rt. The reaction was quenched with water, extracted with CH_2Cl_2 (4 x 10 mL), the combined organic layers dried over $MgSO_4$ and the solvent was evaporated. Purification by FCC using hexane:AcOEt 1:1 gave the pure product in 3 % yield (7.0 mg).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.38-7.25 (m, 5H), 5.1 (d, 1H, *J* = 9.0), 3.75 (d, 1H, *J* = 2.5), 3.1 (t, 1H, *J* = 3.0), 2.95 (d, 1H, *J* = 10.5), 2.90 (br s, 1H), 2.68 (m, 2H), 2.10-1.80 (m, 4H).

2-((R)-Hydroxy(phenyl)methyl)-4-((S)-hydroxy(phenyl)methyl)-8-thiabicyclo[3.2.1]octan-3-one[22]



67

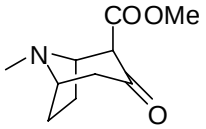
Modiefied procedure was adapted from reference **93**

MgI_2 etherate (462 mg, 1.3 mmol) was added into a solution of TBON **53** (52 mg, 0.37 mmol) in dry CH_2Cl_2 (2.0 mL). Benzaldehyde (0.09 mL, 0.9 mmol) was then added dropwise followed by the addition of $EtN(i\text{-}Pr)_2$ (0.24 mL, 1.4 mmol). The reaction was stirred 1 h at rt then quenched with saturated NH_4Cl. The mixture was extracted with CH_2Cl_2 (4 x 10 mL), dried over $MgSO_4$ and solvent was evaporated. Purification by FCC using CH_2Cl_2:MeOH 98:2 gave the titled compound as a single diastereoisomer in 78% yield (104.0 mg).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.51 (d, 4H, *J* = 7.0), 7.27 (m, 4H), 7.21 (t, 2H, *J* = 7.0), 5.58 (dd, 2H, *J* = 3.0, 10.0), 3.09 (br s, 2H), 3.06 (m, 2H), 2.90 (dd, 2H, *J* = 3.0, 10.0), 1.50 (m, 2H), 1.40 (m, 2H).

^{13}C NMR (500 MHz, $CDCl_3$) δ: 209.9, 147.7, 129.5, 129.4, 129.2, 129.0, 70.0, 50.7, 34.4.

Methyl 8-methyl-3-oxo-8-azabicyclo[3.2.1]octane-2-carboxylate[24]



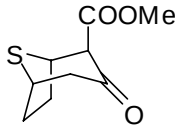
85

n-Butyllithium (0.59 mL, 1.48 mmol, 2.5 M solution in hexanes) was added dropwise into a solution of DIA (0.21 mL, 1.48 mmol) in dry THF (5.0 mL) under nitrogen atmosphere. The reaction was stirred at 0 ºC for 0.5 h and then cooled to -78 ^{o}C. A solution of tropinone **52** (188 mg, 1.35 mmol) in dry THF (1.0 mL) was added at the same temperature and the mixture was stirred for another 0.5 h. Methyl cyanoformate (0.16 mL, 2.0 mmol) was then added and the reaction left to stir for 1 h at the same temperature. The reaction was quenched by addition of $AgNO_3$ in water, AcOH and THF (0.17 g, 0.25 mL: 0.25 mL:1.0 mL), followed by addition of NH_4OH (till pH was 8). The mixture was extracted with $CHCl_3$ (4 x 10 mL), the combined organic layers were dried over $MgSO_4$ and the solvent was evaporated. Purification by FCC using hexane:AcOEt 1:1 → CH_2Cl_2:MeOH 9:1 gave the pure product as a mixture of 3 tautomers, in 60 % yield (160 mg).

mp.: 103-104°C, **Lit. mp.**: 104-105°C

^{1}H NMR (500MHz, $CDCl_3$) δ: 3.85-3.75 (m, 1H), 3.80 (s, 1H), 3.40-3.35 (m, 1H), 2.82-2.71 (m, 1H), 2.40 (s, 3H), 2.29-2.00 (m, 4H), 2.00-1.75 (m, 1H), 1.68-1.52 (m, 1H).

Methyl 3-oxo-8-thiabicyclo[3.2.1]octane-2-carboxylate[23]

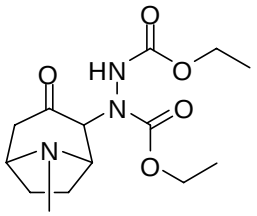


86

A solution of *n*-BuLi in hexane (2.1M, 1.32 mL, 2.73 mmol) was added dropwise to the solution of DIA (0.46 mL, 2.73 mmol) in THF (5.0 mL) at 0 ºC and mixture was stirred for 0.5h. After cooling to -78 ºC, a solution of TBON **53** (400 mg, 1.65 mmol) in THF (2.0 mL) was added and the resulting solution was stirred for another 0.5h. Methyl cyanoformate (0.31 mL, 3.9 mmol) was then added dropwise to the reaction mixture and stirred for 0.5h, followed by quenching with a solution of $AgNO_3$ (0.27 g, 1.65 mmol) in THF (1.0 mL), H_2O (0.5 mL) and AcOH (0.5 mL). After warming up the reaction mixture to rt, it was basified with NH_4OH (pH 8), diluted with water and extracted with $CHCl_3$ (4 x 10 mL). The combined organic layers were dried over $MgSO_4$. Evaporation of the solvent furnished the crude product that was further purified by FCC (hexane:Et_2O) to give the titled compound as a transparent oil (264 mg, 80 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 12.15 (br s, 1H), 4.33 (ap d, 1H, *J* = 5.0), 4.19 (m, 0.5H), 3.95 (m, 0.25 H), 3.89-3.82 (m, 3H), 3.80 (br s, 3H), 3.77 (br s, 0.5H), 3.75 (br s, 1.5H), 3.55 (ap d, 0.5 H, *J* = 3.5), 3.02-2.55 (m, 8H), 2.37-1.88 (m, 7H).

Diethyl-1-(8-methyl-3-oxo-8-azabicyclo[3.2.1]octan-2-yl) hydrazine-1,2-dicarboxylate[24]

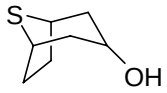


104

n-Butyllithium (4.03 mL, 10.2 mmol, 2.5 M solution in hexanes) was added dropwise into solution of DIA (1.40 mL, 10.2 mmol) in dry THF (5.0 mL) under nitrogen atmosphere. The mixture was stirred at 0 ºC for 0.5 h, cooled down to -78 ºC and tropinone **52** (1.49 g, 10.0 mmol) was added. The mixture was stirred for another 0.5 h followed by the addition of DEAD (3.0 mL, 19 mmol). The reaction mixture was then stirred for 0.5 h at
-78 ºC and quenched with NH_4Cl. The reaction was allowed to warm up to rt and extracted with CH_2Cl_2 (4 x 20 mL), dried over Na_2SO_4 and solvent was evaporated. Purification by column chromatography ($CHCl_3$:MeOH 95:5) afforded the product as a yellowish oil in 75 % yield (2.34 g).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.81-7.09 (br s, 1H), 4.99-5.21 (br s, 1H), 4.13 (q, 4H, *J* = 7.0), 3.68-3.58 (br s, 1H), 3.41 (br s, 1H), 2.69 (d, 1H, *J* = 15.0), 2.52 (br s, 3H), 2.23 (d, 1H, *J* = 15.5), 1.80-2.12 (br s, 3H), 1.49 (m, 1H), 1.19 (tt, 6H, *J* = 7.0).

