New N-Carbamate-2-Methoxy-3-Piperidones as Precursors of Highly Functionalized Piperidines

Dissertation

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Meinem Lehrer, Herrn Prof. Dr. O. Reiser, danke ich herzlich für die Überlassung des interessanten Themas, die Möglichkeit zur Durchführung dieser Arbeit und seine stetige Unterstützung.

to my daughter Liya and my wife Anan

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Acknowledgements

Abbreviations

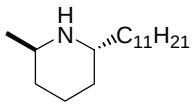
Ac	acetyl group
BSA	(bistrimethylsilyl)acetamide
BTAF	benzyltrimethylammonium fluoride
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-Dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
ds	diastereomeric selectivity
DEPT	distortionless enhancement by polarization transfer
DIBAL-H	diisobutylaluminum hydride
DMAP	4-(N,N-dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	N,N-dimethylformamide
HMPA	hexamethylphosphoramide
HMPT	hexamethylposphorous triamide
KHMDS	Potassium hexamethyldisilazide
LBA	Lewis acid-assisted BrØnsted Acid
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
mCPBA	Meta-chloroperoxybenzoic acid
Ms	Methanesulfonyl
NMO	N-methylmorpholine-N-oxide
NOE	Nuclear Overhauser Effect
Ns	*ortho*-Nitrobenzolsulfonyl
TBAF	tetrabutylammonium fluoride
TBDMS	*t*-Butyldimethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TMEDA	tetramethylethylenediamine
TMSOTf	Trimethylsilyl triflate
Ts	*para*-Toluenesulfonyl

• Chapter 1

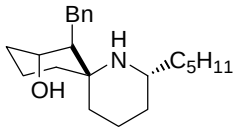
Introduction

1.1 Piperidines: integral components of countless alkaloids

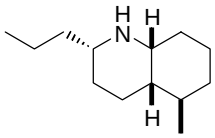
Alkaloids represent a large group of plant and animal compounds with a wide variety of activity. They are not only important pharmacological products, but also interesting models for the design of new drugs. Piperidines are integral components of countless alkaloids, many piperidine alkaloids possess biological and medicinal activity. Thus construction of these fragments is often a central step in the synthesis of alkaloids. Up to now at least 700 piperidine alkaloids are known. [1] Moreover, simple substituted piperidines are often biologically active. Scheme 1-1 shows some examples of piperidine containing natural products. [1-6]



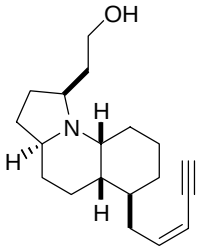
Solenopsin A **1**



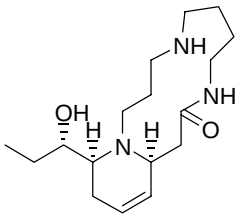
Perhydrohistrionicotoxin **2**



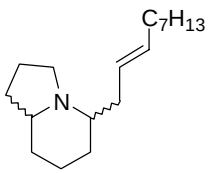
Pumiliotoxin C **3**



Gephyrotoxin **4**



Palustrine **5**



Piclavine A **6**

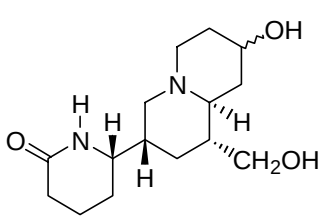
Scheme 1-1. Examples of piperidine-containing natural products with biological activity.

Among piperidine derivatives, piperidones are important substrates from a synthetic standpoint as the development of the synthetic chemistry of piperidones is associated with their use as intermediates, particularly in the preparation of alkaloids and useful medicinal drugs. Therefore, we summarize simply some recent progress of reactions of 2-, 3-, and 4-piperidones.

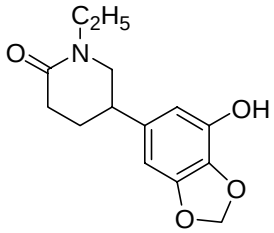
1.2 Recent development of the reactions of N-protected-piperidones

1.2.1 N-protected-2-piperidones

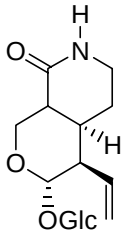
Apart from the fact that 2-piperidones should be considered mainly as important intermediates in the synthesis of quinolizidine alkaloids, some other interesting compounds from the pharmacological standpoint also include the 2-piperidone unit in their structures. For instance, alkaloids such as *Cadiamine* **7**, [7] *Campedine* **8**, [8] and *Bakankoside* **9**, [9] have a substituted 2-piperidone ring (Scheme 1-2).



Cadiamine **7**



Campedine **8**

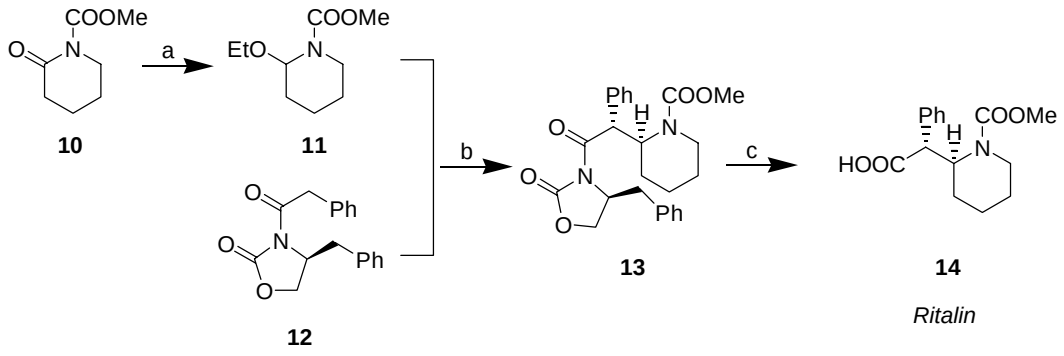


Bakankoside **9**

Scheme 1-2. The structures of *Cadiamine* **7**, *Campedine* **8**, and *Bakankoside* **9**.

Methylphenidate (*Ritalin*) **14** is used to treat attention-deficit-disorder in children. It can be synthesized in three steps from N-carbamate-2-piperidone **10**. [10] The reaction sequence involves the reduction of 2-piperidone, the nucleophilic substitution of N-

acyliminium ions with chiral enolate ions, and hydrolysis of the chiral auxiliary (Scheme 1-3).



Reagents and conditions:

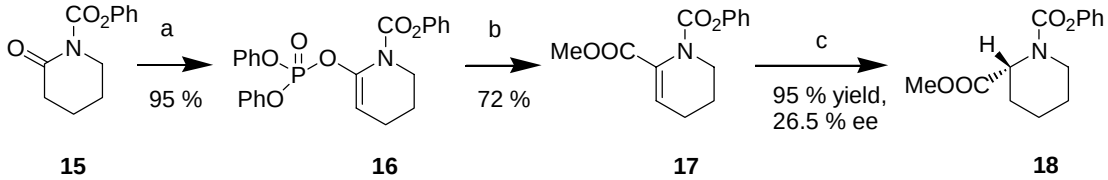
a: (i) $NaBH_4$, EtOH; (ii) EtOH, HCl; (iii) KOH, EtOH.

b: (i) $TiCl_4$, CH_2Cl_2; (ii) $EtN(i\text{-}Pr)_2$, CH_2Cl_2.

c: (i) LiOH, H_2O_2, H_2O, THF; (ii) Na_2SO_3, H_2O; (iii) HCl, H_2O.

Scheme 1-3. The synthesis of *Methylphenidate* (*Ritalin*) **14**.

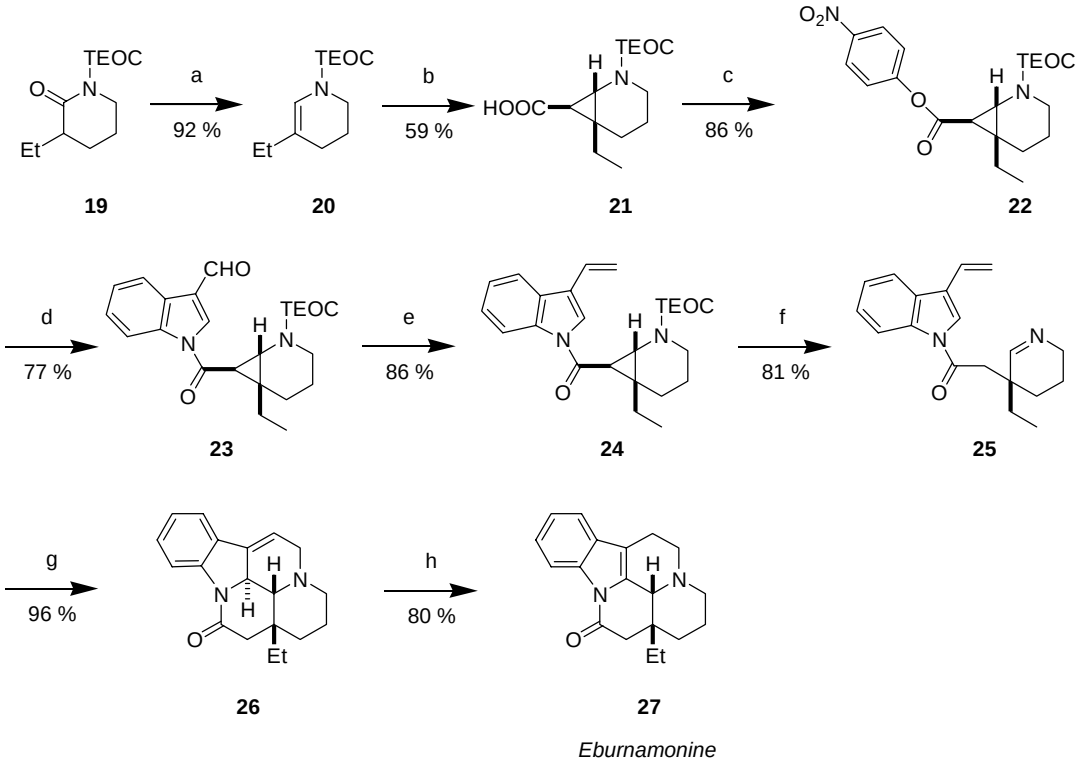
K.C. Nicolaou reported an asymmetric synthesis of cyclic amino acids **18** via Pd(0)-catalyzed carbonylation of their corresponding enol phosphates **16** [11]. These enol phosphate intermediates are stable, easy to form and display good reactivities (Scheme 1-4).



Reagents and conditions: (a) 1.5 eq $(PhO)_2P(O)Cl$, 1.2 eq KHMDS, THF, -78°C, 0.5 h;
(b) (i) CO (1 atm), 0.1 eq $Pd(OAc)_2$, 0.2 eq PPh_3, (ii) 4 eq MeOH, 2 eq NEt_3, DMF, 60 °C, 4h,
(c) H_2 (400 psi), 0.06 eq [Rh(COD)-(-)-(R, R)-Et-DuPHOS]OTf, 70 °C, EtOH.

Scheme 1-4. An asymmetric synthesis of cyclic amino acids **18** from N-protected-2-piperidone **15** via Pd^0-catalyzed carbonylation reaction.

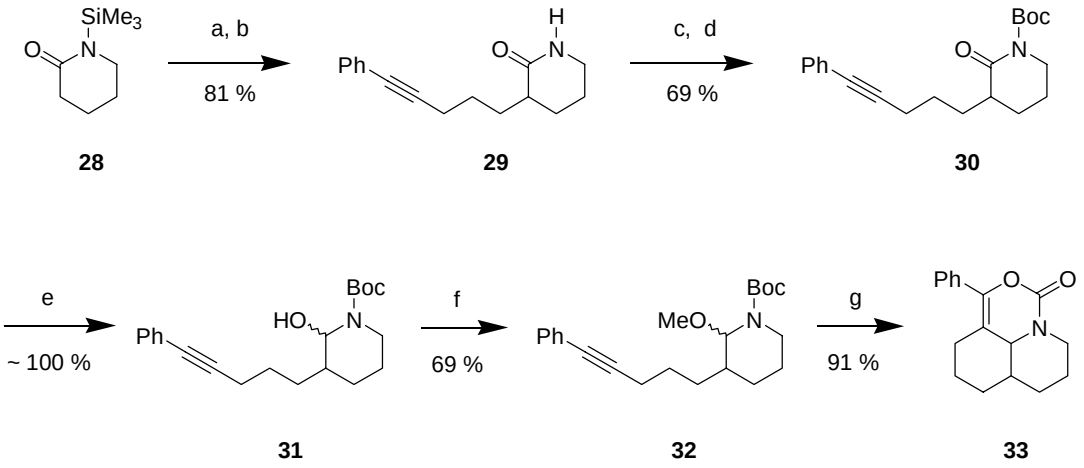
In 1994, Paul A. Grieco et al. reported a novel strategy, involving an intramolecular imino Diels-Alder reaction for the construction of the pentacyclic framework of *Eburnamonine* **27** from N-protected-2-piperidone **19** in eight steps. [12] This synthetic route involves reduction, elimination, cyclopropanation, substitution and Wittig reaction. Most importantly, the intramolecular [4+2] cycloaddition of vinyl indole imine **25** leads to pentacyclic framework **26,** followed by isomerization to form *Eburnamonine* **27** in 19 % total yield (Scheme 1-5).



Reagents and conditions: (a) (i) $(^{t}BuO)_3AlHLi$, (ii) H_2SO_4, Et_2O; (b) (i) Ethyl diazoacetate, copper bronze, 135°C, (ii) 0.15 eq $BF_3.OEt_2$, 0°C, (iii) Saponification; (c) dicyclohexylcarbodimide facilitated esterification; (d) 1.2 eq N-lithioindole-3-carboxaldehyde, -20°C; (e) Ph_3P^+-CH_2^-, THF, low temperature; (f) BTAF, crushed 4A molecular sieves; (g) 5.0 M lithium perchlorate-Et_2O, 10 mol % camphorsulfonic acid; (h) isomerization, reflux, in ethanolic sulfuric acid, 12 h.

Scheme 1-5. The construction of the pentacyclic framework of *Eburnamonine* **27** from N-protected-2-piperidone **19**.

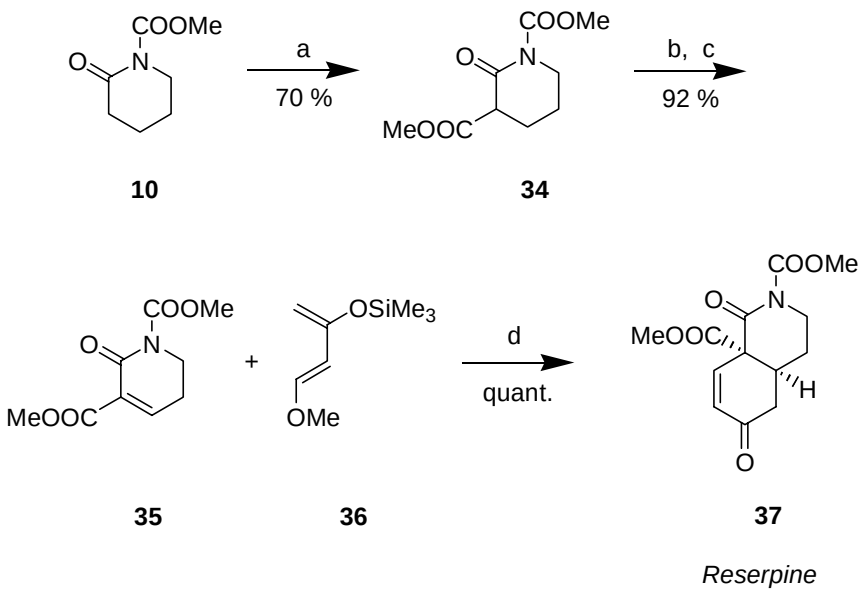
Treatment of N-protected-2-piperidones **28** with LDA, followed by nucleophilic substitution, the 5-phenyl-pent-4-ynyl group was connected to the 3-position of the 2-piperidone ring. Intramolecular cyclocondensation can easily take place by Lewis acid catalysis from compound **32**, forming the tricyclic framework **33** (Scheme 1-6) [13].



Reagents and conditions: (a) LDA, -78°C, $PhCC(CH_2)_3I$; (b) H_2O; (c) LDA, -78°C; (d) Boc_2O; (e) $NaBH_4$ (excess); (f) KH, MeI; (g) $SnCl_4$, -23°C.

Scheme 1-6. The formation of tricyclic framework **33**.

The cis-hydroisoquinoline ring system constitutes an important part of natural products such as in the indole alkaloid *Reserpine* **37**. This compound can be synthesized from N-carbamate-2-piperidone **10** in three steps via an intermolecular Diels-Alder reaction as key step (Scheme 1-7) [14].



Reagents and conditions: (a) LDA, THF, ClCOOMe; (b) NaH, THF, PhSeCl; (c) H_2O_2, CH_2Cl_2; (d) (i) benzene, heat, (ii) CSA, THF.

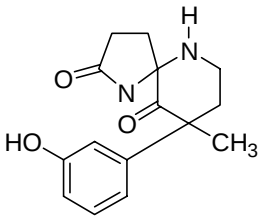
Scheme 1-7. The synthesis of *Reserpine* **37**.

As we can see, two kinds of reactions of N-protected-2-piperidones received wide attention. The first is the nucleophilic substitution of its 2-position. In this strategy the carbonyl group is first reduced and then alkylated to form an alkoxy group, which is a good leaving group. Under Lewis acid condition, it forms N-acyliminium ions which is attacked by nucleophilic reagents.

The other is the formation of an enolate under basic condition. The carbanion in 3-position can attack other electrophilic reagents to form carbon-carbon single bonds. In the enolate chemistry of 2-piperidones, there is no problem of selectivity because only one adjacent α-H exists.

1.2.2 N-protected-3-piperidones

Despite of the relatively small amout of publications about the reactions of 3-piperidones, they are synthetic precursors of many biologically active compounds. Some natural products, such as *Canthiphytine* **38**, include a 3-piperidone moiety in their structures (Scheme 1-8).

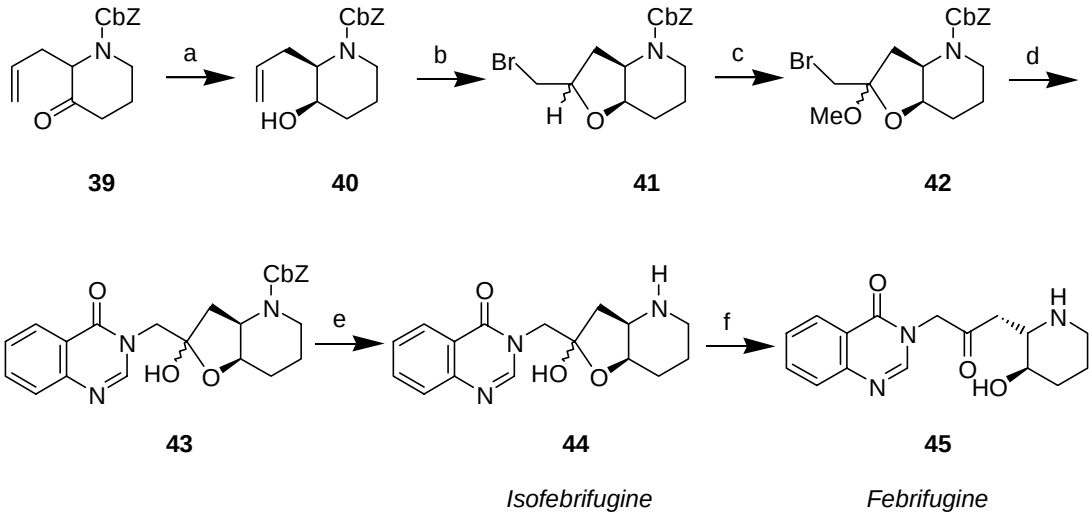


38

Canthiphytine

Scheme 1-8. The structures of *Canthiphytine* **38** with 3-piperidone moiety.

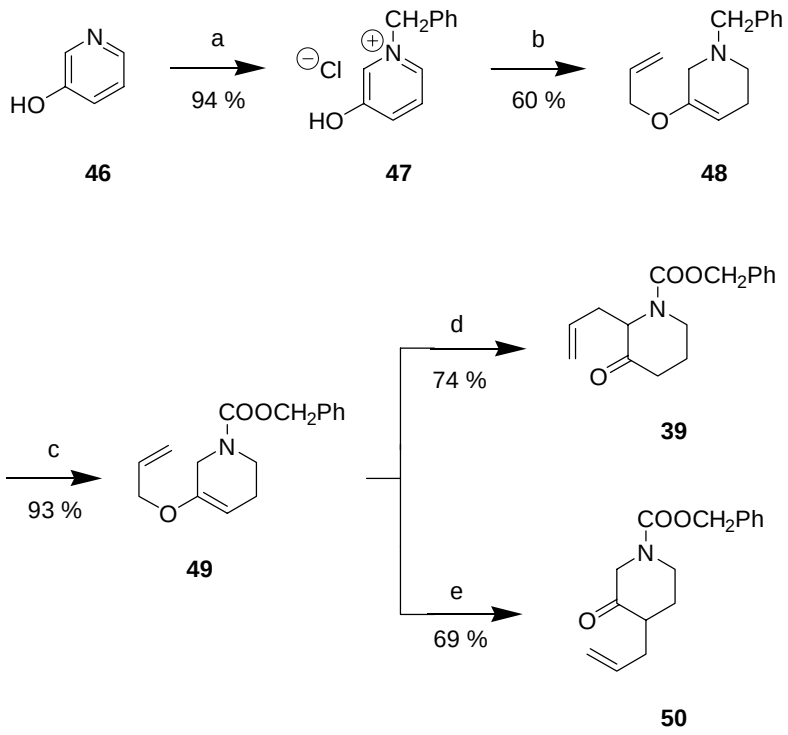
Y. Takeuchi et al. reported a synthetic route of *Isofebrifugine* **44** and *Febrifugine* **45** from 3-piperidone derivatives **39** (Scheme 1-9). [15]



Reagents and conditions: (a) Baker's Yeast, Sucrose in EtOH/H_2O, K_2CO_3, RT, 90 h, 62 % yield, 97 %ee; (b) NBS, MeCN, RT, 0.5 h, 87 %; (c) (i) ^{t}-BuOK, THF, 0°C, 0.25 h, (ii) NMS, MeOH, RT, 1 h, 90 %; (d) (i) H^+, MeCN, RT, 1 h, (ii) 4(3H)-quinazolinone, K_2CO_3, DMF, RT, 1 h, 75 %; (e) H_2, 20 %-$Pd(OH)_2$/C, MeOH, RT, 4 h, 62 %; (f) (i) H_2O, 80°C, 15 min, (ii) H^+, 73 %.

Scheme 1-9. A synthetic route of *Isofebrifugine* **44** and *Febrifugine* **45**.

The starting material 3-piperidone **39** was synthesized from commercially available 3-hydroxypyridine **46** in four steps (Scheme 1-10). [16] The step **d** involved the unusual Claisen rearrangement in the presence of boron trifluoride-diethyl ether complex at room temperature. On the other hand, the Claisen rearrangement of **49** at 130°C in *p*-cymene proceeded smoothly to give 4-allylpiperidin-3-one derivative **50** in 69 % yield. These two different results show that in the presence of a Lewis acid, the isomerization [17] of the double bond on the piperidine ring of **49** proceeds before the migration [18] of the allyl group.



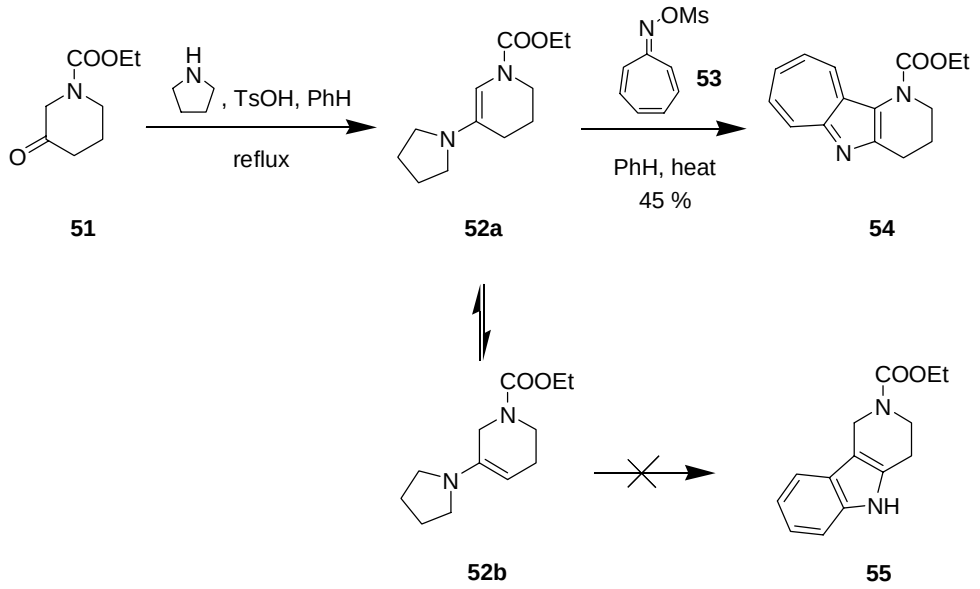
46 **47** **48** **49** **39** **50**

Reagents and conditions:

(a) $PhCH_2Cl$, PhMe, reflux, 1 h;
(b) (i) allyl bromide, NaH, MeOH, reflux, 4 h; (ii) $NaBH_4$, MeOH, 0°C, 0.5 h;
(c) $ClCOOCH_2Ph$, THF, rt, 1 h;
(d) $BF_3.OEt_2$, MeCN, rt, 1.5 h;
(e) *p*-cymene, 130°C, 1h.

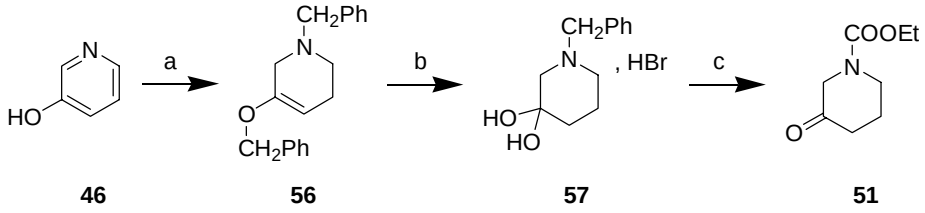
Scheme 1-10. The synthesis of 3-piperidone **39**.

The 1-azaazulene derivative **54** has attracted much attention from the viewpoint of their pharmacological activities, [19] and it can be synthesized from N-ethoxycarbonyl-3-piperidone **51** and troponimine **53** (Scheme 1-11). [20] It should be noted that from 3-piperidone **51**, the isomeric mixture of two enamines **52a** and **52b** was formed. Treatment of the isomeric mixtures **52a** and **52b** with troponimine **53,** only one product 1-azaazulene derivatives **54** is formed.



Scheme 1-11. The synthesis of 1-azaazulene derivative **54** from N-ethoxycarbonyl-3-piperidone **51** and troponimines **53**.

The starting material N-ethoxycarbonyl-3-piperidone **51** can also be synthesized from 3-hydroxypyridine **46** via reduction reaction (Scheme 1-12). [21]

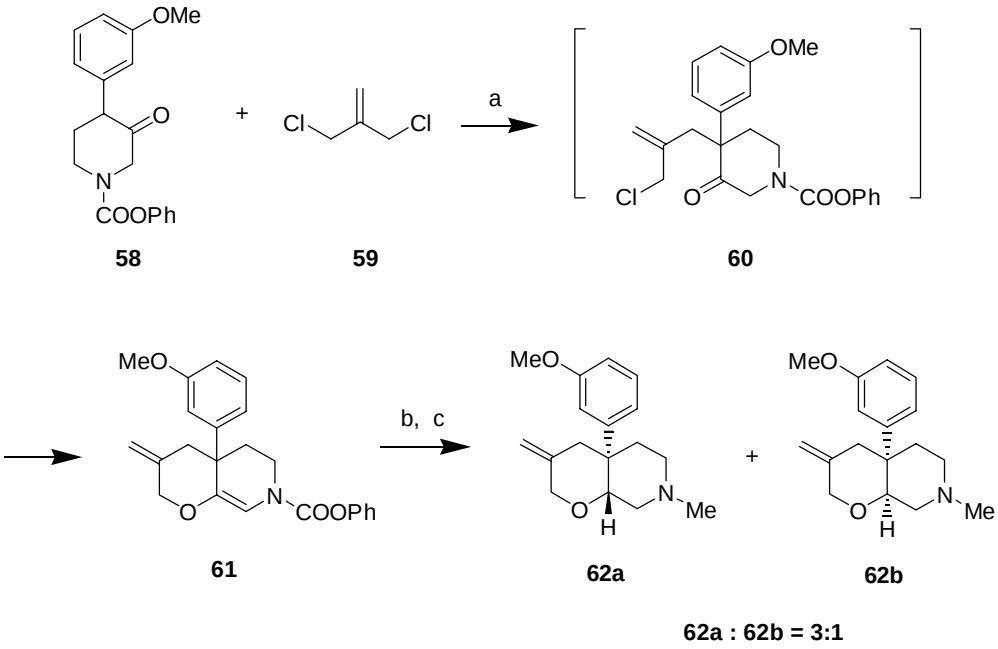


Reagents and conditions:

(a) (i) $NaOCH_3$, $PhCH_2Cl$, (ii) $NaBH_4$;
(b) HBr, RT, 3 h;
(c) (i) H_2, Pd-C, (ii) K_2CO_3, ClCOOEt.

Scheme 1-12. The synthesis of N-ethoxycarbonyl-3-piperidone **51**.

It was reported that compound **62a** has antinociceptive activity and a simple, efficient synthetic route through enolate was developed (Scheme 1-13). [22] The crucial alkylation of **58** with **59**, using sodium hydride in DMF at –50°C, generated the intermediate **60** which the alkyl group was introduced in the required 4-position due to the presence of the phenyl substituent. Subsequent reduction produced two isomers **62a** and **62b** in a 3:1 ratio which could be separated by column chromatography.

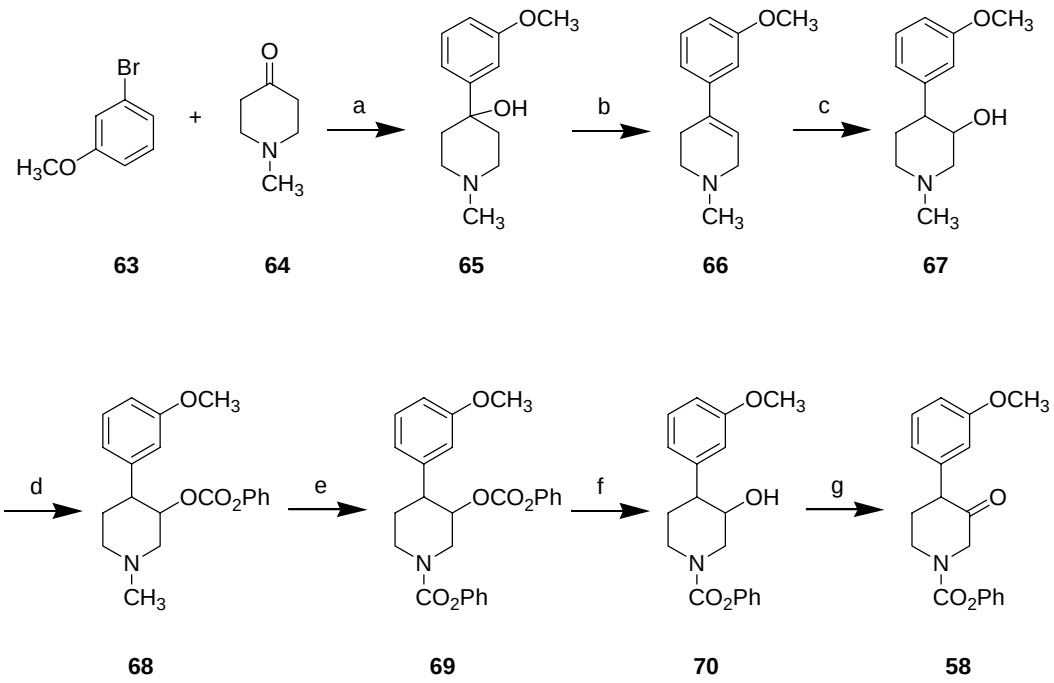


Reagents and conditions:

(a) NaH, DMF; (b) $LiALH_4$, THF; (c) NH_4OAc, $NaBH_3CN$, MeOH, pH 6.5-8.

Scheme 1-13. The synthesis of **62a** from N-protected-3-piperidones-4-substituted **58**.

The starting material **58** was synthesized from commercially available compounds **63** and **64** in seven steps (Scheme 1-14). [22, 23]



63 **64** **65** **66** **67**

68 **69** **70** **58**

Reagents and conditions:

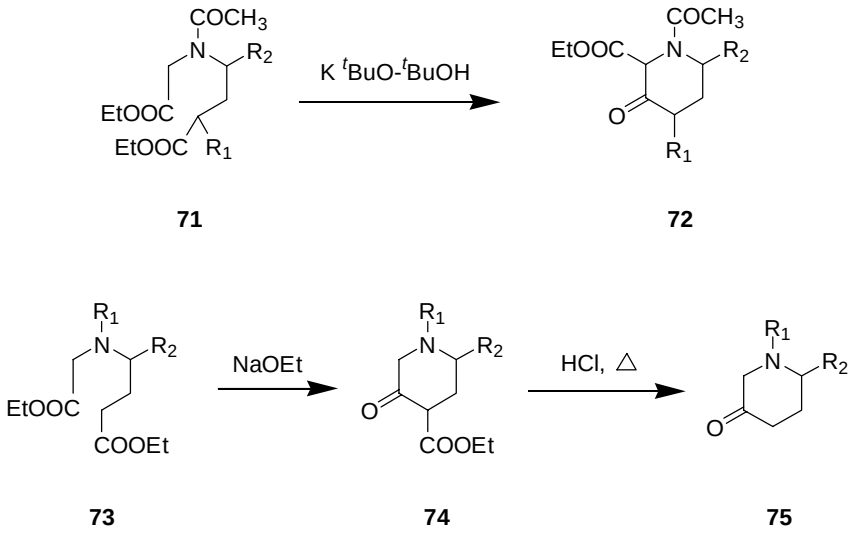
(a) n-BuLi, THF, hexane, -50°C, 2h; (b) *p*-TsOH, toluene, 2h, reflux;
(c) (i) $NaBH_4$, $BF_3.OEt_2$, diglyme, (ii) H_2O_2, NaOH; (d) $ClCO_2Ph$, rt, K_2CO_3, 1.2-dichloroethane; (e) $ClCO_2Ph$, K_2CO_3, 1,2-dichloroethane, reflux;
(f) K_2CO_3, MeOH, H_2O, 58°C, 40 min; (g) $(COCl)_2$, DMSO, NEt_3, -78°C.

Scheme 1-14. Preparation of compound **58** from commercially available compounds **63** and **64**.

Unlike 2-piperidones, there are two α-positions to the carbonyl group in the structures of N-protected-3-piperidones, so two different enolates can be formed under basic condition. However, an electron-withdrawing group or conjugated system conneceted with α-carbon will greatly improve the regioselectivity in the formation of enolates from N-protected-3-piperidones.

The preparation of N-protected-3-piperidones is one of the main topics in my research. According to the published procedures, reduction of 3-hydroxypyridine **46** is a common and effective method. Examples are the preparations of compounds **39** and **51** (Scheme 1-10 and 1-12). However, the most widely used method to obtain 3-piperidones is the

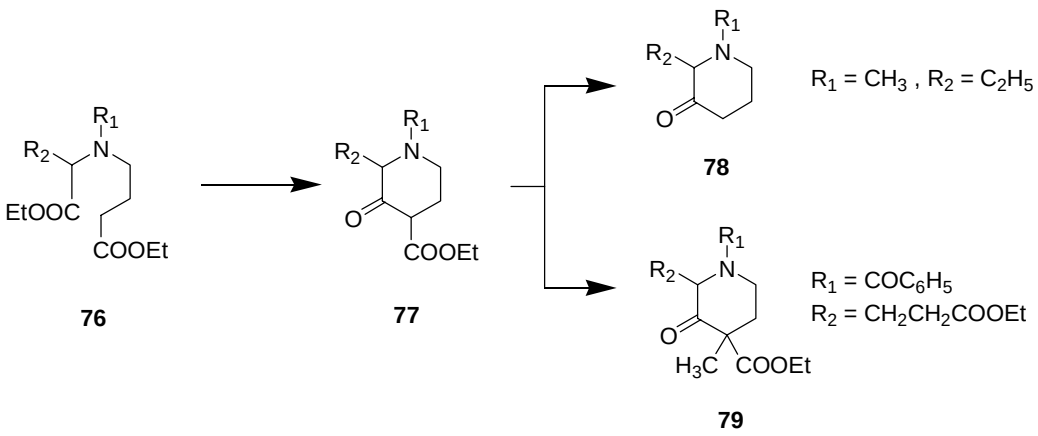
Dieckmann cyclization of amino or amidodiesters. [24,25,26] It is well known that this reaction is regioselective when the cyclization is carried out with an unsymmetrical diester. In the presence of an appropriate base, the differences in acidity of the two α-methylene groups and the stability of the two possible cyclized products are sufficient to ensure an umambiguous course of the reaction (Scheme 1-15).



$R_1 = CH_3$, R_2= H	Ref. 25
$R_1 = CH_2Ph$, R_2 = H	Ref. 26,27
R_1 = COPh , R_2 = COOEt	Ref. 28,29
R_1 = Et , R_2 = H	Ref. 29
R_1 = COOEt , R_2 = H	Ref. 30

Scheme 1-15. The published preparations of N-protected-3-piperidones via Dieckmann cyclization.

Formation of 4-ethoxycarbonyl-3-piperidones **77**, substituted at C-2 by an alkyl group [31] or an alkoxycarbonylalkyl chain has also been described (Scheme 1-16). [32]



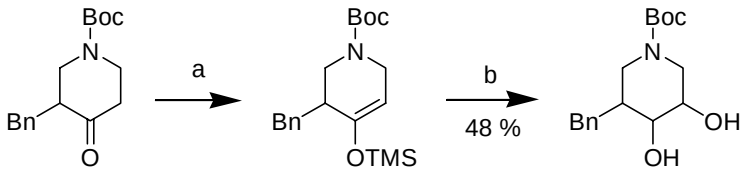
Scheme 1-16. The published preparations of N-protected-2-substituted-3-piperidones via Dieckmann cyclization.

In addition to these methods, as part of this thesis, I have developed an efficient route to synthesize the N-carbamate-2-methoxy-3-piperidones derivatives from piperidine, which is an inexpensive starting material. This approach will be introduced in detail in Chapter 2.

1.2.3 N-protected-4-piperidones

The synthetic reactions of 4-piperidones have been most widely studied among the piperidones because many natural products and medicinal drugs with great effect upon the central nervous system can be synthesized from them. [33] The carbonyl group is the main functional group in the ring and most reactions, such as formation of double bond via Wittig and HWE reaction, [34] formation of C-N bond via addition of amine, [35,36] formation of C-C bond via nucleophilic addition, [37] are based on this group.

4,5-Diols **82** can be synthesized via enolation and desilylation from 4-piperidone **80** (Scheme 1-17). [38] Kinetic deprotonation of ketone **80** was performed with LDA in THF at –78°C, and reaction of the resulting lithium enolate with TMSCl gave silyl enol ether **81**.

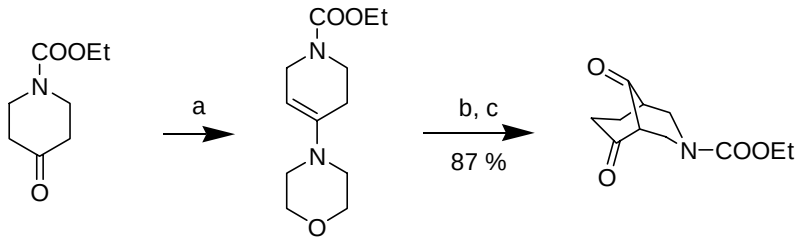


80 **81** **82**

Reagents and conditions: (a) (i) LDA, THF, -78°C, (ii)TMSCl, -78°C-rt; (b) (i) $BH_3.SMe_2$, THF, 0°C-rt, (ii) H_2O_2, NaOH. (iii) TBAF, THF, rt.

Scheme 1-17. The synthesis of 4,5-diols **82** from 4-piperidone **80**.

Substituted 3-azabicyclo[3.3.1]nonanes are a structurally fascinating and practically significant class of compounds that have attracted attention for their pharmacological properties. A one pot synthesis of 3-azabicyclo[3.3.1]nonane-6,9-diones **85** is described via the addition of acryloyl chloride to enamines of N-carboxy-4-piperidones **83** (Scheme 1-18). The yield was highest when the addition reaction was made to vigorously boiling solutions of morpholine enamines. [39]



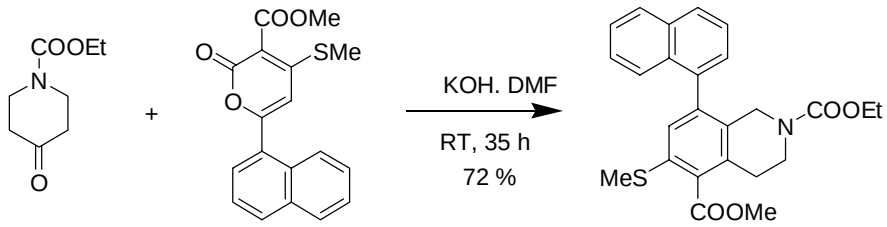
83 **84** **85**

Reagents and conditions:

(a) TsOH, morpholine, benzene; (b) acryloyl chloride; (c) water.

Scheme 1-18. A one pot synthesis of 3-azabicyclo[3.3.1]nonane-6, 9-diones **85**.

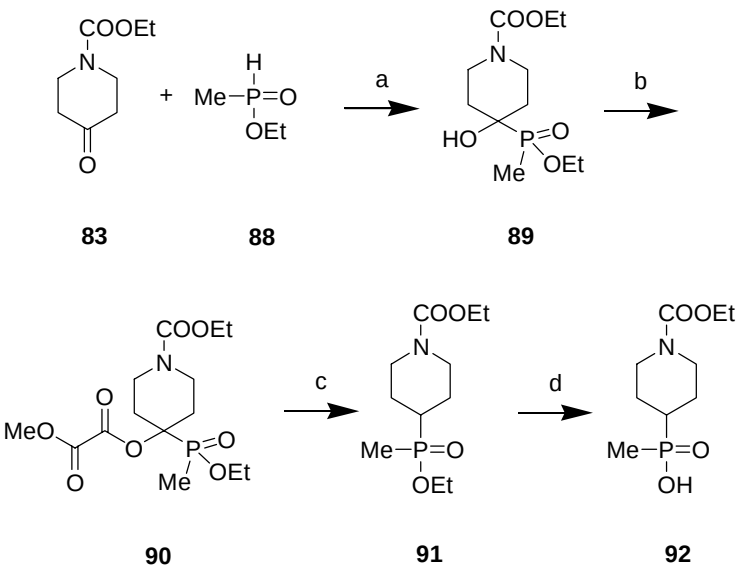
V. J. Ram reported a highly convenient and efficient synthesis of unsymmetrical biaryls **87** through base-induced ring transformation reaction. This reaction in many ways is superior to other procedures because of its versatility, mild reaction conditions, high yield and use of inexpensive reactants (Scheme 1-19). [40]



83 **86** **87**

Scheme 1-19. A highly convenient and efficient synthesis of unsymmetrical biaryls **87** through base-induced ring transformation reaction.

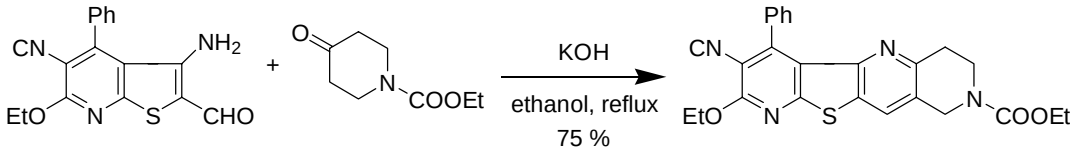
The methylphosphinic acid group continues to attract considerable interest as bioisosteric replacement for carboxylic acid groups, being potential regulators, mediators or inhibitors of metabolic processes. [41] J. Kehler reported a simple route to *sec*-alkylmethyl phosphinates **91** from N-protected-4-piperidone **83** and the easily obtainable ethyl methylphosphinate **88** using sequential Pudovik/Abramov-Barton/McCombie reactions (Scheme 1-20). [42]



Reagents and conditions: (a) Et_3N; (b) $ClCOCO_2Me$, 4-DMAP, MeCN; (c) AIBN, Bu_3SnH, PhMe, 90 °C; (d) HCl.