8-Thiabicyclo[3.2.1]octan-3-ol[112]



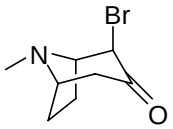
159

$NaBH_4$ (69 mg, 1.85 mmol) was added in small portions to the solution of TBON **53** (50 mg, 0.35 mmol) in EtOH (2.0 mL) at -78 ºC. NH_4Cl (saturated solution in water, 0.5 ml) was added and the mixture was stirred at the same temperature for 3 h. The mixture was then allowed to warm up to rt and AcOH (5 %, 1.0 mL) was added. The mixture was extracted with $CHCl_3$ (4 x 10 mL) and the combined organic layers were washed with sat solution of Na_2CO_3, water, dried over $MgSO_4$ and the solvent was evaporated to afford the crude product as a mixture of 2 diastereoisomers in 3.4:1 ratio. FCC using hexane:Et_2O 1:9 gave the pure products in 57 % combined yield (29.0 mg).

^{1}H NMR (500 MHz, $CDCl_3$, major diastereoisomer) δ: 3.95 (m, 1H), 3.65 (m, 2H), 2.33-2.78 (m, 2H), 2.08-1.97 (m, 3H), 1.77 (ap t, 2H, *J* = 12), 1.31 (m, 2H).

^{1}H NMR (500 MHz, $CDCl_3$, minor diastereoisomer) δ: 4.16 (ap t, 1H, *J* = 5.0), 3.61 (m, 2H), 2.49 (m, 2H), 2.30 (m, 2H), 2.10-2.05 (m, 4H).

2-Bromo-8-methyl-8-azabicyclo[3.2.1]octan-3-one[113]

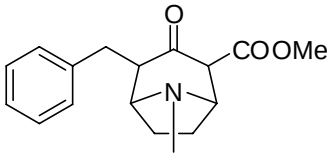


181

n-Buthyllithium (0.6 mL, 1.5 mmol, 2.5 M solution in hexane) was added dropwise into solution of DIA (0.21 mL, 1.5 mmol) in dry THF under nitrogen atmosphere. The solution was stirred at 0 ºC for 0.5 h, cooled down to -78 ºC and tropinone **52** (188 mg, 1.35 mmol) in dry THF (1.0 mL) was added dropwise. After 0.5 h at the same temperature, NBS (238 mg, 1.35 mmol) in dry THF (1.0 mL) was added and mixture was stirred for 1.5 h while the temperature was allowed to rise to -10 ºC. The reaction was quenched with saturated NH_4Cl and extracted with CH_2Cl_2. After drying over $MgSO_4$ and evaporation of solvent crude product was obtained (128 mg). Product was purified by column chromatography (deactivation of silica gel, hexane:AcOEt 1:1 → CH_2Cl_2:MeOH 9:1) to give pure compound in 7 % yield (24.0 mg).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.88 (dd, 1H, *J* = 5.0, 8.0), 4.16 (m, 2H), 3.93 (ddd, 1H, *J* = 4.5, 7.5, 8.0), 2.68 (br s, 4H), 2.42 (m, 1H), 2.36 (m, 1H), 2.19 (m, 1H), 1.97 (m, 1H).

Methyl 4-benzyl-8-methyl-3-oxo-8-azabicyclo[3.2.1]octane-2-carboxylate [114]

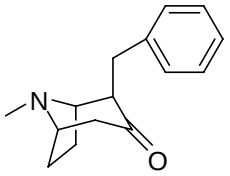


213

n-Butyllithium (0.32 mL, 0.78 mmol, 2.5 M solution in hexanes) was added dropwise into a solution of DIA (0.11 mL, 0.78 mmol) in dry THF (5.0 mL) under nitrogen atmosphere. The reaction was stirred at 0 ºC for 0.5 h and then cooled to -78 ^{o}C. A solution of tropinone ester **219** (66.6 mg, 0.34 mmol) in dry THF (1.0 mL) was added at the same temperature and the mixture was stirred for another 0.5 h. Benzyl chloride (0.04 mL, 0.37 mmol) was then added and the mixture stirred while warming up to rt for 17.5 h. The reaction mixture was then poured into a saturated NH_4Cl, extracted with Et_2O (4 x 10 mL), the combined organic layers dried over $MgSO_4$ and the solvent was evaporated. Purification by PTLC (deactivation of silica gel, hexane:AcOEt 1:1) gave the product in
7 % yield (7.0 mg).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.45-7.10 (m, 5H), 3.92-3.80 (dd, 1H), 3.80-3.73 (s, 3H), 3.58-3.48 (m, 1H), 3.38-3.21 (m, 1H), 3.17-2.94 (m, 1H), 2.94-2.82 (m, 2H), 2.38 (s, 3H), 2.35-2.25 (m, 2H), 1.80-1.40 (m, 2H).

2-Benzyl-8-methyl-8-azabicyclo[3.2.1]octan-3-one



214

n-Buthyllithium (0.56 mL, 1.17 mmol, 2.1 M solution in hexanes) was added dropwise into a solution of DIA (0.18 mL, 1.28 mmol) in dry toluene (6.0 mL) under nitrogen atmosphere. The solution was stirred at 0 ºC for 0.5 h, cooled down to -45 ºC and a solution of tropinone **52** (147.3 mg, 1.06 mmol) in dry toluene (2.0 mL) and N^1-(2-(dimethylamino)ethyl)-N^1, N^2, N^3-trimethylethane-1,2-diamine (0.66 mL, 3.17mmol) were added. The reaction mixture was stirred at the same temperature for 50 min followed by the addition of benzyl bromide (0.63 ml, 5.30 mmol) and warmed up to -23 ºC. The reaction was stirred at -23 ºC for another 50 min, quenched with citric acid (40 %, 10 mL) and allowed to warm up to rt. The reaction mixture was extracted with AcOEt (4 x 30 mL) and the combined organic layers were washed with $NaHCO_3$ (10 mL), brine, dried over $MgSO_4$ and the solvent was evaporated to give crude product as a mixture of diastereoisomers in 1:1.5 ratio. FCC using hexane:AcOEt 8:2 → $CHCl_3$:MeOH 9:1 afforded the major isomer in 11 % yield (29.0 mg).

^{1}H NMR (500MHz, $CDCl_3$) δ**:** 7.30 (ap t, 2H, *J* = 7.5), 7.21 (t, 1H, *J* = 7.5), 7.15 (ap d, 1H, *J* = 7.5), 3.45 (br s, 1H), 3.33 (dd, 1H, *J* = 4.5, 15), 3.16 (br s, 1H), 2.98 (br s, 1H), 2.79 (br s, 1H), 2.45 (br s, 3H), 2.35 (dd, 1H, *J* = 9.5, 15), 2.23 (d, 1H, *J* = 15), 2.10 (m, 1H), 1.94 (m, 1H), 1.75 (m, 1H), 1.60 (m, 1H).