Scheme 1-20. A simple route to *sec*-alkylmethylphosphinates **91** from N-protected-4-piperidone **83** and the easily obtainable ethyl methylphosphinate **88**.

Numerous N-heteroaromatic carbaldehydes are extensively used as versatile synthetic building blocks for the preparation of condensed heterocyclic system. The formation of ring compounds from substituted heterocyclic amino aldehyde **93** is often the method of choice for the synthesis of polycondensed materials consisting of many fused rings. The enolate of 4-piperidone **83** formed under basic condition attacks the aldehyde and the ketone carbonyl group is attacked by amino group to form the piperidine ring (Scheme 1-21). [43]



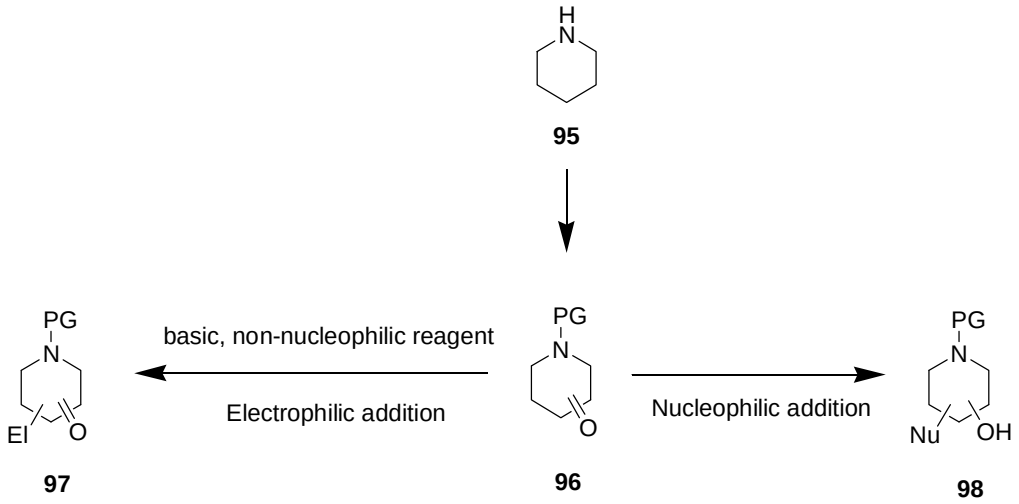
93 **83** **94**

Scheme 1-21. The synthesis of polycondensed materials **94**.

1.3 Aim of this work

Functionalized piperidines are among the most ubiquitous heterocyclic building blocks in natural products and the huge amount of works on the synthesis of piperidines and pyrrolidines derivatives testify to their importance. However, the studies about the changes of functional groups from one to another around the ring with N-protected piperidine and the direct introductions of new functional groups to the piperidine rings, especially the reaction of carbon-carbon formation, are not so much.

The basic purpose of synthetic organic chemistry is the construction of organic molecules and one of the key elements in this field is the formation of carbon-carbon bond. The exploration of carbon-carbon bond formation on the piperidine ring, which is an important heterocyclic compound and also a component of many alkaloids, is undoubtfully significant. Among the continuously developing carbon-carbon formation methods, the nucleophilic addition of the carbanion on a carbonyl group is of course the most important method. Thus, we tried to first induce a carbonyl group on the piperidine ring, and then connect with different nucleophilic groups to form a series of new piperidine derivatives. Moreover, under non-nucleophilic basic conditions, piperidones can be transformed in an enolate, which then can be attacked by an electrophile. This is also a main carbon-carbon bond formation method (Scheme 1-22).



Scheme 1-22. N-protected-piperidone as both of electrophilic reagents and nucleophilic reagents.

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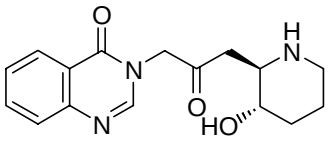
• Chapter 2

Syntheses of N-Carbamate-2-Methoxy-3-Piperidones Derivatives

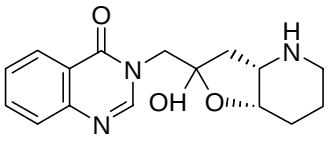
2.1 Introduction

Many nitrogen-containing six-member cyclic compounds are widely distributed in biologically important natural products and pharmaceuticals. *Febrifugine* **99** and *Isofebrifugine* **100** are alkaloids first found in the Chinese plant *Dichroafebrifuga* [1] and later in the common hydrangea (Scheme 2-1). [2] These compounds have attracted great attention because of their potential powerful antimalarial activities. [1,2, 3]



Febrifugine (2R, 3S)

99

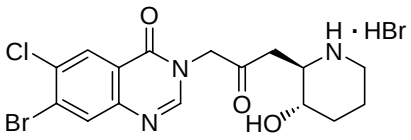


Isofebrifugine (2S, 3S)

100

Scheme 2-1. Structures of *Febrifugine* **99** and *Isofebrifugine* **100**.

Halofuginone has been used as an antiparasitic feed additive for the prevention of coccidiosis in poultry production. [4] Recently, it has been reported that *Halofuginone* **101** inhibits collagen production (collagene synthesis inhibitor) and is now undergoing clinical trials for treatment of scleroderma in human (Scheme 2-2). [4]

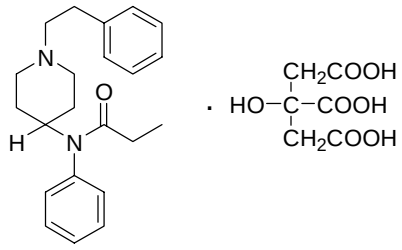


Halofuginone Hydrobromide (dl-trans)

101

Scheme 2-2. Structure of Halofuginone Hydrobromide (dl-trans) **101**.

A major achievement in the creation of effective analgesic pharmaceuticals has been the synthesis and investigation of the pharmaceutical properties of piperidine-type analgesics such as *fentanyl citrate* **102** (Scheme 2-3). [5]



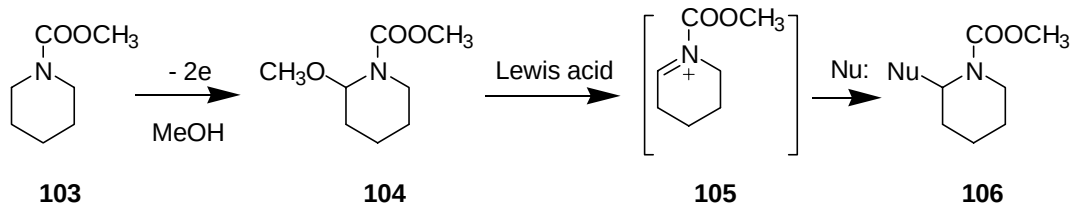
fentanyl citrate

102

Scheme 2-3. Structure of *fentanyl citrate* **102**.

From a synthetic point of view, the reactive properties of the α-position of N-protected piperidines are most widely studied. [6] Anodic methoxylation of compound **103** allows the easy preparation of α-methoxycarbamates **104**. These compounds constitute interesting synthetic intermediates because of their facile conversion into the corresponding N-acyliminium ions **105**, which have been shown to be versatile electrophiles (Scheme 2-4). The combination of anodic methoxylation and nucleophilic

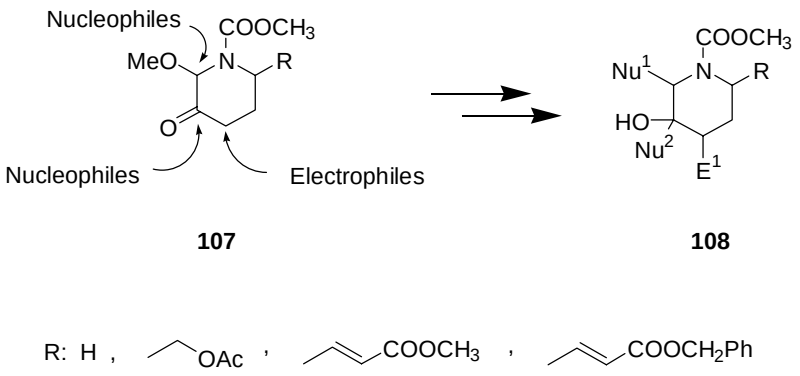
substitution, e.g., with silyl enol ethers, appears to be a main method for the introduction of a new C-C bond α to the nitrogen atom of piperidines. [6]



103 **104** **105** **106**

Scheme 2-4. Introduction of a new C-C bond α to the nitrogen atom of piperidines.

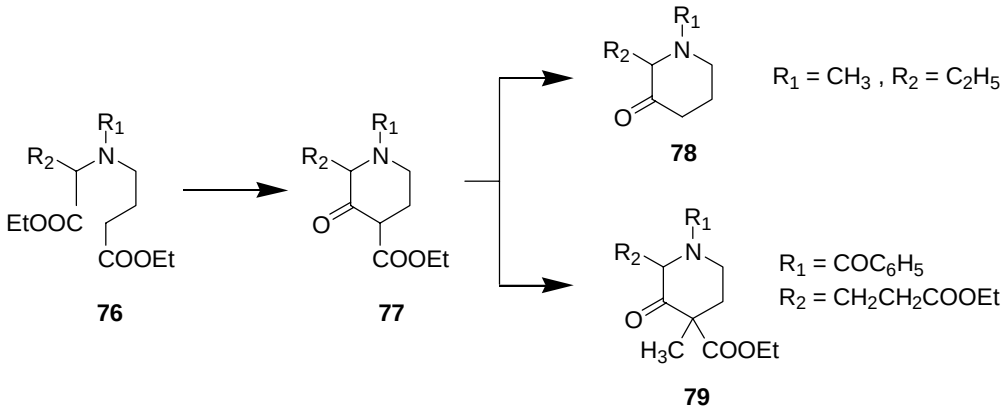
Recently, it was reported that the introduction of substituents into the 3- and 4- position is important to the biological activities of piperidine derivatives. [7] However, up to now the derivatives substituted in 3- and 4- positions did not receive as much attention as that of 2-position, which is most likely due to the chemical inaccessibility of those positions. We therefore proposed that a carbonyl group being introduced to the 3-position, both the 3- and 4- position would become active to many reagents. Consequently, it would be easy to introduce a series of functional groups by the reactions common of carbonyl and enolates. Therefore, a synthetic method should be developed that would lead to N-carbamate-3-piperidones. In addition, if at the same time a methoxy group would be present in 2-position, nucleophilic substitutions might be feasible here as well (Scheme 2-5).



Scheme 2-5. Target compounds: N-carbamate-2-methoxy-3-piperidones and their derivatives.

2.2 Background and the design of the synthesis of N-protected-3-piperidones

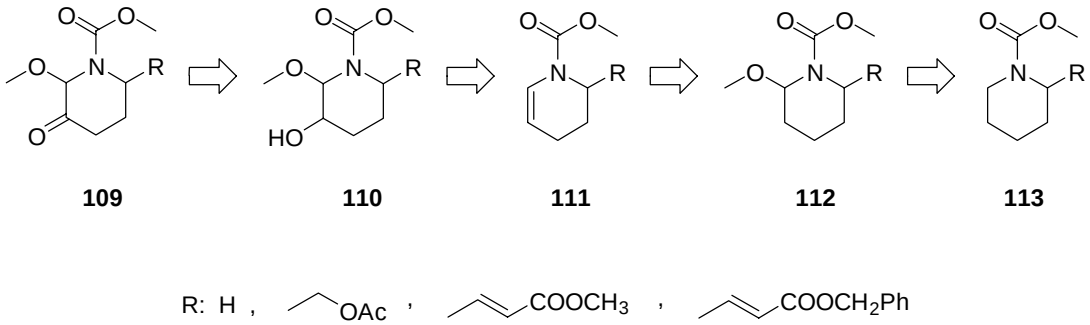
In Chapter 1, we once introduced that the most widely used method to obtain 3-piperidones is the Dieckmann cyclization of amino- or amido- diesters (Scheme 2-6). [8, 9, 10]



Scheme 2-6. The preparation of N-protected-2-substituted-3-piperidones via Dieckmann cyclization.

In the methods used for the preparation of compound **77**, the 2-positions of N-protected-3-piperidones were unsubstituted or monoalkylated, and further introduction of other

functional groups proved to be difficult. In contrast, methoxy group at 2-position should allow a flexible functionalization with a variety of functional groups via nucleophilic substitution. In order to synthesize 3-piperidones **109**, the following route to **109** was envisioned (Scheme 2-7).



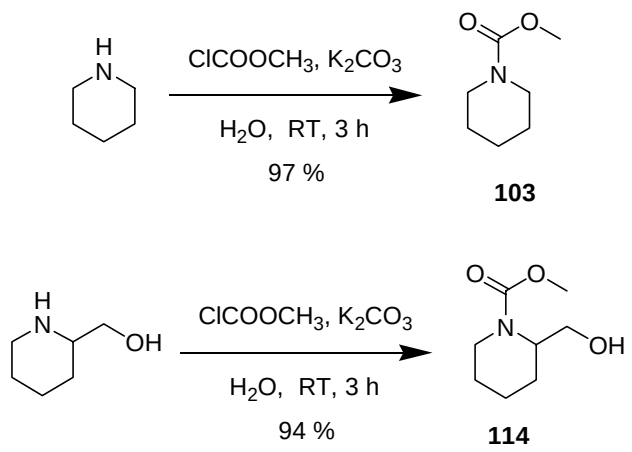
Scheme 2-7. Retrosynthesis of target compounds.

As key intermediates, the enecarbamate **111** could be readily available from **113** by electrochemical oxidation followed by elimination of methanol. Dihydroxylation or epoxidation and nucleophilic ring opening by alcohols should lead to **110**, which then could be oxidated to aim compound **109**.

2.3 Synthesis of N-carbamate-2-methoxy-3-piperidones

2.3.1 Protection of N-H bond of piperidine ring

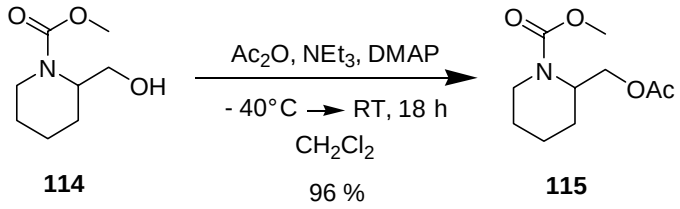
Before the subsequent reaction, the N-H bond should be first protected. We choose carbamate as protecting group. Acylation of the nitrogen atom of the piperidines with methyl chloroformate under Schotten-Baumann condition [11] yielded quantitatively the carbamate (Scheme 2-8).



Scheme 2-8. Protection of piperidines with carbamate.

2.3.2 Protection of hydroxy group and the Swern-Wittig reaction

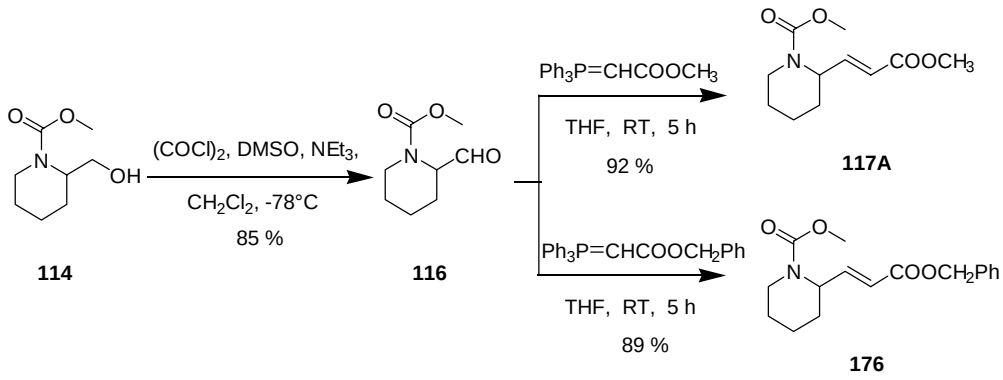
The hydroxy group in 2- side chain is protected by acetoxy group. Compound **114** reacts with 1 eq acetic anhydride, 1.05 eq triethylamine and 0.05 eq DMAP in dry dichloromethane leading to the protected compound **115** in 96 % yield (Scheme 2-9).



Scheme 2-9. Protection of hydroxy group.

Swern oxidation is a mild, high-yielding method which oxidates many kinds of alcohols, including saturated, unsatuated, acetylenic, and steroidal alcohols, to carbonyls with ‘‘activated‘‘ DMSO and successful ‘‘activator‘‘oxalyl chloride in very low temperature (-78 °C). [12] Followed with Wittig or HWE reaction, it is now the generally used method to

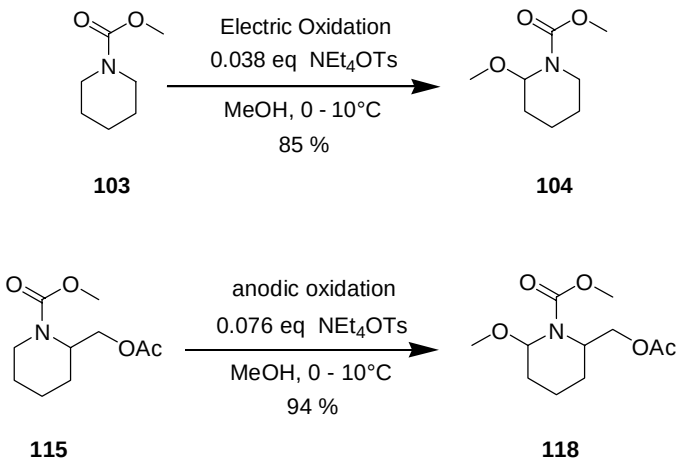
form a carbon-carbon double bond (Scheme 2-10). [13] Using Wittig reaction, the product is totally stereospecific with only E product. The stereochemistry of Wittig reaction will be discussed in detail in Chapter 5.

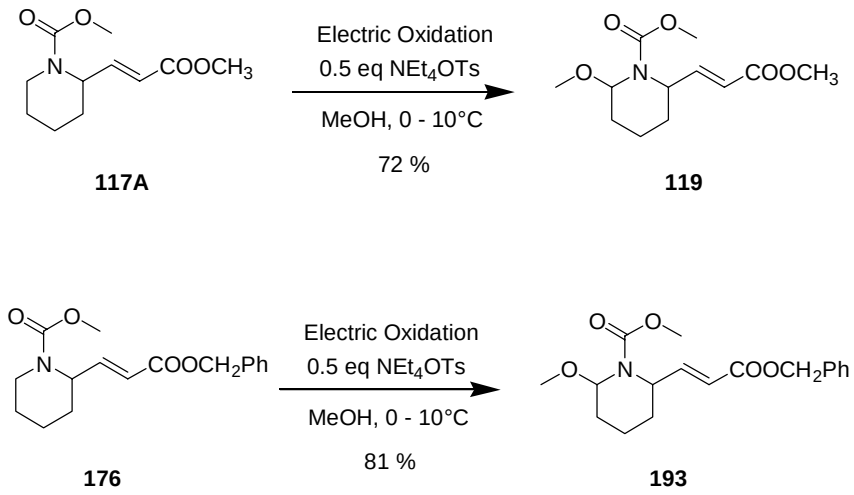


Scheme 2-10. Synthesis of **117A** and **176** via Wittig reactions.

2.3.3 The anodic oxidations

In 1975 Shono [14] and Nyberg [15] first developed the anodic oxidations in carbamate piperidine and pyrrolidine ring. The oxidation is regiospecific, only in the α-position of less substituted side (Scheme 2-11).





Scheme 2-11. Electric oxidations of piperidines derivatives.

All anodic oxidations performed in this study were carried out by cooling of water in methanol containing NEt_4OTs as a supporting electrolyte, in an undivided container equipped with eight carbon electrodes, a constant potential of 10.00 V was applied. The oxidation is monitored by ^{1}H-NMR spectrum. In agreement with the structures of the oxidation products, the ^{13}C-NMR spectrum showed the presence of only four methylene groups in piperidine ring (Figure 2-1). In the ^{1}H-NMR spectrum ($CDCl_3$, 250 MHz), the proton signals at both sides of the two α-positions are broad peaks. A broadening of signals, due to the slow rotation around the N-$COOCH_3$ bond, is observed for all the compounds of this series (Scheme 2-12).

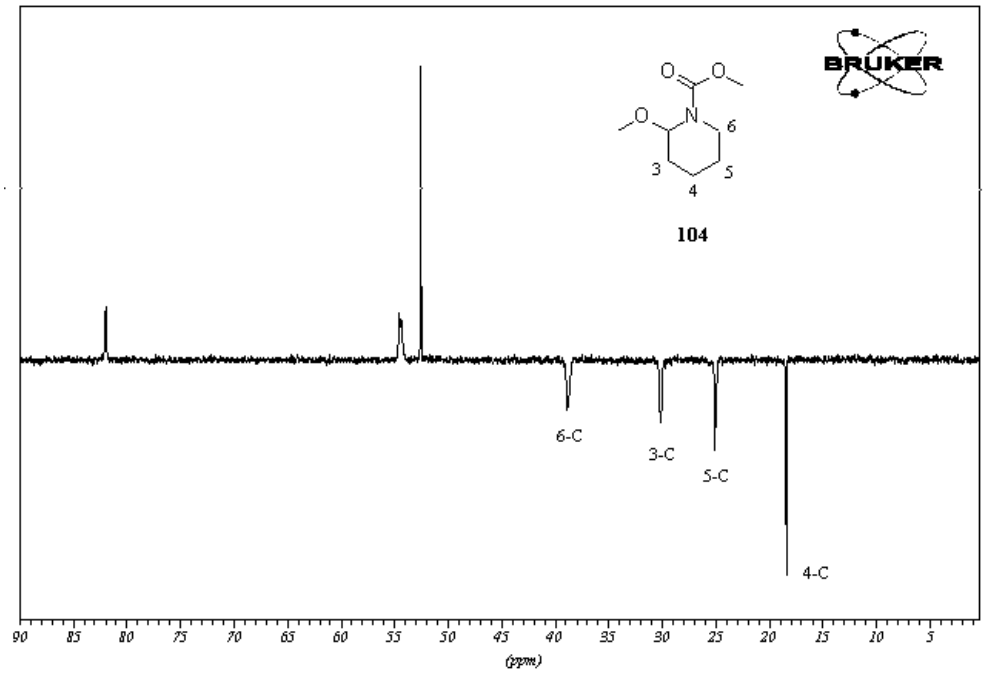
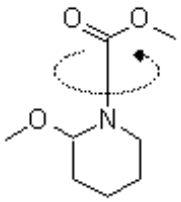


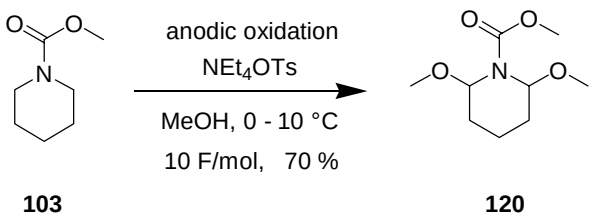
Figure 2-1. ^{13}C-NMR (DEPT135) spectrum of 2-methoxy-piperidine-1-carboxylic acid methyl ester **104**.



104

Scheme 2-12. Broad proton signals in 2-, 6-position caused by the slow rotation of N-C bond due to the substitution of methoxy group in 2-position.

Anodic dimethoxylation of carbamate **103** to yield α,α'-dimethoxy carbamate **120** is possible if sufficient amount of electricity is used. When a large excess of electricity (10 F/mol) was passed, **120** was obtained in a 70 % yield from **103** (Scheme 2-13).



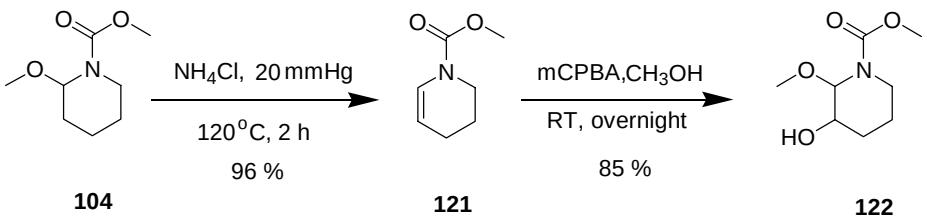
Scheme 2-13. Anodic dimethoxylation of carbamate **103**.

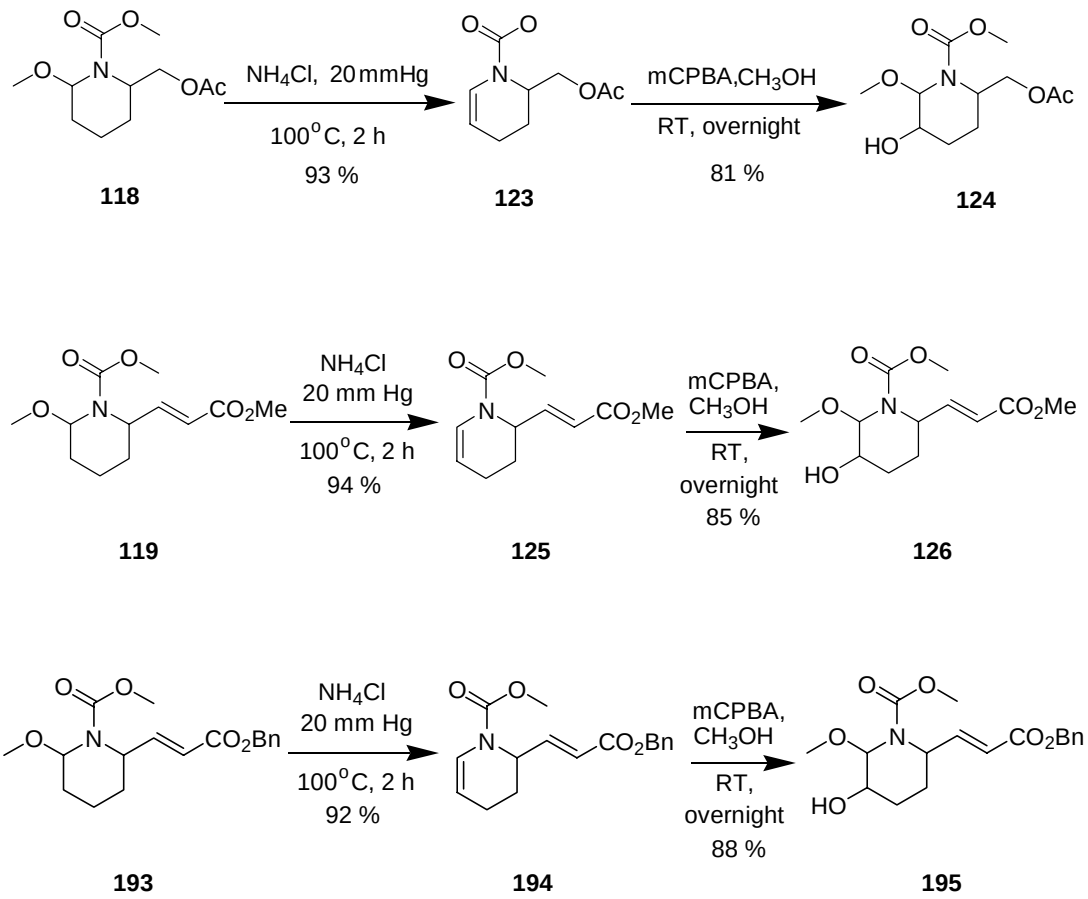
Therefore, the control of reaction time is very important if we only need mono-methoxylation product. When 2.7 F/mol is passed, we can get mono-substituted product 2-methoxy-piperidine-1-carboxylic acid methyl ester **104** in 85 % yield.

2.3.4 Elimination and epoxidation followed by ring-opening reaction

With catalytic amounts of ammonium chloride and under reduced pressure at high temperature, elimination reaction can take place quantitatively. The products **121, 123, 125** and **194** are useful synthetic intermediates which can be transformed into a number of nitrogen-containing natural pruducts by electrophilic addition.

Oxidations of **121, 123, 125** and **194** with 1.1eq mCPBA in methanol proceeded cleanly to afford N-carbamate-3-hydroxy-2-methoxy-piperidines derivatives **122, 124, 126** and **195** in good yields (Scheme 2-14). These results are in sharp contrast with recent results reported by Burgess and coworkers who obtained complex mixtures by reacting enecarbamates with peracids.[16]

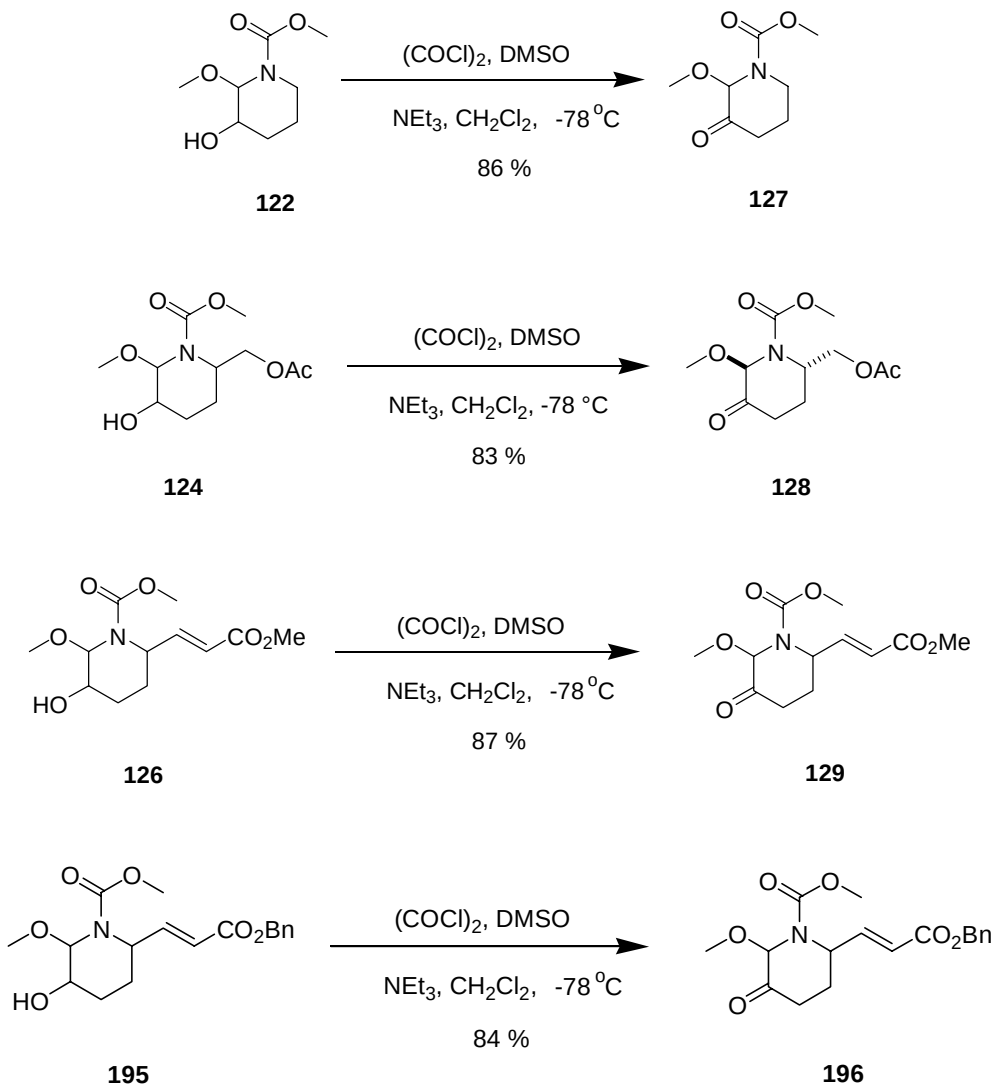




Scheme 2-14. Elimination and epoxidation followed by ring-opening reaction.

2.3.5 Swern Oxidation of alcohol to carbonyls

The subsequent oxidations of the 3-hydroxy group could be accomplished in high yield with Swern oxidations to yield 3-piperidones **127, 128, 129** and **196** (Scheme 2-15).



Scheme 2-15. Swern oxidation of 3-hydroxypiperidines derivatives.

Formation of the keto group in 3-position was readily confirmed by ^{13}C-NMR spectrum. E.g., the ^{13}C-NMR spectrum of **127** showed a signal at 202 ppm, which is typical for a carbonyl group in cyclohexanone (Figure 2-2). In IR spectrum, there are two C=O absorptions in the region of 1720-1706 cm $^{-1}$, which can be assigned to both ketone and ester carbonyl groups.

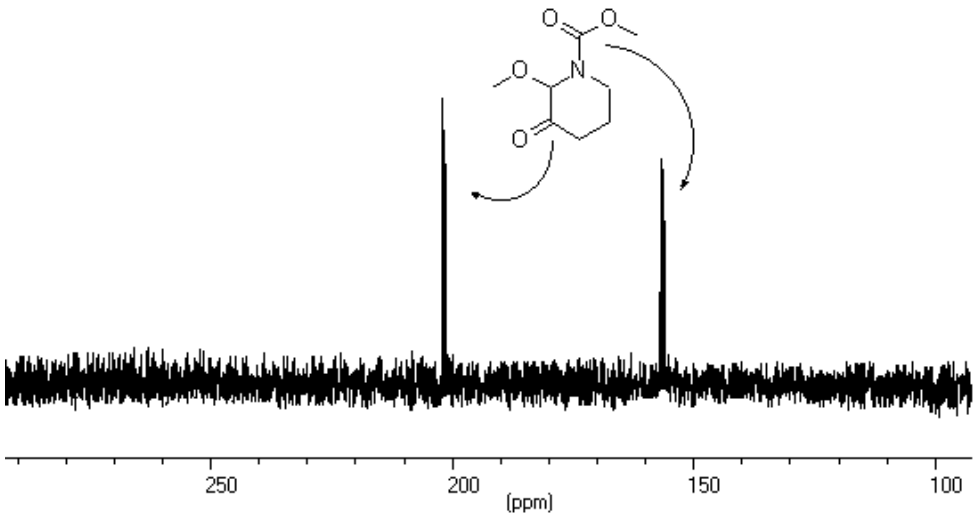
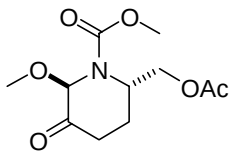


Figure 2-2. ^{13}C-NMR spectrum of carbonyl groups of 2-methoxy-3-oxo-piperidine-1-carboxylic acid methyl ester **127**.

The ^{1}H-NMR spectrum of **128** shows that only one diastereomer exists. From the subsequent ring-closing reaction product **188**, the structure of compound **128** is proved to be that with methoxy and acetoxymethyl groups located at different sides (Scheme 2-16). This will be described in detail in Chapter 5.



128

Scheme 2-16. Stereo structure of compound **128**.

In summary, a general route to 2-methoxy-3-oxo-piperidines **127**, **128**, **129** and **196** could be developed from the commercially available and inexpensive starting materials (Table

2-1). These synthetic steps involved are easy to carry out, high yielding and require mild reaction conditions.

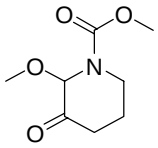
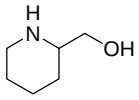
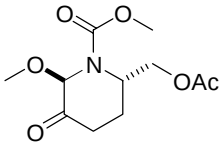
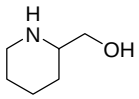
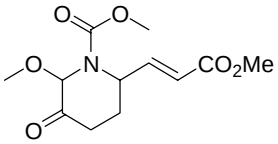
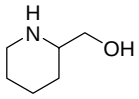
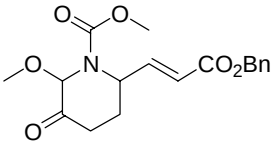
Materials	Steps	Total yield (%)	Aim compound
	**5**	**58**	 **127**
	**6**	**53**	 **128**
	**6**	**37**	 **129**
	**6**	**39**	 **196**

Table 2-1. Total yields of N-carbamate-2-methoxy-3-piperidones derivatives.

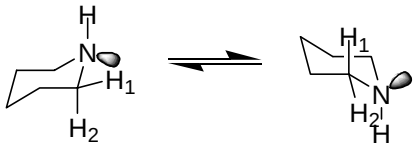
2.4 The ^{1}H-NMR studies of some piperidine derivatives

The ^{1}H-NMR technique has made a remarkable contribution to the knowledge of the stereochemistry of piperidines, both for configurational and conformational aspects. The structural resemblance between piperidine and cyclohexane with regard to conformational mobility has permitted the extrapolation of part of the knowledge acquired for the cyclohexane derivatives. Nevertheless, the presence of the heteroatom and the possibility of a conformational equilibrium based on nitrogen atom inversion has

introduced a new degree of complexity, which has motivated the development of numerous studies.

2.4.1 ^{1}H-NMR of piperidine and methylpiperidine

At room temperature the two conformations of piperidine ring can interchange quickly, so only one peak can be seen at δ 2.77 of both of the axial and equatorial protons of 2-H (Figure 2-3).

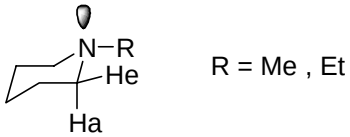


H_1, H_2 : δ 2.77 ($CDCl_3$, 500 MHz)

Figure 2-3. Quick interchange of two chair forms.

At low temperature, the chemical shift difference between axial and equatorial protons is δae = 0.4 ppm, with the axial proton found at higher field. [17]

In the case of methylpiperidine, the different chemical shift of axial and equatorial protons is both caused by the fact that an axial proton is more shielded than its equatorial proton, and influenced by the orientation of the lone electron pair on the heteroatom. Thus, an equatorial proton is usually more deshielded because it is syn with respect to the nitrogen lone pair (Figure 2-4). [18]



$\Delta\delta_{ax\text{-}eq}$ = 0.94 – 1.05

Figure 2-4. Equatorial proton is more deshielded at low temperature.

2.4.2 ^{1}H-NMR analysis of N-carbamate-piperidines

The interest in piperidine ring system in the biological field has led to the study of the conformational behavior of N-acylpiperidine. The simplest example of an N-acylpiperidine is N-formylpiperidine. When the piperidine ring is unsubstituted, all of the axial and equatorial protons of each carbon atom in the ring, are magnetically equivalent due to the rapid ring inversion between the two equivalent chair forms (Figure 2-5, 2-6).

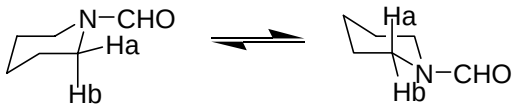


Figure 2-5. The rapid ring inversion between the two equivalent chair forms.

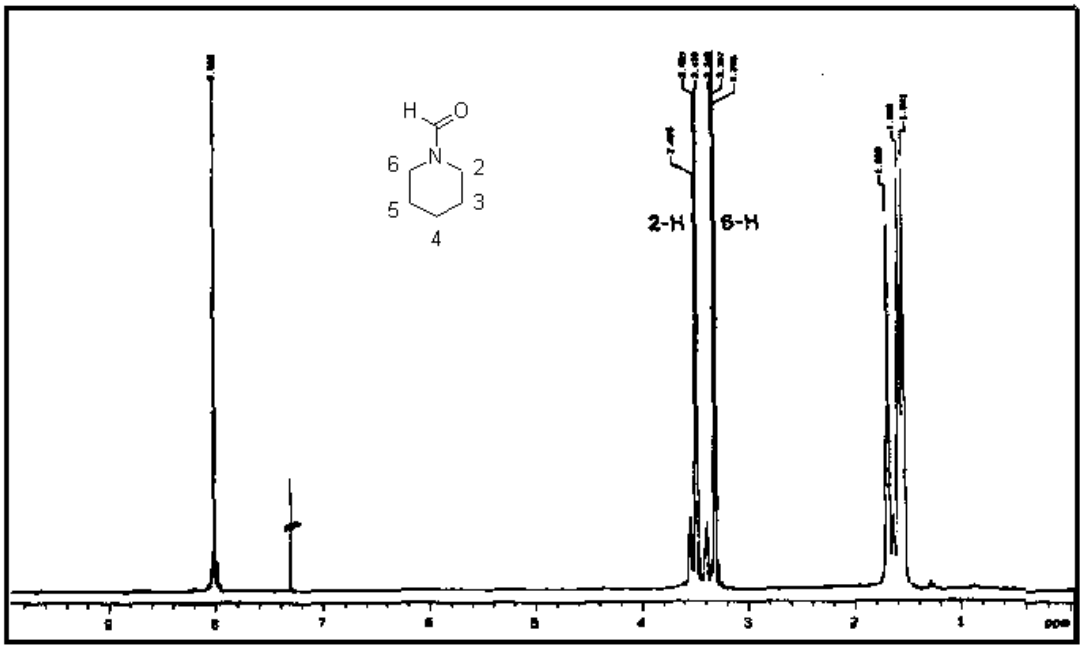


Figure 2-6. ^{1}H-NMR (200 MHz) of N-formylpiperidine in $CDCl_3$ at 30 °C.

From the ^{1}H-NMR spectrum of N-formylpiperidine, it can be seen that the chemical shifts of 2- and 6- protons are different because the rotation of the C-N is hindered under room temperature (Figure 2-7). The 2-proton is more deshielded, for they are in *cis* with the carbonyl oxygen atom.

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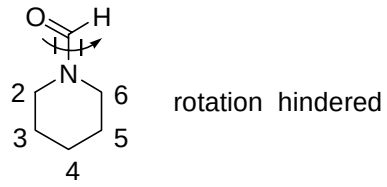

Figure 2-7. The rotation of C-N bond hindered.

The carbamate rotation barrier is much lower than the amide barrier in the tethehydropyridine system, because of the lower C-N bond order caused by the precense of ester resonance (Figure 2-8).

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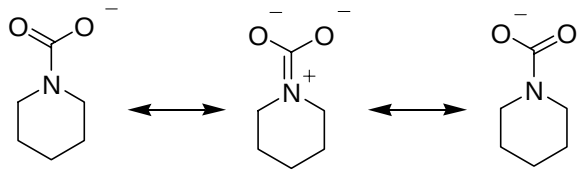

Figure 2-8. The resonance of carbamate.

At room temperature, because of the free rotation of the C-N bond of the carbamate, the 2- and 6- position protons are chemically equivalent (Figure 2-9).

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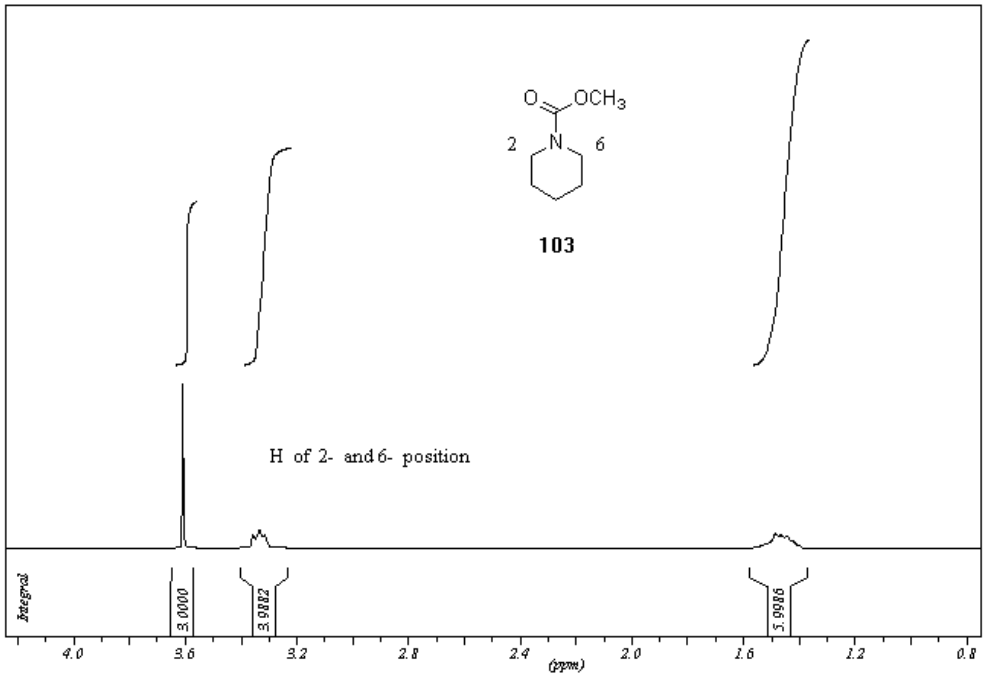

Figure 2-9. ^{1}H-NMR spectrum of piperidine-1-carboxylic acid methyl ester **103**.

The substitution of the piperidine ring complicates the situation as ring reversal provides two non-equivalent conformers. 2-Methoxy-piperidine-1-carboxylic acid methyl ester **104** is an example of α-substituted-N-carbamate piperidine. In the conformational equilibrium, the A $^{(1,3)}$ strain forces the methoxy group on C-2 predominantly axial (Figure 2-10). [19]

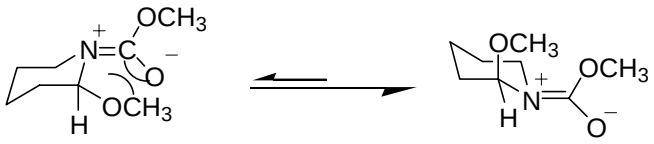

Figure 2-10. The methoxy group on C-2 predominantly axial due to the A $^{(1,3)}$ strain.