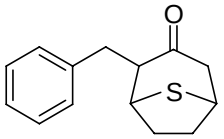
^{13}C NMR (125MHz, $CDCl_3$) δ: 209.8, 140.0, 129.2, 128.7, 126.3, 64.5, 62.1, 55.8, 47.7, 38.5, 32.1, 27.6, 23.4.

IR (**D**RIFT) ν_{max}: 1706, 1347, 1127, 751, 699 cm^{-1}.

LRMS (EI), *m/z* (relative intensity): 229 ($[M]^+$, 38), 110 (7), 97 (24), 91 (10), 82 (100).

HRMS *m/z* calcd. for $C_{15}H_{19}NO$: 229.1467; found: 229.1467.

2-Benzyl-8-thiabicyclo[3.2.1]octan-3-one[23]

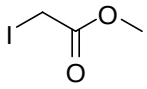


216

Benzylated ester of TBON **223** (15.2 mg, 0.05 mmol) was dissolved in H_2SO_4 (10 %, 2.0 mL) and refluxed over 3 h. The reaction was allowed to cool down to rt. and extracted with Et_2O (4 x 10 mL). The combined organic layers were washed with saturated $NaHCO_3$, dried over $MgSO_4$ and solvent was evaporated. Purification by PTLC (hexane:AcOEt 7:3) afforded pure product as a mixture of 2 diastereoisomers in 1:1.5 ratio in 14 % yield (2.0 mg).

^{1}H NMR (500 MHz, $CDCl_3$, major diastereoisomer) δ: 7.35-7.19 (m, 5H), 3.72 (br s, 1H), 3.35 (br s, 1H), 3.09 (dd, 1H, *J* = 13.5, 11.0), 2.88 (dd, 1H, *J* = 13.5, 4.5), 2.81 (d, 1H, *J* = 14.0), 2.68 (d, 1H, *J* = 9.0), 2.57 (dd, 1H, *J* = 17.0, 3.0), 2.12 (m, 2H), 1.92 (m, 2H).

Methyl 2-iodoacetate[115]

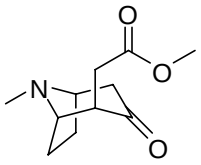


218

Methyl 2-chloroacetate (4.5 mL, 50 mmol) and NaI (15 g, 100 mmol) were dissolved in acetone (30 mL) and refluxed for 2.5 h. After cooling down to rt., the mixture was filtered through Celite, the residue washed with Et_2O and the combined solvent was evaporated to afford yellowish liquid in 83 % (8.26 g).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.75 (br s, 3H), 3.70 (br s, 2H).

Methyl 2-(8-methyl-3-oxo-8-azabicyclo[3.2.1]octan-2-yl)acetate



219

A solution of *n*-BuLi in hexane (2.1M, 0.19 mL, 0.40 mmol) was added dropwise to the solution of DIA (0.05 mL, 0.40 mmol) in THF (5.0 mL) at 0 ºC under nitrogen atmosphere and the mixture was stirred for 0.5h. After cooling to -78 ºC, a solution of tropinone **52** (50.0 mg, 0.37 mmol) in THF (1.0 mL) was added and the resulting solution was stirred for another 0.5h. Methyl iodoacetate (86.0 mg, 0.56 mmol) was added and the reaction was allowed to warm up to rt while stirring overnight. The reaction was quenched with saturated NH_4Cl, extracted with CH_2Cl_2 (4 x 10 mL), the combined organic layers dried over $MgSO_4$ and the solvent was evaporated. Purification by FCC (CH_2Cl_2:MeOH 9:1) gave the titled compound in 53 % yield (42.0 mg).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.70 (s, 3H), 3.49 (m, 1H), 3.35 (ddd, 1H, *J* = 1.5, 4.0, 7.0), 3.28 (dddd, 1H, *J* = 1.5, 5.0, 6.5, 7.0), 2.86 (dd, 1H, *J* = 7.0, 16.5), 2.59 (s, 3H), 2.7 (m, 1H), 2.18 (dd, 1H, *J* = 3.0, 15.0), 2.06 (m, 1H), 2.04 (dd, 1H, *J* = 6.5, 16.5), 1.98 (m, 1H), 1.56-1.47 (m, 2H).

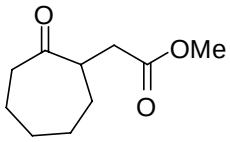
^{13}C NMR (500MHz, $CDCl_3$) δ: 208.7, 173.3, 65.7, 62.0, 52.1, 49.8, 46.0, 37.3, 31.4, 27.9, 24.2

IR (**D**RIFT) ν_{max}: 1736, 1708 cm^{-1}.

LRMS (EI), *m/z* (relative intensity): 211 ($[M]^+$, 21), 180 (13), 152 (49), 96 (15), 82 (100).

HRMS *m/z* calcd. for $C_{11}H_{17}NO_3$: 211.1208; found: 211.1208.

Methyl 2-(2-oxocycloheptyl)acetate[116]

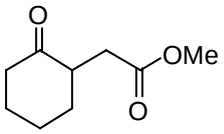


231a

A solution of *n*-BuLi in hexane (2.1 M, 0.19 mL, 0.40 mmol) was added dropwise to the solution of DIA (0.05 mL, 0.40 mmol) in THF (5.0 mL) at 0 ºC under nitrogen atmosphere and the mixture was stirred for 0.5h. After cooling to -78 ºC, a solution of cycloheptanone (0.40 mL, 0.37 mmol) in THF (1.0 mL) was added and the resulting solution was stirred for another 0.5h. Methyl iodoacetate (86.0 mg, 0.56 mmol) was added and the reaction was allowed to warm up to rt while stirring overnight. The reaction was quenched with saturated NH_4Cl, extracted with CH_2Cl_2 (4 x 10 mL), the combined organic layers dried over $MgSO_4$ and the solvent was evaporated. Purification by FCC (hexane:AcOEt 4:6) gave the titled compound in 30 % yield (31.0 mg).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.68 (br s, 3H), 3.14 (dddd, 1H, *J* = 2.5, 5.5, 8.5, 11.0), 2.95 (dd, 1H, *J* = 8.5, 16.5), 2.67 (dddd, 1H, *J* = 1.0, 4.5, 5.0, 16.0), 2.48 (ddd, 1H, *J* = 4.5, 11.5, 16.0), 2.33 (dd, 1H, *J* = 5.5, 16.5), 1.97-1.73 (m, 5H), 1.63-1.54 (m, 1H), 1.44-1.28 (m, 2H).

Methyl 2-(2-oxocyclohexyl)acetate[117]

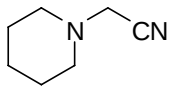


231b

A solution of *n*-BuLi in hexane (2.1M, 0.19 mL, 0.40 mmol) was added dropwise to the solution of DIA (0.05 mL, 0.40 mmol) in THF (5.0 mL) at 0 ºC under nitrogen atmosphere and the mixture was stirred for 0.5h. After cooling to -78 ºC, a solution of cyclohexanone (0.40 mL, 0.37 mmol) in THF (1.0 mL) was added and the resulting solution was stirred for another 0.5h. Methyl iodoacetate (86.0 mg, 0.56 mmol) was added and the reaction was allowed to warm up to rt while stirring overnight. The reaction was quenched with saturated NH_4Cl, extracted with CH_2Cl_2 (4 x 10 mL), the combined organic layers dried over $MgSO_4$ and the solvent was evaporated. Purification by FCC (hexane:AcOEt 7:3) gave the titled compound in 49 % yield (30.0 mg).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.74 (br s, 3H), 3.45-3.31 (m, 2H), 2.79-2.62 (m, 2H), 2.38-2.30 (m, 3H), 2.15-2.02 (m, 2H), 1.71-1.59 (m, 2H).

2-(Piperidin-1-yl)acetonitrile[90]



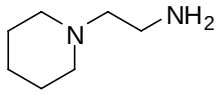
240

Chloroacetonitrile (11.9 g, 155 mmol) and Na_2CO_3 (8.29 g, 78.2 mmol) were stirred together in dry benzene (40 ml) at rt for 15 min. Piperidine (17.7 g, 20.8 mmol) dissolved in dry benzene (20 mL) was added dropwise at rt. After refluxing for 9 h, the reaction was cooled down to rt. and washed with brine (20 mL). The organic layer was dried over Na_2SO_4 and solvent was evaporated. Distillation gave the pure product in 96 % yield (18.4 g)

b.p.: 90-92 ºC/0.2 mmHg, **Lit b.p.**: 109-110 ºC/11mmHg

^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.51 (br s, 2H), 2.54 (ap t, 4H, *J* = 5.5), 1.64 (m, 4H), 1.46 (m, 2H).

2-(Piperidin-1-yl)ethanamine[90]



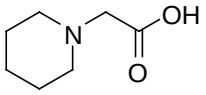
241

$LiAlH_4$ (4.97 g, 128.4 mmol) in dry Et_2O (60 ml) was stirred at rt for 0.5 h. Temperature was cooled down to 0 ºC and solution of 2-(piperidin-1-yl)acetonitrile **245** (15.9 g,128.4 mmol) in Et_2O was added dropwise. The mixture was refluxed for 5 h in air with a $CaCl_2$ drying tube on top of the condenser. The reaction was then cooled down to rt and ice and water was added slowly followed by addition of a solution of potassium, sodium tartrate (20 %, 20 mL). The mixture was stirred at rt for 1 h, extracted with CH_2Cl_2 (4 x 20 mL), dried over $MgSO_4$ and solvent was evaporated to give a yellowish oil in 77 % yield. Distillation of crude product gave a colorless liquid in 68 % yield (11.16 g)

b.p.: 50-52ºC/0.2mmHg, **Lit. b.p.**: 79-80 ºC/2.0mmHg

^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.74 (m, 2H), 2.34-2.31 (m, 6H), 1.56-1.51 (m, 4H), 1.39 (m, 2H).

1-Piperidineacetic acid[118]



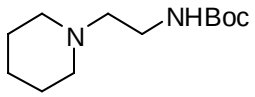
243

A solution of chloroacetic acid (5.30 g, 55.9 mmol) in dry Et_2O (20 mL) was added dropwise to the solution of piperidine (11.0 mL, 111.8 mmol) in Et_2O (50 mL) at rt. The mixture was allowed to stir for 12 h. The white crystals were filtered and washed with Et_2O (3 x 20 mL) to give the product in 99 % yield (7.91 g).

m.p.: 205-206ºC, **Lit. m.p.**: 204-205 ºC

^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.04 (br s, 1H), 3.18 (br s, 4H), 2.07 (br s, 2H), 1.97-1.92 (m, 4H), 1.72-1.67 (m, 2H).

***tert*-Butyl 2-(piperidin-1-yl)ethylcarbamate**[119]

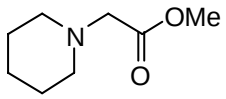


245

2-(Piperidin-1-yl)ethanamine **246** (0.2 g, 1.4 mmol) and di-*tert*-butyl dicarbonate (0.6 g, 2.8 mmol) were refluxed together in Et_3N and DMF (10 %, 10 mL) for 0.5 h. The mixture was cooled down to the rt and stirred another 0.5 h. The solvent was removed with toluene (3 x 10 mL) under vacuum to give desired product in 97 % yield (0.31 g)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.09 (br s, 1H), 3.24 (br s, 2H), 2.42 (br s, 6H), 1.59 (br s, 4H), 1.47 (br s, 11H).

Methyl 2-(piperidin-1-yl)acetate[120]

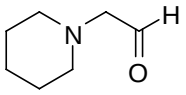


248

Methyl chloroacetate (5.0 g, 46.0 mmol) was added dropwise to a solution of piperidine (4.5 mL, 46.0 mmol) at rt. After stirring for 2 h (reaction monitored by TLC), a white precipitation was filtered off, and filtrate was concentrated to yield crude product that was purified by dry flash column chromatography (hexane : AcOEt 6:4) to give yellow oil in 69 % yield (4.98 g).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.75 (br s, 3H), 3.39 (br s, 2H), 2.73 (br s, 4H), 1.75 (br s, 4H), 1.51 (br s, 2H).

2-(Piperidin-1-yl)acetaldehyde[121]

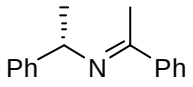


249

DIBAL-H (2.27 mL, 3.4 mmol) was added dropwise to a stirred solution of methyl 2-(piperidin-1-yl)acetate **254** (0.53 g, 3.4 mmol) in dry THF (15 mL) at -78 ºC under nitrogen atmosphere. The reaction was left to stir for 1 h, warmed up to rt and MeOH (2.0 mL) followed by saturated solution of potassium, sodium tartrate (10 mL) was added. After stirring for 0.5 h at rt, the mixture was extracted with CH_2Cl_2 (3 x 10 mL), dried over Na_2SO_4, filtered and evaporated to yield the unstable product in 58 % yield (0.197g) and 22 % alcohol (2.5:1 ratio aldehyde:alcohol by ^{1}H NMR).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.62 (t, 1H, *J* = 1.5), 4.06 (d, 2H, *J* = 1.5), 3.76-3.73 (m, 4H), 1.87-1.84 (m, 4H), 1.63-1.60 (m, 2H).