Thus the axial and equatorial protons in 6- position have separate signals in ^{1}H-NMR spectrum due to the different chemical environment (Figure 2-11).

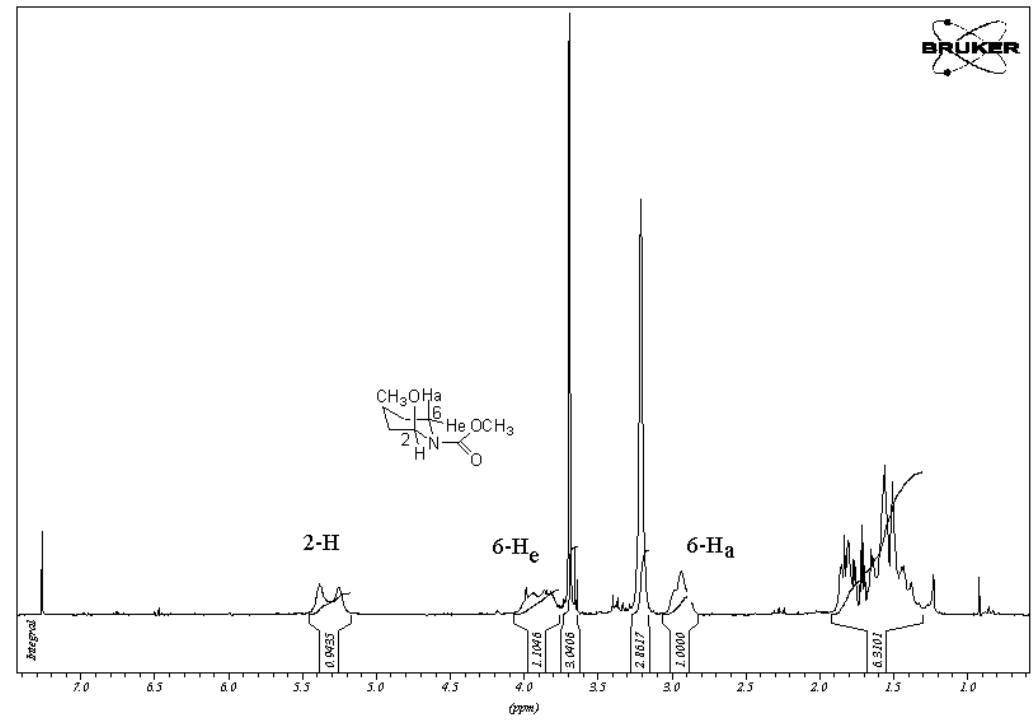

Figure 2-11. ^{1}H-NMR spectrum of 2-methoxy-piperidine-1-carboxylic acid methyl ester **104**.

The equatorial proton signal appears at low field resulting from a deshielding effect of a carbonyl group near to equatorial proton of 6-position (Figure 2-12).

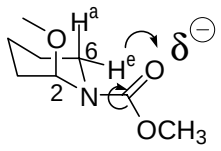

Figure 2-12. Deshielding effect of a carbonyl group near to equatorial proton of 6-position of **104**.

References

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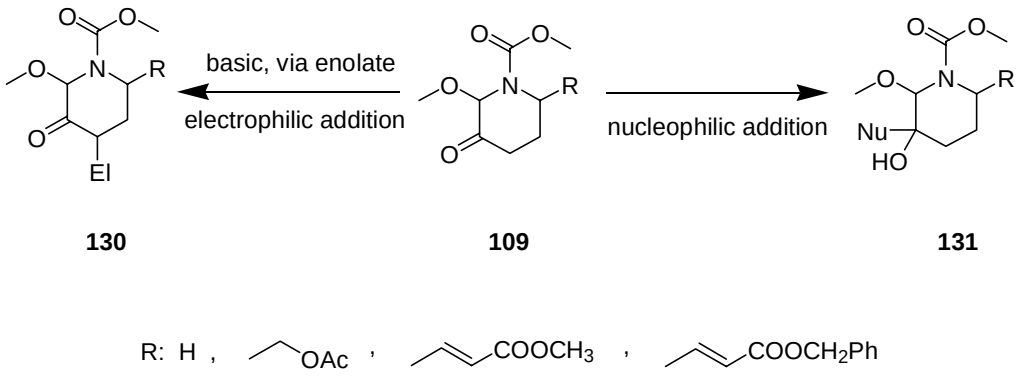
• Chapter 3

Reactions of Piperidine-3-ones on the Carbonyl Group

The carbonyl group is undoubtedly one of the most important functional groups in organic chemistry, both in its role as reactive center for synthesis and as crucial feature for special structural or physiological properties. [1] In the structures of N-carbamate-2-methoxy-3-piperidones derivatives, the carbonyl group is the main functional group. Through nucleophilic addition and electrophilic addition via enolates, a carbon-carbon bond can be introduced into both of the 3- and 4-positions, thus various kinds of other functional groups will be successfully connected (Scheme 3-1).



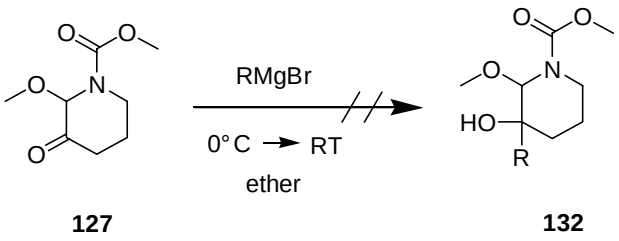
Scheme 3-1. Formation of carbon-carbon bond in 3- and 4-positions.

In this chapter, we will discuss some nucleophilic additions on the carbonyl group of the N-carbamate-2-methoxy-3-piperidones derivatives and other interesting reactions based on the addition products.

3.1 Nucleophilic addition on the carbonyl group

3.1.1 The addition reaction with 2-furyllithium

The nucleophilic addition to carbonyl groups by Grignard reagents is a general reaction in organic chemistry. However, treatment of N-carbamate-2-methoxy-3-piperidones **127** with Grignard reagents, no selective formation of addition products was achieved due to the presence of the carbamate carbonyl group, which also might react with strong nucleophilic reagents (Scheme 3-2).

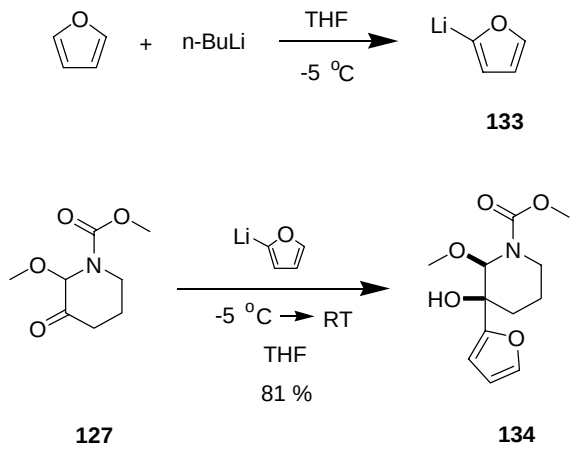


Scheme 3-2. Nucleophilic additions with Grignard reagents to compound **127** failed.

Organolithium reagents are as important as the Grignard reagents for organic synthesis. The reactions of organolithium reagents parallel those of Grignard reagents in many ways. It was also reported that organolithium reagents can easily add to hindered ketones to form alcohols. [2] Thus, organolithium reagents were investigated instead of Grignard reagents in the reaction with **127**. Meanwhile, 2-furylalcohol is an interesting compound, which can be changed to spiro heterocycles via oxidation-rearrangement. This will be discussed in detail in section 3.3.1. Therefore, the nucleophilic addition to N-carbamate-2-methoxy-3-piperidones **127** was tried with furyllithium.

Furan can be deprotonated by organolithium, such as *n*-butyllithium, and the α-position shows the highest reactivity. Treatment of 2-methoxy-3-oxo-piperidine-1-carboxylic acid

methyl ester **127** with 2-furyllithium **133** yielded the corresponding 3-(2-furyl)-3-hydroxy-2-methoxy-piperidine-1-carboxylic acid methyl ester **134** in 81 % yield as single diastereomer (Scheme 3-3).



Scheme 3-3. Nucleophilic addition with 2-furyllithium **133**.

In the ^{1}H-NMR spectrum, no diastereomeric mixture was found. Due to the chelation effect of Li^{+}, the stereochemistry of addition product **134** can be assumed to be determined via a transition state **127A** (Figure 3-1).

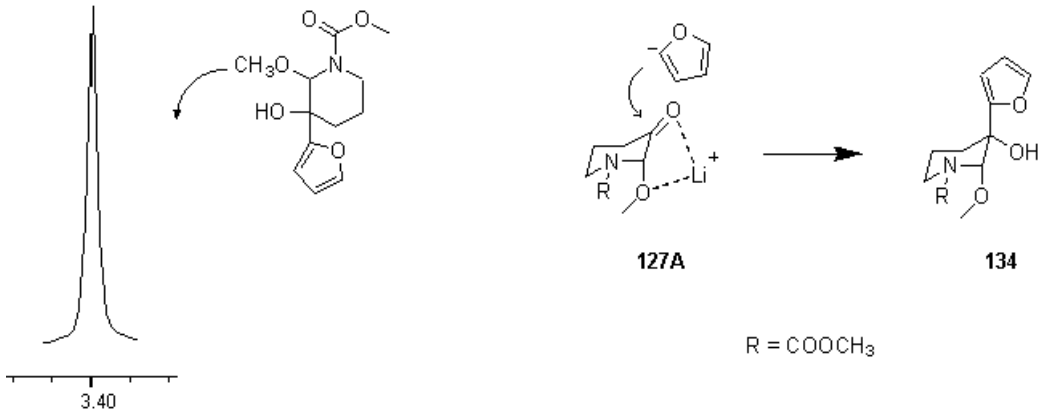
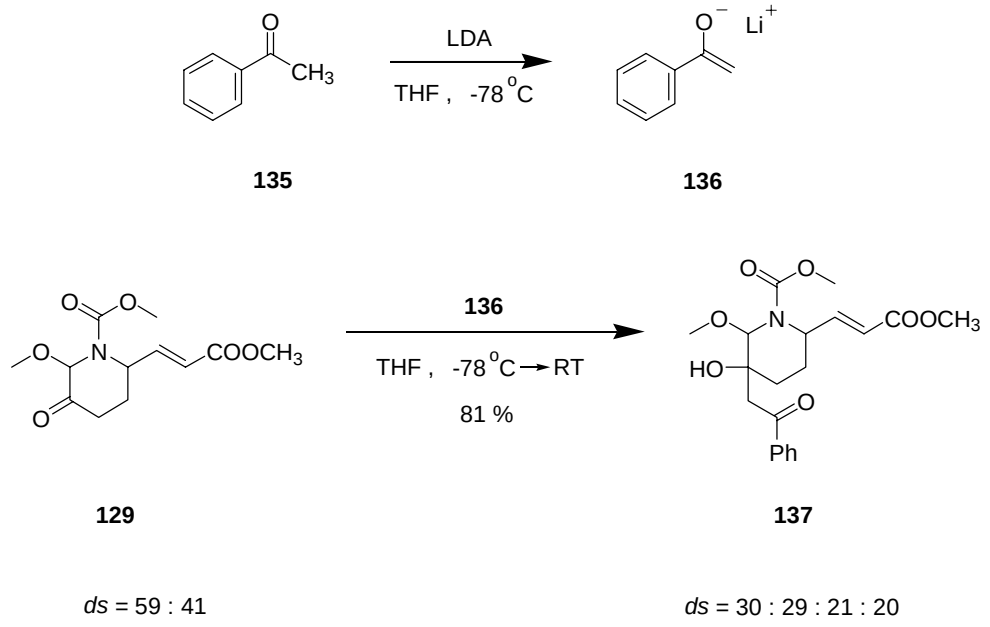


Figure 3-1. Part of ^{1}H-NMR spectrum of **134** (363K, DMSO-d_6) and the chelation effect of Li^{+} leading to one diastereomer.

3.1.2 The aldol reaction of N-carbamate-2-methoxy-3-piperidones derivatives

The aldol reaction is an extremely important carbon-carbon formation method and has led to many applications in organic synthesis. We tried both of ketone enolates and ester enolates as nucleophilic reagents in the reactions of piperidine-3-ones **127-129**.

Lithium enolates are stable at low temperature (-78 °C) but reactive enough to be useful as reagents with ketones. Treatment of acetophenone **135** with LDA (freshly made from *n*-butyllithium and diisopropylamine at 0°C) yielded the intermediate lithium enolate **136**. Treatment of compound **129** (*ds* = 59:41) with **136** gave the product 3-hydroxy-(N-carbamate-2-methoxy-6-(2-methoxycarbonyl-vinyl)-[3]-piperidyl)-acetophenone **137** in 81 % yield as diastereomeric mixture (*ds* = 30:29:21:20) (Scheme 3-4).



Scheme 3-4. Aldol reaction of 2-methoxy-6-(2-methoxycarbonyl-vinyl)-3-oxo-piperidine-1-carboxylic acid methyl ester **129** with acetophenone.

The diastereomeric ratios of starting material **129** and product **137** were determined by ^{1}H-NMR spectra (Figure 3-2).

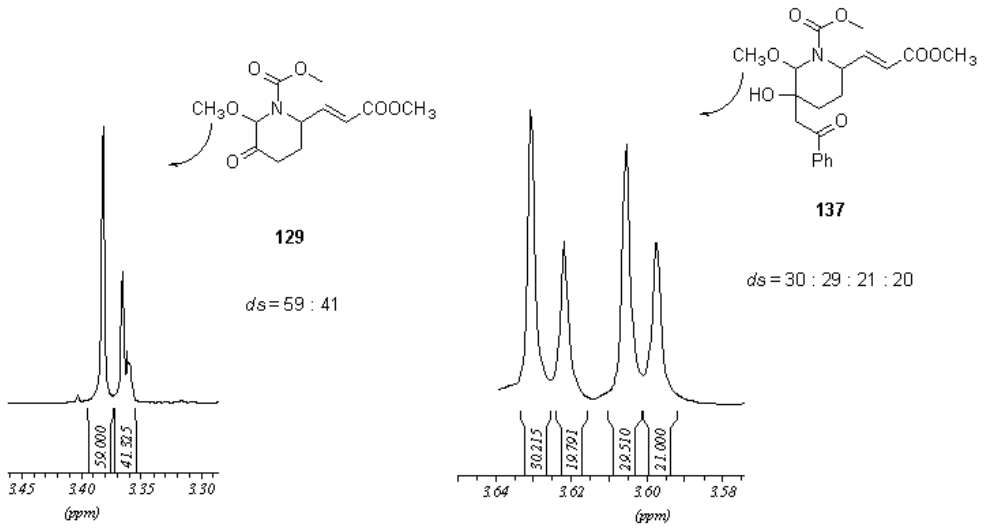
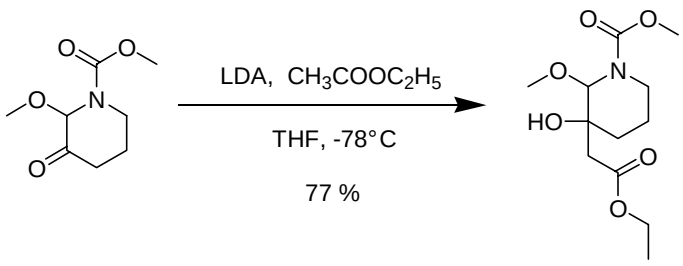


Figure 3-2. The diastereomeric ratios of starting material **129** and product **137** were determined by ^{1}H-NMR spectra (363K, DMSO-d_6).

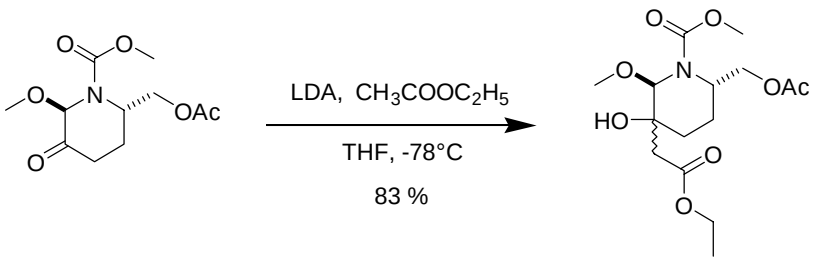
The ^{1}H-NMR spectra were performed at high temperature (363 K) to exclude the possibilities of rotamers.

Likewise, ester enolates gave high yields in the reactions of various 3-piperidones **127-129** (Scheme 3-5).



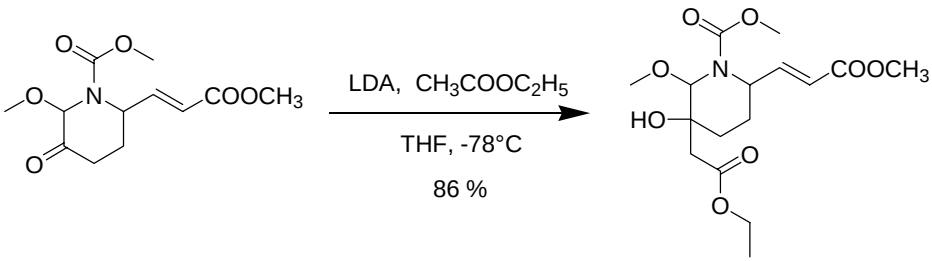
127 **138**

ds = 48 : 52



128 **139**

ds = 53 : 47



129 **140**

ds = 59 : 41 *ds* = 28 : 40 : 14 :18

Scheme 3-5. Aldol reactions of N-carbamate-2-methoxy-3-piperidones derivatives **127-129** with ethyl acetate.

The diastereomeric ratios of the addition products **138-140** were determined by ^{1}H-NMR spectra (363K, DMSO-d_6) (Figure 3-3).

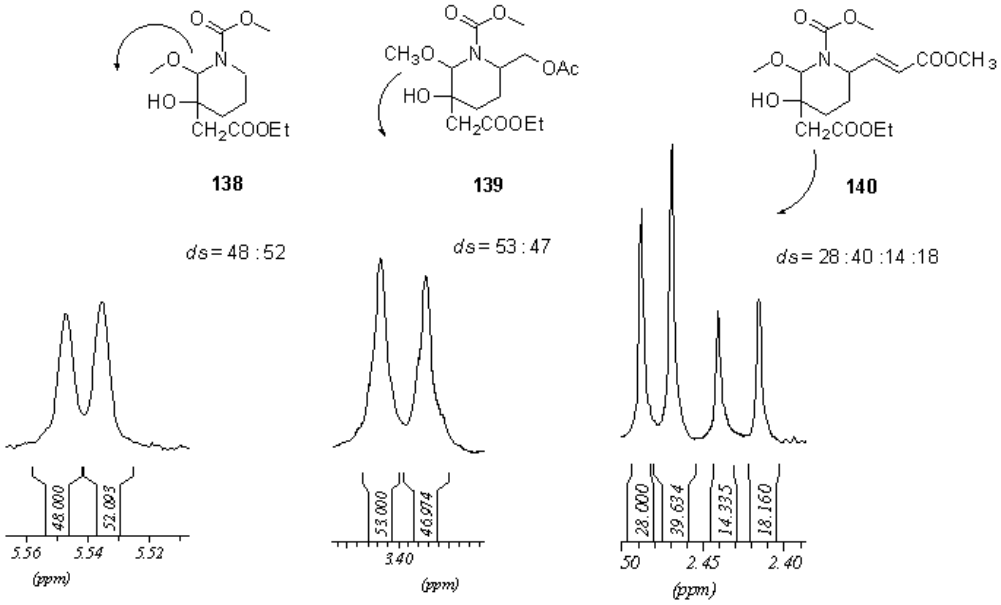
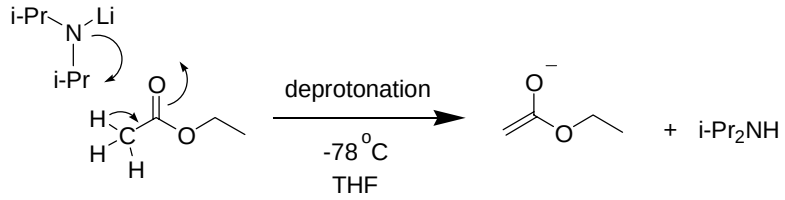
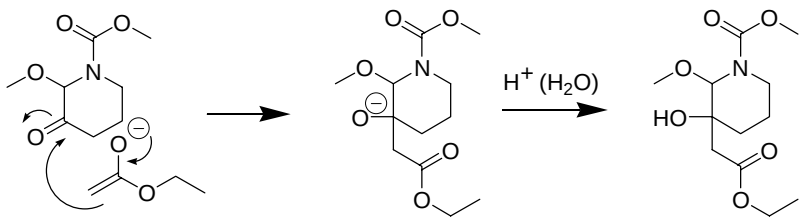


Figure 3-3. The diastereomeric ratios of the addition products **138-140** were determined by ^{1}H-NMR spectra (363K, DMSO-d_6).

The mechanism of the reactions can be explained as following (Scheme 3-6):





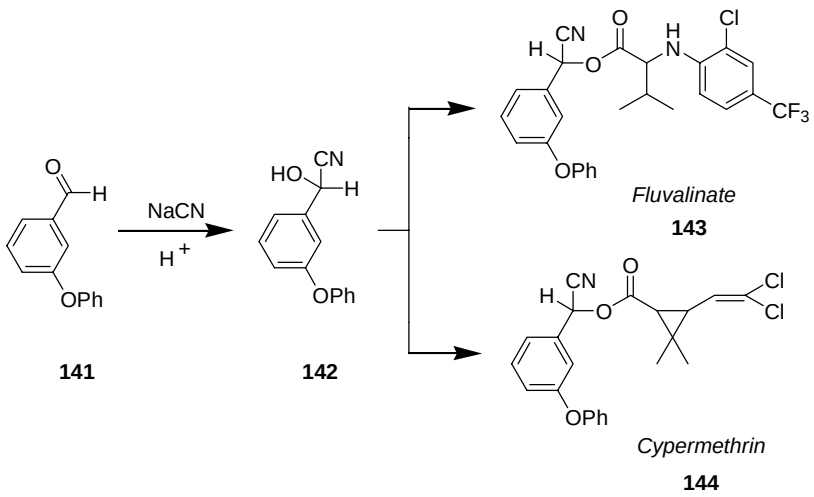
Scheme 3-6. Mechanism of aldol reaction of **127** with ethyl acetate.

The proton comes from the work up procedure. The reaction mixture was washed with 2N H_2SO_4 solution for several times, extracted by ether, further purified by flash column chromatography.

Simple ester enolate anions can be prepared in THF solution using lithiumamide bases and stored at -78 °C, but if they are warmed to room temperature, they will give β-keto ester enolates. This occurs even though no free ester was present. As a consequence, the reactions of simple ester enolates should generally be carried out at -78 °C. In the addtion of ester enolate anions to a ketone, the anion is prepared first and then ketone is added, otherwise the base would produce the anion of the ketone instead.

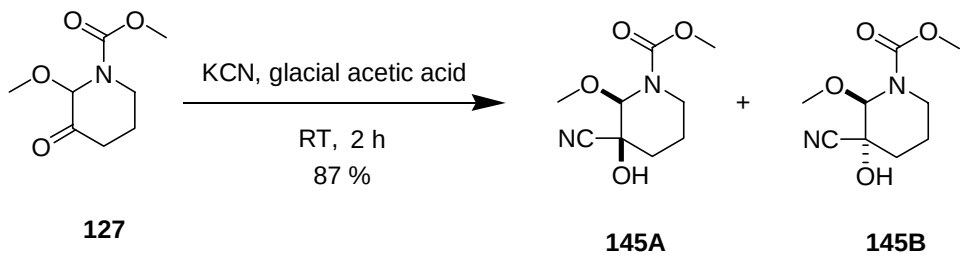
3.1.3 The addition reaction with potassium cyanide.

Cyanohydrins are important synthetic intermediates, and components of many natural and industrial products, such as the insecticides *Fluvalinate* **143** and *Cypermethrin* **144** (Scheme 3-7).



Scheme 3-7. Cyanohydrin is an important intermediate of *Fluvalinate* **143** and *Cypermethrin* **144**.

Cyanohydrin formation is reverisible. The equilibrium is more favorable for aldehyde cyanohydrins than for ketone cyanohydrins, and the reason is the size of the groups attached to the carbonyl carbon atom. As the carbonyl carbon atom changes from sp^2 to sp^3, its bond angles change from about 120 ° to about 109 °, that is to say, the substituents it carries move closer together. In a ketone with large alkyl groups, this steric effect can disfavor the addition reaction. In the structure of 2-methoxy-3-oxo-piperidine-1-carboxylic acid methyl ester **127**, the two α- alkyl groups are not large enough to hinder the attack of cyanide ion on carbonyl group, so we get good yield of the addition product. In glacial acetic acid, treatment of 2-methoxy-3-oxo-piperidine-1-carboxylic acid methyl ester **127** with potassium cyanide under room temperature produced **145A/145B** in 87 % yield as diastereomeric mixture (*ds* = 85:15) (Scheme 3-8).



127 **145A** **145B**

ds (**145A** : **145B**) = 85:15

Scheme 3-8. Synthesis of cyanohydrin **145A** and **145B** as diastereomeric mixture.

The structures of major and minor diastereomers were determined by NOESY spectrum of **145** (Figure 3-4). From this spectrum we can see that the 2-position proton (δ 5.35) and the hydroxy proton of 3-position (δ 6.59) show a small NOE effect, this is caused by the minor diastereomer, in which these two protons are located at same side.

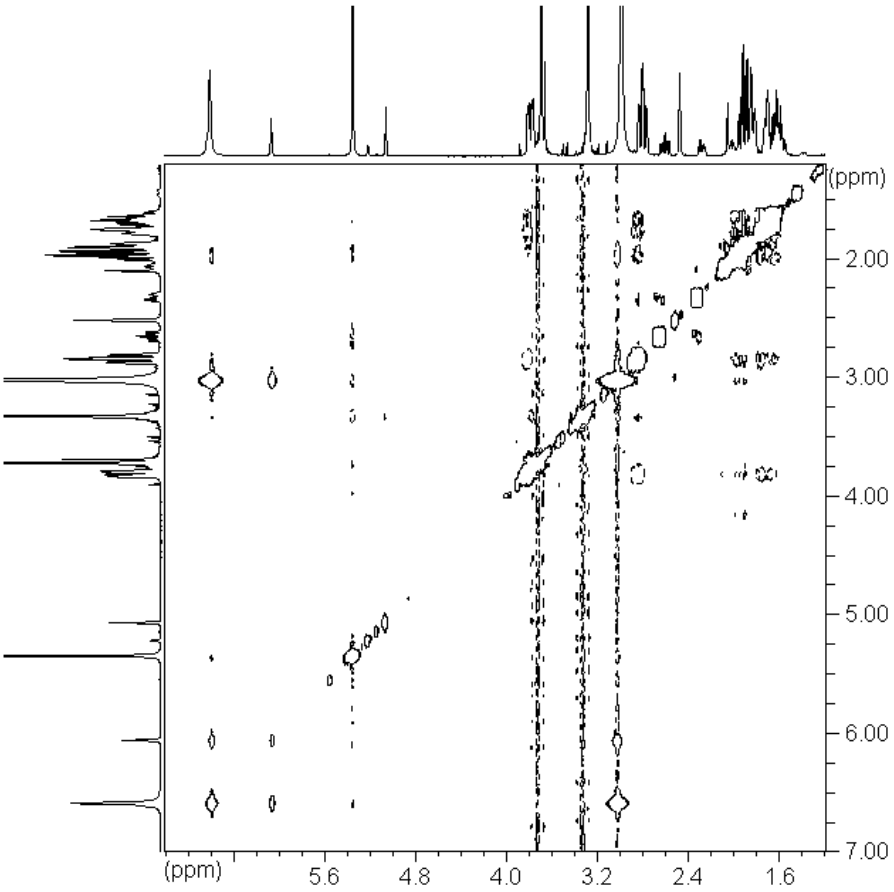


Figure 3-4. NOESY spectrum of **145** at high temperature. (363 K, DMSO-d_6).

The diastereomeric ratio was determined by part of ^{1}H-NMR and ^{13}C-NMR spectra of **145** at high temperature (363 K, DMSO-d_6) (Figure 3-5).

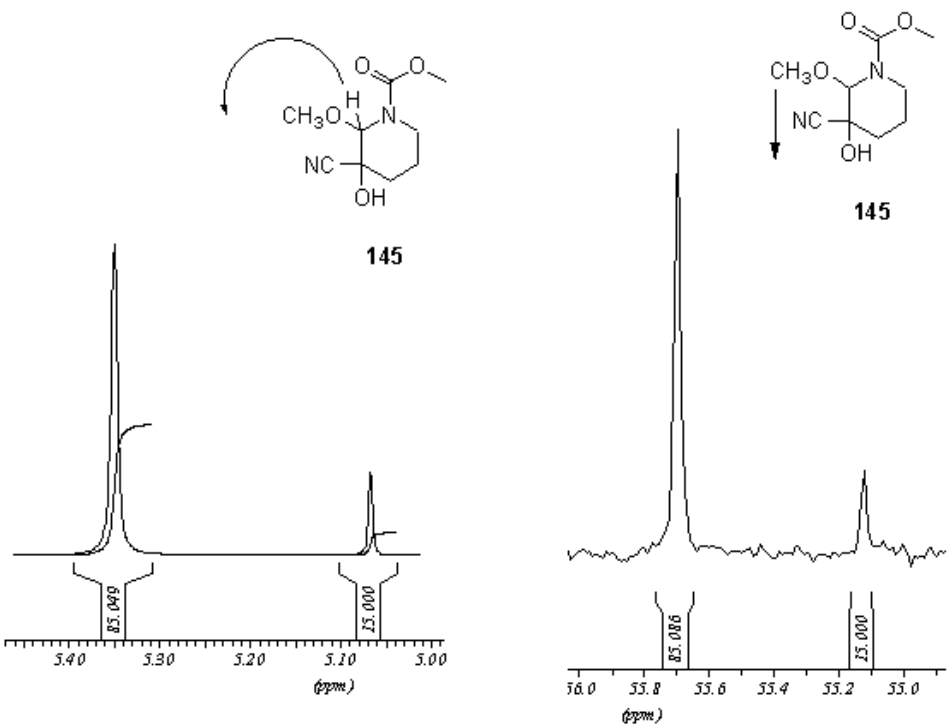
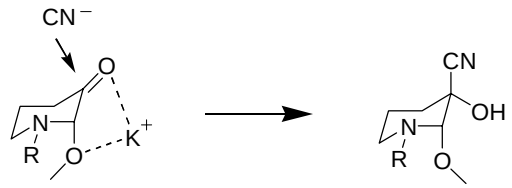


Figure 3-5. Part of the ^{1}H-NMR and ^{13}C-NMR spectra of **145** (363 K, DMSO-d_6).

The formation of cyanohydrin is diastereoselective (*ds* = 85:15). This can be explained by the chelation effect of K^+ (although K^+ is not a very good chelating metal). CN^- attacks the carbonyl group in axial direction, thus the addition product **145A** with methoxy and hydroxy group at same side is predominant (Scheme 3-8 and 3-9).



145A

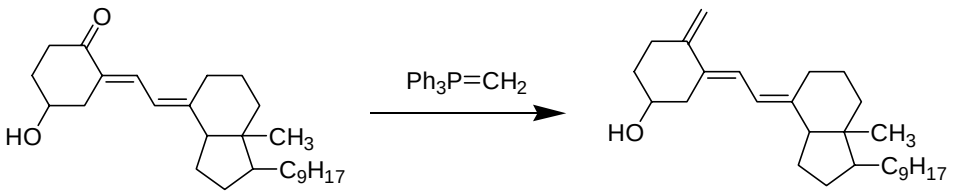
R = $COOCH_3$

Scheme 3-9. Diastereoselective formation of cyanohydrin.

The presence of glacial acetic acid in solution helps to strengthen the polarity of the carbon-oxygen double bond. The electrons in that bond are strongly attracted towards the hydrogen ions in the solution. It is easy to think that the more acid added, the more we could increase the polarity of the carbon-oxygen double bond. Unfortunately, there is a competing effect. The more acid we add, the more the cyanide ions get converted into hydrogen cyanide. Since cyanide ions are what actually attack the slightly positive carbon, removing them is not helpful. A pH of 4 - 5 is found experimentally to give the best rate of reaction. So we choose glacial acetic acid (pH = 4.8) as the solvent in this reaction. It increases the polarity of the double bond by a useful amount, but without removing too many of the cyanide ions as HCN.

3.2 Wittig and HWE reactions

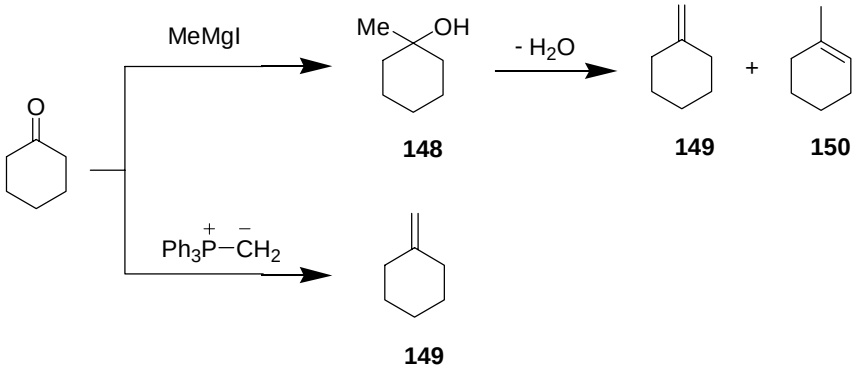
Wittig reaction is an efficient method to synthesize compound with a semicyclic double bond. [3] It has found great application in natural product synthesis. For example, immediately after the first publication from Wittig about this reaction, [4] Inhoffen et al. utilized this method to synthesize a moiety of Vitamin D_2 (Scheme 3-10). [5]



146 **147**

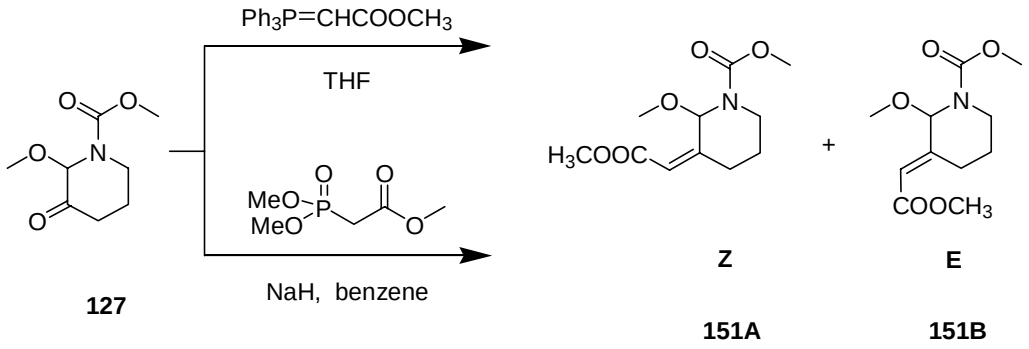
Scheme 3-10. Inhoffen et al utilized Wittig reaction to synthesize a moiety of Vitamin D_2.

A semicyclic double bond can also be achieved by the Grignard addition and dehydration sequence, but it generally proceeds with the formation of isomeric mixtures and thus is not as good as Wittig reaction in the synthesis of semicyclic double bond (Scheme 3-11).



Scheme 3-11. Grignard addition and dehydration sequence generally proceeds with the formation of isomeric mixtures.

The stereochemistry of formation of semicyclic double bond is relatively complicated and different results were reported in literatures with Wittig and HWE olefination. [6-9]
In Chapter 2, we once used Wittig reaction to acquire stereoselective E-alkene from aldehyde. Here with both Wittig and HWE reactions we got E and Z-alkene with different ratios (Scheme 3-12, Table 3-1).

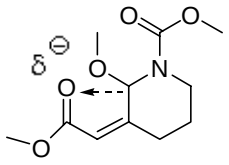


Scheme 3-12. Wittig and HWE reactions of **127** led to both Z and E porducts.

Method	Z / E Ratio	Yield (%)
Wittig Reaction	36 : 64	71
HWE Reaction	63 : 37	63

Table 3-1. Wittig and HWE olefinations with different Z/E ratios and yields.

The stereochemistry of olefins **151A** and **151B** was tentatively assigned as Z and E respectively on the basis of their NMR spectra. In the ^{1}H-NMR spectrum of compound **151A**, the 2-H appeared at δ 5.40, and the methoxy group appeared at δ 3.30. In contrast, the 2-H of isomer **151B** was observed at δ 5.32 and the methoxy group at δ 3.35. Similar phenomena have been reported in the E and Z derivatives of a hexofuranose, [7,9] presumably resulting from a deshielding effect of a carbonyl group *cis* to 2-proton (Scheme 3-13).[7]



Z

151A

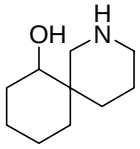
Scheme 3-13. The deshielding effect of a carbonyl group *cis* to 2-proton.

3.3 Some interesting reactions based on nucleophilic addition products

3.3.1 The oxidation-rearrangement of compound 134

Azaspiro[5.5]undecanes are recognized to be important as constituents of a growing variety of naturally occurring compounds. [10] Especially, the 2-azaspiro[5.5]undecane

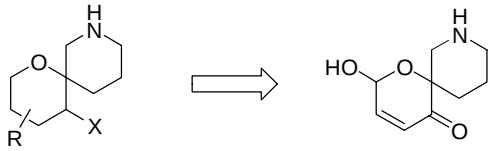
moiety comprises the skeleton of *Isonitramine* **152**, which is alkaloid isolated from plants of the *Nitraria* family with important biological activity (Scheme 3-14). [11,12] Thus, many approaches have been developed towards the facile and convenient synthesis of azaspiro[5.5]undecanes and their derivatives and analogues. [13]



152

Scheme 3-14. Structure of *Isonitramine* **152**.

Therefore, it would be interesting to study the synthesis and use of 6-hydroxy-2-spiropyran-3(6H)-ones **153** as key intermediates for the facile and efficient preparation of several novel biologically interesting 8-aza-1-oxaspiro[5.5]undecane **154** derivatives (Scheme 3-15). This synthetic approach also leads to the synthesis of novel oxygen-containing isosteres of *Isonitramine*. It is evident that the multitude of the reactions which can be carried out on the α,β-unsaturated ketone system as well as the hydroxy and oxo groups of these synthetic intermediates allows the incorporation of a wide variety of substituents and functionalities leading to a great series of derivatives.

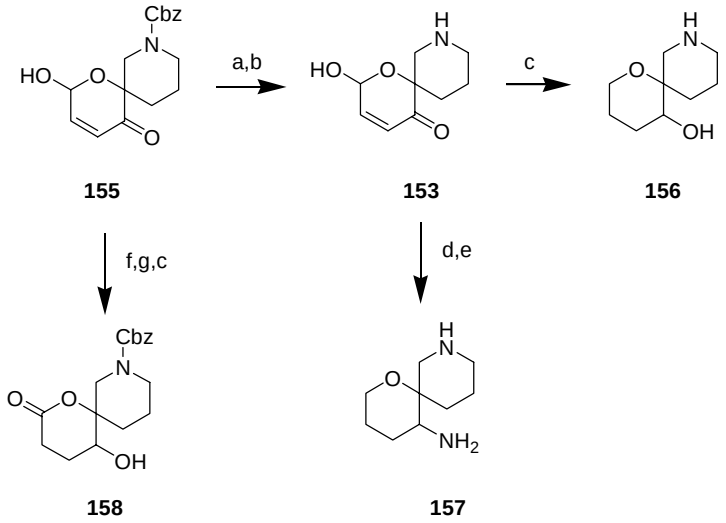


154 **153**

X = -OH, $-NH_2$

Scheme 3-15. Retrosynthesis of 8-aza-1-oxaspiro[5.5]undecane derivatives **154** from 6-hydroxy-2-spiropyran-3(6H)-ones **153**.

Apostolopoulos et al. reported a synthetic method of oxygen containing isosteres of *Nitramine* and *Isonitramine* and their analogues from 6-hydroxy-2-spiropyran-3(6H)-ones **153** derivative (Scheme 3-16). [14]



Reagents and conditions:

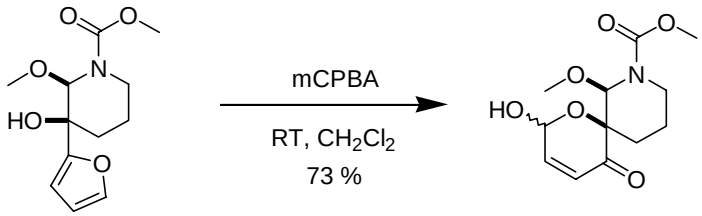
(a) $ClCOOC_2H_5$, NEt_3, CH_2Cl_2, -5° C to rt, 2 h; (b) H_2/Pd-C, CH_3OH, rt, 20 psi, 2h;
(c) $NaBH_4$, CH_3OH; (d) NH_2OH/HCl, CH_3COONa, CH_3OH/H_2O, rt, 1 h;
(e) H_2/PtO_2, C_2H_5OH/HCl, 45 psi, 3 h; (f) Jones reagent, $(CH_3)_2CO$, 0° C to rt, 0.5 h;
(g) H_2/Pd-C, $CH_3COOC_2H_5$, rt, 20 psi, 1h.

Scheme 3-16. Synthesis of oxygen-containing isosteres of *Nitramine* and *Isonitramine* and their analogues from 6-hydroxy-2-spiropyran-3(6H)-ones **153** derivative.

The reactions in which the carbon skeleton of the molecule is rearranged to give a structural isomer of the original molecule are known as rearrangement reactions. Usually in such reaction atoms or groups shift from one position to another within the molecule resulting in a new molecular structure. Various kinds of rearrangement reactions have been widely used in organic synthesis. The changes of carbon skeleton usually lead to some interesting and unexpected structures otherwise not readily available. Here through oxidation-rearrangement we successfully synthesized the 6-hydroxy-2-spiropyran-3(6H)-ones **159** derivatives from furanmethanol **134** which is the addition product from ketone

127 and 2-furyllithium.

The reaction of furanmethanol 3-(2-furyl)-3-hydroxy-2-methoxy-piperidine-1-carboxylic acid methyl ester **134** with mCPBA under room temperature undergoes an oxidation-rearrangement sequence on the furan nucleus affording the pyranone derivative **159** in 73 % yield as diastereomeric mixture (*ds* = 62:38) (Scheme 3-17).



134 **159**

ds = 62 : 38

Scheme 3-17. The oxidation-rearrangement of furanmethanol **134** with mCPBA.

The diastereomeric ratio was determined by ^{1}H-NMR spectrum (peaks of methoxy group) of **159** (Figure3-6).

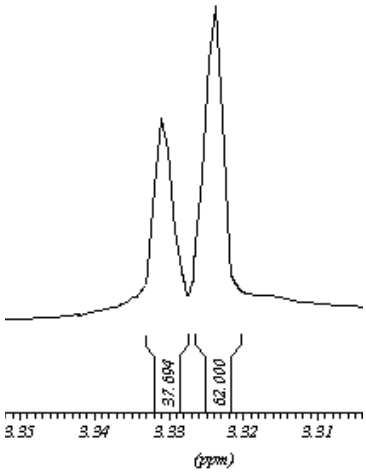
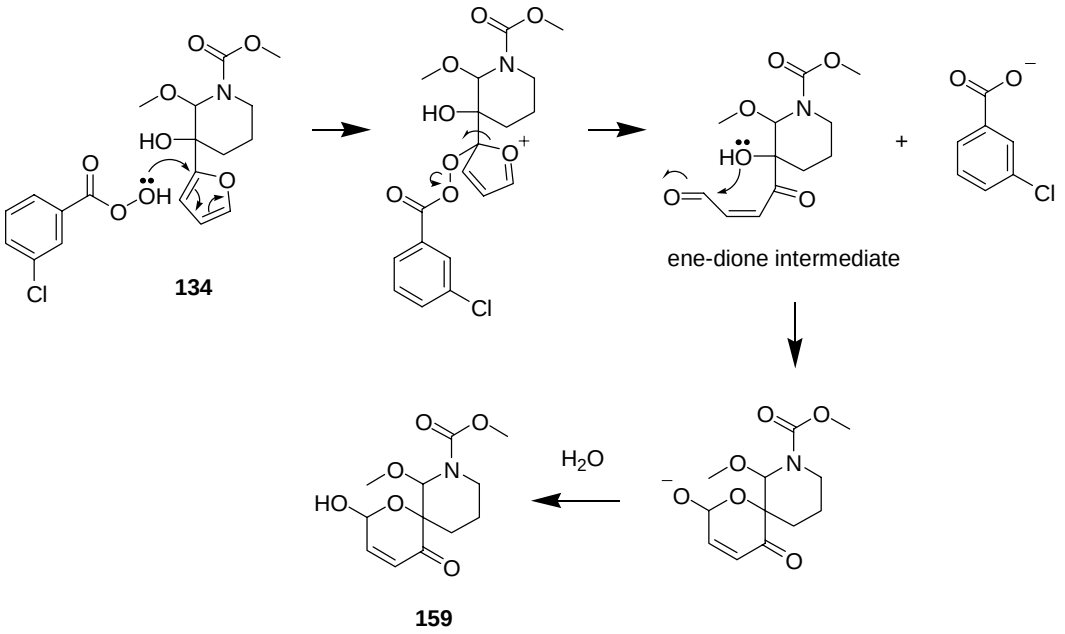


Figure 3-6. The diastereomeric ratio of **159** can be determined as 62:38 according to the ^{1}H-NMR spectrum (363K, DMSO-d_6).