(*S*,*E*)-1-phenyl-N-(1-phenylethylidene)ethanamine[29]

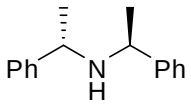


277

A mixture of (S)-(-)-α-methylbezylamine (18.46 g, 152 mmol), acetophenone (24.2 g, 202 mmol) and p-TsOH (0.38g, 2.0 mmol) was dissolved in dry benzene (100 mL) and refluxed in Soxhlet apparatus containing molecular sieves (4A) for 7 days. After the mixture was cooled down, it was washed with saturated K_2CO_3 and dried over $MgSO_4$. Evaporation of solvent gave the crude product (32.5 g, 96 %) that was used in the next step.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.95-7.88 (m, 2H), 7.57-7.23 (m, 8H), 4.90 (q, 1H, J = 6.5), 2.33 (s, 3H), 1.62 (d, 3H, J = 6.5).

(*S*)-Bis((*S*)-1-phenylethyl)amine[29]

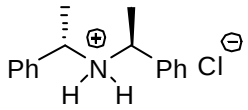


278

The crude imine **279** (32.5 g, 145.7 mmol) was dissolved in dry THF (50 mL) and hydrogenated on 30 % Pd/C catalyst (0.86 g) in a Paar apparatus for 17 h. When reaction was completed (monitored by ^{1}H NMR), the solution was filtered through celite and the solvent was evaporated to afford the crude product (31.7 g, 97 %). Distillation (118-120 ºC) gave the pure product in 84% yield (27.9 g).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.43-7.22 (m, 10H), 3.55 (q, 2H, J = 6.5), 1.50 (br s, 1H), 1.35 (d, 6H, J = 6.5).

(*S*)-Bis((*S*)-1-phenylethyl)amine hydrochloride[29]



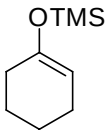
279

Amine **280** (27.9 g, 123.9 mmol) was diluted with EtOH (30 ml) and poured carefully into a boiling mixture of water (90 ml), EtOH (60 ml) and conc. HCl (14 ml). The resulting solution was set aside to crystallize. Filtration to collect the crystals afforded pure amine hydrochloride in 75 % yield (24.3 g).

m.p. 264-266ºC; **Lit. mp.:** > 300ºC

$[\alpha]^{25}_{D}$ = -85.8 (c 4.0, 95% EtOH); **Lit.** $[\alpha]^{25}_{D}$ = -71.8 (c 4.0, 100% EtOH)

Cyclohexenyloxytrimethylsilane[122]

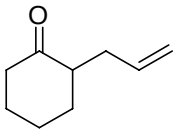


280

n-Buthyllithium (0.44 mL, 1.1 mmol, 2.5 M solution in hexanes) was added dropwise into a solution of DIA (0.15 mL, 1.1 mmol) in dry THF (5.0 mL) under nitrogen atmosphere. The solution was stirred at 0 ºC for 0.5 h, cooled down to -78 ºC followed by the addition of TMSCl (0.69 mL, 5.5 mmol). The reaction mixture was stirred for another 5 min and cyclohexanone (0.11 mL, 1.1 mmol) in dry THF (2.0 mL) was added. The solution was stirred for another 20 min at -78º C and Et_3N (0.98 mL, 7.0 mmol) added. The reaction was allowed to warm up to rt and solvent removed on a rotavap. The precipitate was suspended in dry hexane and filtered through celite and $MgSO_4$. After evaporation of the solvent the pure product was obtained in 70 % yield (131.0 mg)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.87 (br s, 1H), 2.35 (ap t, 2H, *J* = 6.5), 2.03-1.98 (m, 4H), 1.90-1.85 (m, 2H), 1.73 (m, 1H), 1.68-1.64 (m, 2H), 1.58-1.49 (m, 3H), 0.18 (br s, 9H).

2-Allylcyclohexanone[123]



281

A solution of *n*-BuLi in hexane (2.5 M, 4.03 mL, 10.2 mmol) was added dropwise to the solution of DIA (1.40 mL, 10.2 mmol) in THF (5.0 mL) at 0 ºC under nitrogen atmosphere and the mixture was stirred for 0.5h. After cooling to -78 ºC, cyclohexanone (1.0 mL, 10.0 mmol) followed by HMPA (5.2 mL, 30.6 mmol) was added and the resulting solution was stirred for another 0.5 h. Allyl bromide (4.5 mL, 51 mmol) was then added and the reaction stirred for 4 h at the same temperature. The reaction was quenched with saturated NH_4Cl, extracted with Et_2O (4 x 20 mL), the combined organic layers dried over Na_2SO_4 and the solvent was evaporated. Purification by FCC (hexane:AcOEt 8:2) gave the titled compound in 28 % yield (0.39 g).

Alternative approach A:

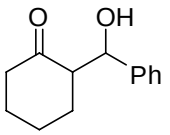
TMS-cyclohexanone **282** (130.6 mg, 0.77 mmol) was dissolved in dry THF (3.0 mL) and cooled down to 0 ºC. MeLi.LiBr (0.51 mL, 0.77 mmol) was added dropwise and stirred at the same temperature for 1 h. The reaction was cooled down to -78 ºC and HMPA (0.39 mL, 2.31mmol) was added, followed by addition of allyl bromide (0.44 mL, 0.77 mmol). After stirring for 4 h at the same temperature, the reaction was quenched with saturated NH_4Cl, extracted with Et_2O (4 x 10 mL), washed with brine (10 mL) and dried over $MgSO_4$. The solvent was evaporated to afford crude product that was purified on column chromatography (hexane:AcOEt 8:2) to give the titled compound in 52 % yield (45.0 mg).

Alternative approach B:

A solution of *n*-BuLi in hexane (2.5 M, 0.17 mL, 0.43 mmol) was added dropwise to the solution of DIA (0.06 mL, 0.43 mmol) in THF (2.0 mL) at 0 ºC under nitrogen atmosphere and the mixture was stirred for 0.5h. After cooling to -78 ºC, cyclohexanone (0.04 mL, 0.43 mmol) was added and the resulting solution was stirred for another 10 min. Chiral tropinone enolate {obtained by stirring TMS-tropinone **54** (96.6 mg, 0.43 mmol) in dry THF (3.0 mL) with MeLi. LiBr (0.38 mL, 0.43 mmol) at 0 ºC for 1 h} was then added and the reaction stirred for 0.5 h at the same temperature. HMPA (0.22 mL, 1.29 mmol) was added followed by allyl bromide (0.19 mL, 2.15 mmol) and the resulting solution was stirred for 19 h while warning to rt. The reaction was quenched with saturated NH_4Cl, extracted with Et_2O (4 x 20 mL), the combined organic layers dried over Na_2SO_4 and the solvent was evaporated. Purification by FCC (hexane:AcOEt 8:2) gave a mixture of diastereoisomers in 26 % yield (14.0 mg).

^{1}H NMR (500 MHz, $CDCl_3$) δ**:** 5.81-5.61 (m, 1H), 5.05-4.97 (m, 2H), 2.55-2.43 (m, 1H), 2.40-2.01 (m, 5H), 2.00-1.58 (m, 4H), 1.38-1.23 (m, 1H).

2-(Hydroxy(phenyl)methyl)cyclohexanone[124]



287

A solution of *n*-BuLi in hexane (2.5 M, 4.03 mL, 10.2 mmol) was added dropwise to the solution of DIA (1.40 mL, 10.2 mmol) in THF (5.0 mL) at 0 ºC under nitrogen atmosphere and the mixture was stirred for 0.5h. After cooling to -78 ºC, cyclohexanone (1.0 mL, 10.0 mmol) followed by HMPA (5.2 mL, 30.6 mmol) was added and the resulting solution was stirred for another 0.5 h. Benzaldehyde (1.5 mL, 15 mmol) was then added and the reaction stirred for 2 mins at the same temperature. The reaction was quenched with saturated NH_4Cl, warmed up to rt, extracted with CH_2Cl_2 (4 x 10 mL), the combined organic layers dried over Na_2SO_4 and the solvent was evaporated. Purification by FCC (hexane:AcOEt 8:2) gave a mixture of 2 diastereoisomers in 1:13 ratio in 68 % combined yield (0.95 g).

Alternative approach:

A solution of *n*-BuLi in hexane (2.5 M, 0.17 mL, 0.43 mmol,) was added dropwise to the solution of DIA (0.06 mL, 0.43 mmol)) in THF (2.0 mL) at 0 ºC under nitrogen atmosphere and the mixture was stirred for 0.5h. After cooling to -78 ºC, cyclohexanone (0.04 mL, 0.43 mmol) and the resulting solution was stirred for another 10 min. Chiral tropinone enolate {obtained by stirring TMS-tropinone **54** (96.6 mg, 0.43 mmol) in dry THF (3.0 mL) with MeLi. LiBr (0.38 mL, 0.43 mmol) at 0 ºC for 1 h} was then added and the reaction stirred for 1 h at the same temperature. Benzaldehyde (0.22 mL, 2.15 mmol) was then added dropwise and the reaction was stirred for another 5 min followed by addition of saturated NH_4Cl.The reaction was warmed up to rt, extracted with CH_2Cl_2 (4 x 10 mL), the combined organic layers dried over $MgSO_4$ and the

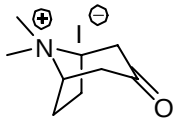
solvent was evaporated. Purification by FCC (hexane:AcOEt 8:2) gave a mixture of 2 diastereoisomers in 1:26.7 ratio in 40 % combined yield (35 mg).

Note: When the reaction was carried out with achiral tropinone enolate, the yield of product was 60 % (54.0 mg) as a mixture of 2 diastereoisomers in 1:7.6 ratio.

$[\alpha]^{22}_{D}$ = 0.1 (c 1.2, $CHCl_3$); **Lit.** $[\alpha]^{24}_{D}$ = - 24.2 (c 1.03, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.37-7.28 (m, 5H), 4.80 (dd, 1H, *J* = 2.5, 8.5), 3.90 (d, 1H, *J* = 2.5), 2.63 (ddd, 1H, *J* = 5.5, 8.5, 13.0), 2.50 (dddd, 1H, *J* = 1.5, 3.0, 4.5, 13.5), 2.37 (ddd, 1H, *J* = 6.0, 13.5, 13.5), 2.10 (dddd, 1H, *J* = 3.0, 3.0, 6.0, 13.0), 1.80 (m, 1H), 1.73-1.52 (m, 3H), 1.32 (m, 1H).

8,8-Dimethyl-3-oxo-8-azoniabicyclo[3.2.1]octane iodide[76]

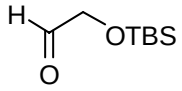


288

Methyl iodide (2.95 mL, 47.3 mmol) was added dropwise to a solution of tropinone **52** (4.97 g, 35.8 mmol) in EtOH (30 mL) at r.t. The mixture was stirred at the same temp for 2h and the solvent was evaporated to give a brownish white precipitate (9.71 g) that was homogenous by ^{1}H NMR. The crude product was directly used in next step. A sample for measurement of melting point was re-crystallized from MeOH:H_2O (1:1).

mp.: 260-263 ºC, **Lit. mp**.: 263-265 ºC

2-(tert-Butyldimethylsilyloxy)acetaldehyde[125]

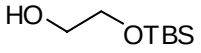


289

A solution of TBSCl (1.25 g, 8.25 mmol) in dry CH_2Cl_2 (8.0 mL) was added dropwise at - 50ºC to a mixture of glycerol (11.75 mL, 165.5 mmol) and imidazole (1.68 g, 24.75 mmol) in dry CH_2Cl_2 and DMF (2.5:1, 35 mL). The cold bath was removed and the mixture stirred for 1 h at rt followed by the addition of water. The reaction mixture was the extracted with CH_2Cl_2 (4 x 30 mL) and the combined organic layers were washed with water, brine, dried over $MgSO_4$, and the solvent evaporated to afford TBS-glycerol as clear a colorless oil (2.93 g). This material was dissolved in CH_2Cl_2 (25 mL) and $NaOI_4$ (4.6 g, 8.4 mmol) in water (25 mL) was added. The reaction mixture was the stirred for 3 h at rt. The organic layer was separated, was washed with water, brine and dried over Na_2SO_4. After evaporation of the solvent, the crude product was obtained in 49 % yield (0.71 g) with >90% purity by ^{1}H NMR and used in the next step.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.71 (br s, 1H), 4.22 (s, 2H), 0.94 (br s, 9H), 0.11 (br s, 6H).

2-(*tert*-Butyldimethylsilyloxy)ethanol[126]

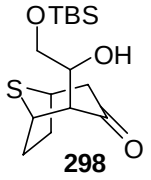


295

Ethylene glycol (5.0 mL, 90 mmol) was added dropwise to a suspension of NaH (80 %, 2.7 g, 90 mmol) in THF at 0 ^{o}C. After stirring at rt for 45 min., TBSCl (13.5 g, 90 mmol) was added in small portions and the mixture was allowed to stir at rt for another 1.5 h. The solvent was evaporated, water was added and the mixture extracted with CH_2Cl_2 (4 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. FCC using hexane → AcOEt gave the pure product in 45 % yield (7.4 g).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.77-3.64 (m, 4H), 1.95 (br s, 1H), 0.92 (br s, 9H), 0.10 (br s, 3H), 0.09 (br s 3H).

2-(2-(*tert*-Butyldimethylsilyloxy)-1-hydroxyethyl)-8-thiabicylclo[3.2.1]octan-3-one



298

Modiefied procedure was adapted from reference **39**

n-Butyllithium (0.05 mL, 0.11 mmol, 2.20 M solution in hexane) was added dropwise in to solution of DIA (0.02 mL, 0.11 mmol) in dry THF (5.0 mL) at 0 ºC under nitrogen atmosphere. The solution was stirred at the same temperature for 0.5 h and than cooled down to -78 ºC. A solution of TBON **53** (14.2 mg, 0.1 mmol) in THF (0.5 mL) was added dropwise over 30 s. The reaction mixture was the stirred for another 1 h at the same followed by the addition of the solution of aldehyde **292** (18.5 mg, 0.1 mmol) in THF (0.5 mL). After stirring for 2.5 h at -78 ºC, the reaction was quenched with NH_4Cl aq. The mixture was stirred for another 0.5 h at rt, then poured into 1:1 mixture of Et_2O and water (10 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (4 x 10 mL). The Combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated. Purification by column chromatography (hexane: AcOEt 7:3) gave the titled compound in 90 % yield (28 mg).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.13 (m, 1H), 3.79 (m, 1H), 3.71-3.67 (m, 3H), 2.87-2.83 (m, 2H), 2.69 (dd, 1H, *J* = 3.0, 7.0), 2.63 (dd, 1H, *J* = 3.0, 16.0), 2.24-2.09 (m, 2H), 2.02-1.96 (m, 2H), 0.90 (br s, 9H), 0.09 (br s, 3H), 0.08 (br s, 3H).