It is obvious that this synthetic route provides a convenient route to the not easily available functionalized 8-aza-1-oxaspiro[5.5]undecanes which are valuable intermediates for the synthesis of natural products and their analogues.

The mechanism of the oxidation-rearrangement invloves ring closure of ene-dione intermediate which can be offered as following (Scheme 3-18):

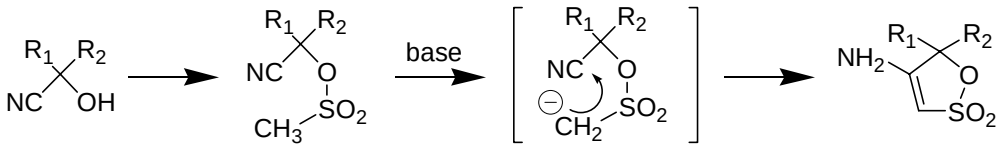


Scheme 3-18. The mechanism of the oxidation-rearrangement.

3.3.2 Study of the CSIC reaction

The CSIC (Carbanion Mediated Sulfonate Intramolecular Cyclization) reaction is an aldol type cyclization that takes place when alkanesulfonates of cyanohydrins are treated with non-nucleophilic bases such as DBU or sodium hydride to yield the 4-amino-5*H*-1,2-oxathiole-2,2-dioxide ring system. [15] The mechanism involves the removal of a

proton from the methylene neighbouring the SO_2 group under non-nucleophilic basic condition, and the carbanion which is generated attacks the cyano group to produce the cyclic enamine system (Scheme 3-19). [16] This reaction is rapid and clean with mild condition, easy work up procedure and high yield.

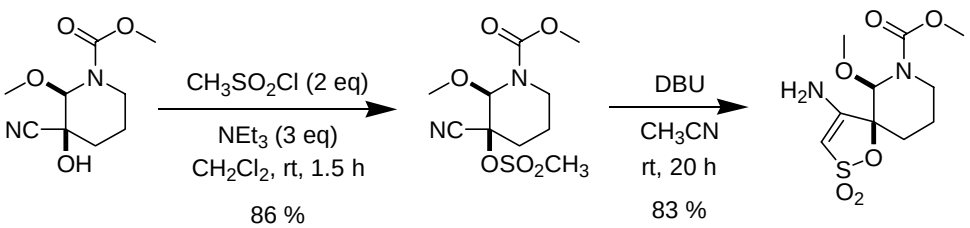


160 **161** **162** **163**

Scheme 3-19. The procedure and mechanism of the CSIC reaction.

Recently it was reported that complex polyoxygenated derivatives from sugars or nucleosides, simple ketones and aliphatic aldehydes could all be successfully used as the starting materials in the CSIC reaction. [17] This important discovery in the CSIC reaction has opened this protocol to new structural and functional possibilities, enriched the chemical reactions of simple heterocycles.

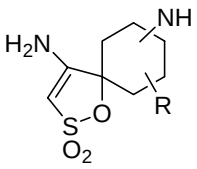
3-Cyano-3-hydroxy-2-methoxy-piperidine-1-carboxylic acid methyl ester **145A** is a cyanohydrin synthesized from compound ketone **127**. We used **145A** as the starting material of the CSIC reaction. Treatment of the cyanohydrin **145A** with methanesulfonyl chloride and triethylamine in dichloromethane under room temperature yielded 3-cyano-3-methanesulfonyloxy-2-methoxy-piperidine-1-carboxylic acid methyl ester **164** in 86 % yield. Treatment of **164** in acetonitrile with 0.6 eq DBU gave the 4-amino-7-aza-7-carbamate-6-methoxy-1-oxa-2-thiaspiro[4.5]dec-3-ene 2,2-dioxide **165** in 83 % yield as a single diastereomer. (Scheme 3-20).



145A **164** **165**

Scheme 3-20. The CSIC reaction of cyanohydrin **145A**.

Above all, the CSIC reaction of 3-cyano-3-hydroxy-2-methoxy-piperidine-1-carboxylic acid methyl ester **145A** proceeded smoothly and the resulting heterocycle has been obtained in good yield. Marco et al. reported that N-protected-4-piperidones are good starting compounds for this reaction [15] and we found that CSIC reaction of N-carbamate-3-piperidone with 2-methoxy substituted can also be well performed. It has been reported that some aza 4-amino-1-oxa-2-thiaspiro[4.5]dec-3-ene 2,2-dioxide derivatives **166** could show interesting biological activities (Scheme 3-21), [18] so the exploration of CSIC reaction of 3-cyano-3-hydroxy-2-methoxy-piperidine-1-carboxylic acid methyl ester **145A** should be significant.



166

Scheme 3-21. Some aza 4-amino-1-oxa-2-thiaspiro[4.5]dec-3-ene 2,2-dioxide derivatives **166** show interesting biological activities.

References

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• Chapter 4

Regioselective Formation of Enol Acetates and the Aldol Reaction

4.1 Introduction

Organic reactions involving intermediate enolate ions were first discovered in the middle of the nineteenth century and we now know a number of these reactions as efficient methods for the formation of carbon-carbon bonds. Since the discovery of lithium diisopropylamide (LDA) in 1950, [1] one of the most useful strong base, great achievements have been made and a huge number of papers applying this base were published. Among these publications, the improvement of the selectivity of enolate formation was the main topic. Many methods have been reported to form the kinetic and thermodynamic selective enolates. Table 4-1 shows some reagents and reaction conditions favored to kinetic and thermodynamic enolates.

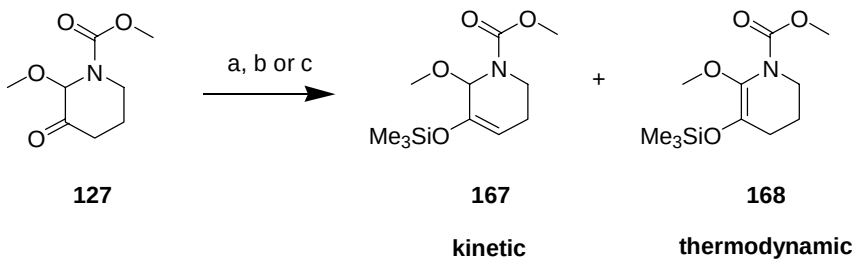
Table 4-1. Reagents and conditions favored to kinetic and thermodynamic enolates

	Favored to kinetic enolates	**Favored to thermo -dynamic enolates**
General favored condition	forms faster, favored by strong, hindered bases, low temperature, short reaction time	more stable, favored by excess ketone, high temperature, long reaction time
Reagents and other conditions	1, LDA, DME, TMSCl, -78 °C [3] 2, Ph_3Cli, THF, DME [4] 3, LICA, THF, -78 °C [5] 4, KH, THF, -78 °C [6] 5, $TiCl_4$, NEt_3, CH_2Cl_2 [7] 6, 9-BBNOTf, *i*-Pr_2NEt [7] 7, TMSOTf, NEt_3, 0°C, CH_2Cl_2 [10]	1, *t*-BuOK, *t*-BuOH, heat [8,11] 2, TMSCl, NEt_3, DMF [9,18] 3, TMSCl, NaI, NEt_3, CH_3CN [2] 4, KH, THF, TMSCl, 20 °C [6] 5, Ph_3CK, glyme, 20 °C [12] 6, BSA, NBu_4Br, 105 °C [13] 7, BMDA, TMSCl, HMPA, NEt_3 [14] 8, NBu_4NF, $TMSCH_2COOEt$ [15] 9, $FeCl_3$, MeMgBr, TMSCl, NEt_3, HMPA, RT [17]

4.2 Formation of silyl enol ethers

Silyl enol ethers have become extremely important intermediates in organic synthesis. Mukaiyama aldol reaction, formation of β-hydroxy ketones via reaction of silyl enol ethers with aldehydes in presence of a Lewis acid, such as titanium tetrachloride, tin tetrachloride or boron trifluoride etherate, is a general carbon-carbon formation reactions

which received wide attention. 2-Methoxy-3-oxo-piperidine-1-carboxylic acid methyl ester **127** is an interesting compound first synthesized in my work which is described in Chapter 2. To explore its reactivity, aldol reactions in 4- position based on kinetic enolates were first attempted. Treatment of **127** with LDA, and subsequent trapping with TMSCl, both kinetic and thermodynamic silyl enol ethers were obtained, favoring the kinetic product **167** (68:32). In contrast, treatment of **127** with TMSOTf and NEt_3 in dry CH_2Cl_2 at 0 °C, only the kinetic silyl enol ether **167** was obtained. Treatment of **127** with TMSCl, NaI, and NEt_3 in dry CH_3CN at 0°C, which is normally used as a standard thermodynamic product formation method, [2] surprisingly, the kinetic silyl enol ether was formed as the only product (Scheme 4-1).



127 **167** **168**

kinetic **thermodynamic**

Reagents and Condition:

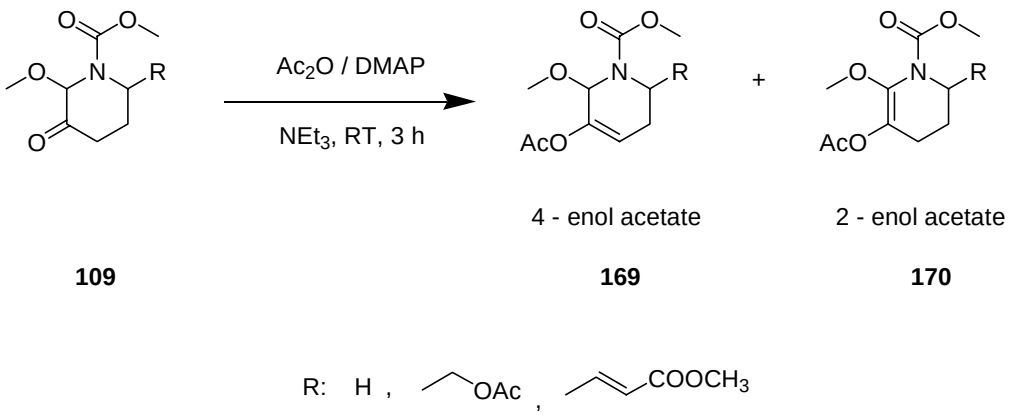
(a) LDA, TMSCl, THF, -78°C. **167**:**168** = 68 : 32
(b) TMSOTf, NEt_3, CH_2Cl_2, 0°C. **167**:**168** = 100 : 0
(c) TMSCl, NaI, NEt_3,CH_3CN, 0°C. **167**:**168** = 100 : 0

Scheme 4-1. Formation of kinetic and thermodynamic enolates under different conditions.

Although the pure kinetic silyl enol ether **167** can be made with method (b) and (c), its boiling point is unfortunately very high, therefore, purification by distillation, even at 150°C/0.02 mm Hg, was not possible. Higher temperature will lead to the decomposition of the silyl enol ether. Thus it is difficult to isolate pure **167**, preventing its further application in organic synthesis.

4.3 Formation of enol acetates

Since the pionnering works of Stork [19] and House [20] on the formation of lithium enolates by cleavage of silyl enol ethers and enol acetates with methyllithium, this method has been widely used in synthetic organic chemistry. Although not so common as silyl enol ethers, enol acetates have also been considered to be efficient enolate precursors. Due to the drawbacks of the silyl enol ether **167** of 2-methoxy-3-oxo-piperidine-1-carboxylic acid methyl ester mentioned above, I tried to synthesize the enol acetate of compound **127**. Indeed, a good method of preparing for **169** was developed, resulting in high regioselectivity and yields (Scheme 4-2, Table 4-2), favoring greatly the kinetic product **169**.



Scheme 4-2. Formation of enol acetates of 6-substituted N-carbamate-2-methoxy-3-piperidones **109**.

Unlike the silyl enol ethers, pure enol acetates are easily isolated by column chromatography and also they are stable at room temperature. To those silyl enol ethers whose boiling points are too high to be distilled for purification, the preparation of their corresponding enol acetates should be a method of choice because the latter can be purified by column chromatography.

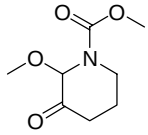
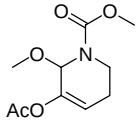
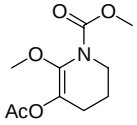
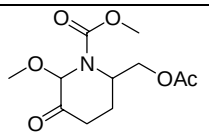
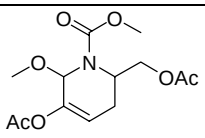
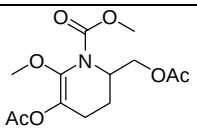
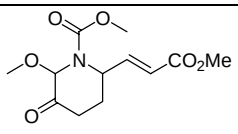
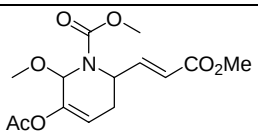
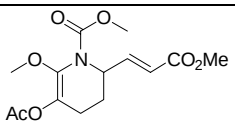
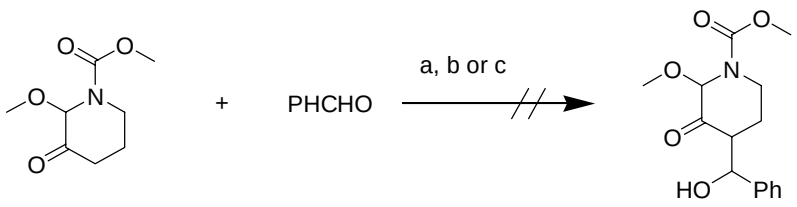
Entry	Substrate	Kinetic enol acetate (169)	Thermodynamic enol acetate (170)	Regio-select. 169:170	Yield (%)
1				**100 : 0**	**82**
2				**98 : 2**	**72**
3				**97 : 3**	**77**

Table 4-2. Regioselectivities and yields of the formation of enol acetates of 6-substituted N-carbamate-2-methoxy-3-piperidones derivatives **109**.

4.4 Attempts of aldol reactions of 127 with lithium enolates, silyl enol ethers and titanium enolates

The aldol reaction is an extremely useful carbon-carbon bond forming reaction in organic synthesis. The selective formation of C-C bonds in 4-position of **127** would be useful for further preparation of piperidine alkaloids. Lithium enolates, [24] silyl enol ethers [25] and titanium enolates [26] have been widely applied in aldol reaction. With these reagents under corresponding conditions, no clean aldol reactions could be performed (Scheme 4-3).



127 **171**

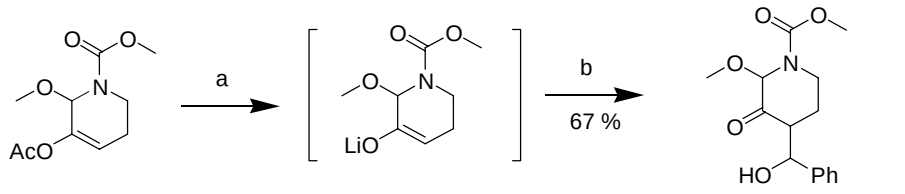
Reagents and conditions:

(a) LDA, -78°C, THF.
(b) (i) LDA, TMSCl, -78°C, THF. (ii) $TiCl_4$, CH_2Cl_2, -78°C.
(c) $TiCl_4$, $^{i}Pr_2NEt$, -78°C.

Scheme 4-3. Attempted aldol reactions with **127** and benzaldehyde.

4.5 Aldol reaction with enol acetate 172

In Section 4.3, a method was described to prepare the pure enol acetate **172**. Treatment of **172** with methyllithium gave rise to the lithium enolate **173**, which was treated with benzaldehyde in the presence of $ZnCl_2$. Indeed, **171** was isolated in 67 % yield as mixture of four diastereomers. (Scheme 4-4). The diastereomeric ratio was determined by ^{1}H-NMR spectrum.



172 **173** **171**

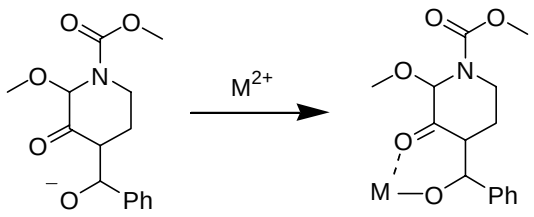
ds = 6 : 21 : 35 : 38

Reagents and conditions:

(a) CH_3Li, DME, 2.2´-bipyridyl, -10°C. (b) anhydrous $ZnCl_2$, PhCHO, 0°C.

Scheme 4-4. Aldol reaction of enol acetate **172** with benzaldehyde.

In this aldol reaction, the keto alkoxide **175** was chelated by metal cation Zn^{2+}, which favored the aldol reaction and avoided comman side reactions (Scheme 4-5). [27]



174 **175**

Scheme 4-5. Metal chelate favors the aldol reaction.

Although theoretically lithium may serve as the chelating metal cation in nonpolar solvents at low temperature, the aldol reaction failed without a further chelating metal. The zinc cation has a greater positive charge than lithium cation, while the ionic radius of these two cations is similar (Li^{+}: 0.78 Å; Zn^{2+}: 0.69 Å). In additin to zinc chloride, magnesium bromide is also a good chelating reagent. [27]

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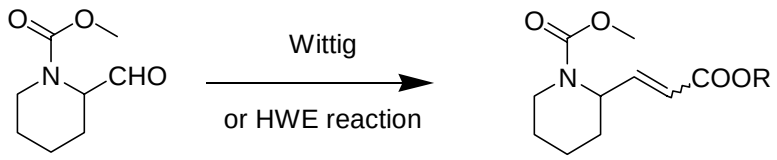
• Chapter 5

Reactions on 6-Side Chain of N-Carbamate Piperidines Derivatives

5.1 Stereoselectivities of Wittig and HWE Reactions in 6-side chain

The Wittig and the Horner-Wadsworth-Emmons (HWE) reactions are most useful methods for selectively constructing carbon-carbon double bond. In one of the steps of the preparation of 6-substituted N-carbamate-3-piperidones **129**, we tried both Wittig and HWE reaction to form the double bond in 6-side chain. We got different E/Z-selectivities in these two types of alkene formation reactions (Scheme 5-1).



116 **117, 176**

R = CH_3, **117,** Wittig reaction product: **117A**

HWE reaction product: **117B**

R = CH_2Ph, **176,** Wittig reaction product.

Scheme 5-1. The Wittig and HWE reactions from **116**.

With the HWE reaction, we got the product **117B** in 86 % yield with E/Z ratio 65:35. The two isomers can not be separated by column chromatography. With Wittig reaction we got totally stereospecific **117A** and **176** in 92 % and 89 % yields (Table 5-1).

React.	**Reagent**	**Solv.**	**Condition**	**E/Z**	**Yield**	**Product**
HWE	$(MeO)_2P(O)CHCO_2CH_3$ **177**	THF	NaH, RT, 3 h	65:35	86 %	**117B**
Wittig	$Ph_3P=CHCOOCH_3$ **178**	THF	RT, 5 h	100:0	92 %	**117A**
Wittig	$Ph_3P=CHCOOCH_2Ph$ **179**	THF	RT, 5h	100:0	89 %	**176**

Table 5-1. Reagents, conditions, E/Z ratios, and yields of Wittig and HWE reactions.

The mechanism of the stereoselectivity of the Wittig reaction can be explained by the stabilized structure of the ylid which includes electron-withdrawing methoxycarbonyl group. It is reasonable to suppose that the thermodynamically more stable of the oxaphosphetanes is the trans-diastereoisomer, with the two bulky groups on opposite side of the ring. The elimination of Ph_3PO from trans-diastereoisomer gives E-alkene. Figure 5-1 shows the mechanism of the stereoselectivity of Wittig reaction.

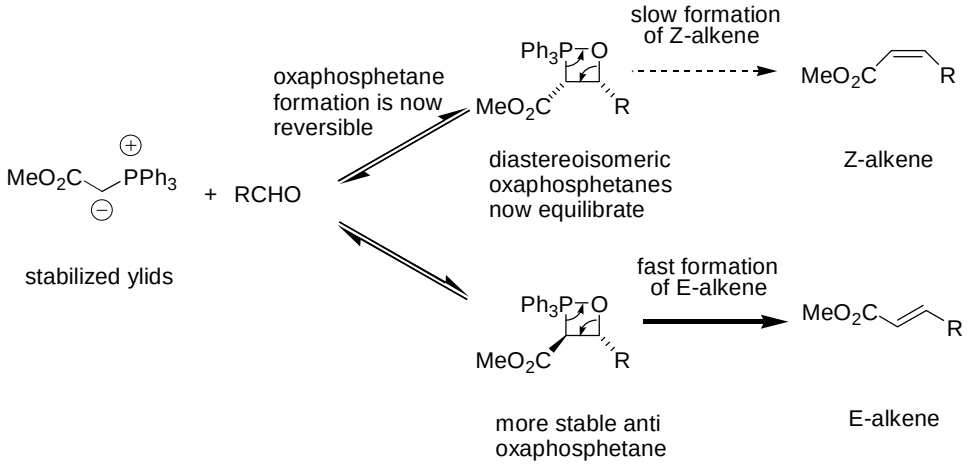


Figure 5-1. The mechanism of the stereoselectivity of Wittig reaction.

The ratio of E/Z can be determined from analyzing of the Figure 5-2. The two olefin-H appeared at δ 6.81-6.93 and δ 5.77-5.88, having the coupling constant $^{3}J_{trans}$ = 15.78 Hz, being typical for *trans*-alkene.

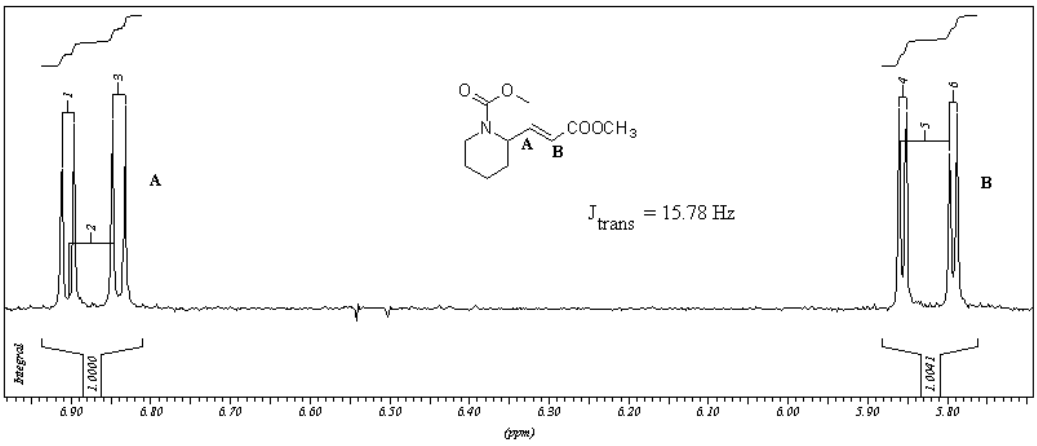


Figure 5-2. ^{1}H-NMR of olefin-H of Wittig reaction product **117A**, pure E-olefin.

Figure 5-3 shows the ^{1}H-NMR spectrum of the olefin-H part of compound **117B**, being obtained with a E/Z ratio of 65:35.

The olefinic protons of the (Z)-isomer appear at δ 6.37-6.49 and δ 5.77-5.88, with a coupling constant of $^{3}J_{cis}$ = 10.70 Hz, being in the typical range for (Z)-alkenes.

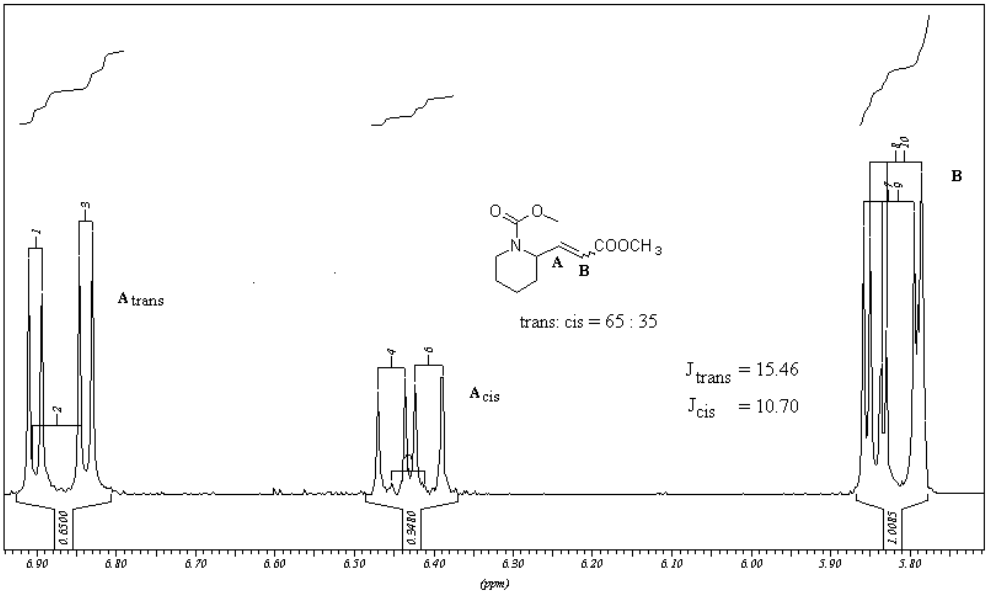
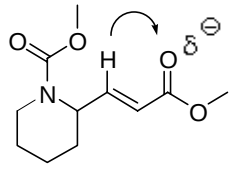


Figure 5-3. ^{1}H-NMR of olefin-H of HWE reaction product **117B**, E:Z = 65:35.

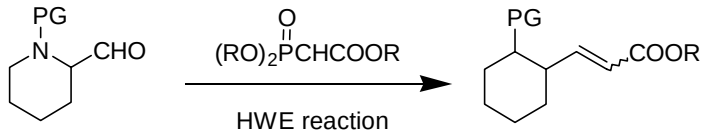
The chemical shift of olefin δ H_{cis} is at higher field than that of δ H_{trans}, This is understandable because in the E structure of **117A**, the olefin proton is affected by a deshielding effect of a carbonyl group *cis* to olefin-proton (Scheme 5-2).



(E)-**117A**

Scheme 5-2. Deshielding effect of a carbonyl group *cis* to olefin-proton.

R. Kreuder [11] and K. Bodmann [12] studied the HWE reaction of N-protected piperidine aldehyde. They used Dpp, Ts, Ns, Cbz as N-protecting groups and got different E/Z ratios (Table5-2). The HWE reaction result with N-carbamate-piperidine aldehyde **116** is supplementary to their conclusions. According to their results, under same condition, best E/Z ratio was reached with Ts protected starting material. It should be noted that the stereoselectivity of Wittig reaction of N-carbamate-piperidine derivative is better than that of HWE reaction. Not only totally stereospecific E product but also better yield is reached.



180 **181**

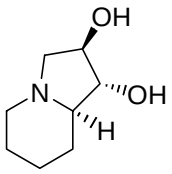
PG	R	E/Z Ratio	Yield (%)	Reference
Dpp	Me	89:11	90	[11]
Ts	Et	95:5	95	[12]
Ns	Et	94:6	96	[12]
CBz	Et	84:16	80	[12]
Carbamate	Me	65:35	86	-

Table 5-2. The HWE reactions results with different protecting groups.

5.2 Synthesis of 1,2-dihydroxyhexahydroindolizidine-3-on

5.2.1 Introduction

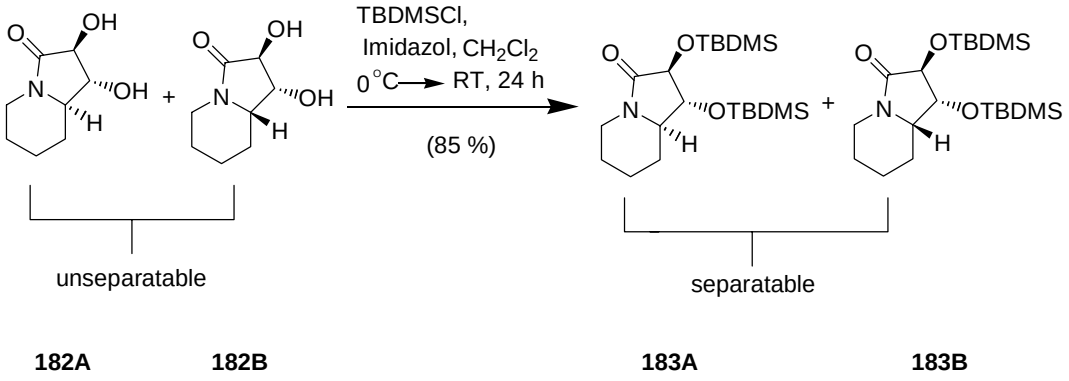
Polyhydroxylated indolizidine alkaloids are sugar mimics which inhibit glycosidases with promising potential as drugs against viruses, cancers and diabetes. [1] A large number of representative structures were isolated from natural sources and the synthesis of the corresponding stereoisomers and analogues is actively pursued particularly for structure-activity studies. [1,2] A variety of methods have been reported for the synthesis of indolizidine alkaloids and among them, *(-)-Lentiginosine* **202** maybe ranks as the most popular synthetic target (Scheme 5-3). [3]



202

Scheme 5-3. Structure of *(-)-Lentiginosine* **202**.

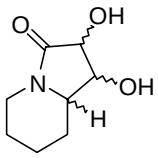
Recently, D. Raatz [13] successfully developed a resolution method to separate the epimeric mixture of **182A** and **182B**. While the two diastereoisomers **182A** and **182B** themselves are difficult to separate, after protections with TBDMSCl to **183A** and **183B**, they can be easily separated using preparative medium-pressure chromatography (Scheme 5-4). [4]



Scheme 5-4. Protection of the hydroxy groups of **182A** and **182B** with TBDMSCl.

After de-protection and reduction, *(-)-Lentiginosin*e **202** can be successfully synthesized via this route.

Therefore, the racemic 1,2-dihydroxyhexahydroindolizin-3-on **182** is an important precursor of *(-)-Lentiginosin* **202** (Scheme 5-5). Thus, the exploration of the synthesis of racemic 1,2-dihydroxyhexahydroindolizin-3-on **182** is significant.

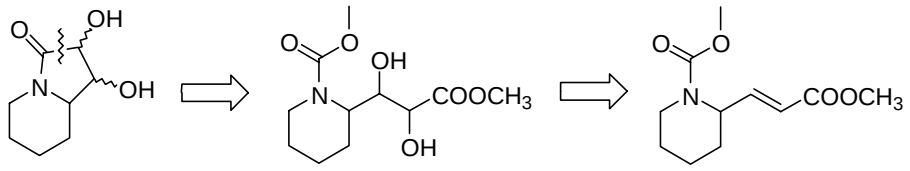


182

Scheme 5-5. Structure of racemic 1,2-dihydroxyhexahydroindolizin-3-on **182**.

5.2.2 Synthesis of racemic 1,2-dihydroxyhexahydroindolizidine-3-on 184

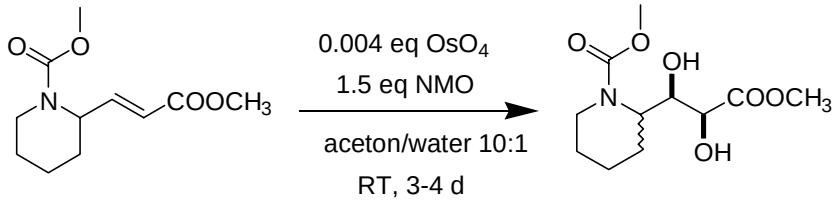
In Chapter 2, (E)-2-(2-methoxycarbonyl-vinyl)-piperidine-1-carboxylic acid methyl ester **117A** was prepared, which should be a suitable precursor to indolizidine **182** (Scheme 5-6).



182 **185** **117A**

Scheme 5-6. Retrosynthesis of 1,2-dihydroxyhexahydroindolizidine-3-on **182**.

Therefore, **117A** was dihydroxylated with catalytic amount of osmium tetraoxid and NMO as the stochiometric oxidant, resulting in **185** as diastereomeric mixture (*ds* = 58 : 42) (Scheme 5-7). The structures of major and minor diastereomers can not be assigned.



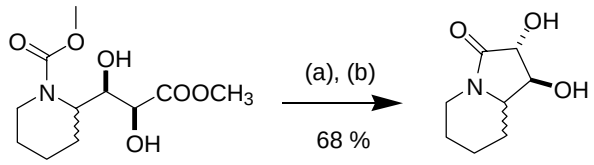
117A **185**

ds = 58 : 42

Scheme 5-7. Dihydroxylation of **117A**.

The cleavage of the N-carbamate in diastereomeric mixture **185** was attempted. Iodotrimethylsilane, developed independently by Olah [5,6,7] and Jung [8,9], received wide application in the cleavage of esters, [5-8] ethers, [9] and carbamates. [10] However, iodotrimethylsilane itself has some disadvantages. First, it should be prepared freshly and used under strictly anhydrous conditions, as it fumes in air and turns purple on standing, making prolonged storage undesirable. Also, it is until now a relatively expensive commercial reagent (Fluka 2001-2002: 5ml = 18.50 Euro). Instead, in a simple and inexpensive alternative, a mixture of chlorotrimethylsilane and sodium iodide in acetonitrile solution can be used which generates iodotrimethylsilane *in situ*.

Cleavage of methyl carbamate is the most difficult among the methyl, benzyl and *tert*-butyl carbamates. Therefore, heating of **185** under reflux for 24 h was required, followed by acidic treatment to cleave the silyl carbamate formed *in situ*, which led to the formation of diastereomeric mixture **184** (*ds* = 58:42) in 68 % yield as white solid (Scheme 5-8).



185 **184**

ds = 58 : 42

Reagents and Conditions:

(a) TMSCl, NaI, CH_3CN, reflux, 24 h.
(b) MeOH / HCl, 10 % $Na_2S_2O_3$ solution.

Scheme 5-8. Formation of diastereomeric mixture **184** (*ds* = 58:42).

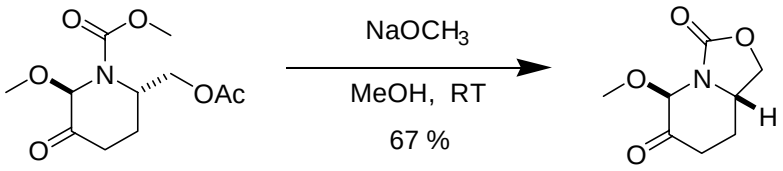
5.3 Synthesis of 5-methoxy-tetrahydro-oxazolo[3,4-a]pyridin-3,6-dione 188

5-Methoxy-hexahydro-oxazolo[3,4-a]pyridin-3-one **186** is an important precursor of a great number of natural alkaloids. Many preparation methods have been reported. [14-17] Here we give a synthetic method of 5-methoxy-tetrahydro-oxazolo[3,4-a]pyridin-3,6-dione **187**, which allows further functionalization at the 6-oxo group (Scheme 5-9).

186 **187**

Scheme 5-9. Structures of compounds **186** and **187**.

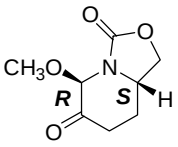
The synthesis of enantiomeric mixture **128** was described in Chapter 2. Treatment of **128** with sodium methoxide in methanol under room temperature, 5-methoxy-tetrahydro-oxazolo[3,4-a]pyridin-3,6-dione **188** was formed in 67 % yield as single diastereomer (Scheme 5-10).



128 **188**

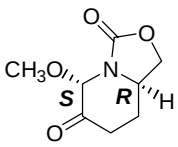
Scheme 5-10. The formation of 5-methoxy-tetrahydro-oxazolo[3,4-a]pyridin-3,6-dione **188** as single diastereomer.

There are two chiral centers in the structure of compound **188**. From the NOESY spectrum, we can assign their stereo structures to two enantioisomers (Scheme 5-11).



188A

(1S, 5R)-5-methoxy-tetrahydro-oxazolo[3,4-a]pyridin-3,6-dione



188B

(1R, 5S)-5-methoxy-tetrahydro-oxazolo[3,4-a]pyridin-3,6-dione

Scheme 5-11. Two enantioisomers of compound **188**.

The NOESY spectrum of the compound **188** shows that the 1-position proton (δ 4.31) and 5-position proton (δ 4.85) are located at different side because no NOE effect exists between the two protons (Figure 5-5).

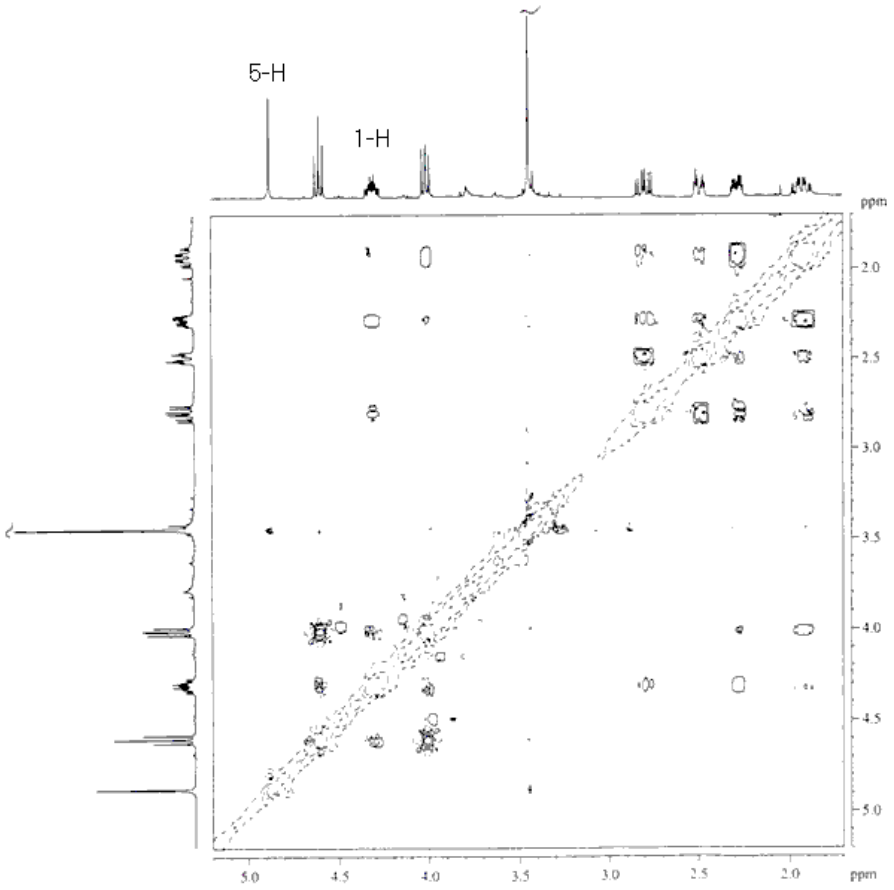


Figure 5-5. NOESY spectrum of compound **188.**

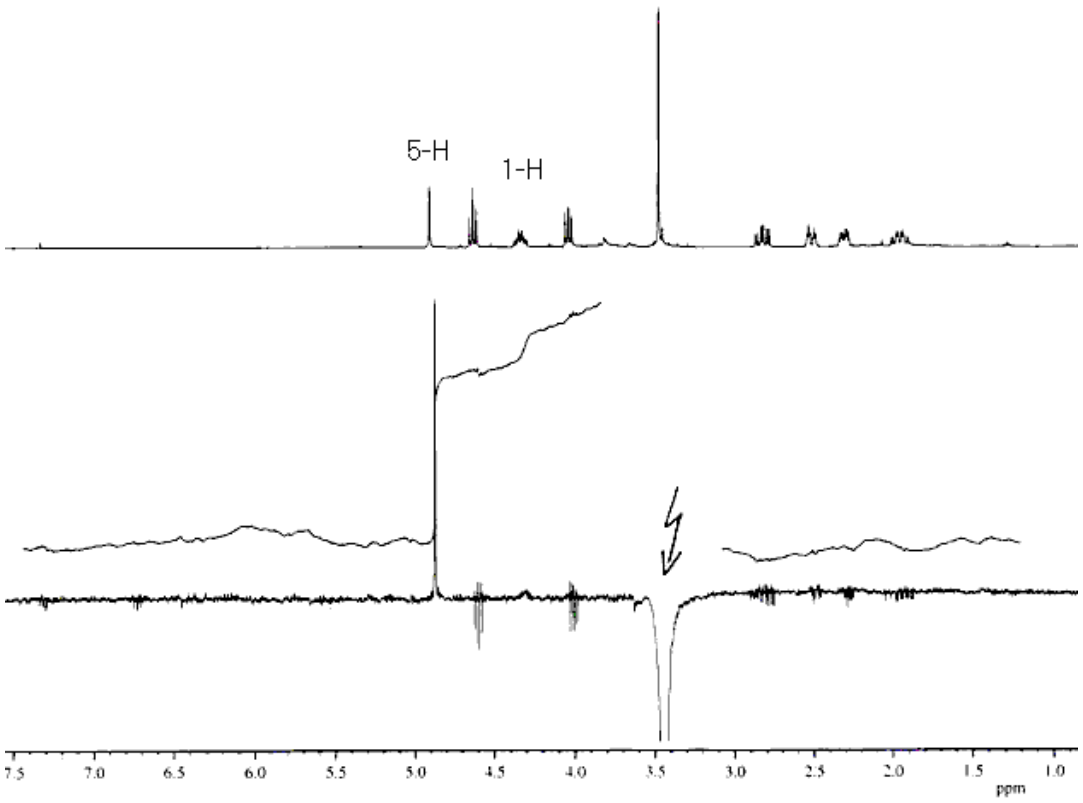


Figure 5-6. NOE spectrum of 5-methoxy-tetrahydro-oxazolo[3,4-a] pyridin-3,6-dione **188**.

When irradating the protons of methoxy group, in addition to the exist of NOE effect of 5-position proton (δ 4.85), a small NOE effect of 1-position proton (δ 4.31) was also found (Figure 5-6). This can be explained by conformation analysis. Inspite of the rotation of the axial C-OCH_3 single bond, the favored conformation should be that the CH_3 groups stay at far side to the 1-position proton because of the steric crowding (Figure 5-7).

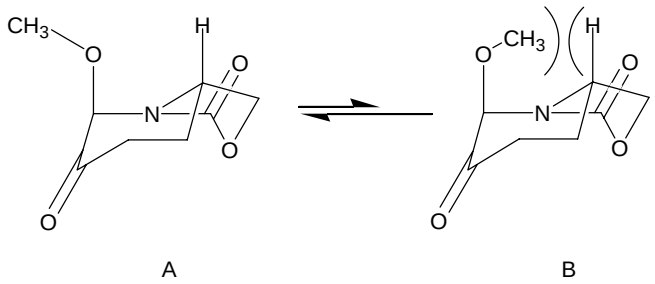
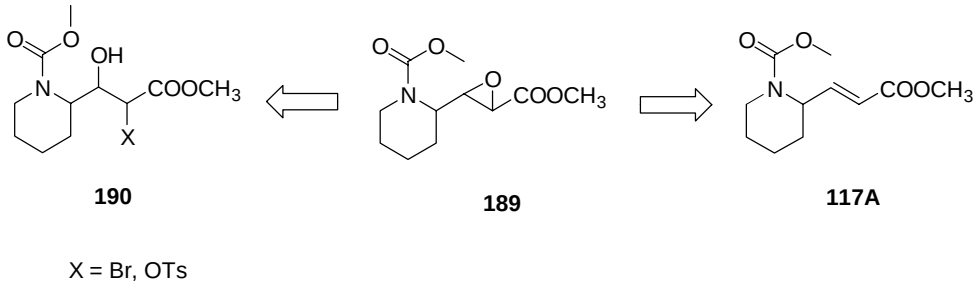


Figure 5-7. Conformation A is predominant because of the steric crowding.

In Chapter 3, it was discussed that in N-carbamate-2-methoxy-piperidine derivatives, the methoxy group stands predominantly axial because of the $A^{(1,3)}$ strain between the methoxy group and carbamate group. [18] In the structure of **188**, the 6-proton is also predominantly axial to avoid the axial-axial strain between 2- and 6-position.

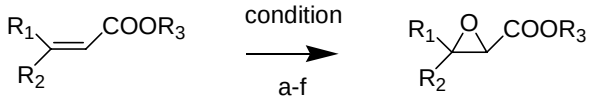
5.4 Exploration of epoxidation reactions

Epoxides occupy an important role in organic synthesis and have been the focus of interest of many research groups around the world. In order to further modify the side chain in piperidine-acrylates **117A**, the epoxidation of **117A** followed by ring-opening with nucleophiles was envisioned (Scheme 5-12).