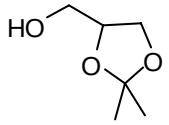
^{13}C NMR (500 MHz, $CDCl_3$) δ: 209.8, 73.6, 64.5, 61.5, 52.4, 49.3, 46.4, 34.2, 33.9, 26.1, 18.5, -5.1, -5.2.

IR (**D**RIFT) ν_{max}: 3474, 1705 cm^{-1}.

LRMS (CI), *m/z* (relative intensity): 334 ($[M+17]^+$)

HRMS *m/z* calcd. for $C_{15}H_{29}O_3SSi$: 316.1528 (M + H = 317.1607); found: 317.1608

(2,2-Dimethyl-1,3-dioxolan-4-yl)methanol[127]

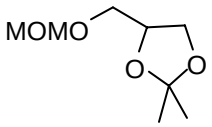


303

Glycerol (2.0 mL, 27.6 mmol), 2,2-dimethoxymethane (6.78 mL, 55.2 mmol) and p-TsOH (cat. amount) were dissolved in CH_2Cl_2 (10 mL) and stirred at rt for 1 h. The mixture was washed with $NaHCO_3$ and the organic solvent evaporated. The crude product was dissolved in Et_2O and the solution was filtered through a short silica gel pad. After evaporation of the solvent *in vacuo*, the product was obtained in 80 % yield (2.91 g).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.25 (dddd, 1H, *J* = 3.5, 5.5, 6.5, 6.5), 4.04 (dd, 1H, *J* = 6.5, 8.0), 3.80 (dd, 1H, *J* = 6.5, 8.0), 3.74 (ddd, 1H, *J* = 4.0, 6.0, 11.5), 3.60 (ddd, 1H, *J* = 5.0, 6.5, 11.5), 1.45 (s, 3H), 1.38 (s, 3H).

4-((Methoxymethoxy)methyl)-2,2-dimethyl-1,3-dioxolane[128]

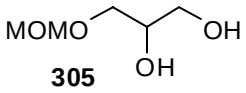


304

Protected alcohol **304** (1.28 g, 11.0 mmol) in dry THF (5.0 mL) was added dropwise to suspension of NaH (0.32 g, 11.0 mmol) in dry THF (10 mL) under nitrogen atmosphere. The reaction mixture was stirred at rt for 0.5 h and then MOMCl (0.84 mL, 11.0 mmol) was added. After stirring for 2 h at rt, the reaction was quenched with NH_4Cl aq. and the mixture extracted with CH_2Cl_2 (4 x 30 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated to give the titled compound as colorless oil in
61 % yield (1.18 g).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.66 (br s, 2H), 4.30 (ddd, 1H, *J* = 6.0, 6.0, 12.0), 4.08 (dd, 1H, *J* = 6.5, 8.0), 3.74 (dd, 1H, *J* = 6.5, 8.0), 3.58 (dd, 1H, *J* = 2.0, 6.0), 3.37 (br s, 2H), 1.43 (br s, 3H), 1.37 (br s, 3H).

3-(Methoxymethoxy)propane-1,2-diol[126]

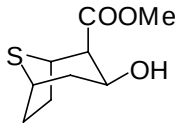


305

MOM protected alcohol **305** (1.18 g, 6. 71 mmol) was dissolved in acetic acid (80 % solution in water, 20 mL) and refluxed. After 1 h the solution was allowed to cool down to rt and extracted with AcOEt (4 x 20 mL). The combined organic layers were washed with $NaHCO_3$, dried over $MgSO_4$ and solvent the evaporated to furnish the product homogenous by ^1H NMR in 34 % yield (0.31 g).

^1H NMR (500 MHz, $CDCl_3$) δ: 4.67 (br s, 2H), 3.76-3.59 (m, 5H), 3.41 (br s, 3H).

Methyl 3-hydroxy-8-thiabicyclo[3.2.1]octane-2-carboxylate



***cis*-307**

The β–ketoester **222** (100 mg, 0.48 mmol) was dissolved in absolute EtOH (2.0 mL) at rt. The solution was cooled to -78 ^{o}C, $NaBH_4$ (108 mg, 2.8 mmol) was added in one portion followed by slow addition of NH_4Cl aq. (excess) at same temperature. The reaction mixture was stirred for 3h while warming up to r.t, quenched with AcOH and diluted with water. The reaction mixture was extracted with $CHCl_3$ (4 x 10 mL) and the combined organic layers were dried over Na_2SO_4. Evaporation of the solvent furnished a yellowish oil in 1:1 diastereoisomeric ratio. Column chromatography (hexane:Et_2O, 6:4) afforded two separable diastereoisomers (58 mg, 60 % combined yield).

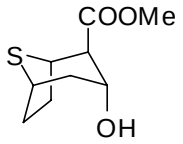
^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.43 (ddd, 1H, *J* = 3.0, 3.0, 6.0), 3.93 (ap d, 1H, *J* = 5), 3.78, (br s, 3H), 3.62 (m, 1H), 3.11 (m, 1H), 3.06 (ap d, 1H, *J* = 2.5), 2.57-2.46 (m, 2H), 2.24 (m, 2H), 2.08-2.00 (m, 2H).

^{13}C NMR (500 MHz, $CDCl_3$) δ: 173.7, 66.5, 54.0, 52.3, 46.3, 45.4, 41.9, 33.8, 32.1.

IR (**D**RIFT) ν_{max}: 3555, 1735 cm^{-1}.

LRMS (EI), *m/z* (relative intensity): 202 ([M]$^{+}$, 100), 184 (17), 148 (29), 137 (25), 81 (35).

HRMS *m/z* calcd. for $C_9H_{14}O_3S$: 202.0664; found: 202.0664.



***trans*-307**

^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.99 (t, 1H, *J* = 5.0), 3.87-3.79 (m, 2H), 3.76 (br s, 3H), 3.60 (m, 1H), 3.13 (t, 1H, *J* = 5.0), 2.22-1.95 (m, 6H).

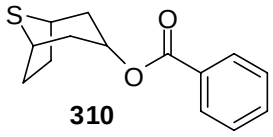
^{13}C NMR (500 MHz, $CDCl_3$) δ: 173.4, 66.8, 52.1, 48.4, 45.8, 41.6, 33.5, 32.4, 31.2.

IR (**D**RIFT) ν_{max}: 3555, 1735 cm^{-1}.