Scheme 5-12. Retrosynthesis of the epoxide **189**.

α,β-Unsaturated ester **117A** is an electrophilic alkene due to the substituted electron-withdrawing ester group. The studies of epoxidation of electrophilic alkene received great attention in recent years and several methods were reported (Scheme 5-13). [19-23]



200 **201**

a: (i) ^{t}BuOOH, BuLi, THF, -78°C , (ii) RT,16 h.
b: mCPBA, CH_2Cl_2, reflux.
c: H_2O_2, K_2CO_3.
d: (i) OsO_4, NMO, Aceton, H_2O, (ii) TsCl, NEt_3, CH_2Cl_2, (iii) K_2CO_3, EtOH, RT.
e: (i) OsO_4, NMO, Aceton, H_2O, (ii) HBr, HOAc, 40°C, (iii) K_2CO_3, EtOH, RT.
f: ^{t}BuOK, ^{t}BuOOH, NH_3, THF, - 40°C.

Scheme 5-13. Published methods of synthesis of electrophilic epoxides.

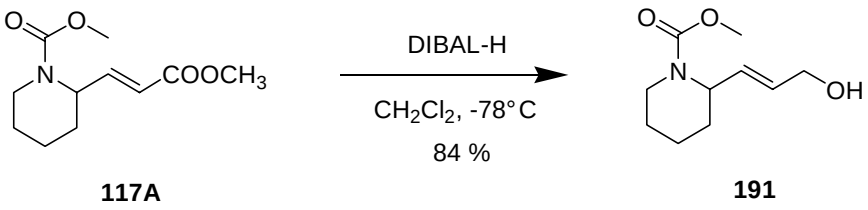
We tried the six preparation methods to synthesize electrophilic epoxide under corresponding conditions from compound (E)-2-(2-methoxycarbonyl-vinyl)-piperidine-1-carboxylic acid methyl ester **117A**, but all the efforts of epoxidation reactions failed. Table 5-3 shows the results of epoxidation of compound **117A** under corresponding conditions as listed in Scheme 5-13.

condition	**a**	**b**	**c**	**d**	**e**	**f**
result	Starting material decomposed	no reaction	no reaction	The last step failed *	The last step failed *	Starting material decomposed

* The tosylate and bromide were successfully obtained, but the epoxidations failed.

Table 5-3. Epoxidation reactions of compound **117A** under corresponding conditions and the results.

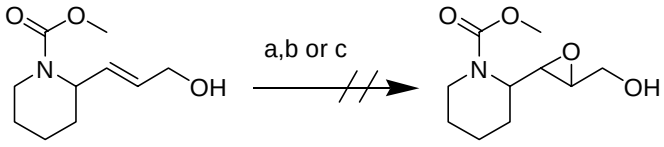
The epoxidation of allylic alcohols is a well known reaction developed by Sharpless, which works reliabally with a great number of substrates. In order to use this reaction, the carbonylmethoxy group of compound **117A** was reduced to yield the allylic alcohol **191** in 84 % yield (Scheme 5-14).



117A **191**

Scheme 5-14. The reduction of compound **117A**.

Oxidation with mCPBA is a general method used in epoxidation reaction of various kinds of allylic alcohols. [24] To our surprise, under similar condition, the epoxidation of allylic alcohol **191** with mCPBA failed. The starting material remained unchanged without giving the epoxide **192** (Scheme 5-15).



191 **192**

Reagents and conditions:

a: mCPBA, CH_2Cl_2, RT.
b: mCPBA, $NaHCO_3$, CH_2Cl_2, reflux.
c: mCPBA, $NaHCO_3$, H_2O.

Scheme 5-15. The epoxidations of allylic alcohol **191** are unsuccessful.

The epoxidation of allylic alcohol **191** will be further investigated.

References

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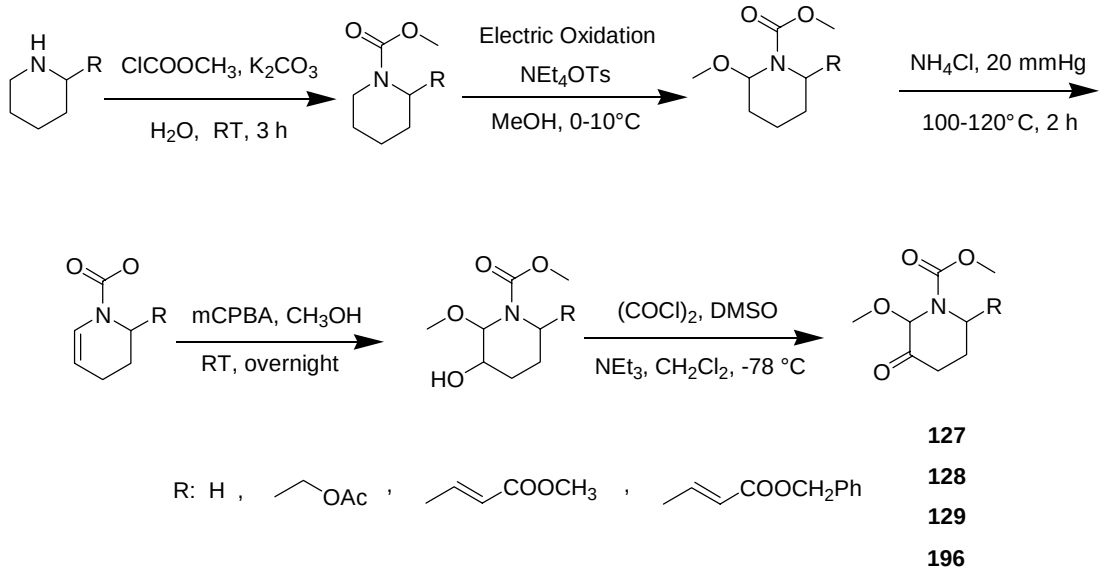
• Chapter 6

Summary

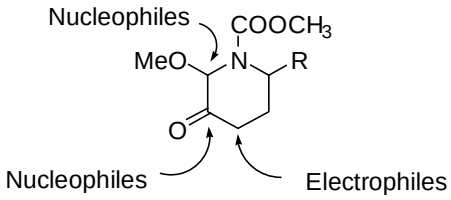
This work involved the new synthesis of N-carbamate-2-methoxy-3-piperidones derivatives and further studies of their reactions with nucleophiles, regioselective enolate formation and other reactions at side chain in 6-position.

First, a general route leading to N-carbamate-2-methoxy-3-piperidone derivatives **(127, 128, 129** and **196)** was successfully developed from commercially available and inexpensive starting materials. The synthetic steps involved are easy to carry out, high yielding and require mild reaction conditions. The total yield is 37-58 % with 5-6 steps (Scheme 6-1).

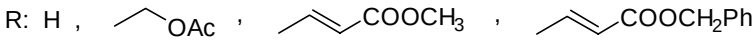


Scheme 6-1. A general route leading to N-carbamate-2-methoxy-3-piperidones derivatives.

The methoxy group at 2-position allows a flexible functionalization with a variety of functional groups via nucleophilic substitution. Thus, the 2-, 3- and 4-positions are reactive to nucleophiles or electrophiles respectively (Scheme 6-2). Obviously, this structure should be of great significance to the introductions of various functional groups and the further formations of piperidine alkaloids.

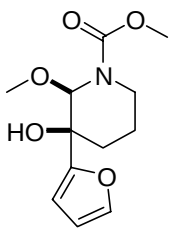


109



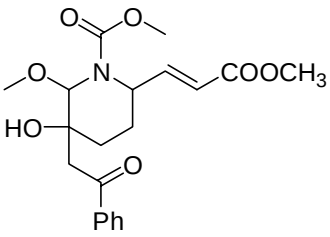
Scheme 6-2. The reactivities of 2,3,4-positions of N-carbamate-2-methoxy-3-piperidones **109**.

Secondly, the nucleophilic addition on the carbonyl group was studied. 2-Furyllithium, ketone enolates, ester enolates and potassium cyanide were used as nucleophiles. The corresponding addition products (**134**, **137**, **138**, **139**, **140**, **145**) could be obtained in 77-87 % yield with different diastereomeric selectivities (Scheme 6-3).



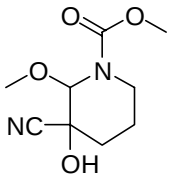
134

1 diastereomer



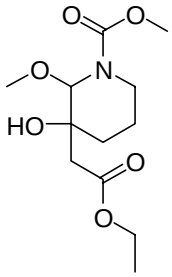
137

ds = 30 : 29 : 21 : 20



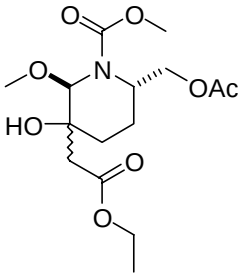
145

ds = 85 :15



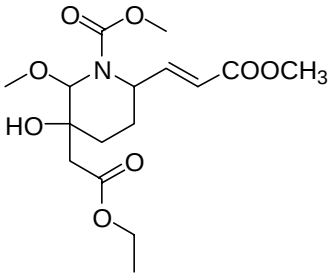
138

ds = 1 : 1



139

ds = 53 : 47

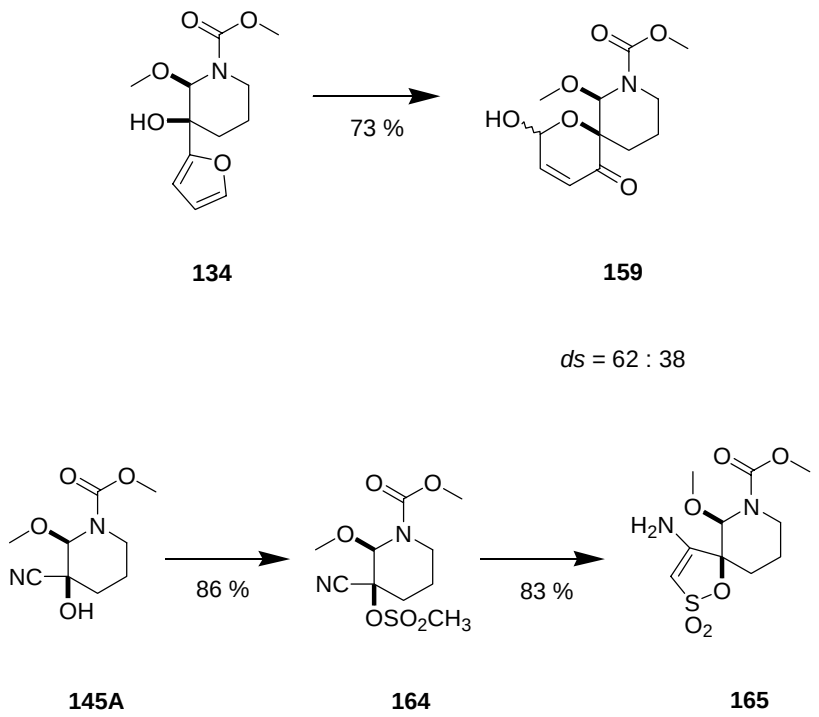


140

ds = 28 : 40 : 14 : 18

Scheme 6-3. The structures of addition products with different diastereomeric ratios.

Furthermore, the oxidation-rearrangement of furanmethanol **134** and the CSIC (Carbanion Mediated Sulfonate Intramolecular Cyclization) reaction of alkanesulfonates **164** were studied. With these rearrangement and aldol type cyclization reactions, the interesting spiro heterocycles of 8-aza-1-oxaspiro[5.5]undecane **159** (diastereomeric mixture, *ds* = 62:38) and 4-amino-7-aza-7-carbamate-6-methoxy-1-oxa-2-thiaspiro[4.5] dec-3-ene 2,2-dioxide **165** (single diastereomer) were successfully synthesized with good yields (Scheme 6-4).



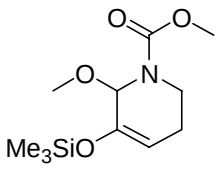
134 **159**

ds = 62 : 38

145A **164** **165**

Scheme 6-4. Formations of spiro heterocycles **159** and **165**.

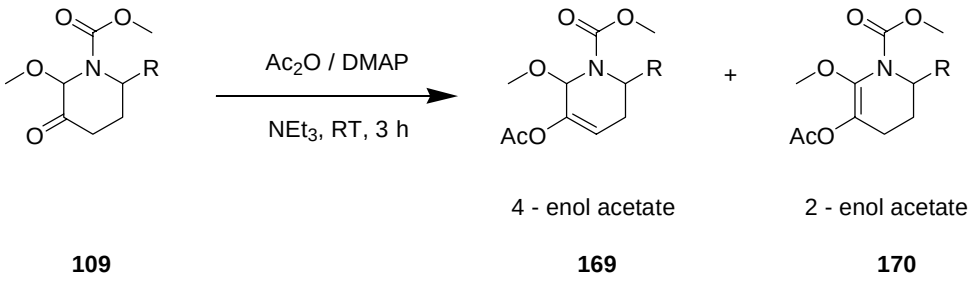
Furthermore, the reactions of enolates derived from 3-piperidones derivatives were studied. Although selective formation of the kinetic silyl enol ether of N-carbamate-2-methoxy-3-piperidone **167** was achieved, it could not be isolated in pure form because of its high boiling point, thus preventing its further application in organic synthesis (Scheme 6-5).



167

Scheme 6-5. The structure of silyl enol ether **167**.

Therefore, the synthesis of the enol acetates of N-carbamate-2-methoxy-3-piperidone **169** was developed with high regioselectivities and high yields (Scheme 6-6 and Table 6-1).



Scheme 6-6. Formation of enol acetates of 6-substituted N-carbamate-2-methoxy-3-piperidones **109**.

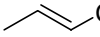
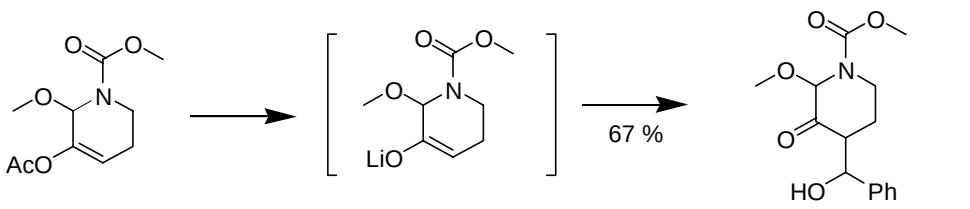
Substituted Groups (R)	Product Ratios (kinetic : thermodynamic)	Yields (%)
H	100 : 0	82
	98 : 2	72
	97 : 3	77

Table 6-1: Selectivities and yields of formation of enol acetates of 6-substituted N-carbamate-2-methoxy-3-piperidones **109**.

Formation of lithium enolates by cleavage of enol acetates with methyllithium makes the regioselective aldol reaction successful (Scheme 6-7).



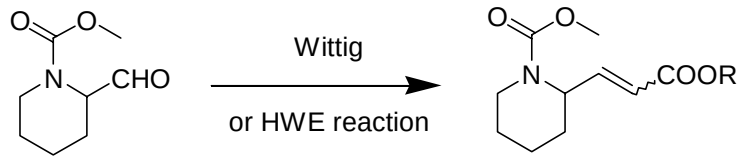
172 **173** **171**

ds = 6 : 21 : 35 : 38

Scheme 6-7. Aldol reaction of enol acetate **172** with benzaldehyde.

To those silyl enol ethers whose boiling points are too high thus difficult to be distilled out for purification, the preparation of their enol acetates should be a method of choice because they can be purified by column chromatography.

Finally, reactions on the 6-side chain of N-carbamate-piperidine derivatives were studied. Wittig reaction of aldehyde **116** leads to pure E olefin, while HWE reaction leads to the *trans*- and *cis*- mixture of olefin (E:Z=65:35) (Scheme 6-8).

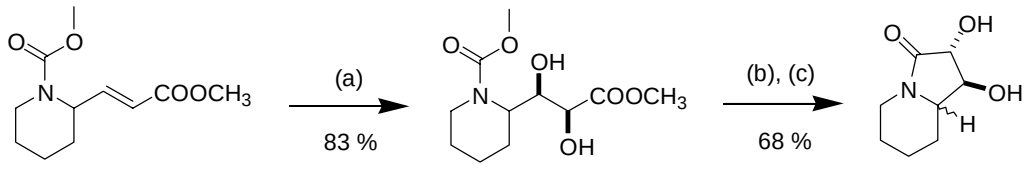


116 **117, 176**

Wittig reaction: R = CH_3 (**117A**), E/Z = 100:0, 92 % yield.
R = CH_2Ph (**176**), E/Z = 100:0, 89 % yield.
HWE reaction: R = CH_3 (**117B**), E/Z = 65:35, 86 % yield.

Scheme 6-8. Wittig and HWE reactions of aldehyde **116**.

The compound 1,2-dihydroxyhexahydroindolizidine-3-on **184** is an important precursor of *(-)-Lentiginosine,* we developed a synthetic route to the diastereomeric mixture **184** (*ds* = 58:42) from **117A**, which involved the dihydroxylation and deprotection reaction (Scheme 6-9).



117A **185** **184**

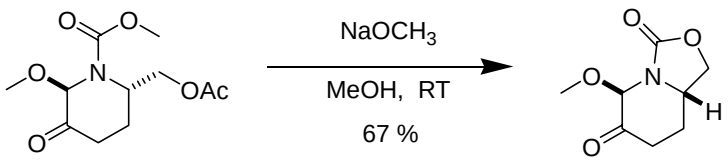
ds = 58 : 42

Reagents and Conditions:

(a) 0.004 eq OsO_4, 1.5 eq NMO, aceton/water 10:1, RT, 3-4 d.
(b) TMSCl, NaI, CH_3CN, reflux, 24 h.
(c) MeOH / HCl, 10 % $Na_2S_2O_3$ solution.

Scheme 6-9. Formation of diastereomeric mixture **184**.

The compound 5-methoxy-tetrahydro-oxazolo[3,4-a]pyridin-3,6-dione **188** is a structural analogue of precursor of natural alkaloids. From the enantiomeric mixture 3-piperidones **128, 188** was synthesized in 67 % yield as single diastereomer (Scheme 6-10).



128 **188**

Scheme 6-10. Formation of 5-methoxy-tetrahydro-oxazolo[3,4-a]pyridin-3,6-dione **188**.

• Chapter 7

Experimental Section

7.1 Instruments and general techniques

^{1}H-NMR Bruker ARX 400 (400 MHz), Bruker ARX 300 (300 MHz), Bruker AC 250 (250 MHz). The chemical shifts are reported in ä (ppm) relative to chloroform ($CDCl_3$, 7.26 ppm), dimethylsulfoxide (DMSO-d_6, 2.49 ppm), methanol (CD_3OD, 3.34 ppm) and tetramethylsilane (TMS, 0 ppm). The spectra were analysed by first order, the coupling constants are reported in Hertz (Hz). Characterisation of signals: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, dd = double douplet, dt = double triplet, dq = double quartet, ddd = double double doublet. Integration is determined as the relative number of atoms. Diastereomeric ratios were determined by comparing the integrals of corresponding protons in the ^{1}H-NMR spectra.

^{13}C-NMR Bruker ARX 400 (100.6 MHz), Bruker ARX 400 (75.5 MHz), Bruker AC 250 (62.9 MHz). The chemical shifts are reported in ä (ppm) relative to chloroform ($CDCl_3$, 77.0 ppm), dimethylsulfoxide (DMSO-d_6, 36.9 ppm), methanol (CD_3OD, 49.0 ppm) and tetramethylsilane (TMS, 0 ppm).

^{13}C-NMR resonance assignment were aided by the use of the DEPT 135 (DEPT = distortionless enhancement by polarisation transfer) technique to determine the number of hydrogens attached to each carbon atom and is declared as: + = primary or tertiary (positive DEPT signal intensity), - = secondary (negative DEPT signal) and quart = quarternary (no DEPT signal intensity) carbon atoms. In some cases DEPT 90 spectra were recorded to distinguish between primary and tertiary carbon atoms. This is marked with the CH or CH_3 notation at the corresponding signal.

2D-NMR Bruker ARX-400 spectrometer operating at a basic 1H frequency of 400 MHz at 300 K and 363K.

IR-spectra were recorded with an ATI Mattson Genesis Series FT-IR.

MS-spectra: masspectroscopy department of the University of Regensburg, Varian Mat 311 A.

Elemental analysis: microanalytical department of the University of Regensburg.

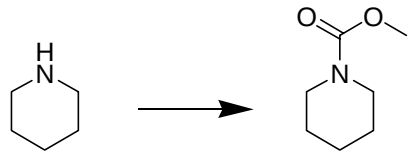
Thin layer chromatography (TLC) was performed on alumina plates coated with silica gel (Merck silica gel 60 F 254, layer thickness 0.2 mm). Visualisation was accomplished by Uvlight (wavelength 254 nm) and a vanillin/sulphuric acid solution.

Column chromatography was performed on silica gel Geduran SI 60 (70-230 mesh) purchased from Merck and flash chromatography on flash-silica gel 60 (230-400 mesh ASTM) purchased from Merck.

Solvents were purified according to standard laboratory methods. THF, diethyl ether and toluene were distilled over sodium/benzophenone before use. Dichlormethane, DMSO and DMF were distilled over calcium hydride and acetonitrile over P_2O_5. Methanol was refluxed 2h over magnesia, distilled and stored under nitrogen over 4Å molecular sieves. The hexanes used had a boiling point of 40-60 °C. All solvents were distilled before use. Some chemicals were purchased from commercial suppliers and used as received. Others were redistilled before use. All reactions with oxygen or moisture sensitive reactants were performed under nitrogen atmosphere.

7.2 Synthesis of the compounds

7.2.1 Synthesis of N-carbamate-2-methoxy-3-piperidones derivatives



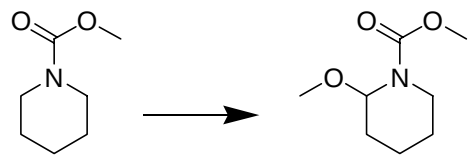
103

*Piperidine-1-carboxylic acid methyl ester **103***

Potassium carbonate (55.20 g, 0.4 mol) and methyl chloroformate (47.25 g, 0.5 mol) were successively added to a stirred solution of piperidine (8.52g, 0.1 mol) in water (600 ml). After 3 h, 50 ml $NH_3 \bullet H_2O$ solution was added to stop the reaction and the basic solution was extracted three times with ethyl acetate. The combined organic layers were evaporated and the residue was filtered to afford the crude product as colorless oil. The crude oily product is distilled under reduced pressure through a Claisen flask to get pure product piperidine-1-carboxylic acid methyl ester **103** (13.87 g, 97 % yield, bp 90°C/20 mm Hg) as colorless oil.

R_f = 0.76 (PE/EE =1:1) -^{1}H-NMR (250MHz, $CDCl_3$) δ = 1.37-1.58 (m, 6H, CH_2), 3.26-3.40 (t, 4H, NCH_2), 3.60 (s, 3H, $COOCH_3$). -^{13}C-NMR (62.9MHz, $CDCl_3$) δ = 24.34 (-, 4-CH_2), 25.77 (-, 3-CH_2, 5-CH_2), 44.38 (-, 2-CH_2, 6-CH_2), 52.42 (+, OCH_3), 155.95 (C_{quart}, Carbonyl-C). -IR (Film): ν = 2935, 2856, 1701, 1446, 1410, 1263, 1238, 1151, 1089, 1029, 947, 852, 768, 497 cm $^{-1}$. -MS (EI(70eV)): m/z (%) = 143 (35) [M^+], 128 (100), 112 (8) [M-OCH_3], 102 (11), 84 (28) [M-CO_2CH_3].

$C_7H_{13}NO_2$ (143.18)	Anal.calcd:	C: 58.72	H: 9.15	N: 9.78
	Found:	C: 57.89	H: 9.22	N: 9.95



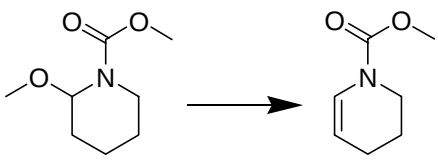
103 **104**

*2-Methoxy-piperidine-1-carboxylic acid methyl ester **104***

A solution of piperidine-1-carboxylic acid methyl ester **103** (12.54 g, 87.6 mmol) in methanol (40 ml) containing tetraethylammonium *p*-toluenesulfonate (1.00 g, 3.3 mmol) as an electrolyte was placed into an electrolysis cell equipped with carbon electrodes. A constant current (3A) was passed through the solution which was externally cooled with water. After 2.7 F / mol of electricity was passed, the reaction was stopped and the solvent was evaporated under reduced pressure. After water (20 ml) was added to the residue, it was extracted with CH_2Cl_2 (2 × 15 ml) to get crude product, which was distilled to get pure product 2-methoxy-piperidine-1-carboxylic acid methyl ester **104** as red oil. (12.90 g, 85 % yield), bp 64 °C (4 mm Hg).

R_f = 0.78 (PE/EE =1:1) -^{1}H-NMR (250MHz, $CDCl_3$) δ = 1.39-1.88 (m, 6H, CH_2), 2.82-3.03 (t, 1H, NCH_2), 3.20 (s, 3H, OCH_3), 3.69 (s, 3H, $COOCH_3$), 3.81- 4.04 (m, 1H, NCH_2), 5.17-5.47 (br, d, 1H, CH_3OCHN). -^{13}C-NMR (62.9MHz, $CDCl_3$) δ = 18.31 (-, 4-CH_2), 24.93 (-, 5-CH_2), 29.96 (-, 3-CH_2), 38.57 (-, 6-CH_2), 52.24 (+, $R_2NCOOCH_3$), 54.35 (+, CH_3OCHN), 82.38 (+, CH_3OCHN), 156.31 (C_{quart}, Carbonyl-C). -IR (Film): ν = 2941, 2870, 1705, 1444, 1410, 1342, 1269, 1171, 1088, 1031, 955, 762 cm $^{-1}$. -MS (PI-EIMS(70eV)): m/z (%) = 173 (1) [M^+], 158 (8), 142 (100) [M-OCH_3], 126 (21).

$C_8H_{15}NO_3$ (173.21)	Anal.calcd:	C: 55.47	H: 8.73	N: 8.09
	Found:	C: 55.39	H: 8.52	N: 8.29

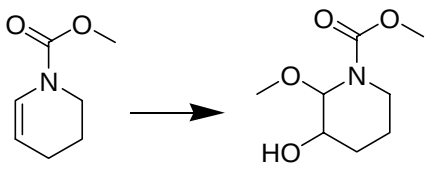


104 **121**

*3,4-Dihydro-2H-pyridine-1-carboxylic acid methyl ester **121***

To 2-methoxy-piperidine-1-carboxylic acid methyl ester **104** (4.47 g, 25.8 mmol) in a 25-ml flask was added 241mg (4.50 mmol) ammonium chloride, and then heated to 100°C for 2h under reduced pressure (20 Torr). After cooling, saturated sodium hydrogen carbonate and sodium chloride solution was added and washed. The solution was extracted by dichloromethane, dried over sodium sulfate. The solvent was evaporated. The crude product was further purified by column chromatography on silica gel (PE/EE 1:1) to afford 3,4-dihydro-2H-pyridine-1-carboxylic acid methyl ester **121** (3.50 g, 96 % yield).

R_f = 0.80 (PE/EE = 1:1) -^{1}H-NMR (250MHz, $CDCl_3$) δ = 1.69-1.87 (m, 2H, 5-CH_2), 1.90-2.07 (dt, 2H, 4-CH_2), 3.49-3.62 (t, 2H, NCH_2), 3.69 (s, 3H, $COOCH_3$), 4.73- 5.02 (dt, 1H, 3-olefin-H), 6.51-6.90 (dd, 1H, 2-olefin-H). -^{13}C-NMR (62.9MHz, $CDCl_3$) δ = 21.36 (-, 4-CH_2, Rotamer), 21.65 (-, 4-CH_2, Rotamer), 26.10 (-, 5-CH_2), 42.13 (-, 6-CH_2, Rotamer), 42.31(-, 6-CH_2, Rotamer), 52.82 (+, OCH_3), 106.27 (+, NCH=*C*H, Rotamer), 106.48 (+, NCH=*C*H, Rotamer), 124.90 (+, N*C*H=CH, Rotamer), 125.40 (+, N*C*H=CH, Rotamer), 153.83 (C_{quart}, Carbonyl-C, Rotamer), 154.20 (C_{quart}, Carbonyl-C, Rotamer). -IR (Film): ν = 2996, 2952, 2864, 1706, 1654, 1446, 1360, 1260, 1192, 1118, 1057, 998, 963, 768, 717 cm $^{-1}$. -MS (PI-EIMS(70eV)): m/z (%) = 141 (88) [M^+], 126 (100), 82 (38) [M-$COOCH_3$].



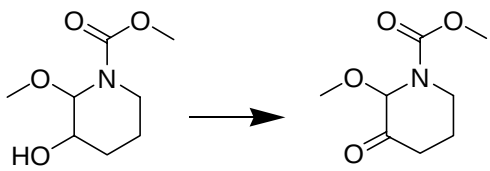
121 **122**

*3-Hydroxy-2-methoxy-piperidine-1-carboxylic acid methyl ester **122***

To a solution of 3,4-dihydro-2H-pyridine-1-carboxylic acid methyl ester **121** (2.20 g, 15.6 mmol) in dry methanol (20 ml) was added mCPBA (4.10 g, 72 % in oil, 17.2 mmol) and stirred overnight under room temperature. Saturated sodium hydrogencarbonate solution was added and washed, extracted by dichloromethane. The solvent was evaporated and the crude product was further purified by column chromatography on silica gel (PE/EE 1:1) to afford 3-hydroxy-2-methoxy-piperidine-1-carboxylic acid methyl ester **122** as yellow oil (2.51 g, 85 % yield).

R_f = 0.51 (PE/EE = 1:1) -^{1}H-NMR (250MHz, $CDCl_3$) δ = 1.45 (s, 1H, OH), 1.56-1.77 (m, 2H, 5-CH_2), 1.78-2.07 (dt, 2H, 4-CH_2), 2.73-3.07 (m, 1H, NCH_2), 3.30 (s, 3H, OCH_3), 3.50-3.60 (dt, 1H, 3-C*H*OH), 3.73 (s, 3H, $COOCH_3$), 3.81-4.03 (m, 2H, NCH_2, 3-C*H*OH), 5.12-5.50 (br, d, 1H, 2-CH_3OCHN). -^{13}C-NMR (100.6MHz, $CDCl_3$) δ = 18.63 (-, 5-CH_2), 27.91 (-, 4-CH_2), 37.60 (-, NCH_2, Rotamer), 38.37 (-, NCH_2, Rotamer), 52.71 (+, $R_2NCOOCH_3$,), 54.70 (+, OCH_3, Rotamer), 55.29 (+, OCH_3, Rotamer), 69.07 (+, 3-CHOH), 84.26 (+, CH_3OCHN, Rotamer), 85.25 (+, CH_3OCHN, Rotamer), 156.34 (C_{quart}, Carbonyl-C, Rotamer), 157.38 (C_{quart}, Carbonyl-C, Rotamer). -IR (Film): ν = 3443, 2950, 2877, 2830, 1809, 1705, 1447, 1409, 1374, 1266, 1195, 1132, 1081, 965, 770 cm $^{-1}$. -MS (CI-MS/DCl): m/z (%) = 207 (2) [M+NH_4^+], 175 (18), 158 (100) [M-CH_3O], 142 (30).

$C_8H_{15}NO_4$ (189.21)	Anal.calcd:	C: 50.78	H: 7.99	N: 7.40
	Found:	C: 50.01	H: 7.88	N: 7.72



122 **127**

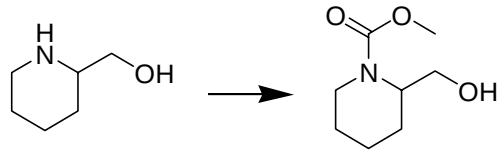
*2-Methoxy-3-oxo-piperidine-1-carboxylic acid methyl ester **127***

DMSO (0.55 ml, 7.68 mmol) in dichloromethane (2 ml) was added to a stirred solution of oxalyl chloride (0.33 ml, 3.84 mmol) in dichloromethane (7 ml) at -78°C. The mixture was stirred for 3 min, and the alcohol 3-hydroxy-2-methoxy-piperidine-1-carboxylic acid methyl ester **122** (0.66 g, 3.49 mmol) in dichloromethane (3 ml) was added over a 5-min period. Stirring was continued for an additional 15 min, and triethylamine (2.43 ml, 17.45 mmol) was added. The reaction mixture was stirred for 5 min and then allowed to warm to room temperature. Water (15 ml) was added, the organic layer was separated, and the aqueous layer was further extracted with dichloromethane (30 ml). The combined organic phases were washed with saturated aqueous sodium chloride solution and dried, and the solvent was removed to give a yellow oil. This crude product was purified by column chromatography on silica gel (PE/EE 1:1) to afford 2-methoxy-3-oxo-piperidine-1-carboxylic acid methyl ester **127** (0.56 g, 86 % yield).

R_f = 0.41 (PE/EE = 1:1) -^{1}H-NMR (250MHz, $CDCl_3$) δ = 1.79-2.45 (m, 4H, 4-, 5- CH_2), 2.57-2.81 (m, 1H, NCH_2), 3.29 (s, 3H, OCH_3), 3.67 (s, 3H, $COOCH_3$), 3.75-4.04 (m, 1H, NCH_2), 4.96-5.34 (d, 1H, CH_3OCHN). -^{13}C-NMR (62.9MHz, $CDCl_3$) δ = 24.23 (-, 5-CH_2, Rotamer), 24.57 (-, 5-CH_2, Rotamer), 28.61 (-, 4-CH_2, Rotamer), 31.39 (-, 4-CH_2, Rotamer), 38.51 (-, 6-CH_2, Rotamer), 39.09 (-, 6-CH_2, Rotamer), 53.13 (+, $R_2NCOOCH_3$, Rotamer), 53.45 (+, $R_2NCOOCH_3$, Rotamer), 55.50 (+, OCH_3, Rotamer), 55.95 (+, OCH_3, Rotamer), 86.65 (+, CH_3OCHN, Rotamer), 87.07 (+, CH_3OCHN, Rotamer), 156.00 (C_{quart}, $COOCH_3$, Rotamer), 156.59 (C_{quart}, $COOCH_3$, Rotamer), 201.69 (C_{quart}, 3-Carbonyl-C). -IR (Film): ν = 2956, 2878, 2831, 1713,1708, 1447, 1402, 1303, 1190,

1070, 955, 770 cm $^{-1}$. -MS (EI(70eV)): m/z (%) = 187 (1) [M^+], 159 (11), 143 (13), 128 (100) [M-CO_2CH_3].

$C_8H_{13}NO_4$ (187.19)	Anal.calcd:	C: 51.33	H: 7.00	N: 7.48
	Found:	C: 50.86	H: 7.00	N: 7.69



114

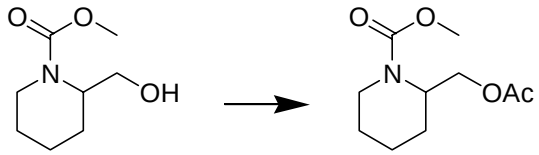
*2-Hydroxymethyl-piperidine-1-carboxylic acid methyl ester **114***

Potassium carbonate (5.52 g, 40 mmol) and methyl chloroformate (4.73 g, 50 mmol) were successively added to a stirred solution of 2-hydroxymethyl-piperidine (1.15 g, 10 mmol) in water (60 ml). After 3 h, 20 ml NH_3•H_2O solution was added to stop the reaction and the basic solution was extracted three times with ethyl acetate. The combined organic layers were evaporated and the residue was filtered to afford the crude product as colorless oil. The crude oily product was distilled under reduced pressure through a Claisen flask to get pure product carbamate 2-hydroxymethyl-piperidine-1-carboxylic acid methyl ester **114** as yellow oil (1.63g, 94 % yield).

R_f = 0.15 (PE/EE = 2:1) -^{1}H-NMR (250MHz, $CDCl_3$) δ = 1.38-1.84 (m, 6H, CH_2), 2.33 (s, 1H, CH_2O*H*,), 2.78-3.05 (t, 1H, NCH_2), 3.56-3.66 (m, 1H, C*H*$_2$OH), 3.71 (s, 3H, OCH_3), 3.76-3.90 (m, 1H, C*H*$_2$OH), 3.92-4.09 (m, 1H, NCH_2), 4.25-4.43 (m, 1H, CHN). -^{13}C-NMR (62.9MHz, $CDCl_3$) δ = 19.54 (-, 4-CH_2), 25.21 (-, 3-, 5-CH_2), 40.07 (-, NCH_2), 52.68 (+, OCH_3), 52.86 (+, N*C*HCH_2), 61.30 (-, CH_2OH), 157.27 (C_{quart}, Carbonyl-C). -IR (Film) ν = 3434, 2939, 2866, 1665, 1448, 1410, 1369, 1340, 1313,

1267, 1174, 1142, 1084, 1052, 1021, 927, 769, 579, 537 cm^{-1}. -MS(CI-MS/DCl) m/z (%) = 191 (19) [M+ NH_4^+], 174 (100) [MH^+], 159 (81) , 142 (14) [M-OCH_3].

$C_8H_{15}NO_3$ (173.21)	Anal.calcd:	C: 55.47	H: 8.73	N: 8.09
	Found:	C: 55.04	H: 8.78	N: 8.34



114 **115**

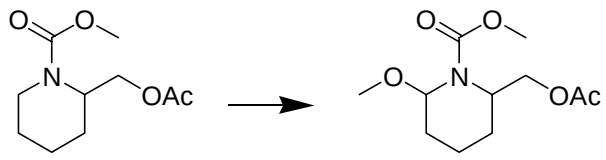
*2-(Acetoxy)methyl-piperidine-1-carboxylic acid methyl ester **115***

To a solution of 2-hydroxymethyl-piperidine-1-carboxylic acid methyl ester **114** (4.33 g, 25 mmol), NEt_3 (5 ml, 37.5 mmol) and DMAP (250 mg, 2 mmol) in 50 ml CH_2Cl_2 was added dropwise acetic anhydride (3.49 ml, 37.5 mmol) at - 40°C. The solution was warmed to room temperature and stirred for 18 h. The reaction was stopped with 100 ml of 0.1 M $KHSO_4$ solution. The aqueous phase was extracted with ethyl acetate, washed with water and saturated NaCl solution, dried over $MgSO_4$. The solvent was removed and filtered through a short column with silica gel to give crude product, which was distilled to get pure product 2-(acetoxy)methyl-piperidine-1-carboxylic acid methyl ester **115** as colorless oil. (5.17 g, 96 % yield, bp 104-107°C / 0.05 mm Hg).

R_f = 0.54 (PE/EE =1:1) -^{1}H-NMR (300MHz, $CDCl_3$) δ = 1.31-1.79 (m, 6H, 3,4,5-CH_2), 2.05 (s, 3H, CH_3COOR), 2.77-2.95 (t, 1H, NCH_2), 3.68 (s, 3H, $COOCH_3$), 3.96-4.10 (m, 1H, NCH_2), 4.14 (dd, J = 6.58, 11.25 Hz, 1H, CH_2OAc), 4.24 (dd, J = 8.51, 11.25 Hz, 1H, CH_2OAc), 4.51 (br, s, 1H, CHN). -^{13}C-NMR (75.5MHz, $CDCl_3$) δ = 19.20 (-, 4-CH_2), 20.78 (+, *C*H_3COOCH_2R), 25.10 (-, 3-CH_2), 25.31 (-, 5-CH_2), 39.64 (-, NCH_2), 49.04 (+, N*C*HCH_2), 52.53 (+, $R_2NCOOCH3$), 61.68 (-, CH_3COOCH_2R), 156.35 (C_{quart},

$R_2NCOOCH_3$), 170.79 (C_{quart}, CH_3COOCH_2R), -IR (Film) ν = 2939, 2860, 1752, 1718, 1452, 1413, 1390, 1370, 1270, 1182, 1148, 1102, 1055, 845, 776 cm^{-1}. -MS (PI-DCIMS(NH_3)): m/z (%) = 233 (100) [$M+NH_4^+$], 216 (42) [MH^+].

$C_{10}H_{17}NO_4$ (215.25)	Anal.calcd:	C: 55.80	H: 7.96	N: 6.51
	Found:	C: 55.44	H: 8.03	N: 6.96



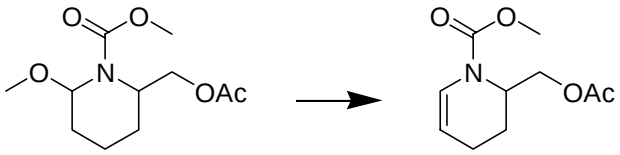
115 **118**

*6-(Acetoxy)methyl-2-methoxy-piperidine-1-carboxylic acid methyl ester **118***

A solution of 2-(acetoxy)methyl-piperidine-1-carboxylic acid methyl ester **115** (18.86 g, 87.6 mmol) in methanol (40 ml) containing tetraethylammonium *p*-toluenesulfonate (2.00 g, 6.6 mmol) as an electrolyte was placed into an electrolysis cell equipped with carbon electrodes. Set up the U = 10 V, I = 0.32 A and the solution was externally cooled with water. After 11 h the reaction was finished checked by ^{1}H-NMR. The solvent was evaporated under reduced pressure. Water (20 ml) was added to the residue, and it was extracted with ethyl acetate (2 × 15 ml) to get crude product, which was distilled to get pure product 6-(acetoxy)methyl-2-methoxy-piperidine-1-carboxylic acid methyl ester **118** as red oil (20.22 g, 94 % yield, bp 100-103 °C / 0.05 mm Hg).

R_f = 0.28 (PE/EE = 5:1) -^{1}H-NMR (250MHz, $CDCl_3$) δ = 1.34-1.90 (m, 6H, CH_2), 1.98 (s, 3H, CH_3COOR), 3.22 (s, 3H, CH_3O), 3.67 (s, 3H, $R_2NCO_2CH_3$), 4.06-4.13 (m, 1H, NC*H*CH_2OAc), 4.24-4.48 (m, 2H, CH_2OAc), 5.21-5.44 (br, d, 1H, CH_3OCHN). -^{13}C-

NMR (62.9MHz, $CDCl_3$) δ = 13.46 (-, 4-CH_2), 20.78 (+, *C*H_3CO_2R), 24.79 (-, 5-CH_2), 30.09 (-, 3-CH_2), 48.37 (+, N*C*HCH_2OAc, Rotamer), 48.54 (+, N*C*HCH_2OAc, Rotamer), 52.63 (+, $R_2NCO_2CH_3$), 54.91 (+, *C*H_3OCHN, Rotamer), 55.32 (+, *C*H_3OCHN, Rotamer), 63.95 (-, *C*H_2OAc, Rotamer), 64.42 (-, *C*H_2OAc, Rotamer), 81.64 (+, CH_3OCHN, Rotamer), 81.86 (+, CH_3OCHN, Rotamer), 156.24 (C_{quart}, $R_2NCO_2CH_3$, Rotamer), 156.93 (C_{quart}, $R_2NCO_2CH_3$, Rotamer), 179.52 (C_{quart}, CH_3CO_2R). -IR (Film) ν = 2950, 1748, 1715, 1450, 1416, 1322, 1232, 1101, 1060, 1000, 932, 772, 724 cm^{-1}. -MS (EI(70ev)) m/z (%) = 214 (19) [M-OCH_3], 185(6), 172 (100), 140 (21).



118 **123**

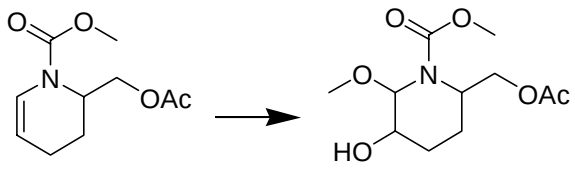
*6-(Acetoxy)methyl-4,5-dihydro-pyridine-1-carboxylic acid methyl ester **123***

6-(Acetoxy)methyl-2-methoxy-piperidine-1-carboxylic acid methyl ester **118** (7.50 g, 30.6 mmol) in a 25-ml flask was added 290 mg (5.42 mmol) ammonium chloride, and then heated to 135°C for 2 h under reduced pressure (20 Torr). After cooling, saturated sodium hydrogen carbonate and sodium chloride solution was added and washed. The solution was extracted by CH_2Cl_2, dried over sodium sulfate. The solvent was evaporated. The crude product was further purified by column chromatography on silica gel (PE/EE 5:1), to 6-(acetoxy)methyl-4,5-dihydro-pyridine-1-carboxylic acid methyl ester **123** (6.06 g, 93 % yield).

R_f = 0.26 (PE/EE =5:1) -^{1}H-NMR (250MHz, $CDCl_3$) δ = 1.64-2.03 (m, 4H, CH_2), 2.03 (s, 3H, CH_3COOR), 3.73 (s, 3H, $COOCH_3$), 3.96-4.08 (m, 1H, CH_2OAc), 4.10-4.24 (m, 1H, CH_2OAc), 4.46-4.72 (m, 1H, NCH), 4.79-5.04 (m, 1H, NCH=C*H*CH_2), 6.61-6.98 (m, 1H,

NC*H*=CHCH$_2$). -^{13}C-NMR (62.9MHz, $CDCl_3$) δ = 17.24 (-, 4-CH_2, Rotamer), 17.46 (-, 4-CH_2, Rotamer), 20.71 (+, *C*H_3CO_2R), 21.79 (-, 5-CH_2), 48.37 (+, N*C*HCH$_2$OAc, Rotamer), 48.68 (+, N*C*HCH$_2$OAc, Rotamer), 52.92 (+, $R_2NCO_2CH_3$), 61.95 (-, *C*H$_2$OAc, Rotamer), 62.07 (-, *C*H$_2$OAc, Rotamer), 105.32 (+, NCH=*C*H, Rotamer), 105.73 (+, NCH=*C*H, Rotamer), 123.46 (+, N*C*H=CH, Rotamer), 124.78 (+, N*C*H=CH, Rotamer), 154.24 (C_{quart}, $R_2NCO_2CH_3$, Rotamer), 154.43 (C_{quart}, $R_2NCO_2CH_3$, Rotamer), 171.52 (C_{quart}, CH_3CO_2R). -IR (Film): ν = 2952, 1744, 1705, 1655, 1445, 1411, 1362, 1237, 1191, 1119, 1074, 1046, 966, 768, 715 cm $^{-1}$. -MS (PI-DCIMS(NH_3)): m/z (%) = 231 (100) [M+NH_4^+], 214 (96) [MH^+].

$C_{10}H_{15}NO_4$ (213.23)	Anal.calcd:	C: 56.33	H: 7.09	N: 6.57
	Found:	C: 56.05	H: 7.31	N: 6.84



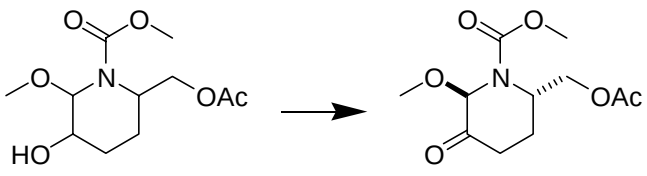
123 **124**

*6-(Acetoxy)methyl-3-hydroxy-2-methoxy-piperidine-1-carboxylic acid methyl ester **124***

6-(Acetoxy)methyl-4,5-dihydro-pyridine-1-carboxylic acid methyl ester **123** (3.33 g, 15.6 mmol) in dry methanol (20 ml) was added mCPBA (4.10 g, 72 % in oil, 17.2 mmol) and stirred overnight under room temperature. Saturated sodium hydrogencarbonate solution was added and washed, extracted by dichloromethane. The solvent was evaporated and the crude product was further purified by column chromatography on silica gel (PE/EE 5:1) to afford 6-(acetoxy)methyl-3-hydroxy-2-methoxy-piperidine-1-carboxylic acid methyl ester **124** as yellow oil (3.30 g, 81 % yield).

R_f = 0.15 (PE/EE =5:1) - ^{1}H-NMR (300MHz, $CDCl_3$) δ = 1.32–2.07 (m, 4H, 4-, 5-CH_2), 1.98 (s, 3H, C*H*$_3$COOR), 2.46 (s, 1H, OH), 3.27 (s, 3H, OCH_3), 3.41-3.54 (m, 1H, 3-C*H*OH), 3.67 (s, 3H, $COOCH_3$), 3.78-3.91 (m, 1H, CH_3COOCH_2R), 3.91-4.13 (m, 1H, CH_3COOCH_2R), 4.17-4.52 (m, 2H, NC*H*CH_2, 3-C*H*OH), 5.01-5.52 (m, 1H, CH_3OCHN). -^{13}C-NMR (75.5MHz, $CDCl_3$) δ = 17.09 (-, 5-CH_2), 19.88 (+, *C*H_3COOCH_2R), 22.34 (-, 4-CH_2), 47.56 (+, NC*H*CH_2), 52.05 (+, CH_3O), 54.52 (+, $R_2NCOOCH_3$, Rotamer), 54.92 (+, $R_2NCOOCH_3$, Rotamer), 63.15 (-, CH_3COOCH_2R, Rotamer), 63.45 (-, CH_3COOCH_2R, Rotamer), 64.82 (+, CHOH), 84.40 (+, CH_3OCHN, Rotamer), 84.82 (+, CH_3OCHN, Rotamer), 156.14 (C_{quart}, $R_2NCOOCH_3$, Rotamer), 157.11 (C_{quart}, $R_2NCOOCH_3$, Rotamer), 169.71 (C_{quart}, CH_3COOCH_2R, Rotamer), 169.79 (C_{quart}, CH_3COOCH_2R, Rotamer). -IR (Film) ν = 3440, 2940, 2810, 1738, 1700, 1670, 1440, 1406, 1368, 1302, 1230, 1188, 1160, 1130, 1090, 1061, 958, 772 cm^{-1}. -MS (PI-DCIMS(NH_3)): m/z (%) = 279 (16) [M+NH_4^+], 247 (100), 230 (39) [M-CH_3O].

$C_{11}H_{19}NO_6$ (261.27)	Anal.calcd:	C: 50.57	H: 7.33	N: 5.36
	Found:	C: 49.99	H: 6.98	N: 5.25



124 **128**

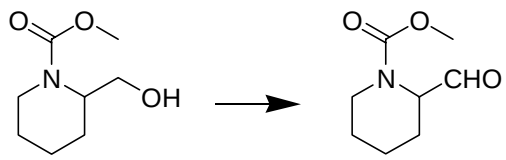
*6-(Acetoxy)methyl-2-methoxy-3-oxo-piperidine-1-carboxylic acid methyl ester **128***

DMSO (0.55 ml, 7.68 mmol) in dichloromethane (2 ml) was added to a stirred solution of oxalyl chloride (0.33 ml, 3.84 mmol) in dichloromethane (7 ml) at -78°C. The mixture was stirred for 3 min, and the alcohol 6-(acetoxy)methyl-3-hydroxy-2-methoxy-piperidine-1-carboxylic acid methyl ester **124** (0.91 g, 3.49 mmol) in dichloromethane (3

ml) was added over a 5-min period. Stirring was continued for an additional 15 min, and triethylamine (2.43 ml, 17.45 mmol) was added. The reaction mixture was stirred for 5 min and then allowed to warm to room temperature. Water (15 ml) was added, the organic layer was separated, and the aqueous layer was further extracted with dichloromethane (30 ml). The combined organic phases were washed with saturated aqueous sodium chloride solution and dried, and the solvent was removed to give a yellow oil. This crude product was purified by column chromatography on silica gel (EE) to afford 6-(acetoxy)methyl-2-methoxy-3-oxo-piperidine-1-carboxylic acid methyl ester **128** as single diastereomer (0.75 g, 83 % yield).

R_f = 0.70 (EE) -^{1}H-NMR (250MHz, $CDCl_3$) δ = 2.03 (s, 3H, CH_3COOR), 2.04–2.73 (m, 4H, 4,5-CH_2), 3.38 (s, 3H, OCH_3), 3.72 (s, 3H, $COOCH_3$), 3.96-4.20 (m, 2H, $CH_3COOC\mathit{H}_2$), 4.21-4.44 (m, 1H, $NC\mathit{H}CH_2$), 5.06-5.34 (br, d, 1H, $CH_3OC\mathit{H}N$). -^{13}C-NMR (62.9MHz, $CDCl_3$) δ = 20.79 (+, $\mathit{C}H_3COOCH_2R$), 22.78 (-, 5-CH_2), 33.09 (-, 4-CH_2), 49.78 (+, 6-NCH), 53.27 (+, $R_2NCOO\mathit{C}H_3$), 56.42 (+, OCH_3, Rotamer), 56.69 (+, OCH_3, Rotamer), 64.66 (-, $R\mathit{C}H_2OAc$, Rotamer), 65.25 (-, $R\mathit{C}H_2OAc$, Rotamer), 86.39 (+, $CH_3O\mathit{C}HN$), 155.92 (C_{quart}, $R_2N\mathit{C}OOCH_3$, Rotamer), 156.97 (C_{quart}, $R_2N\mathit{C}OOCH_3$, Rotamer), 170.64 (C_{quart}, $CH_3\mathit{C}OOR$). 201.29 (C_{quart}, 3-Carbonyl-C). -IR (Film) ν = 2961, 2841, 1740, 1722, 1703, 1439, 1388, 1348, 1295, 1230, 1195, 1166, 1070, 970, 772 cm^{-1}. - MS (CI-MS/DCl) m/z (%) = 536 (1) [2M+NH_4^+], 277 (37) [M+ NH_4^+], 245 (100).

$C_{11}H_{17}NO_6$ (259.26)	Anal.calcd:	C: 50.96	H: 6.61	N: 5.40
	Found:	C: 50.39	H: 6.69	N: 5.80

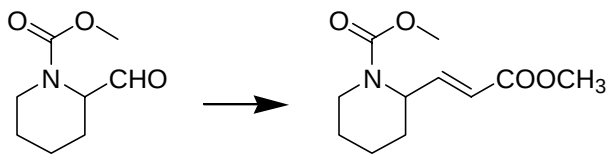


114 **116**

*2-Formyl-piperidine-1-carboxylic acid methyl ester **116***

$(COCl)_2$ (2.42 mmol, 208ul) was dissolved in CH_2Cl_2 (16 ml) at –78 °C under nitrogen. DMSO (4.78 mmol, 340 ul) in CH_2Cl_2 (4 ml) was added dropwise via a syringe. 2-Hydroxy-piperidine-1-carboxylic acid methyl ester **114** (346 mg, 2 mmol) in CH_2Cl_2 (12 ml) was injected 10 min later. The reaction mixture was stirred for 35 min before NEt_3 (9.88 mmol. 1.38 ml) was added. After 40 min at - 60°C the reaction mixture was allowed to reach ambient temperature over 1h. The solvent was evaporated and the residue was washed twice with hexane and once with ethyl acetate. These solution were combined and then evaporated. This crude product was purified by column chromatography on silica gel (PE/EE 1:1) to afford 2-formyl-piperidine-1-carboxylic acid methyl ester **116** as light yellow oil (290 mg, 85 % yield).

R_f = 0.52 (PE/EE = 1:1) -^{1}H-NMR (250MHz, $CDCl_3$) δ = 1.12-1.50 (m, 2H, 4-CH_2), 1.51-1.75 (m, 3H, 3-CH_2, 5-CH_2), 2.11-2.29 (m, 1H, 3-CH_2), 2.72-3.02 (t, 1H, 6-NCH_2), 3.68 (s, 3H, OCH_3), 3.82-4.19 (t, 1H, 6-NCH_2), 4.52-4.71 (m, 1H, 2-CHN), 9.52 (s, 1H, CHO). -^{13}C-NMR (62.9MHz, $CDCl_3$) δ = 20.76 (-, 4-CH_2), 23.48 (-, 3-CH_2), 24.65 (-, 5-CH_2), 42.59 (-, 6-CH_2N), 52.91 (+, COO*C*H_3), 61.02 (+, N*C*HCHO), 157.02(C_{quart}, *C*OOCH$_3$), 201.08 (+, CHO). -IR (Film): ν = 2944, 2865, 1707, 1446, 1393, 1263, 1190, 1121, 1047, 983, 768 cm $^{-1}$. -MS (CI-MS/DCI): m/z (%) = 172 (51) [MH^+], 142 (100).

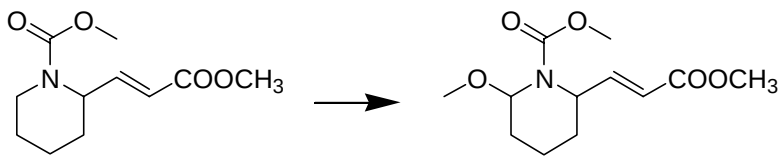


116 **117A**

*E-2-(2-Methoxycarbonyl-vinyl)-piperidine-1-carboxylic acid methyl ester **117A***

To a solution of 2-formyl-piperidine-1-carboxylic acid methyl ester **116** (1.71 g, 10 mmol) in 10 ml dry THF was added (carbomethoxymethylene)triphenylphosphorane **178** (3.34 g, 10 mmol) under room temperature. The solution was stirred for 5 h. The solvent was removed under vacuum and the residue was dissolved in the minium amount of CH_2Cl_2. This crude product was purified by column chromatography on silica gel (PE/EE 1:1) to afford E-2-(2-methoxycarbonyl-vinyl)-piperidine-1-carboxylic acid methyl ester **117A** as yellow oil (2.09 g, 92 % yield).

R_f = 0.67 (PE/EE = 1:1) -^{1}H-NMR (400MHz,$CDCl_3$) δ = 1.35-1.87 (m, 6H, CH_2), 2.84-2.91 (t, 1H, NCH_2), 3.70 (s, 3H, CH=CHCOOC*H*$_3$), 3.74 (s, 3H, $R_2NCOOCH_3$), 4.02-4.05 (m, 1H, NCH_2), 4.96-5.02 (m, 1H, CHN), 5.77-5.88 (dd, J = 2.38, 15.78 Hz, 1H, Olefin-H), 6.78-6.97 (dd, J = 3.96, 15.78 Hz, 1H, Olefin-H). -^{13}C-NMR (100.6 MHz, $CDCl_3$) δ = 19.79 (-, 4-CH_2), 25.29 (-, 5-CH_2), 28.95 (-, 3-CH_2), 40.37 (-, 6-CH_2), 51.63 (+, $R_2NCOOCH_3$), 51.94 (+, 2-NCH), 52.80 (+, CH=CHCOO*C*H_3), 121.99 CH=*C*HCOOCH$_3$),147.37 (+, *C*H=CHCOOCH$_3$), 156.22 (C_{quart}, $R_2NCOOCH_3$), 166.60 (C_{quart}, CH=CH*C*OOCH$_3$). -IR (Film): ν = 3010, 2970, 2885, 1730, 1700, 1660, 1455, 1412, 1380, 1318, 1282, 1200, 1180, 1145, 1050, 775 cm $^{-1}$. -MS (PI-EIMS(70eV)): m/z (%) = 227 (17) [M^+], 196 (39) [M-OCH_3], 168 (92) [M-CO_2CH_3], 140 (57), 136 (55), 75 (100).

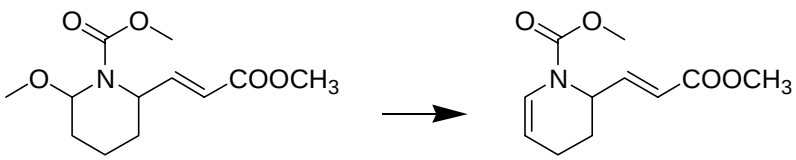


117A **119**

2-Methoxy-6-(2-methoxycarbonyl-vinyl)-piperidine-1-carboxylic acid methyl ester ***119***

A solution of 2-(2-methoxycarbonyl-vinyl)-piperidine-1-carboxylic acid methyl ester **117A** (2.98 g, 13.1 mmol) in methanol (75 ml) containing tetraethylammonium *p*-toluenesulfonate (1.98 g, 6.55 mmol) as an electrolyte was placed into an electrolysis cell equipped with carbon electrodes. Set up the U = 10 V, I = 0.25-0.28 A and the solution was externally cooled with water. After 17 hour the reaction was finished checked by ^{1}H-NMR. The solvent was evaporated under reduced pressure. Water (30 ml) was added to the residue, and it was extracted with ethyl acetate (2 × 30 ml) to get crude product, which was further purified by column chromatography on silica gel (PE/EE 1:1), to get pure 2-methoxy-6-(2-methoxycarbonyl-vinyl)-piperidine-1-carboxylic acid methyl ester **119** as yellow oil (2.43 g, 72 % yield).

R_f = 0.75 (PE/EE = 1:1) -^{1}H-NMR (400MHz, $CDCl_3$) δ = 1.13-2.58 (m, 6H, CH_2), 3.25 (s, 3H, OCH_3), 3.71 (s, 3H, CH=CHCOOC*H*$_3$), 3.74 (s, 3H, $R_2NCOOCH_3$), 3.96-4.12 (m, 1H, NC*H*CH_2), 4.81-5.12 (m, 1H, CH_3OC*H*NR_2), 5.72-5.90 (dd, 1H, Olefin-H), 6.73-7.00 (dd, 1H, Olefin-H). -^{13}C-NMR (100.6 MHz, $CDCl_3$) δ = 19.78 (-, 4-CH_2), 25.29 (-, 5-CH_2), 28.89 (-, 3-CH_2), 51.62 (+, 2-NCH), 51.94 (+, $R_2NCOOCH_3$), 52.77 (+, OCH_3), 53.16 (+, $COOCH_3$), 105.99 (+, CH_3OCHN), 122.00 (+, Olefin-C), 147.34 (+, Olefin-C), 156.24 (C_{quart}, N-*C*$OOCH_3$), 166.59 (C_{quart}, *C*$OOCH_3$). -IR (Film): ν = 2960, 2919, 2825, 1750, 1660, 1460, 1420, 1350, 1250, 1060, 980, 850, 775, 720.

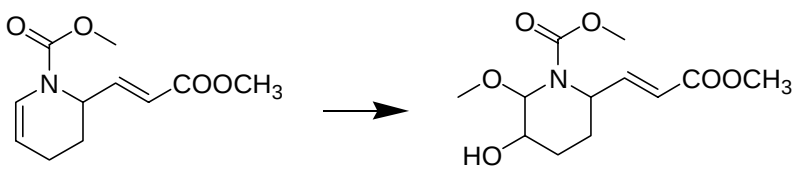


119 **125**

*3,4-Dihydro-2-(2-methoxycarbonyl-vinyl)-pyridine-1-carboxylic acid methyl ester **125***

2-Methoxy-6-(2-methoxycarbonyl-vinyl)-piperidine-1-carboxylic acid methyl ester **119** (2.29 g, 8.9 mmol) in a 25-ml flask was added 83mg (1.55 mmol) ammonium chloride, and then heated to 120 °C for 2 h under reduced pressure (20 Torr). After cooling, saturated sodium hydrogen carbonate and sodium chloride solution was added and washed. The solution was extracted by CH_2Cl_2, dried over sodium sulfate. The solvent was evaporated. The crude product was further purified by column chromatography on silica gel (PE/EE 6:4) to afford 3,4-dihydro-2-(2-methoxycarbonyl-vinyl)-pyridine-1-carboxylic acid methyl ester **125** (1.88 g, 94 % yield) as red oil.

R_f = 0.76 (PE/EE = 6:4) -^{1}H-NMR (400MHz, $CDCl_3$) δ = 1.60-2.05 (m, 4H, CH_2), 3.61 (s, 3H, CH=CHCOOC*H*$_3$), 3.70 (s, 3H, $R_2NCOOCH_3$), 4.70-4.85 (m, 1H, NC*H*CH_2), 4.86-5.10 (dt, 1H, NCH=C*H*CH_2), 5.70-5.85 (dd, 1H, CH=C*H*$COOCH_3$), 6.68-6.80 (dd, 1H, C*H*=CHCOOCH$_3$), 6.82-6.92 (dd, 1H, NC*H*=CHCH_2). -IR (Film): ν = 2988, 2953, 2846, 1715, 1655, 1444, 1360, 1308, 1275, 1232, 1194, 1171, 1117, 1074, 975, 768 cm^{-1}. -MS (PI-EIMS(70eV)): m/z (%) = 225 (15) [M^+], 166 (32) (M-CO_2CH_3), 140 (100), 134 (37).

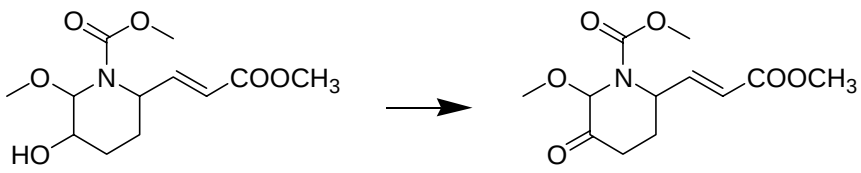


125 **126**

*3-Hydroxy-2-methoxy-6-(2-methoxycarbonyl-vinyl)-piperidine-1-carboxylic acid methyl ester **126***

3,4-Dihydro-2-(2-methoxycarbonyl-vinyl)-pyridine-1-carboxylic acid methyl ester **125** (3.51 g, 15.6 mmol) in dry methanol (20 ml) was added mCPBA (4.10 g, 72 % in oil, 17.2 mmol) and stirred overnight under room temperature. Saturated sodium hydrogencarbonate solution was added and washed, extracted with dichloromethane. The solvent was evaporated and the crude product was further purified by column chromatography on silica gel (PE/EE 6:4) to afford 3-hydroxy-2-methoxy-6-(2-methoxycarbonyl-vinyl)-piperidine-1-carboxylic acid methyl ester **126** as yellow oil (3.62 g, 85 % yield).

R_f = 0.39 (PE/EE = 6:4) -^{1}H-NMR (250MHz, $CDCl_3$) δ = 1.55-2.38 (m, 4H, CH_2), 3.37 (s, 3H, OCH_3), 3.69 (s, 3H, $R_2NCOOCH_3$), 3.71 (s, 3H, CH=CHCOOC*H*$_3$), 3.90-4.02 (dt, 1H, 3-C*H*OH), 4.12 (s, 1H, OH), 4.81-4.92 (m, 1H, NC*H*CH_2), 5.20-5.39 (br, d, 1H, CH_3OC*H*N), 5.91-6.05 (dt, 1H, CH=C*H*$COOCH_3$), 7.05-7.19 (dd, 1H, C*H*=$CHCOOCH_3$). -IR (Film) 3430, 2962, 1738, 1705, 1670, 1451, 1408, 1330, 1298, 1270, 1261, 1200, 1075, 975, 855, 770, 670 cm^{-1}.



126 **129**

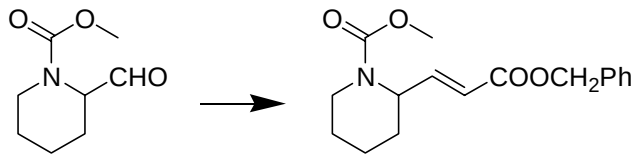
2-Methoxy-6-(2-methoxycarbonyl-vinyl)-3-oxo-piperidine-1-carboxylic acid methyl ester ***129***

DMSO (0.55 ml, 7.68 mmol) in dichloromethane (2 ml) was added to a stirred solution of oxalyl chloride (0.33 ml, 3.84 mmol) in dichloromethane (7 ml) at -78°C. The mixture was stirred for 3 min, and the alcohol 3-hydroxy-2-methoxy-6-(2-methoxycarbonyl-vinyl)-piperidine-1-carboxylic acid methyl ester **126** (0.95 g, 3.49 mmol) in dichloromethane (3 ml) was added over a 5-min period. Stirring was continued for an additional 15 min, and triethylamine (2.43 ml, 17.45 mmol) was added. The reaction mixture was stirred for 5 min and then allowed to warm to room temperature. Water (15 ml) was added, the organic layer was separated, and the aqueous layer was further extracted with dichloromethane (30 ml). The combined organic phases were washed with saturated aqueous sodium chloride solution and dried, and the solvent was removed to give a yellow oil. This crude product was purified by column chromatography on silica gel (PE/EE 6:4) to afford 2-methoxy-6-(2-methoxycarbonyl-vinyl)-3-oxo-piperidine-1-carboxylic acid methyl ester **129** as yellow oil (0.82 g, 87 % yield).

R_f = 0.63 (PE/EE = 6:4) -^{1}H-NMR (250MHz, $CDCl_3$) δ = 1.87-2.41 (m, 4H, 4-, 5-CH_2), 2.52-2.75 (t, 1H, NC*H*CH_2), 3.39 (s, 3H, OCH_3), 3.73 (s, 6H, $COOCH_3$), 4.45-4.79 (m, 1H, NC*H*CH_2), 4.99-5.40 (d, 1H, CH_3OCHNR_2), 5.83-6.11 (dd, 1H, CH=C*H*$COOCH_3$), 6.71-7.04 (dd, 1H, C*H*=$CHCOOCH_3$). -^{13}C-NMR (100.6 MHz, $CDCl_3$) δ = 25.00 (-, 5-CH_2, Rotamer), 25.29 (-, 5-CH_2, Rotamer), 33.40 (-, 4-CH_2), 50.85 (+, N*C*HCH_2, Rotamer), 51.69 (+, N*C*HCH_2, Rotamer), 52.59 (+, $R_2NCOOCH_3$), 53.18 (+, OCH_3, Rotamer), 53.37 (+, OCH_3, Rotamer), 56.76 (+, CH=$CHCOOCH_3$), 86.21 (+, CH_3OCHN,

Rotamer), 86.72 (+, CH_3OCHN, Rotamer), 121.95 (+, $CH=CHCOOCH_3$, Rotamer), 122.33 (+, $CH=CHCOOCH_3$, Rotamer), 146.67 (+, $CH=CHCOOCH_3$, Rotamer), 147.54 (+, $CH=CHCOOCH_3$, Rotamer), 155.94 (C_{quart}, N-$COOCH_3$, Rotamer), 156.55 (C_{quart}, N-$COOCH_3$, Rotamer), 166.14 (C_{quart}, $CH=CHCOOCH_3$, Rotamer), 166.60 (C_{quart}, $CH=CHCOOCH_3$, Rotamer), 200.70 (C_{quart}, 3-Carbonyl-C, Rotamer), 201.92 (C_{quart}, 3-Carbonyl-C, Rotamer). -IR (Film): ν = 2950, 2830, 1740, 1685, 1442, 1383, 1340, 1310, 1265, 1255, 1188, 1108, 1068, 1045, 962, 850, 770, 740 cm^{-1}. -MS (EI(70eV)): m/z (%) = 271 (5) [M^+], 213 (67) [MH^+-$COOCH_3$], 212 (62) [M^+-$COOCH_3$], 158 (92), 144 (100).

$C_{12}H_{17}NO_6$ (271.27)	Anal.calcd:	C: 53.13	H: 6.32	N: 5.16
	Found:	C: 52.70	H: 6.58	N: 5.13



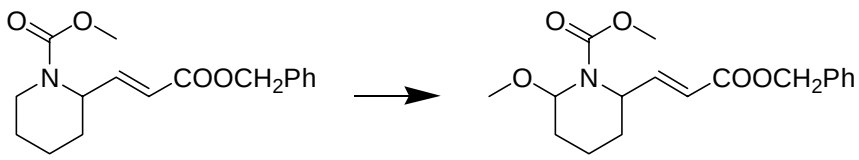
116 **176**

*(E)-2-(2-methoxycarbonyl-vinyl)-piperidine-1-carboxylic acid benzyl ester **176***

To a solution of 2-formyl-piperidine-1-carboxylic acid methyl ester **116** (1.71 g, 10 mmol) in 10 ml dry THF was added (carbobenzoxymethylene)triphenylphosphorane **179** (4.10 g, 10 mmol) under room temperature. The solution was stirred for 5h. The solvent was removed under vacuum and the residue was dissolved in the minium amount of CH_2Cl_2. This crude product was purified by column chromatography on silica gel (PE/EE 1:1) to (E)-2-(2-methoxycarbonyl-vinyl)-piperidine-1-carboxylic acid benzyl ester **176** as yellow oil (2.70 g, 89 % yield).

R_f = 0.75 (PE/EE = 1:1) -^{1}H-NMR (300MHz, $CDCl_3$) δ = 1.34-1.84 (m, 6H, CH_2), 2.77-2.92 (t, 1H, NCH_2), 3.68 (s, 3H, $R_2NCOOCH_3$), 3.95-4.11 (d, 1H, NCH_2), 4.93-5.05 (m,

1H, CHN), 5.13 (s, 2H, $COOCH_2Ph$), 5.82-5.95 (dd, J = 2.46, 15.37 Hz, 1H, CH=C*H*$COOCH_2Ph$), 6.84-6.99 (dd, J = 4.12, 15.37 Hz, 1H, C*H*=$CHCOOCH_2Ph$), 7.23-7.43 (m, 5H, Aryl-H). -^{13}C-NMR (100.6 MHz, $CDCl_3$) δ = 19.72 (-, 4-CH_2), 25.18 (-, 5-CH_2), 28.83 (-, 3-CH_2), 40.27 (-, 6-CH_2), 51.89 (+, 2-NCH), 52.65 (+, $R_2NCOOCH_3$), 66.25 (-, $CH=CHCOOCH_2Ph$), 122.00 (+, $CH=CHCOOCH_2Ph$), 128.20 (+, 4'-Aryl-C), 128.27 (+, 2', 6'-Aryl-C), 128.50 (+, 3', 5'-Aryl-C), 135.89 ($C_{quart,}$ 1'-Aryl-C), 147.66 (+, $CH=CHCOOCH_2Ph$), 156.06 (C_{quart}, $R_2NCOOCH_2Ph$), 165.77 (C_{quart}, $CH=CHCOOCH_3$). -IR (Film): ν = 3020, 2965, 2900, 1720, 1690, 1645, 1440, 1400, 1369, 1300, 1162, 1133, 1088, 1040, 980, 740, 691 cm $^{-1}$. -MS (PI-DCIMS(NH_3)): m/z (%) = 321 (100) [$M+NH_4^+$], 304 (40) [MH^+].

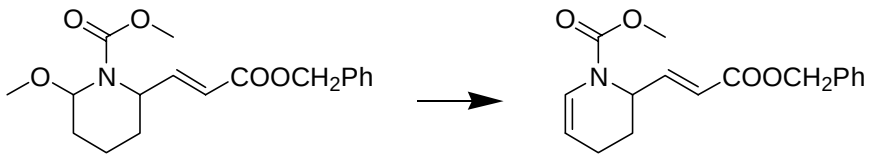


176 **193**

*2-Methoxy-6-(2-methoxycarbonyl-vinyl)-piperidine-1-carboxylic acid benzyl ester **193***

A solution of 2-(2-methoxycarbonyl-vinyl)-piperidine-1-carboxylic acid benzyl ester **176** (3.98 g, 13.1 mmol) in methanol (75 ml) containing tetraethylammonium *p*-toluenesulfonate (1.98 g, 6.55 mmol) as an electrolyte was placed into an electrolysis cell equipped with carbon electrodes. Set up the U = 10 V, I = 0.27-0.30 A and the solution was externally cooled with water. After 18 hour the reaction was finished checked by ^{1}H-NMR. The solvent was evaporated under reduced pressure. Water (30 ml) was added to the residue, and it was extracted with ethyl acetate (2 × 30 ml) to get crude product, which was further purified by column chromatography on silica gel (PE/EE 1:1) to get pure 2-methoxy-6-(2-methoxycarbonyl-vinyl)-piperidine-1-carboxylic acid benzyl ester **193** as red oil (3.54 g, 81 % yield).

R_f = 0.84 (PE/EE = 1:1) -^{1}H-NMR (400MHz, $CDCl_3$) δ = 1.39-2.22 (m, 6H, CH_2), 3.26 (s, 3H, OCH_3), 3.74 (s, 3H, $R_2NCOOCH_3$), 3.58-3.94 (m, 1H, NC*H*CH_2), 4.74-5.06 (m, 1H, CH_3OCHNR_2), 5.07-5.27 (s, 2H, $COOCH_2Ph$), 5.72-6.10 (dd, 1H, CH=C*H*-COOBn), 6.71-6.96 (dd, 1H, C*H*=CH-COOBn), 7.05-7.46 (m, 5H, Aryl-H). -IR (Film): ν = 2960, 2878, 1730, 1710, 1650, 1440, 1402, 1352, 1300, 1258, 1190, 1160, 1112, 1075, 1050, 975, 765, 738, 695 cm $^{-1}$. -MS (PI-DCIMS(NH_3)): m/z (%) = 319 (100) [M+NH_4^+-CH_3OH], 302 (60) [M-CH_3O].

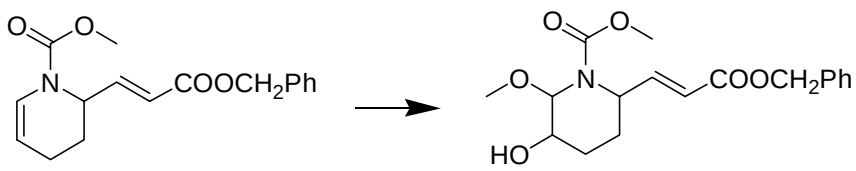


193 **194**

*3,4-Dihydro-2-(2-methoxycarbonyl-vinyl)-pyridine-1-carboxylic acid benzyl ester **194***

2-Methoxy-6-(2-methoxycarbonyl-vinyl)-piperidine-1-carboxylic acid benzyl ester **193** (2.97 g, 8.9 mmol) in a 25-ml flask was added ammonium chloride (83mg, 1.55 mmol), and then heated to 125 °C for 2 h under reduced pressure (20 Torr). After cooling, saturated sodium hydrogen carbonate and sodium chloride solution was added and washed. The solution was extracted by CH_2Cl_2, dried by sodium sulfate. The solvent was evaporated. The crude product was further purified by column chromatography on silica gel (PE/EE 1:1) to afford 3,4-dihydro-2-(2-methoxycarbonyl-vinyl)-pyridine-1-carboxylic acid methyl ester **194** (2.47 g, 92 % yield) as red oil.

R_f = 0.74 (PE/EE = 1:1) -^{1}H-NMR (400MHz, $CDCl_3$) δ = 1.50-2.56 (m, 4H, CH_2), 2.77-2.98 (t, 1H, NC*H*CH_2), 3.70 (s, 3H, $R_2NCOOCH_3$), 4.20-4.45 (m, 1H, NC*H*CH_2), 4.94 (s, 2H, CH=CHCOOC*H*$_2$Ph), 5.09-5.21 (dt, 1H, NCH=C*H*CH_2), 5.71-5.96 (dt, 1H, CH=C*H*$COOCH_3$), 6.59-6.98 (d, 1H, NC*H*=$CHCH_2$), 6.59-6.98 (dd, 1H, C*H*=$CHCOOCH_3$), 7.24-7.44 (m, 5H, Aryl-H). -^{13}C-NMR (100.6MHz, $CDCl_3$) δ = 17.41 (-, 4-CH_2, Rotamer), 17.89 (-, 4-CH_2, Rotamer), 24.86 (-, 5-CH_2, Rotamer), 25.23 (-, 5-CH_2, Rotamer), 51.53 (+, $R_2NCO_2CH_3$, Rotamer), 51.99 (+, $R_2NCO_2CH_3$, Rotamer), 52.74 (+, N*C*HCH=CHCOOPh, Rotamer), 53.13 (+, N*C*HCH=CHCOOPh, Rotamer), 66.24 (-, CH=CHCOO*C*H_2Ph, Rotamer), 66.39 (-, CH=CHCOO*C*H_2Ph, Rotamer), 105.96 (+, NCH=*C*H, Rotamer), 106.26 (+, NCH=*C*H, Rotamer), 121.69 (+, CH=*C*HCOOCH_2Ph, Rotamer), 122.04 (+, CH=*C*HCOOCH_2Ph, Rotamer), 123.50 (+, N*C*H=CH, Rotamer), 123.91 (+, N*C*H=CH, Rotamer), 128.12-128.65 (+, 5C, Aryl-C), 135.88 (C_{quart}, Aryl-C, Rotamer), 136.07 (C_{quart}, Aryl-C, Rotamer), 145.74 (+, *C*H=CHCOOCH_2Ph, Rotamer), 145.93 (+, *C*H=CHCOOCH_2Ph, Rotamer), 153.46 (C_{quart}, $R_2NCO_2CH_3$, Rotamer), 153.90 (C_{quart}, $R_2NCO_2CH_3$, Rotamer), 165.95 (C_{quart}, CH=CH*C*OOCH_2Ph, Rotamer), 166.58 (C_{quart}, CH=CH*C*OOCH_2Ph, Rotamer). -IR (Film): ν = 3005, 2880, 1720, 1705, 1690, 1442, 1408, 1359, 1303, 1262, 1230, 1186, 1115, 1070, 975, 768, 690 cm $^{-1}$. -MS (PI-DCIMS(NH_3)): m/z (%) = 319 (100) [M+NH_4^+], 302 (61) [MH^+].

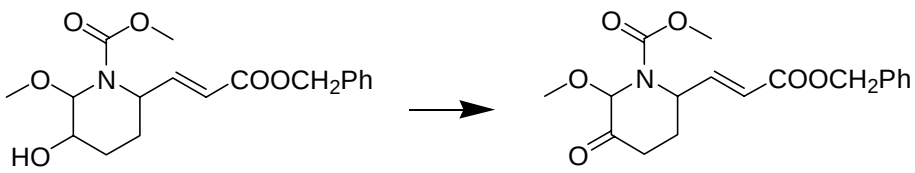


194 **195**

*3-Hydroxy-2-methoxy-6-(2-methoxycarbonyl-vinyl)-piperidine-1-carboxylic acid benzyl ester **195***

3,4-Dihydro-2-(2-methoxycarbonyl-vinyl)-pyridine-1-carboxylic acid methyl ester **194** (4.70 g, 15.6 mmol) in dry methanol (20 ml) was added mCPBA (4.10 g, 72 % in oil, 17.2 mmol) and stirred up overnight under room temperature. Saturated sodium hydrogencarbonate solution was added and washed, extracted by dichloromethane. The solvent was evaporated and the crude product was further purified by column chromatography on silica gel (PE/EE 1:1) to afford 3-hydroxy-2-methoxy-6-(2-methoxycarbonyl-vinyl)-piperidine-1-carboxylic acid methyl ester **195** as yellow oil (4.80 g, 88 % yield).

R_f = 0.36 (PE/EE = 1:1) -^{1}H-NMR (250MHz, $CDCl_3$) δ = 1.39-2.28 (m, 4H, CH_2), 3.27 (s, 3H, CH_3O), 3.48-3.52 (dt, 1H, 3-C*H*OH), 3.72 (s, 3H, $R_2NCOOCH_3$), 3.85-4.02 (m, 1H, NC*H*CH_2), 4.84 (s, 1H, OH), 5.15 (s, 2H, CH=CHCOOC*H*$_2$Ph), 5.21-5.32 (br, d, 1H, CH_3OC*H*N), 5.91-6.07 (dt, 1H, CH=C*H*$COOCH_3$), 7.05-7.18 (dd, 1H, C*H*=CH$COOCH_3$), 7.25-7.41 (m, 5H, Aryl-H). -IR (Film) ν = 3440, 2958, 1720, 1705, 1685, 1642, 1496, 1445, 1405, 1370, 1352, 1300, 1262, 1180, 1162, 1120, 1080, 1060, 962, 840, 772, 738, 695 cm^{-1}.



195 **196**

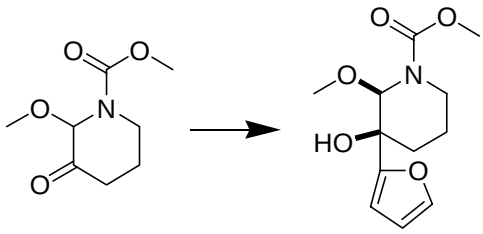
2-Methoxy-6-(2-methoxycarbonyl-vinyl)-3-oxo-piperidine-1-carboxylic acid benzyl ester ***196***

DMSO (0.55 ml, 7.68 mmol) in dichloromethane (2 ml) was added to a stirred solution of oxalyl chloride (0.33 ml, 3.84 mmol) in dichloromethane (7 ml) at -78°C. The mixture was stirred for 3 min, and the alcohol 3-hydroxy-2-methoxy-6-(2-methoxycarbonyl-vinyl)-piperidine-1-carboxylic acid benzyl ester **195** (1.22 g, 3.49 mmol) in dichloromethane (3 ml) was added over a 5-min period. Stirring was continued for an additional 15 min, and triethylamine (2.43 ml, 17.45 mmol) was added. The reaction mixture was stirred for 5 min and then allowed to warm to room temperature. Water (15 ml) was added, the organic layer was separated, and the aqueous layer was further extracted with dichloromethane (30 ml). The combined organic phases were washed with saturated aqueous sodium chloride solution and dried, and the solvent was removed to give a red oil. This crude product was purified by column chromatography on silica gel (PE/EE 1:1) to afford 2-methoxy-6-(2-methoxycarbonyl-vinyl)-3-oxo-piperidine-1-carboxylic acid benzyl ester **196** as yellow oil (1.02 g, 84 % yield).

R_f = 0.57 (PE/EE = 1:1) -^{1}H-NMR (400MHz, $CDCl_3$) δ = 1.78-2.43 (m, 4H, 4-, 5-CH_2), 2.46-2.67 (t, 1H, NC*H*CH_2), 3.27 (s, 3H, OCH_3), 3.63 (s, 6H, $COOCH_3$), 4.42-4.74 (m, 1H, NC*H*CH_2), 5.01-5.37 (d, 1H, CH_3OC*H*NR_2), 5.07 (s, 2H, CH=CHCOOC*H*$_2$Ph), 5.81-6.08 (dd, 1H, CH=C*H*$COOCH_3$), 6.69-6.98 (dd, 1H, C*H*=$CHCOOCH_3$). 7.17-7.40 (m, 5H, Aryl-H). -^{13}C-NMR (100.6 MHz, $CDCl_3$) δ = 25.00 (-, 5-CH_2, Rotamer), 25.27 (-, 5-CH_2, Rotamer), 30.86 (-, 4-CH_2, Rotamer), 31.64 (-, 4-CH_2, Rotamer), 50.89 (+, $R_2NCOOCH_3$, Rotamer), 51.68 (+, $R_2NCOOCH_3$, Rotamer), 53.17 (+, NC*H*CH_2,

Rotamer), 53.42 (+, N*C*HCH$_2$, Rotamer), 56.56 (+, OCH$_3$, Rotamer), 56.74 (+, OCH$_3$, Rotamer), 66.21 (-, CH=CHCOO*C*H$_2$Ph, Rotamer), 66.35 (-, CH=CHCOO*C*H$_2$Ph, Rotamer), 86.30 (+, CH$_3$O*C*HN, Rotamer), 86.76 (+, CH$_3$O*C*HN, Rotamer), 121.97 (+, CH=*C*HCOOCH$_3$, Rotamer), 122.26 (+, CH=*C*HCOOCH$_3$, Rotamer), 127.97-128.84 (+, 5C, Aryl-C), 135.86 (C$_{quart}$, Aryl-C, Rotamer), 135.98 (C$_{quart}$, Aryl-C, Rotamer), 147.28 (+, *C*H=CHCOOCH$_3$, Rotamer), 147.74 (+, *C*H=CHCOOCH$_3$, Rotamer), 156.11 (C$_{quart}$, N-*C*OOCH$_3$, Rotamer), 156.72 (C$_{quart}$, N-*C*OOCH$_3$, Rotamer), 165.96 (C$_{quart}$, CH=CH*C*OOCH$_2$Ph, Rotamer), 166.54 (C$_{quart}$, CH=CH*C*OOCH$_2$Ph, Rotamer), 200.62 (C$_{quart}$, 3-Carbonyl-C, Rotamer), 201.95 (C$_{quart}$, 3-Carbonyl-C, Rotamer). -IR (Film): ν = 3032, 2990, 2880, 1735, 1720, 1690, 1435, 1380, 1345, 1290, 1260, 1163, 1110, 1063, 970, 850, 770, 735, 692 cm $^{-1}$. -MS (PI-DCIMS(NH$_3$)): m/z (%) = 365 (89) [M+NH$_4^+$], 333 (39), 316 (4) [M$^+$- CH$_3$O].

7.2.2 Reactions of 3-piperidones derivatives



127 **134**

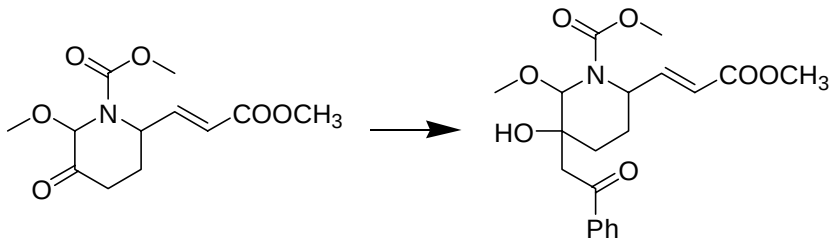
*3-(2-Furyl)-3-hydroxy-2-methoxy-piperidine-1-carboxylic acid methyl ester **134***

To a solution of freshly distilled furan (0.6 ml, 8.25 mmol) in anhydrous THF (2 ml), *n*-butyllithium in hexane (15%, 2 ml) was added dropwise under nitrogen while the temperature was maintained below -5°C. The reaction was allowed to reach room temperature and was stirred for an additional hour. The mixture was cooled to 0°C and a

solution of 2-methoxy-3-oxo-piperidine-1-carboxylic acid methyl ester **127** (0.37 g, 2 mmol) in 6 ml anhydrous THF was added dropwise over a period of 2 min and the stirring was continued under room temperature for 3 hours. Then the mixture was poured into ice water (30 ml), stirred for 15 min and the product was taken by extraction with ethyl acetate (2 × 10 ml). The organic layers, were pooled together, washed with water, dried over magnesium sulfate and evaporated under reduced pressure to yield the crude product as a yellow oil. This crude product was purified by column chromatography on silica gel (PE/EE 1:1) to afford single diastereomer of 3-(2-furyl)-3-hydroxy-2-methoxy-piperidine-1-carboxylic acid methyl ester **134** as dark red oil (0.41 g, 81 % yield).