LRMS (EI), *m/z* (relative intensity): 202 ($[M]^+$, 100), 184 (17), 148 (29), 137 (25), 81 (35).

HRMS *m/z* calcd. for $C_9H_{14}O_3S$: 202.0664; found: 202.0664.

8-Thiabicyclo[3.2.1]octan-3-yl benzoate[129]



310

Benzoyl chloride (0.02 mL, 0.19 mmol) followed by Et_3N (0.05 mL, 0.36 mmol) were added to solution of the alcohol **165** (14 mg, 0.09 mmol) in dry CH_2Cl_2 (1.0 mL). the mixture was stirred for 1.5 h at rt, washed with water and brine. The organic layer was dried over $MgSO_4$ and the solvent was evaporated. Purification by PTLC (hexane:AcOEt 7:3) afforded the pure product in 56 % yield (12.0 mg).

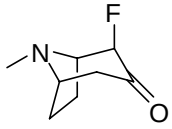
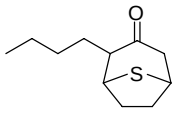
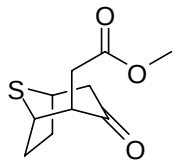
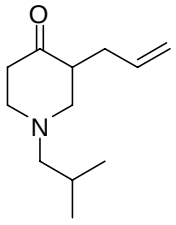
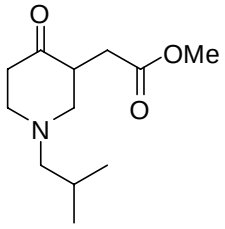
^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.02 (ap d, 2H, *J* = 8.5), 7.56 (ap t, 1H, *J* = 7.5), 7.44 (ap t, 2H, *J* = 7.5), 5.34 (m, 1H), 3.69 (br s, 2H), 2.39 (ddd, 2H, *J* = 5.5, 5.5, 12.5), 2.19-2.11 (m, 4H), 2.01 (ap t, 2H, *J* = 12.0).

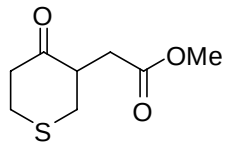
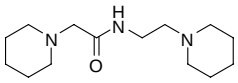
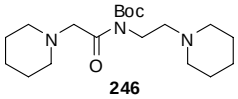
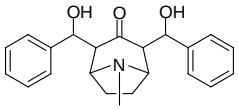
Magnesium iodide etherate

$MgI_2.Et_2O$

Magnesium tunings (1.0 g, 41.7 mmol) and I_2 (9.5 g, 37.4 mmol) were dissolved in dry Et_2O (50 mL) and refluxed for 3 h. The reaction was allowed to cool down and excess magnesium was filtered off. After removal of solvent, a white solid was obtained in 90% yield (11.8 g, 33.7 mmol).

Table 3-1. ^{1}H NMR data for compounds not fully characterized due to low yields from the reaction and/or inability to separate the compounds

	STRUCTURE	***^{1}H NMR (500 MHz, $CDCl_3$) δ:***	***YIELD***
1.	 **179**	4.42 (m, 1H), 3.99 (ap t, 1H *J* = 5.0), 3.92 (ap d, 1H, *J* = 5.0), 3.83 (m, 1H), 3.60 (m, 2H), 3.13-3.10 (m, 2H), 2.96 (br s, 2H), 2.89 (br s, 3H), 2.86-2.80 (m, 4H), 2.55-2.47 (m, 2H), 2.23 (ap t, 2H, *J* = 2.0), 2.07-1.94 (m, 3H)	9 % (mixture of 2 diaster. in 1:1 ratio)
2.	 **217**	3.82-3.79 (m, 1H), 3.73-3.63 (m, 2H), 2.83-2.76 (m, 2H), 2.70-2.67 (m, 1H), 2.64 (dd, 1H, *J* = 3.5, 15.5), 2.52 (dd, 1H, *J* = 3.5, 15.5), 2.44 (m, 1H), 2.27-2.21 (m, 1H), 2.14-1.92 (m, 3H), 1.80-1.73 (m, 1H), 1.69-1.62 (m, 1H), 1.33 (t, 3H, *J* = 6.5)	10 % (mixture of 2 diaster. in 1:1 ratio)
3.	 **220**	3.84 (m, 1H), 3.74 (m, 1H), 3.713 (br s, 3H), 3.708 (br s, 3H), 3.66 (m, 1H), 3.51 (m, 2H), 3.40 (m, 1H), 2.95 (dd, 1H, *J* = 7.0, 16.5), 2.88 (m, 1H), 2.74 (m, 1H), 2.68 (dd, 1H, *J* = 3.5, 16.0), 2.69 (m 1H), 2.30 (m 1H), 2.20-1.91 (m, 10H)	10 % (mixture of 2 diaster. in 1:1.4 ratio)
4.	 **228**	5.76 (m, 1H), 5.06-5.01 (m, 2H), 3.01-2.95 (m, 2H), 2.58-2.53 (m, 3H), 2.46-2.35 (m, 2H), 2.21-2.14 (m, 3H), 2.05 (ap q, 1H, *J* = 9.5), 1.77 (h, 1H, *J* = 6.5), 0.94 (d, 3H, *J* = 1.5), 0.93 (d, 3H, *J* = 1.5)	58 % (LDA) 50 % (**13**)
5.	 **231c**	3.69 (br s, 6H), 3.16-3.08 (m, 6H), 2.79 (d, 1H, *J* = 6.5), 2.76 (d, 1H, *J* = 6.5), 2.72-2.63 (m, 3H), 2.46-2.32 (m, 5H), 2.22-2.12 (m, 7H), 1.78 (sep, 2H, *J* = 6.5), 0.944 (d, 6H, *J* = 6.5), 0.940 (d, 6H, *J* = 6.5), 0.91-0.84 (m, 3H)	40 % (mixture of disaster. in 1:1 ratio),

6.	 **231d**	3.70 (br s, 3H), 3.03-2.93 (m, 3H), 2.84 (dd, 1H, *J* = 7.0, 17.0), 2.79-2.77 (m, 3H), 2.33 (dd, 1H, *J* = 6.0, 17.0)	3 %
7.	 **244**	4.01 (m, 2H), 3.49 (m, 2H), 1.97-1.92 (m, 4H), 1.73-1.68 (m, 4H), 1.63-1.59 (m, 2H), 1.40-1.31 (m, 6H), 1.18-1.06 (m, 6H)	65 %
8.	 **246**	3.27-3.17 (m, 2H), 3.09 (ap t, 1H, *J* = 5.5), 2.47 (br s, 5H), 2.00-1.55 (m, 12H), 1.36-1.08 (m, 6H)	37 %
9.	 **253**	7.44-7.31 (m, 10H), 5.42 (d, 2H, *J* = 7.5), 3.12 (m, 2H), 2.49 (d, 2H, *J* = 7.5), 2.37 (br s, 3H), 2.13 (m, 2H), 1.63 (br s, 2H), 1.49 (d, 2H, *J* = 8.5)	44 % (mixture of disaster.)

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