R_f =0.38 (PE/EE =1:1) -^{1}H-NMR (400MHz, $CDCl_3$) δ = 1.33-1.70 (m, 2H, 5-CH_2), 1.83-2.00 (t, 1H, 4-CH_2), 2.24-2.47 (m, 1H, 4-CH_2), 2.83-2.96 (m, 1H, NCH_2), 2.99 (s, 1H, OH), 3.31 (s, 3H, OCH_3), 3.68 (s, 3H, $COOCH_3$), 3.74-4.02 (m, 1H, NCH_2), 5.48-5.83 (d, 1H, 2-NC*H*OCH_3), 6.25-6.48 (m, 2H, 3´,4´-H of furan ring), 7.32-7.45 (d, 1H, 5´- of furan ring). -^{13}C-NMR (100.6 MHz, $CDCl_3$) δ = 22.67 (-, 4-CH_2, Rotamer), 22.96 (-, 4-CH_2, Rotamer), 31.09 (-, 5-CH_2), 37.35 (-, 6-CH_2, Rotamer), 37.77 (-, 6-CH_2, Rotamer), 52.85 (+, $R_2NCOOCH_3$), 55.21 (+, OCH_3, Rotamer), 55.52 (+, OCH_3, Rotamer), 70.54 (C_{quart}, 3-C), 84.89 (+, CH_3OCHN, Rotamer), 85.45 (+, CH_3OCHN, Rotamer), 107.50 (+, 3-C of furan ring), 110.20 (+, 4-C of furan ring), 142.17 (+, 5-C of furan ring), 153.66 (C_{quart}, 2-C of furan ring), 156.01 (C_{quart}, Carbonyl-C, Rotamer), 156.37 (C_{quart}, Carbonyl-C, Rotamer). -IR (Film): ν = 3454, 2952, 2874, 2831, 1809, 1703, 1501, 1446, 1406, 1369, 1337, 1276, 1191, 1153, 1083, 954, 891, 859, 745 cm^{-1}.

$C_{12}H_{17}NO_5$ (255.27)	Anal.calcd:	C: 56.46	H: 6.71	N: 5.49
	Found:	C: 56.19	H: 6.56	N: 5.26



129 **137**

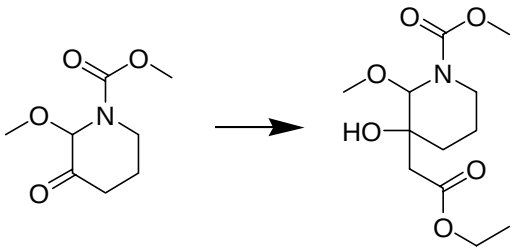
*3-Hydroxy-(N-carbamate-2-methoxy-6-(2-methoxycarbonyl-vinyl)-[3]-piperidyl)-acetophenone **137***

To a stirred solution of LDA prepared from *n*-BuLi (1.7 M hexane solution, 2.81 ml, 4.5 mmol) and diisopropylamine (0.63 ml, 4.5 mmol) in dry THF (4 ml) was added a solution of acetophenone (0.53 ml, 4.5 mmol) in THF (1 ml) at –78 °C, and the resulting mixture was stirred for an additional 30 min. A solution of 2-methoxy-6-(2-methoxycarbonyl-vinyl)-3-oxo-piperidine-1-carboxylic acid methyl ester **129** (406 mg, 1.5 mmol, *ds* = 59:41) in THF (4 ml) was added at –78 °C and the mixture was further stirred for 2 h and warm to room temperature. After addition of saturated aq. NH_4Cl solution (10 ml) and evaporation of the solvent, the organic layer was extracted with ether (3 × 10 ml), followed by standard work up precedure. The residue was purified by column chromatography on silica gel (PE/EE 1:2) to afford diastereomeric mixture (*ds* = 30:29:21:20) of 3-hydroxy-(N-carbamate-2-methoxy-6-(2-methoxycarbonyl-vinyl)-[3]-piperidyl)-acetophenone **137** (0.48 g, 81 % yield) as pale yellow oil.

R_f =0.61 (PE/EE =1:2) -^{1}H-NMR (300MHz, $CDCl_3$) δ =1.40-2.08 (m, 4H, 4-, 5-CH_2), 2.28 (s, 1H, OH), 3.05 (s, 2H, $PhCOCH_2$), 3.37 (s, 3H, OCH_3), 3.65 (s, 6H, $R_2NCOOCH_3$, $COOCH_3$), 4.17-4.44 (m, 1H, NC*H*CH_2), 4.68-4.98 (m, 1H, NC*H*CH_2), 5.10-5.43 (m, 1H, CH_3OCHNR_2), 5.74-6.00 (dd, 1H, CH=C*H*$COOCH_3$), 6.93-7.13 (dd, 1H, C*H*=$CHCOOCH_3$), 7.30-7.98 (m, 5H, Aryl-H). -^{13}C-NMR (75.5 MHz, $CDCl_3$) δ = 21.66 (-, 5-CH_2, Rotamer), 24.48 (-, 5-CH_2, Rotamer), 26.19 (-, 4-CH_2, Rotamer), 28.70

(-, 4-CH_2, Rotamer), 40.98 (-, R*C*H_2COPh, Rotamer), 43.75 (-, R*C*H_2COPh, Rotamer), 48.59 (+, 6-C, Rotamer), 49.12 (+, 6-C, Rotamer), 50.52 (+, R_2NCOO*C*H_3, Rotamer), 50.56 (+, R_2NCOO*C*H_3, Rotamer), 51.96 (+, OCH_3, Rotamer), 52.02 (+, OCH_3, Rotamer), 55.04 (+, COO*C*H_3, Rotamer), 55.09 (+, COO*C*H_3, Rotamer), 69.86 (C_{quart}, 3-C, Rotamer), 70.81 (C_{quart}, 3-C, Rotamer), 85.89 (+, CH_3O*C*HN, Rotamer), 86.30 (+, CH_3O*C*HN, Rotamer), 120.19 (+, CH=*C*HCOOCH_3, Rotamer), 120.43 (+, CH=*C*HCOOCH_3, Rotamer), 127.72, 127.61, 127.50, 127.78 (+, 4 C, Ph-C), 132.34 (+, *p*-Ph-C, Rotamer), 132.82 (+, *p*-Ph-C, Rotamer), 136.02 (C_{quart}, Ph-C, Rotamer), 136.82 (C_{quart}, Ph-C, Rotamer), 146.75 (+, *C*H=*C*HCOOCH_3, Rotamer), 147.33 (+, *C*H=CHCOOCH_3, Rotamer), 155.98 (C_{quart}, R_2N*C*OOCH_3, Rotamer), 156.35 (C_{quart}, R_2N*C*OOCH_3, Rotamer), 165.78 (C_{quart}, *C*OOCH_3, Rotamer), 165.94 (C_{quart}, *C*OOCH_3, Rotamer), 198.43 (C_{quart}, RCH_2*C*OPh, Rotamer), 201.03 (C_{quart}, RCH_2*C*OPh, Rotamer). - MS (PI-DCIMS): m/z (%) = 409 (18) [M+NH_4^+], 360 (43) [M-CH_3O], 259 (100).

$C_{20}H_{25}NO_7$ (391.42)	Anal.calcd:	C: 61.37	H: 6.44	N: 3.58
	Found:	C: 61.75	H: 6.83	N: 3.24



127 **138**

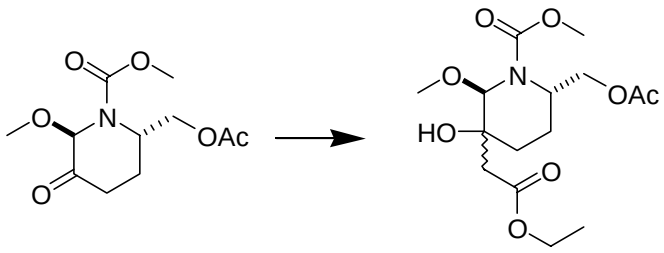
3-Hydroxy-(N-carbamate-2-methoxy-[3]-piperidyl)-propionic acid ethyl ester ***138***

To a stirred solution of LDA prepared from *n*-BuLi (1.7 M hexane solution, 2.72 ml, 4.4 mmol) and diisopropylamine (0.62ml, 4.4 mmol) in dry THF (4 ml) was added a solution

of ethyl acetate (0.43 ml, 4.4 mmol) in THF (1 ml) at –78 °C, and the resulting mixture was stirred for an additional 30 min. A solution of 2-methoxy-3-oxo-piperidine-1-carboxylic acid methyl ester **127** (0.37g, 2 mmol) in THF (4ml) was added at –78 °C and the mixture was further stirred for 2 h. After addition of saturated aq. NH_4Cl solution (10 ml) and evaporation of the solvent, the organic layer was extracted with ether (3×10 ml), followed by standard work up precedure. The residue was purified by column chromatography on silica gel (PE/EE 1:1) to afford diastereomeric mixture (*ds* = 48:52) of 3-hydroxy-(N-carbamate-2-methoxy-[3]-piperidyl)-propionic acid ethyl ester **138** (0.42 g, 77 % yield) as yellow solid.

R_f = 0.30 (PE/EE=1:1) -^{1}H-NMR (400MHz, $CDCl_3$) δ = 1.22-1.34 (t, 3H, $CH_2COOCH_2CH_3$), 1.51-1.67 (m, 2H, 5-CH_2), 1.76-1.95 (m, 2H, 4-CH_2), 2.56 (s, 2H, CH_2COOEt), 2.79-2.99 (m, 1H, NCH_2), 3.25 (s, 1H, OH), 3.34 (s, 3H, OCH_3), 3.73 (s, 3H, $COOCH_3$), 3.71-4.01 (m, 1H, NCH_2), 4.12-4.25 (q, 2H, $COOCH_2CH_3$), 5.16-5.35 (br, d, 1H, CH_3ONCH). -^{13}C-NMR (100.6 MHz, $CDCl_3$) δ = 14.17 (+, $RCH_2COOCH_2CH_3$), 22.23 (-, 5-CH_2, Rotamer), 22.71 (-, 5-CH_2, Rotamer), 31.09 (-, 4-CH_2, Rotamer), 31.47 (-, 4-CH_2, Rotamer), 37.20 (-, $RCH_2COOCH_2CH_3$, Rotamer), 37.64 (-, $RCH_2COOCH_2CH_3$, Rotamer), 39.47 (-, 6-CH_2), 52.88 (+, $R_2NCOOCH_3$), 55.16 (+, OCH_3, Rotamer), 55.48 (+, OCH_3, Rotamer), 60.67 (-, $RCH_2COOCH_2CH_3$), 71.03 (C_{quart}, 3-C), 86.60 (+, CH_3OCHN), 156.28 (C_{quart}, $R_2NCOOCH_3$, Rotamer), 156.57 (C_{quart}, $R_2NCOOCH_3$, Rotamer), 171.11 (C_{quart}, $RCH_2COOCH_2CH_3$). -MS (PI-DCIMS(NH_3)) m/z (%) = 293 (3) [M+ NH_4^+], 276 (1) [MH^+], 261 (21), 244 (100) [M^+-CH_3O].

$C_{12}H_{21}NO_6$ (275.30)	Anal.calcd:	C: 52.35	H: 7.69	N: 5.09
	Found:	C: 51.79	H: 7.57	N: 5.02



128 **139**

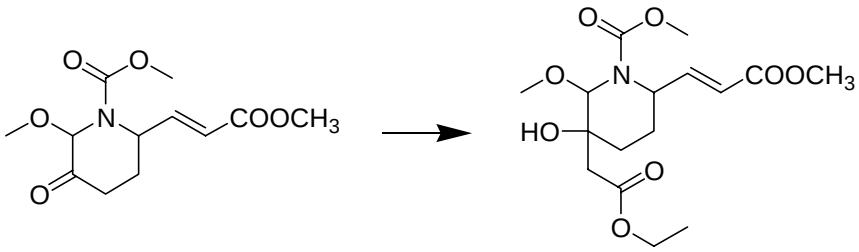
*3-Hydroxy-(N-carbamate-6-(acetoxy)methyl-2-methoxy-[3]-piperidyl)-propionic acid ethyl ester **139***

To a stirred solution of LDA prepared from *n*-BuLi (1.7 M hexane solution, 2.72 ml, 4.4 mmol) and diisopropylamine (0.62 ml, 4.4 mmol) in dry THF (4 ml) was added a solution of ethyl acetate (0.43 ml, 4.4 mmol) in THF(1 ml) at –78 °C, and the resulting mixture was stirred for an additional 30 min. A solution of 6-(acetoxy)methyl-2-methoxy-3-oxo-piperidine-1-carboxylic acid methyl ester **128** (0.519g, 2 mmol) in THF (4 ml) was added at –78 °C and the mixture was further stirred for 2 h. After addition of saturated aq. NH_4Cl solution (10 ml) and evaporation of the solvent, the organic layer was extracted with ether (3 × 10 ml) , followed by standard work up precedure. The residue was purified by column chromatography on silica gel (PE/EE 1:1) to afford diastereomeric mixture (*ds* = 53:47) of 3-hydroxy-(N-carbamate-6-(acetoxy)methyl-2-methoxy-[3]-piperidyl)-propionic acid ethyl ester **139** (0.58 g, 83 % yield) as pale yellow oil.

R_f = 0.32 (PE/EE =1:1) -^{1}H-NMR (250MHz, $CDCl_3$) δ = 1.19-1.33 (t, 3H, CH_3), 1.48-1.97 (m, 4H, 4-, 5-CH_2), 2.03 (s, 3H, C*H*$_3$COOCH$_2$R), 2.53 (s, 2H, C*H*$_2$COOEt), 3.15 (s, 1H, OH), 3.38 (s, 3H, OCH_3), 3.73 (s, 3H, $COOCH_3$), 3.94-4.09 (m, 1H, 6-NC*H*CH=CH), 4.10-4.22 (m, 2H, C*H*$_2$OOCCH$_3$), 4.24-4.41 (q, 2H, COOC*H*$_2$CH$_3$), 5.20-5.47 (d, 1H, 2-NC*H*OCH$_3$). -^{13}C-NMR (62.9 MHz, $CDCl_3$) δ = 14.17 (+, RCH$_2$COOCH$_2$*C*H$_3$), 20.86 (+, *C*H$_3$COOCH$_2$R), 22.23 (-, 5-CH_2, Rotamer), 22.52 (-, 5-CH_2, Rotamer), 26.87 (-, 4-CH_2, Rotamer), 27.30 (-, 4-CH_2, Rotamer), 39.69 (-,

R*C*H_2COOCH_2CH_3), 47.72 (+, 6-CH, Rotamer), 48.01 (+, 6-CH, Rotamer), 53.20 (+, R_2NCOO*C*H_3), 56.48 (+, OCH_3, Rotamer), 57.01 (+, OCH_3, Rotamer), 60.77 (-, R*C*H_2OAc), 63.99 (-, RCH_2COO*C*H_2CH_3, Rotamer), 64.42 (-, RCH_2COO*C*H_2CH_3, Rotamer), 70.84 (C_{quart}, 3-C), 86.95 (+, CH_3O*C*HN), 156.63 (C_{quart}, R_2N*C*OOCH_3, Rotamer), 157.35 (C_{quart}, R_2N*C*OOCH_3, Rotamer), 170.65 (C_{quart}, CH_3*C*OOR). 170.73 (C_{quart}, RCH_2*C*OOCH_2CH_3). -IR (Film) ν = 3480, 2962, 2940, 1738, 1700, 1680, 1432, 1390, 1360, 1290, 1238, 1228, 1218, 1209, 1170, 1060, 1040, 950, 840, 805, 762, 735 cm^{-1}. -MS (CI-MS/DCl(NH_3)) m/z (%) = 365 (11) [M+NH_4^+], 333 (100), 316 (65) [M^+-CH_3O].

$C_{15}H_{25}NO_8$ (347.36)	Anal.calcd:	C: 51.87	H: 7.25	N: 4.03
	Found:	C: 51.51	H: 7.28	N: 4.06



129 **140**

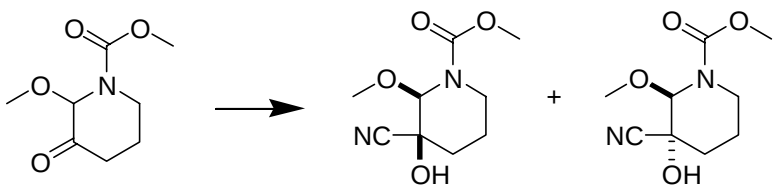
3-Hydroxy-(N-carbamate-2-methoxy-6-(2-methoxycarbonyl-vinyl)-[3]-piperidyl)-propionic acid ethyl ester ***140***

To a stirred solution of LDA prepared from *n*-BuLi (1.7 M hexane solution, 2.72 ml, 4.4 mmol) and diisopropylamine (0.62 ml, 4.4 mmol) in dry THF (4 ml) was added a solution of ethyl acetate (0.43 ml, 4.4 mmol) in THF (1 ml) at –78 °C, and the resulting mixture was stirred for an additional 30 min. A solution of 2-methoxy-6-(2-methoxycarbonyl-vinyl)-3-oxo-piperidine-1-carboxylic acid methyl ester **129** (0.54 g, 2 mmol, *ds* = 59:41) in THF (4 ml) was added at –78 °C and the mixture was further stirred for 2 h. After

addition of saturated aq NH_4Cl solution (10 ml) and evaporation of the solvent, the organic layer was extracted with ether (3 × 10 ml) , followed by standard work up precedure. The residue was purified by column chromatography on silica gel (PE/EE 1:1) to afford diastereomeric mixture (*ds* = 28:40:14:18) of 3-hydroxy-(N-carbamate-2-methoxy-6-(2-methoxycarbonyl-vinyl)-[3]-piperidyl)-propionic acid ethyl ester **140** (0.62 g, 86 % yield) as yellow oil.

R_f = 0.42 (PE/EE =1:1) -^{1}H-NMR (250MHz, $CDCl_3$) δ = 1.15-1.31 (t, 3H, CH_3), 1.55-2.12 (m, 4H, 4-, 5-CH_2), 2.18-2.39 (m, 1H, 6-NC*H*CH=CH), 2.50 (s, 2H, C*H*$_2$COOEt), 3.11 (s, 1H, OH), 3.33 (s, 3H, OCH_3), 3.70 (s, 6H, $R_2NCOOCH_3$, $COOCH_3$), 3.98-4.24 (q, 2H, $RCH_2COOCH_2CH_3$), 4.53-5.03 (m, 1H, NC*H*CH_2), 5.09-5.49 (br, d, 1H, CH_3OCHN), 5.74-6.13 (dd, 1H, Olefin-H), 6.84-7.19 (dd, 1H, Olefin-H). -^{13}C-NMR (62.9MHz, $CDCl_3$) δ = 14.17 (+, $RCH_2COOCH_2CH_3$), 24.92 (-, 5-CH_2, Rotamer), 25.33 (-, 5-CH_2, Rotamer), 27.03 (-, 4-CH_2, Rotamer), 27.63 (-, 4-CH_2, Rotamer), 39.90 (-, $RCH_2COOCH_2CH_3$), 49.37 (+, $R_2NCOOCH_3$), 50.08 (+, 6-CH), 51.60 (+, OCH_3), 53.04 (+, $COOCH_3$, Rotamer), 53.24 (+, $COOCH_3$, Rotamer), 60.07 (-, $RCH_2COOCH_2CH_3$, Rotamer), 60.74 (-, $RCH_2COOCH_2CH_3$, Rotamer), 70.77 (C_{quart}, 3-C, Rotamer), 70.92 (C_{quart}, 3-C, Rotamer), 86.87 (+, CH_3OCHN, Rotamer), 87.40 (+, CH_3OCHN, Rotamer), 121.52 (+, CH=CHCOOCH$_3$), 147.54 (+, CH=CHCOOCH$_3$), 156.72 (C_{quart}, $R_2NCOOCH_3$, Rotamer), 157.41 (C_{quart}, $R_2NCOOCH_3$, Rotamer), 166.78 (C_{quart}, $COOCH_3$, Rotamer), 166.85 (C_{quart}, $COOCH_3$, Rotamer), 170.64 (C_{quart}, $RCH_2COOCH_2CH_3$, Rotamer), 170.76 (C_{quart}, $RCH_2COOCH_2CH_3$, Rotamer). -IR (Film): ν = 3490. 2955, 2840, 1730, 1718, 1708, 1690, 1437, 1365, 1339, 1300, 1240, 1190, 1092, 1070, 1045, 975, 960, 845, 772 cm $^{-1}$. -MS (CI-MS/DCl(NH_3)): m/z (%) = 377 (20) [$M+NH_4^+$], 345 (82), 328 (100) [M^+-CH_3O].

$C_{16}H_{25}O_8N$ (359.37)	Anal.calcd:	C: 53.47	H: 7.01	N: 3.90
	Found:	C: 52.72	H: 6.80	N: 4.13



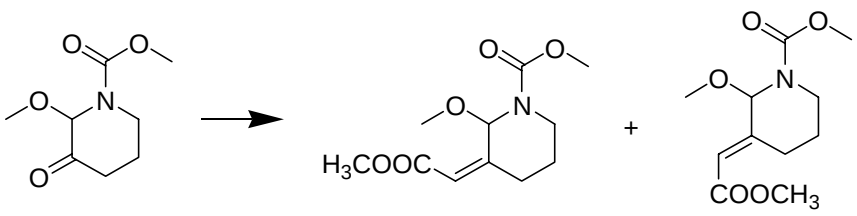
127 **145A** **145B**

*3-Cyano-3-hydroxy-2-methoxy-piperidine-1-carboxylic acid methyl ester **145***

A solution of 2-methoxy-3-oxo-piperidine-1-carboxylic acid methyl ester **127** (3.93 g, 21 mmol) and potassium cyanide (2.1g, 32 mmol) in glacial acetic acid (12 ml) was stirred at room temprature for 0.5 h. After the reaction was over (monitored by TLC), the solvent was evaporated and small amount of ethyl acetate was added, the product was then purified by column chromatography on silica gel (PE/EE 1:1) to afford diastereomeric mixture of 3-cyano-3-hydroxy-2-methoxy-piperidine-1-carboxylic acid methyl ester (**145A**:**145B** = 85:15) as white solid (3.91 g, 87 % yield).

R_f = 0.36 (PE/EE =1:1) -^{1}H-NMR (300 MHz, $CDCl_3$) δ = 1.68-2.14 (m, 4H, 4-CH_2, 5-CH_2), 2.74-2.98 (m, 1H, NCH_2), 3.35 (s, 3H, OCH_3), 3.74 (s, 3H, $COOCH_3$), 3.82-4.13 (m, 1H, NCH_2), 5.33-5.71 (br, d, 1H, 2-NC*H*OCH_3). -^{13}C-NMR (75.5 MHz, $CDCl_3$) δ = 21.70 (-, 5-CH_2, Rotamer), 21.83 (-, 5-CH_2, Rotamer), 29.94 (-, 4-CH_2, Rotamer), 30.41 (-, 4-CH_2, Rotamer), 35.77 (-, 6-CH_2, Rotamer), 36.26 (-, 6-CH_2, Rotamer), 52.41 (+, $R_2NCOOCH_3$), 54.54 (+, OCH_3, Rotamer), 54.96 (+, OCH_3, Rotamer), 68.99 (C_{quart}, 3-C), 82.77 (+, CH_3OCHN, Rotamer), 83.33 (+, CH_3OCHN, Rotamer), 117.19 (C_{quart}, CN), 154.72 (C_{quart}, $R_2NCOOCH_3$, Rotamer), 155.36 (C_{quart}, $R_2NCOOCH_3$, Rotamer). -MS (PI-DCIMS(NH_3)) m/z (%) = 232 (42) [M+NH_4^+], 205 (13) [M+NH_4^+-HCN], 200 (19) [M+ NH_4^+-CH_3OH], 173 (100) [M+ NH_4^+-CH_3OH-HCN].

$C_9H_{14}N_2O_4$ (214.22)	Anal.calcd:	C: 50.46	H: 6.59	N: 13.08
	Found:	C: 50.33	H: 6.60	N: 12.61



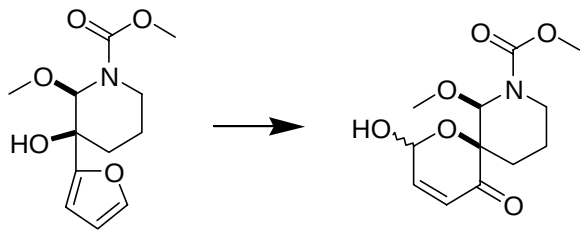
127 **151A** **151B**

*N-Carbamate-2-methoxy-[3]-piperidylidene-acetic acid methyl ester **151A** and **151B***

A dry 10 ml three-necked flask equipped with stirrer, thermometer, condenser, and dropping funnel is purged with dry nitrogen and charged with 80 mg (2 mmol) of a 60 % dispersion of sodium hydride in mineral oil and 2 ml of dry benzene. To this stirred mixture is added dropwise over a 2–4 min period 364 mg (2 mmol) trimethyl phosphonoacetate **177**. During the addition period the temperature is maintained at 30–35°, and cooling is employed if necessary. Vigorous evolution of hydrogen is noted during this portion of the reaction. After the addition of trimethyl phosphonoacetate **177** is completed, the mixture is stirred for 1 hour at room temperature to ensure complete reaction. To this nearly clear solution is added dropwise over a 5–10 minute period 2-methoxy-3-oxo-piperidine-1-carboxylic acid methyl ester **127 (**374 mg, 2 mmol). During the addition the temperature is maintained at 20–30° by appropriate cooling with an ice bath. After approximately one-half of the ketone is added, a gummy precipitate of sodium dimethyl phosphate forms, which in some instances makes stirring difficult. The mixture is then heated at 60–65° for 15 minutes, during which time it is stirred without difficulty. The resulting product is cooled to 15–20°, and the mother liquor is decanted from the precipitate. This gummy precipitate is washed well by mixing it at 60° with several 10 ml portions of benzene and decanting at 20°. Benzene is evaporated and the crude product was then purified by column chromatography on silica gel (PE/EE 1:1) to afford N-carbamate-2-methoxy-[3]-piperidylidene-acetic acid methyl ester **151A** and **151B** (Z/E = 63:37) as yellow oil (306 mg, 63 % yield).

R_f = 0.60 (PE/EE =1:1) - ^{1}H-NMR (400MHz, $CDCl_3$) δ = 1.53-1.94 (m, 2H, 5-CH_2), 2.12–2.53 (m, 2H, 4-CH_2), 2.57-2.73 (m, 1H, NCH_2), 3.25 (s, 3H, OCH_3), 3.74 (s, 6H, $R_2NCOOCH_3$, $COOCH_3$), 3.87-4.09 (m, 1H, NCH_2), 5.30-5.55 (br, d, 1H, CH_3OCHN), 5.80-5.90 (s, 1H, Olefin-H), 6.94-7.14 (s, 1H, Olefin-H). -^{13}C-NMR (100.6 MHz, $CDCl_3$) δ = 23.62 (-, 5-CH_2, Rotamer), 25.21 (-, 5-CH_2, Rotamer), 30.17 (-, 4-CH_2, Rotamer), 30.50 (-, 4-CH_2, Rotamer), 38.90 (-, 6-CH_2, Rotamer), 39.10 (-, 6-CH_2, Rotamer), 51.26 (+, $R_2NCOOCH_3$), 52.91 (+, OCH_3), 54.65 (+, C=CHCOOCH_3, Rotamer), 54.76 (+, C=CHCOOCH_3, Rotamer), 87.14 (+, CH_3OCHN, Rotamer), 87.23 (+, CH_3OCHN, Rotamer), 115.97 (+, Olefin-C), 117.04 (+, Olefin-C), 152.65 (C_{quart}, $R_2NCOOCH_3$, Rotamer), 153.51 (C_{quart}, $R_2NCOOCH_3$, Rotamer), 155.66 (C_{quart}, 3-C-Olefin, Rotamer), 156.20 (C_{quart}, 3-C-Olefin, Rotamer), 165.77 (C_{quart}, C=$CHCOOCH_3$, Rotamer), 166.53 (C_{quart}, C=$CHCOOCH_3$, Rotamer). -IR (Film): ν = 2994, 2952, 2829, 1716, 1664, 1442, 1407, 1312, 1271, 1149, 1069, 963, 882, 770 cm $^{-1}$. -MS (EI(70eV)): m/z (%) = 243 (4) [M^+], 228 (29), 212 (100) [M^+-OCH_3], 196 (44), 184 (51) [M^+-$COOCH_3$].

$C_{11}H_{17}NO_5$ (243.26)	Anal.calcd:	C: 54.31	H: 7.04	N: 5.76
	Found:	C: 53.97	H: 7.14	N: 6.01



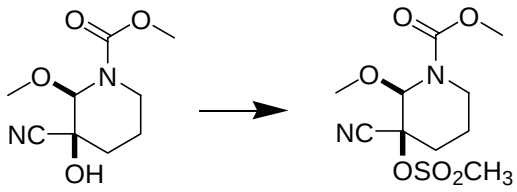
134 **159**

*2-Hydroxy-8-methoxycarbonyl-8-aza-7-methoxy-1-oxaspiro[5.5]undec-3-en-5-one **159***

3-(2-Furyl)-3-hydroxy-2-methoxy-piperidine-1-carboxylic acid methyl ester **134** (0.20 g, 0.78 mmol) was dissolved in methylene chloride (2 ml) and mCPBA (72 %, 0.23 g, 0.94

mmol) was added in portions under stirring, while the temperature was kept between 7 and 15 °C. After being stirred at toom temperature for 3 h the mixture was cooled and the precipitated solid (*m*-chlorobenzoic acid) was filtered. The filtrate was washed successively with 20 % potassium iodide, 30 % sodium thiosulfate, concentrated bicarbonate and water, dried over magnisum sulfate and evaporated to give crude product which was purified by column chromatography on silica gel (EE) to afford diastereomeric mixture (*ds* = 62:38) of 2-hydroxy-8-methoxycarbonyl-8-aza-7-methoxy-1-oxaspiro[5.5]undec-3-en-5-one **159** (0.154 g, 73 % yield) as colorless oil.

R_f = 0.44 (EE) -^{1}H-NMR (300MHz, $CDCl_3$) δ = 1.47-2.10 (m, 4H, 4-CH_2, 5-CH_2), 2.83-3.06 (m, 1H, 6-NCH_2), 3.31 (s, 3H, OCH_3), 3.70 (s, 3H, $COOCH_3$), 3.89 (s, 1H, OH), 4.02-4.29 (m, 1H, NCH_2), 5.33-5.66 (verbr, d, 1H, CH_3OCHN), 5.68-5.87 (d, 1H, HOC*H*-CH=CH), 5.97-6.11 (dt, 1H, HOCH-CH=C*H*), 6.77-6.91 (dt, 1H, HOCH-C*H*=CH). -^{13}C-NMR (75.5 MHz, $CDCl_3$) δ = 20.55 (-, 5-CH_2, Rotamer), 20.64 (-, 5-CH_2, Rotamer), 26.94 (-, 4-CH_2, Rotamer), 28.39 (-, 4-CH_2, Rotamer), 35.78 (-, 6-CH_2, Rotamer), 36.16 (-, 6-CH_2, Rotamer), 51.82 (+, $R_2NCOOCH_3$, Rotamer), 51.92 (+, $R_2NCOOCH_3$, Rotamer), 53.53 (+, OCH_3, Rotamer), 53.81 (+, OCH_3, Rotamer), 76.39 (C_{quart}, 3-C, Rotamer), 77.76 (C_{quart}, 3-C, Rotamer), 82.72 (+, CH_3OCHN), 87.04 (+, HOCHCH=CH), 125.54 (+, CH=CH-CO, Rotamer), 126.32 (+, CH=CH-CO, Rotamer), 142.48 (+, CH=CH-CO, Rotamer), 143.73 (+, CH=CH-CO, Rotamer), 154.98 (C_{quart}, $R_2NCOOCH_3$), 194.24 (C_{quart}, CH=CH-CO, Rotamer), 1904.90 (C_{quart}, CH=CH-CO, Rotamer). -MS (PI-DCIMS(NH_3)): m/z (%) = 289 (43) [$M+NH_4^+$], 272 (10) [MH^+], 257 (100), 240 (98) [M^+-CH_3O].



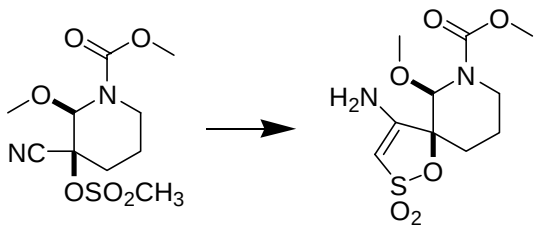
145A **164**

*3-Cyano-3-methanesulfonyloxy-2-methoxy-piperidine-1-carboxylic acid methyl ester **164***

To a solution of 3-cyano-3-hydroxy-2-methoxy-piperidine-1-carboxylic acid methyl ester **145A** (494 mg, 2.3 mmol) and triethylamine (0.97 ml, 6.9 mmol) in dichloromethane (7 ml) was cooled to 0°C and methanesulfonyl chloride (0.35 ml, 4.6 mmol) was added dropwise. The reaction was stirred at 0°C for 30 min and then under room temperature for 1.5 h. The mixture was filtered over celite and was evaporated, the residue was purified by column chromatography (PE/EE 1:1) to give 3-cyano-3-methanesulfonyloxy-2-methoxy-piperidine-1-carboxylic acid methyl ester **164** as a waxy solid (578 mg, 86% yield).

R_f = 0.29 (PE/EE =1:1) -^{1}H-NMR (300MHz, $CDCl_3$) δ = 1.78-2.07 (m, 2H, 5-CH_2), 2.18-2.45 (m, 2H, 4-CH_2), 2.83-3.05 (m, 1H, NCH_2), 3.22 (s, 3H, CH_3SO_2), 3.39 (s, 3H, OCH_3), 3.77 (s, 3H, $COOCH_3$), 3.86-4.17 (d, 1H, NCH_2), 5.82-6.08 (br, d, 1H, 2-NC*H*OCH_3). -^{13}C-NMR (75.5MHz, $CDCl_3$) δ = 22.56 (-, 5-CH_2), 29.60 (-, 4-CH_2), 36.46 (-, 6-CH_2, Rotamer), 36.98 (-, 6-CH_2, Rotamer), 40.25 (+, CH_3SO_2), 53.45 (+, $R_2NCOOCH_3$), 55.66 (+, OCH_3, Rotamer), 56.08 (+, OCH_3, Rotamer), 77.67 (C_{quart}, 3-C), 82.63 (+, CH_3OCHN, Rotamer), 83.02 (+, CH_3OCHN, Rotamer), 115.39 (C_{quart}, CN), 155.33 (C_{quart}, $R_2NCOOCH_3$, Rotamer), 155.88 (C_{quart}, $R_2NCOOCH_3$, Rotamer). -MS (PI-DCIMS(NH_3)): m/z (%) = 310 (100) [M+NH_4^+].

$C_{10}H_{16}N_2O_6S$ (292.31)	Anal.calcd:	C: 41.09	H: 5.52	N: 9.58
	Found:	C: 41.23	H: 5.56	N: 9.26



164 **165**

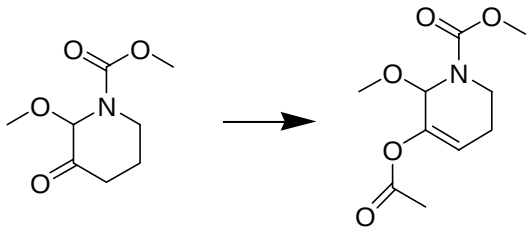
*4-Amino-7-aza-7-carbamate-6-methoxy-1-oxa-2-thiaspiro[4.5]dec-3-ene 2,2-dioxide **165***

To a solution of the 3-cyano-3-methanesulfonyloxy-2-methoxy-piperidine-1-carboxylic acid methyl ester **164** (300 mg, 1.026 mmol) in acetonitrile (1 ml) was added DBU (93.7 mg, 0.616 mmol) and the mixtire was stirred at room temperature for 20 h. After evaporation the crude product was submitted to column chromatography (PE/EE 1:1) to afford 4-amino-7-aza-7-carbamate-6-methoxy-1-oxa-2-thiaspiro[4.5]dec-3-ene 2,2-dioxide **165** as a colorless solid (249 mg, 83 % yield).

R_f = 0.35 (PE/EE =1:1) - ^{1}H-NMR (300MHz, $CDCl_3$) δ = 1.82-1.98 (m, 2H, 5-CH_2), 2.07-2.20 (m, 1H, 4-CH_2), 2.37-2.58 (m, 1H, 4-CH_2), 3.05-3.21 (m, 1H, NCH_2), 3.44 (s, 3H, OCH_3), 3.78 (s, 3H, $COOCH_3$), 3.84-3.96 (d, 1H, NCH_2), 4.64 (s, 2H, NH_2), 5.43 (s, 1H, Olefin-H), 5.50 (s, 1H, 2-NC*H*OCH_3). -^{13}C-NMR (75.5 MHz, $CDCl_3$) δ = 20.01 (-, 5-CH_2), 28.43 (-, 4-CH_2), 36.25 (-, 6-CH_2), 52.87 (+, $R_2NCOOCH_3$), 55.82 (+, OCH_3), 83.99 (+, CH_3OCHN), 85.29 (C_{quart}, 3-C), 85.29 (+, *C*H=C(NH_2)R), 155.90 (C_{quart}, $R_2NCOOCH_3$), 157.76 (C_{quart}, CH=*C*(NH_2)R). -MS (PI-DCIMS(NH_3)): m/z (%) = 310 (100) [M+NH_4^+], 278 (58), 261 (10) [M^+-CH_3O].

$C_{10}H_{16}N_2O_6S$ (292.31)	Anal.calcd:	C: 41.09	H: 5.52	N: 9.58
	Found:	C: 41.18	H: 5.55	N: 9.27

7.2.3 Formation of enol acetate and aldol reaction



127 **172**

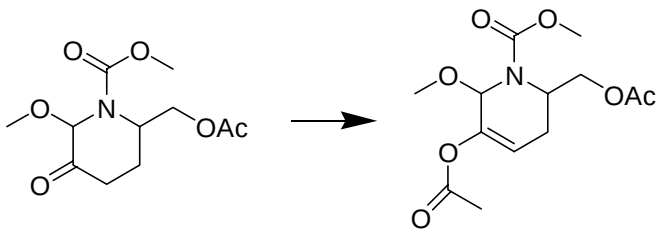
*3-Acetoxy-2-methoxy-5,6-dihydro-1(2H)-pyridinecarboxylic acid methyl ester **172***

To a solution of 2-methoxy-3-oxo-piperidine-1-carboxylic acid methyl ester **127** (0.65 g, 3.45 mmol) and DMAP (42.8 mg, 0.35 mmol) in triethylamine (5 ml) was added acetic anhydride (1 ml, 10.6 mmol) at room temperature. The reaction mixture was stirred for 2.5 h at the same temperature. The reaction was quenched with a saturated aqueous sodium hydrogen carbonate solution at 0 °C and the mixture was extracted with ethyl acetate (twice). The combined organic layers were washed with water, saturated aqueous $NaHCO_3$ solution and brine, dried over sodium sulfate, filtered, and evaporated in vacuo. The crude product was purified by silica gel chromatography to afford 3-acetoxy-2-methoxy-5,6-dihydro-1(2H)-pyridinecarboxylic acid methyl ester **172** (648 mg, 82 % yield) as a light yellow oil.

R_f = 0.59 (PE/EE = 1:1) -^{1}H-NMR (300MHz, $CDCl_3$) δ = 2.03–2.15 (m, 1H, 5-CH_2), 2.19 (s, CH_3COOR), 2.29–2.49 (m, 1H, 5-CH_2), 3.02-3.26 (m, 1H, 6-CH_2), 3.37 (s, 3H, OCH_3), 3.76 (s, 3H, $COOCH_3$), 3.92-4.23 (m, 1H, 6-CH_2), 5.37-5.59 (d, 1H, 2-NC*H*OCH_3), 5.61-5.74 (t, 1H, Olefin-H). -^{13}C-NMR (75.5 MHz, $CDCl_3$) δ = 21.01 (+, *C*H_3COOR), 23.59 (-, 5-CH_2, Rotamer), 24.00 (-, 5-CH_2, Rotamer), 35.16 (-, 6-CH_2, Rotamer), 36.69 (-, 6-CH_2, Rotamer), 52.95 (+, $R_2NCOOCH_3$), 55.70 (+, OCH_3, Rotamer), 55.89 (+, OCH_3, Rotamer), 56.30 (+, OCH_3, Rotamer), 80.10 (+, CH_3OCHN,

Rotamer), 80.29 (+, CH_3OCHN, Rotamer), 116.70 (+, 4-Olefin-C, Rotamer), 117.24 (+, 4-Olefin-C, Rotamer), 144.01 (C_{quart}, 3-Olefin-C), 155.56 (C_{quart}, $R_2NCOOCH_3$, Rotamer), 156.14 (C_{quart}, $R_2NCOOCH_3$, Rotamer), 169.00 (C_{quart}, CH_3COOR, Rotamer), 169.31 (C_{quart}, CH_3COOR, Rotamer). -IR (Film): ν = 2993, 2940, 2833, 1760, 1708, 1446, 1414, 1369, 1335, 1292, 1208, 1152, 1077, 977, 944, 769 cm^{-1}. -MS (CI-MS/DCl) m/z (%) = 198 (100) [M^+-CH_3O].

$C_{10}H_{15}NO_5$ (229.23)	Anal.calcd:	C: 52.40	H: 6.60	N: 6.11
	Found:	C: 52.66	H: 6.59	N: 6.33



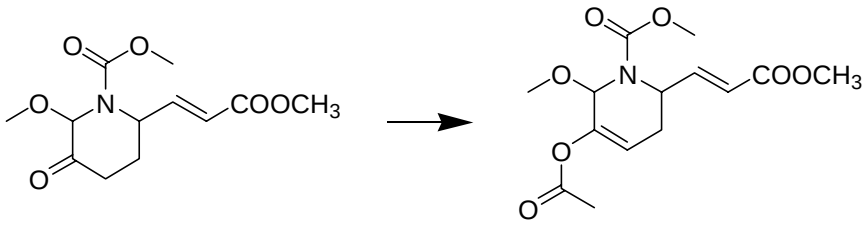
128 **197**

*3-Acetoxy-6-(acetoxy)methyl-2-methoxy-5,6-dihydro-1(2H)-pyridinecarboxylic acid methyl ester **197***

To a solution of 6-(acetoxy)methyl-2-methoxy-3-oxo-piperidine-1-carboxylic acid methyl ester **128** (0.65 g, 3.45 mmol) and DMAP (42.8 mg, 0.35 mmol) in triethylamine (5 ml) was added acetic anhydride (1 ml, 10.6 mmol) at room temperature. The reaction mixture was stirred for 2.5 h at the same temperature. The reaction was quenched with a saturated aqueous sodium hydrogen carbonate solution at 0 °C and the mixture was extracted with ethyl acetate (twice). The combined organic layers were washed with water, saturated aqueous $NaHCO_3$ solution and brine, dried over sodium sulfate, filtered, and evaporated in vacuo. The crude product was purified by silica gel chromatography to

afford 3-acetoxy-6-(acetoxy)methyl-2-methoxy-5,6-dihydro-1(2H)-pyridinecarboxylic acid methyl ester **197** (748 mg, 72 % yield) as a light yellow oil.

R_f = 0.41 (PE/EE =1:1) -^{1}H-NMR (400MHz, $CDCl_3$) δ = 2.05 (s, 3H, C*H*$_3$COOCH$_2$R), 2.20 (s, 3H, C*H*$_3$COOR), 2.28-2.78 (m, 2H, 5-CH_2), 3.41 (s, 3H, OCH_3), 3.78 (s, 3H, $COOCH_3$), 4.13-4.46 (d, 2H,CH_2OAc), 4.54-4.89 (m, 1H, NC*H*CH_2OAc), 5.45-5.67 (m, 2H, 2-NC*H*OCH_3, 4-Olefin-H). -^{13}C-NMR (100.6 MHz, $CDCl_3$) δ = 20.84 (+, *C*H$_3$COOCH$_2$R), 20.97 (+, *C*H$_3$COOR), 24.69 (-, 5-CH_2), 46.08 (+, 6-NC*H*CH_2, Rotamer), 46.53 (+, 6-NC*H*CH_2, Rotamer), 53.21 (+, R$_2$COO*C*H$_3$), 56.65 (+, OCH_3, Rotamer), 57.38 (+, OCH_3, Rotamer), 64.17 (-, R*C*H_2OAc), 79.68 (+, CH$_3$O*C*HN), 113.04 (+, 4-Olefin-C, Rotamer), 113.62 (+, 4-Olefin-C, Rotamer), 143.14 (C_{quart}, 3-Olefin-C), 156.06 (C_{quart}, R$_2$N*C*$OOCH_3$, Rotamer), 156.64 (C_{quart}, R$_2$N*C*$OOCH_3$, Rotamer), 168.89 (C_{quart}, CH$_3$*C*OOR, Rotamer), 169.11 (C_{quart}, CH$_3$*C*OOR, Rotamer), 170.51 (C_{quart}, CH$_3$*C*OOCH$_2$R). -MS (CI-MS/DCl) m/z (%) = 319 (4) [M+NH_4^+], 270(100) [M-CH_3O].



129 **198**

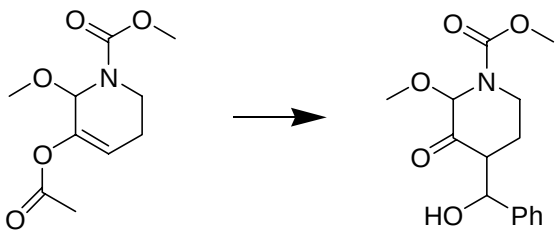
*3-Acetoxy-6-(2-methoxycarbonyl-vinyl)-2-methoxy-5,6-dihydro-1(2H)-pyridinecarboxylic acid methyl ester **198***

To a solution of 2-methoxy-6-(2-methoxycarbonyl-vinyl)-3-oxo-piperidine-1-carboxylic acid methyl ester **129** (0.65 g, 3.45 mmol) and DMAP (42.8 mg, 0.35 mmol) in triethylamine (5 ml) was added acetic anhydride (1 ml, 10.6 mmol) at room temperature.

The reaction mixture was stirred for 2.5 h at the same temperature. The reaction was quenched with a saturated aqueous sodium hydrogen carbonate solution at 0 °C and the mixture was extracted with ethyl acetate (twice). The combined organic layers were washed with water, saturated aqueous $NaHCO_3$ solution and brine, dried over sodium sulfate, filtered, and evaporated in vacuo. The crude product was purified by silica gel chromatography to afford 3-acetoxy-6-(2-methoxycarbonyl-vinyl)-2-methoxy-5,6-dihydro-1(2H)-pyridinecarboxylic acid methyl ester **198** (832 mg, 77 % yield) as light yellow oil.

R_f = 0.47 (PE/EE =1:1) - ^{1}H-NMR (400MHz, $CDCl_3$) δ = 2.20 (s, 3H, C*H*$_3$COOR), 2.28-2.78 (m, 2H, 5-CH_2), 3.42 (s, 3H, OCH_3), 3.70 (s, 3H, $R_2NCOOCH_3$), 3.75 (s, 3H, CH=CHCOOC*H*$_3$), 4.48-4.79 (m, 1H, NC*H*CH_2), 5.00-5.39 (br, d, 1H, CH_3OC*H*N), 5.46-5.68 (m, 1H, C=C*H*CH_2), 5.85-6.20 (d, 1H, CH=C*H*$COOCH_3$), 6.88-7.19 (dt, 1H, C*H*=CHCOOCH_3). -MS (CI-MS/DCl) m/z (%) = 331 (23) [M+NH_4^+], 282 (100) [M^+-CH_3O].

$C_{14}H_{19}NO_7$ (313.30)	Anal.calcd:	C: 53.67	H: 6.11	N: 4.47
	Found:	C: 53.56	H: 6.20	N: 5.07



172 **171**

4-(Hydroxy-phenyl-methyl)-2-methoxy-3-oxo-piperidine-1-carboxylic acid methyl ester ***171***

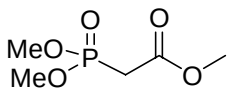
To a cold solution (-78°C) of MeLi (1.44 ml, 2.02 mmol) in 1 ml of DME containing several milligrams of 2,2‘-bipyridyl was added dropwise and with stirring during 3 min, 220 mg (0.96 mmol) of the enol acetate **172**. The resulting purple solution of lithium enolate was stirred at – 40°C for 15 min and warmed to –5°C, treated with freshly fused $ZnCl_2$ (132 mg, 0.97 mmol), and stirred for 10 min. To the resulting light purple, heterogeneous mixture was added, dropwise and with stirring during 1 min, 0.11 ml (0.98 mmol) of benzaldehyde. The resulting cold mixture was stirred for an additional 5 min and then stopped with 1N HCl solution. The solution was extracted with ether and washed successively with aqueous $NaHCO_3$, with water, and with aqueous NaCl and then dried over $MgSO_4$, filtered, and evaporated in vacuo. The crude product was purified by silica gel chromatography (PE/EE = 1:1) to afford diastereomeric mixture (*ds* = 6:21:35:38) of 4-(hydroxy-phenyl-methyl)-2-methoxy-3-oxo-piperidine-1-carboxylic acid methyl ester **171** (189 mg, 67 % yield) as a light yellow oil.

R_f = 0.53 (PE/EE = 1:1) -^{1}H-NMR (400MHz, $CDCl_3$) δ = 1.40 – 2.25 (m, 2H, 5- CH_2), 1.99 (s, 1H, OH), 2.68-3.00 (dt, 1H, 4-C*H*CH_2), 3.01-3.31 (m, 1H, NCH_2), 3.39 (s, 3H, OCH_3), 3.70 (s, 3H, $COOCH_3$), 3.78-4.16 (m, 1H, NCH_2), 4.74-5.09 (m, 1H, PhC*H*OH), 5.13-5.57 (br, d, 1H, CH_3OC*H*N), 7.05-7.67 (m, 5H, Aryl-H). -^{13}C-NMR (100.6 MHz, $CDCl_3$) δ = 19.75 (-, 5-CH_2, Rotamer), 19.96 (-, 5-CH_2, Rotamer), 35.87 (-, 6-CH_2, Rotamer), 36.29 (-, 6-CH_2, Rotamer), 39.52 (+, 4-COC*H*CH_2, Rotamer), 39.74 (+, 4-

COC*H*CH_2, Rotamer), 51.83 (+, $R_2NCOOCH_3$, Rotamer), 52.20 (+, $R_2NCOOCH_3$, Rotamer), 53.90 (+, CH_3O, Rotamer), 54.20 (+, CH_3O, Rotamer), 74.19 (+, CHOHPh, Rotamer), 74.22 (+, CHOHPh, Rotamer), 86.11 (+, CH_3OCHN, Rotamer), 86.46 (+, CH_3OCHN, Rotamer), 123.92-129.22 (+, 5C, Aryl-C), 155.38 (C_{quart}, $R_2NCOOCH_3$, Rotamer), 155.58 (C_{quart}, $R_2NCOOCH_3$, Rotamer), 203.09 (C_{quart}, 3-Carbonyl-C, Rotamer), 203.18 (C_{quart}, 3-Carbonyl-C, Rotamer). -MS (PI-DCIMS(NH_3)): m/z (%) = 311 (5) [$M+NH_4^+$], 279 (29), 262 (10) [$M-CH_3O$], 173 (100).

$C_{15}H_{19}NO_5$ (293.32)	Anal.calcd:	C: 61.42	H: 6.53	N: 4.78
	Found:	C: 61.53	H: 6.37	N: 4.22

7.2.4 Reaction on 6-side chain of N-carbamate piperidines



177

*Trimethyl phosphonoacetate **177***

A mixture of methyl bromoacetate (7.7 g, 50 mmol) and trimethyl phosphite (8.7 g, 70 mmol) was heated in a 50 ml of two-necked, round-bottom flask equipped with a thermometer and a condenser which was connected to a dry-ice acetone trap. As the temperature was increased above 80 °C, methyl bromide began to distill from the reaction and ceased when the reaction temperature reached 160 °C after 2 h. Distillation of the resulting solution gave trimethyl phosphonoacetate **177** as colorless oil (7.3 g, 80 % yield, bp 85-87 °C /0.08 mm Hg).

R_f = 0.80 (PE/EE = 1:1) -^{1}H-NMR (300MHz, $CDCl_3$) δ = 2.85 (s, 2H, CH_2), 3.63 (s, 6H, CH_3O), 3.69 (s, 3H, $COOCH_3$). -^{13}C-NMR (75.5MHz, $CDCl_3$) δ = 33.02 (-, d, CH_2, $^{1}J_{cp}$=134.90 Hz), 52.45 (+, $COOCH_3$), 52.95 (+, CH_3O), 53.05 (+, CH_3O), 165.92(C_{quart}, $^{2}J_{cp}$=6.63 Hz, *C*$OOCH_3$). -MS (PI-EIMS(70eV)): m/z (%) = 182 (4) [M^+], 151 (82) [M^+-OCH_3], 124 (61) [MH^+-$COOCH_3$], 109 (100).

$C_5H_{11}O_5P$ (182.11)	Anal.calcd:	C: 32.98	H: 6.09
	Found:	C: 32.62	H: 6.27

$Ph_3P{=}CHCOOCH_3$

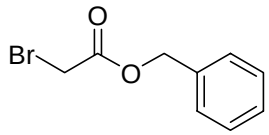
178

*(Carbomethoxymethylene)triphenylphosphorane **178***

Treatment of a solution of 28 g (0.1 mol)of PPh_3 in 80 ml of toluene with 15.3 g (0.1mol) of bromoformiate in 40 ml of toluene under room temperature. The phosphonium salt began precipitating immediately and the temperature reached ca. 70°C within a few minutes. The mixture was shaken vigorously and allowed to stand overnight. The solid was filtered, washed with toluene and pentane, and dried. The salt was dissolved in 250 ml of water, and ca 200 ml of toluene was added. The stirred mixture was brought to the phenolphthalein and pointed by the addition of aqueous NaOH solution. The two layers were separated. The organic layer was dried and concentrated. Careful addition of petroleum ether caused crystallization of the phosphorane. The phosphorane was filtered and dried to get (carbomethoxymethylene)triphenylphosphorane **178** as white solid (32.1 g, 96 % yield).

R_f = 0.24 (PE/EE = 1:1) -^{1}H-NMR (300MHz, $CDCl_3$) δ = 2.90 (s, 1H, C*H*$COOCH_3$), 3.54 (s, 3H, $CHCOOCH_3$), 7.34-7.84 (m, 15H, Aryl-H). -MS (PI-EIMS(70eV)): m/z (%) = 334 (44) [M^+], 333(100).

$C_{21}H_{19}O_2P$ (334.35)	Anal.calcd:	C: 75.44	H: 5.73
	Found:	C: 75.58	H: 5.66



199

Benzyl bromoacetate **199**

To a solution of bromoacetic acid (1.39 g, 10 mmol) in 20 ml THF was added DCC (2.47g, 12 mmol), DMAP (0.37 g, 3 mmol) and benzyl alcohol (2.16g, 20 mmol). The solution was refluxed for 16 h, cooled down, and washed with water and saturated NaCl slution, extracted with CH_2Cl_2, and evaporated in vacuo. The crude product was purified by silica gel chromatography (PE/EE = 1:1) to afford benzyl bromoacetate **199** (1.26 g, 55 % yield) as light yellow oil.

R_f = 0.91 (PE/EE = 1:1) -^{1}H-NMR (400 MHz, $CDCl_3$) δ = 3.83 (s, 2H, $BrCH_2$), 5.17 (s, 2H, $COOCH_2Ph$), 7.28-7.43 (m, 5H, Aryl-H). -^{13}C-NMR (100.6 MHz, $CDCl_3$) δ = 25.84 (-, $BrCH_2$), 67.91 (-, $COOCH_2Ph$), 128.38 (+, Aryl-C), 128.45 (+, Aryl-C), 128.61 (+, Aryl-C), 128.67 (+, Aryl-C), 135.05 (C_{quart}, Aryl-C), 167.03 (C_{quart}, $COOCH_2Ph$).). -IR (Film): ν = 3020, 2922, 2845, 1750, 1720, 1685, 1490, 1445, 1395, 1368, 1270, 1205, 1140, 1105, 1048, 960, 730, 692 cm^{-1}.

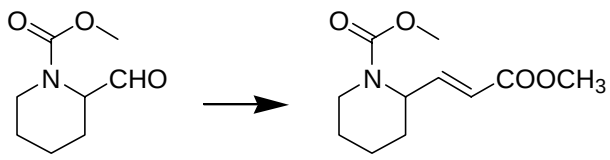
$Ph_3P{=}CHCOOCH_2Ph$

179

*(Carbobenzoxymethylene)triphenylphosphorane **179***

Treatment of a solution of 28.0 g (0.1 mol) of PPh_3 in 80 ml of toluene with 22.9 g (0.1 mol) of benzyl bromoacetate **199** in 40 ml of toluene under room temperature. The phosphonium salt began precipitating immediately and the temperature reached ca. 70°C within a few minutes. The mixture was shaken vigorous and allowed to stand overnight. The solid was filtered, washed with toluene and pentane, and dried. The salt was dissolved in 250 ml of water, and ca 200 ml of toluene was added. The stirred mixture was brought to the phenolphthalein and pointed by the addition of aqueous NaOH. The two layers were separated. The benzene layer was dried and concentrated. Careful addition of petroleum ether caused crystallization of the phosphorane. The phosphorane was filtered and dried over magnesium sulfate to get (carbobenzoxymethylene) triphenylphosphorane **179** as white solid (38.2 g, 93 % yield).

R_f = 0.34 (PE/EE = 1:1) -^{1}H-NMR (300MHz, $CDCl_3$) δ = 2.96 (s, 1H, C*H*$COOCH_2Ph$), 4.93 (s, 2H, $CHCOOC\mathit{H}_2Ph$), 7.05-7.82 (m, 20H, Aryl-H). -MS (PI-EIMS(70eV)): m/z (%) = 410 (100) [M^+].

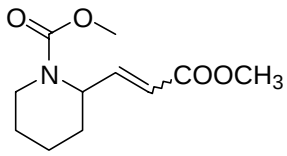


116 **117A**

*E-2-(2-Methoxycarbonyl-vinyl)-piperidine-1-carboxylic acid methyl ester **117A***

To a solution of 2-formyl-piperidine-1-carboxylic acid methyl ester **116** (1.71 g, 10 mmol) in 10 ml dry THF was added (carbomethoxymethylene)triphenylphosphorane **178** (3.34 g, 10 mmol) under room temperature. The solution was stirred up overnight. The solvent was removed under vacuum and the residue was dissolved in the minium amount of CH_2Cl_2. This crude product was purified by column chromatography on silica gel (PE/EE 1:1) to afford E-2-(2-methoxycarbonyl-vinyl)-piperidine-1-carboxylic acid methyl ester **117A** as yellow oil (2.09 g, 92 % yield).

R_f = 0.67 (PE/EE = 1:1) -^{1}H-NMR (400MHz,$CDCl_3$) δ = 1.35-1.87 (m, 6H, CH_2), 2.84-2.91 (t, 1H, NCH_2), 3.70 (s, 3H, CH=CHCOOC*H*$_3$), 3.74 (s, 3H, $R_2NCOOCH_3$), 4.02-4.05 (m, 1H, NCH_2), 4.96-5.02 (m, 1H, CHN), 5.77-5.88 (dd, J = 2.38, 15.78 Hz, 1H, Olefin-H), 6.78-6.97 (dd, J = 3.96, 15.78 Hz, 1H, Olefin-H). -^{13}C-NMR (100.6 MHz, $CDCl_3$) δ = 19.79 (-, 4-CH_2), 25.29 (-, 5-CH_2), 28.95 (-, 3-CH_2), 40.37 (-, 6-CH_2), 51.63 (+, $R_2NCOOCH_3$), 51.94 (+, 2-NCH), 52.80 (+, CH=CHCOO*C*H_3), 121.99 CH=*C*HCOOCH$_3$),147.37 (+, *C*H=CHCOOCH$_3$), 156.22 (C_{quart}, $R_2NCOOCH_3$), 166.60 (C_{quart}, CH=CH*C*OOCH$_3$). -IR (Film): ν = 3010, 2970, 2885, 1730, 1700, 1660, 1455, 1412, 1380, 1318, 1282, 1200, 1180, 1145, 1050, 775 cm $^{-1}$. -MS (PI-EIMS(70eV)): m/z (%) = 227 (17) [M^+], 196 (39) [M-OCH_3], 168 (92) [M-CO_2CH_3], 140 (57), 136 (55), 75 (100).



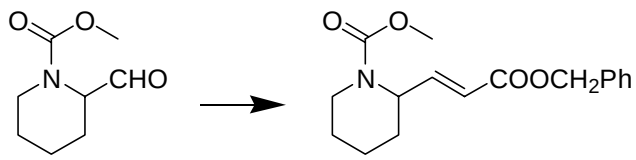
E : Z = 65 : 35

117B

*E, Z-2-(2-Methoxycarbonyl-vinyl)-piperidine-1-carboxylic acid methyl ester **117B***

To a dispersion of NaH (48 mg, 2 mmol) in THF (4 ml) at 0°C under nitrogen atmosphere was added trimethyl phosphonoacetate **177** (364 mg, 2 mmol) in THF (2 ml) and the solution was allowed to react for 1 h before the aldehyde 2-formyl-piperidine-1-carboxylic acid methyl ester **116** (342 mg, 2 mmol), dissolved in dry THF (4 ml) was injected into the mixture, which was then allowed to reach ambient temperature. After 1.5 h, the reaction was complete. The mixture was washed with a pH 7 buffer and water before it was dried over $MgSO_4$ and finally evaporated in vacuum. This crude product was purified by column chromatography on silica gel (PE/EE 1:1) to afford E, Z-2-(2-methoxycarbonyl-vinyl)-piperidine-1-carboxylic acid methyl ester **117B** as yellow oil (390 mg, 86 % yield).

R_f = 0.67 (PE/EE =1:1) -^{1}H-NMR (250MHz, $CDCl_3$) δ = 1.29-1.96 (m, 6H, CH_2), 2.77-3.01 (t, 1H, NCH_2), 3.59-3.75 (s, 6H, CH=CHCOOCH_3, $R_2NCOOCH_3$), 3.95-4.16 (m, 1H, NCH_2), 4.89-5.08 (m, 1H, CHN), 5.77-5.88 (dd, 1H, CH=C*H*$COOCH_3$), 6.37-6.49 (dd, J = 8.71, 10.70 Hz, 1H, Z, C*H*=$CHCOOCH_3$), 6.81-6.94 (dd, J = 4.36, 15.46 Hz, 1H, E, C*H*=$CHCOOCH_3$).

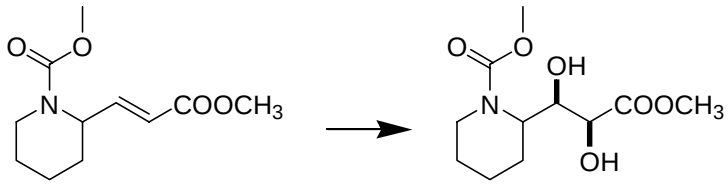


116 **176**

*(E)-2-(2-methoxycarbonyl-vinyl)-piperidine-1-carboxylic acid benzyl ester **176***

To a solution of 2-formyl-piperidine-1-carboxylic acid methyl ester **116** (1.71 g, 10 mmol) in 10 ml dry THF was added (carbobenzoxymethylene)triphenylphosphorane **179** (4.10 g, 10 mmol) under room temperature. The solution was stirred up overnight. The solvent was removed under vacuum and the residue was dissolved in the minium amount of CH_2Cl_2. This crude product was purified by column chromatography on silica gel (PE/EE 1:1), to (E)-2-(2-methoxycarbonyl-vinyl)-piperidine-1-carboxylic acid benzyl ester **176** as yellow oil (2.700 g, 89 % yield).

R_f = 0.75 (PE/EE = 1:1) -^{1}H-NMR (300MHz, $CDCl_3$) δ = 1.34-1.84 (m, 6H, CH_2), 2.77-2.92 (t, 1H, NCH_2), 3.68 (s, 3H, $R_2NCOOCH_3$), 3.95-4.11 (d, 1H, NCH_2), 4.93-5.05 (m, 1H, CHN), 5.13 (s, 2H, $COOCH_2Ph$), 5.82-5.95 (dd, J = 2.46, 15.37 Hz, 1H, CH=C*H*$COOCH_2Ph$), 6.84-6.99 (dd, J = 4.12, 15.37 Hz, 1H, C*H*=$CHCOOCH_2Ph$), 7.23-7.43 (m, 5H, Aryl-H). -^{13}C-NMR (100.6 MHz, $CDCl_3$) δ = 19.72 (-, 4-CH_2), 25.18 (-, 5-CH_2), 28.83 (-, 3-CH_2), 40.27 (-, 6-CH_2), 51.89 (+, 2-NCH), 52.65 (+, $R_2NCOOCH_3$), 66.25 (-, CH=CHCOO*C*H_2Ph), 122.00 (+, CH=*C*H$COOCH_2Ph$), 128.20 (+, 4‘-Aryl-C), 128.27 (+, 2‘, 6‘-Aryl-C), 128.50 (+, 3‘, 5‘-Aryl-C), 135.89 ($C_{quart,}$ 1‘-Aryl-C), 147.66 (+, *C*H=$CHCOOCH_2Ph$), 156.06 (C_{quart}, $R_2NCOOCH_2Ph$), 165.77 (C_{quart}, CH=CH*C*$OOCH_3$). -IR (Film): ν = 3020, 2965, 2900, 1720, 1690, 1645, 1440, 1400, 1369, 1300, 1162, 1133, 1088, 1040, 980, 740, 691 cm $^{-1}$. -MS (PI-DCIMS(NH_3)): m/z (%) = 321 (100) [$M+NH_4^+$], 304 (40) [MH^+].



117A **185**

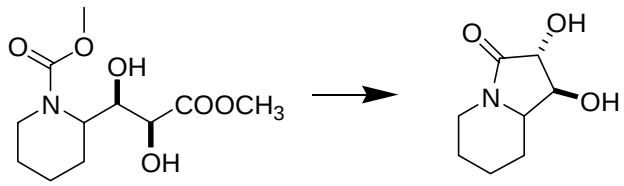
2-(1,2-Dihydroxy-2-methoxycarbonyl-ethyl)-piperidine-1-carboxylic acid methyl ester ***185***

To the mixture solvent aceton/water (15 ml, 10:1) was added OsO_4 (d: 11.2 mg/ml, 0.18 ml, 0.008 mmol) at 0°C and NMO (405 mg, 3 mmol) under room temperature. The solution was stirred for 30 min and then a solution of E-2-(2-methoxycarbonyl-vinyl)-piperidine-1-carboxylic acid methyl ester **117A** (454 mg, 2 mmol) in aceton/water (3 ml, 10:1) was added. The solution was then stirred under room temperature for 3 d. The solution was extracted with ethyl acetate and washed successively with water, and with saturated NaCl solution and then dried over $MgSO_4$, filtered, and evaporated in vacuo. The crude product was purified by silica gel chromatography (PE/EE = 1:1) to afford diastereomeric mixture (*ds* = 58:42) of 2-(1,2-dihydroxy-2-methoxycarbonyl-ethyl)-piperidine-1-carboxylic acid methyl ester **185** as diastereomeric mixture (434 mg, 83 % yield) as colorless oil.

R_f = 0.64 (PE/EE =1:1) -^{1}H-NMR (250MHz, $CDCl_3$) δ = 1.32-1.84 (m, 6H, CH_2), 2.55 (s, 1H, OH), 2.68-3.03 (t, 1H, NCH_2), 3.39 (s, 1H. OH), 3.66 (s, 3H, $COOCH_3$), 3.67 (s, 3H, $R_2NCOOCH_3$), 3.90-4.30 (1H, NCH_2, 2H, RC*H*(OH)C*H*(OH)COOMe) 4.30-4.55 (m, 1H, NC*H*CH2). -^{13}C-NMR (62.9MHz, $CDCl_3$) δ = 18.94 (-, 4-CH_2, Rotamer), 19.45 (-, 4-CH_2, Rotamer), 24.07 (-, 5-CH_2, Rotamer), 24.73 (-, 5-CH_2, Rotamer), 25.03 (-, 3-CH_2, Rotamer), 25.36 (-, 3-CH_2, Rotamer), 51.45 (+, $R_2NCOOCH_3$, Rotamer), 51.99 (+, $R_2NCOOCH_3$, Rotamer), 52.56 (+, $COOCH_3$, Rotamer), 52.88 (+, $COOCH_3$, Rotamer),

53.08 (+, 2-NCH, Rotamer), 53.23 (+, 2-NCH, Rotamer), 69.29 (+, 3-CHOH, Rotamer), 70.26 (+, 3-CHOH, Rotamer), 71.22 (+, 2-CHOH, Rotamer), 72.21 (+, 2-CHOH, Rotamer), 171.15 (C_{quart}, $R_2NCOOCH_3$), 173.54 (C_{quart}, $COOCH_3$). -IR (Film): ν = 3426, 2951, 2866, 1745, 1677, 1452, 1412, 1266, 1178, 1121, 1065, 952, 770. -MS (CI-MS/DCl): m/z (%) = 540 (1) [$2M+NH_4^+$], 279 (100) [$M+NH_4^+$], 262 (87) [MH^+], 247 (64).

$C_{11}H_{19}NO_6$ (261.12)	Anal.calcd:	C: 50.57	H: 7.33	N: 5.36
	Found:	C: 50.74	H: 7.37	N: 5.32



185 **184**

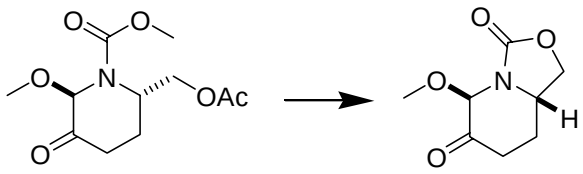
*1,2-Dihydroxyhexahydroindolizidine-3-on **184***

A mixture of 2-(1,2-dihydroxy-2-methoxycarbonyl-ethyl)-piperidine-1-carboxylic acid methyl ester **185** (*ds* = 58:42) (1.31g, 5 mmol), chlorotrimrthylsilane (1.08 g, 10 mmol), and dry sodium iodide (2.25 g, 15 mmol) in dry acetonitrile (15 ml) was heated under reflux in a nitrogen atmosphere. The progress of the reaction was monitored by TLC to check for the disappearance of the starting material. At the end of the reaction (24 h), the mixture was allowed to cool to room temperature. To the cooled mixture, 2 ml of methanol saturated with HCl was carefully added, and the mixture was stirred for 15 min. The volatile materials were then removed from the mixture under reduced pressure, and the residue was dissolved in methanol. Sufficient sodium methoxide was added to render the solution basic. After removal of methanol under reduced pressure, the residue was

shaken with ether (10 ml) and water (10 ml). The aqueous layer was again extracted with ether (10 ml), and the combined ethereal extract were washed with water (3 × 10 ml), sodium thiosulfate solution (10 %, 10 ml), and brine. It was then dried over anhydrous Na_2SO_4. The crude product was further purified by column chromatography on silica gel ($CHCl_3$/CH_3OH 5:1) to afford the diastereomeric mixture (*ds* = 58:42) of **184** as white solid (581 mg, 68 % yield).

R_f =0.42 ($CHCl_3$/CH_3OH = 5:1) -^{1}H-NMR (400MHz, $CDCl_3$) δ = 1.11-1.53 (m, 3H, piperidine-H), 1.60-1.78 (m, 1H, piperidine-H), 1.81-2.25 (m, 2H, piperidine-H), 2.60-2.72 (m, 1H, NCH_2), 3.12-3.21 (m, 1H, NCH), 3.49-3.60 (m, 1H, NCH), 3.83-3.93 (m, 1H, NCHC*H*OH), 4.02-4.15 (m, 1H, NCH_2), 4.27-4.32 (m, 1H, $R_2NC(O)CHOH$), 4.32-4.37 (t, 1H, NCHC*H*OH), 4.33-5.88 (br, s, 2H, CHO*H*CHO*H*). -^{13}C-NMR (100.6 MHz, $CDCl_3$) δ = 22.92, 33.50 (-, $NCH_2CH_2CH_2$), 23.73, 23.99 (-, NCH_2CH_2), 24.95, 25.90 (-, $NCHCH_2$), 39.74, 40.96 (-, NCH_2), 58.64, 58.75 (+, 2-CHN), 73.11, 76.77 (+, NCH*C*HOH), 76.36, 79.69 (+, NC(O)*C*HOH), 171.14, 171.26 (C_{quart}, Carbonyl-C). -MS (CI-MS/DCl): m/z (%) = 343 (10) [$2M+H^+$], 189 (100) [$M+NH_4^+$], 172 (32) [MH^+].

$C_8H_{13}NO_3$ (171.19)	Anal.calcd:	C: 56.13	H: 7.65	N: 8.18
	Found:	C: 55.91	H: 7.71	N: 8.16

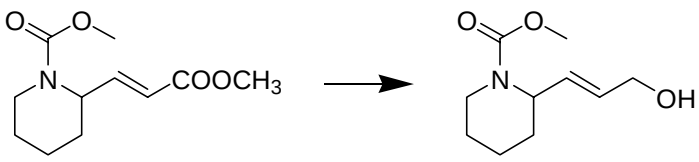


128 **188**

*5-Methoxy-tetrahydro-oxazolo[3,4-a]pyridin-3,6-dione **188***

To 6-(acetoxy)methyl-2-methoxy-3-oxo-piperidine-1-carboxylic acid methyl ester **128** (259 mg, 1 mmol) in dry methanol (10 ml) was added metal sodium (46 mg, 2 mmol) under room temperature. After stirring 2 h, the reaction was finished checked by TLC. The mixture was washed successively with 1N HCl solution, water and saturated NaCl solution, dried over anhydrous Na_2SO_4. The crude product was further purified by column chromatography on silica gel (EE) to afford the product 5-methoxy-tetrahydro-oxazolo[3,4-a]pyridin-3,6-dione **188** (124 mg, 67 % yield) as single diastereomer.

R_f = 0.30 (EE) -^{1}H-NMR (250MHz, $CDCl_3$) δ = 1.82–2.04 (dt, 1H, 5-CH_2), 2.21-2.35 (m, 1H, 5-CH_2), 2.45-2.53 (m, 1H, 4-CH_2), 2.73-2.89 (dt, 1H, 4-CH_2), 3.45 (s, 3H, OCH_3), 3.91-4.04 (t, 1H, NCOOC*H*$_2$), 4.24-4.37 (m, 1H, NC*H*CH_2), 4.56-4.63 (t, 1H, NCOOC*H*$_2$), 4.88 (s, 1H, CH_3OC*H*N). -^{13}C-NMR (62.9MHz, $CDCl_3$) δ = 31.28 (-, 5-CH_2), 34.63 (-, 4-CH_2), 48.94 (+, 6-CHN), 56.44 (+, OCH_3), 68.30 (-, NCOO*C*H_2), 84.88 (+, CH_3O*C*HN), 156.24 (C_{quart}, N*C*OOCH_2), 199.27 (C_{quart}, 3-Carbonyl-C). -IR (Film) ν = 2962, 2940, 1738, 1700, 1680, 1432, 1390, 1360, 1290, 1238, 1228, 1218, 1209, 1170, 1060, 1040, 950, 840, 805, 762, 735 cm^{-1}. -MS (CI-MS/DCl): m/z (%) = 203 (100) [M+NH_4^+].



117A **191**

*3-[1-(Methoxycarbonyl)-2-piperidyl]-2-propen-1-ol **191***

To a well stirred solution of E-2-(2-Methoxycarbonyl-vinyl)-piperidine-1-carboxylic acid methyl ester **117A** (454 mg, 2 mmol) in dry CH_2Cl_2 (25 ml) at –78°C was added DIBAL-H (1.0 M in CH_2Cl_2, 4.2 ml, 4.2 mmol) dropwise over a period of 10 min under a steady stream of nitrogen whilst maintaining the temperature. The mixture was stirred for 10 min, quenched with methanol (30 ml, cooled to -60 °C) and then warmed to room tempeture. CH_2Cl_2 was removed under reduced pressure and the colourless residue dissolved in hydrochloric acid (1M, 600 ml). The aqueous layer was extracted with CH_2Cl_2 (50 ml), the combined organic phases were dried and concentrated by rotary evaporation leading to the crude product which was further purified by column chromatography on silica gel (PE/EE 7:3) to afford the product 3-[1-(methoxycarbonyl)-2-piperidyl]-2-propen-1-ol **191** (335 mg, 84 % yield) as colorless oil.

R_f = 0.73 (PE/EE =7:3) -^{1}H-NMR (300MHz, $CDCl_3$) δ = 1.44-1.75 (m, 6H, 3, 4, 5-CH_2), 2.84 (s, 1H, OH), 2.82-2.95 (t, 1H, NCH_2), 3.67 (s, 3H, $COOCH_3$), 3.89-4.03 (d, 1H, NCH_2), 4.08-4.20 (m, 2H, C*H*$_2$OH), 4.75-4.92 (m, 1H, CHN), 5.62-5.70 (m, 2H, Olefin-H). -^{13}C-NMR (75.5 MHz, $CDCl_3$) δ = 19.38 (-, $NCHCH_2CH_2$), 25.47 (-, NCH_2CH_2), 29.25 (-, $NCHCH_2$), 40.03 (-, NCH_2), 51.82 (+, N*C*H), 52.62 (+, $R_2NCOOCH_3$), 62.93 (-, CH_2OH), 129.46 (+, Olefin-C), 130.83 (+, Olefin-C), 156.46 (C_{quart}, *C*$OOCH_3$). -IR (Film): ν = 3422, 2995, 2939, 2861, 1699, 1448, 1407, 1370, 1337, 1267, 1174, 1125, 1094, 1041, 973, 768 cm^{-1}. -MS (PI-DCIMS(NH_3)): m/z (%) = 217 (99) [M+NH_4^+], 200 (17) [MH^+], 182 (100) [MH^+-H_2O].

$C_{10}H_{17}O_3N$ (199.25)	Anal.calcd:	C: 60.28	H: 8.60	N: 7.03
	Found:	C: 59.61	H: 8.43	N: 6.71

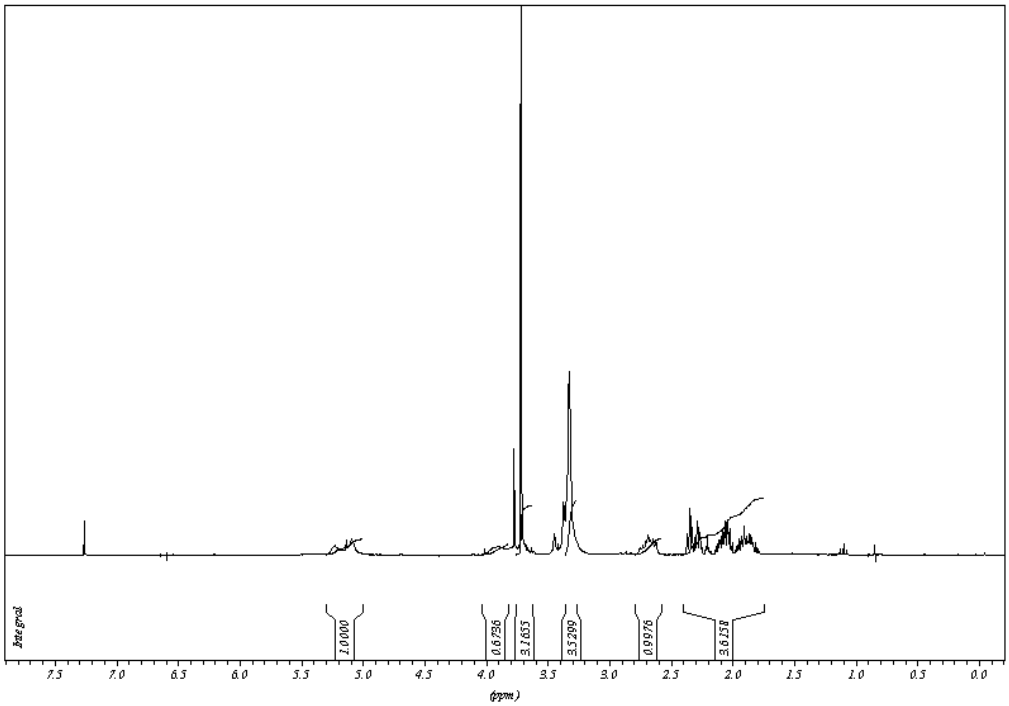
• Chapter 8

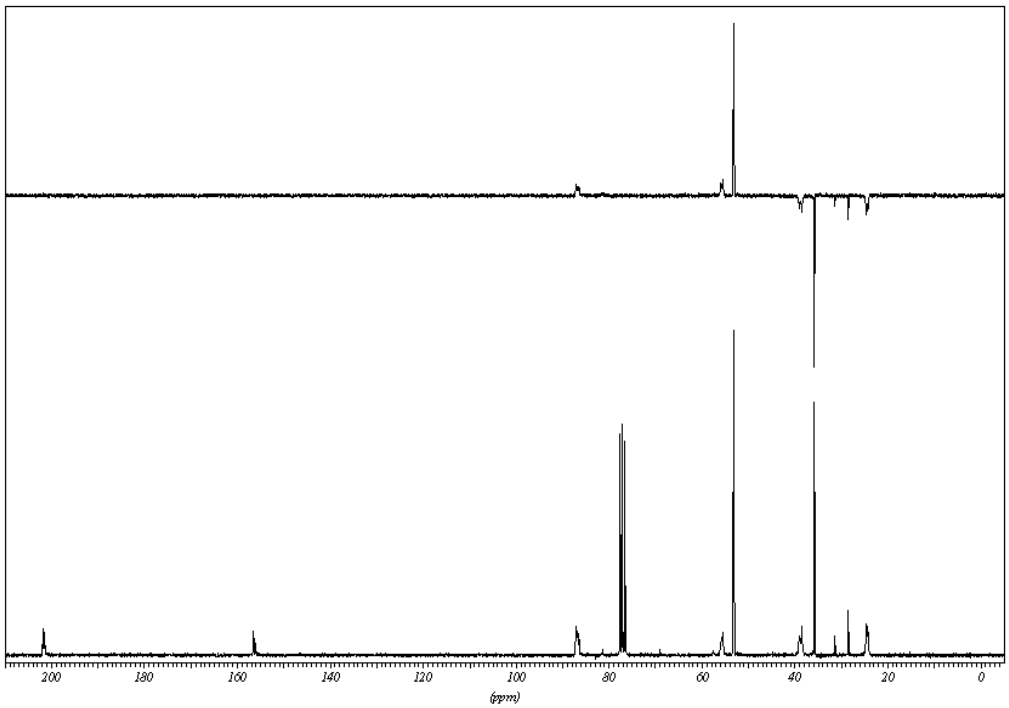
Spectroscopy

NMR

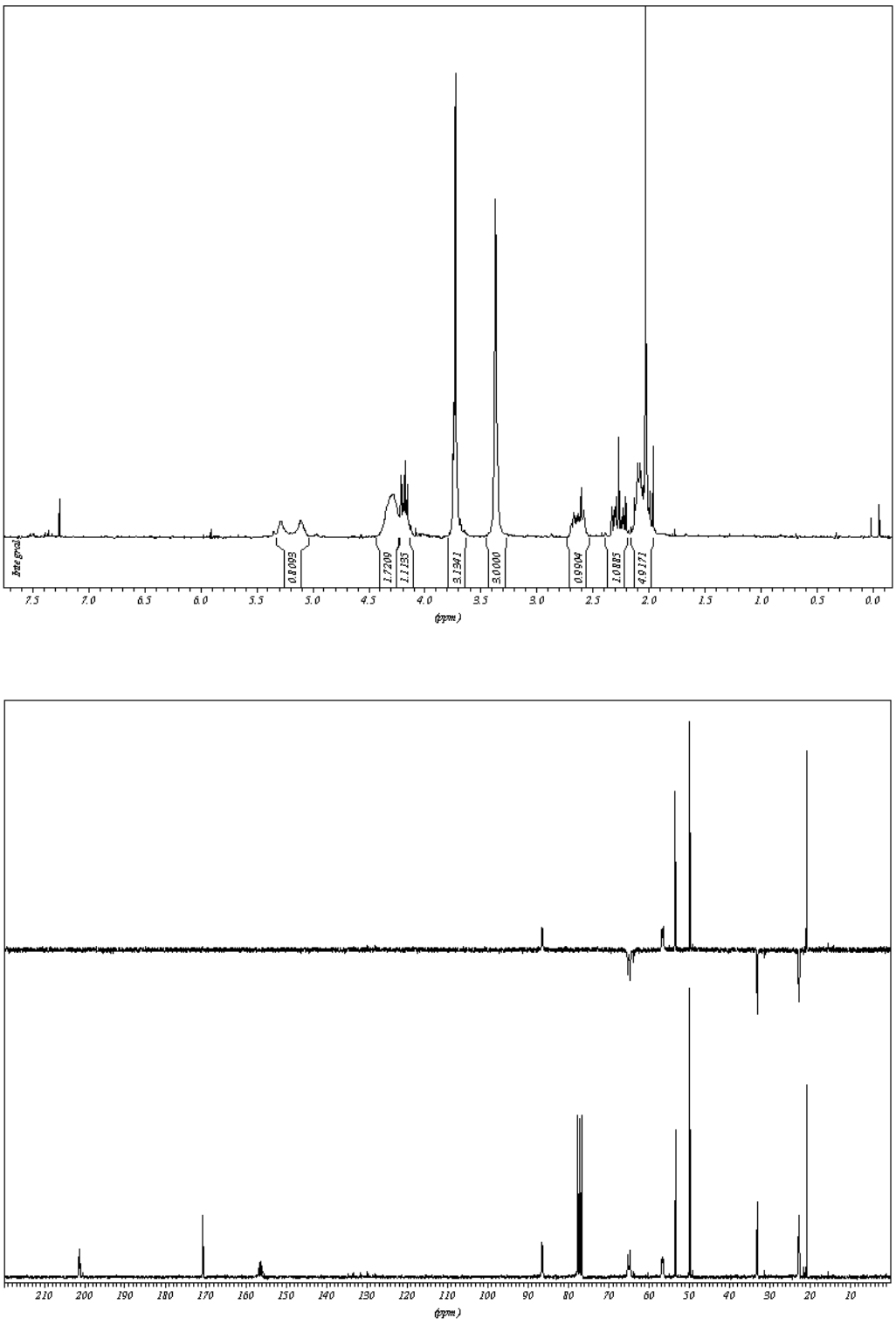
^{1}H-Spectra **(top of the page)**

^{13}C-Spectra (DEPT) **(bottom of the page)**

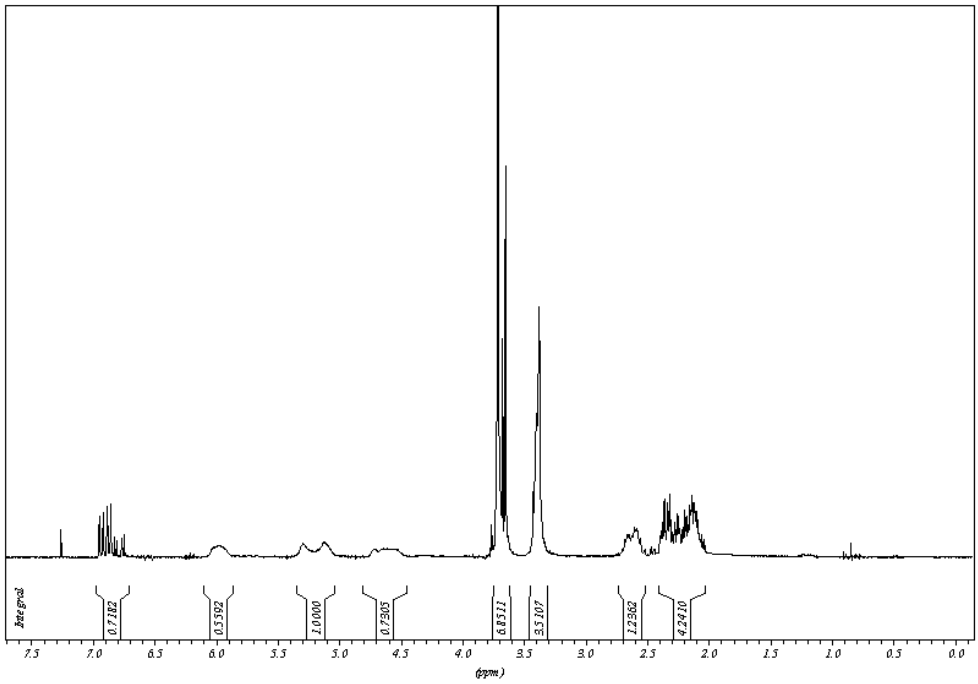


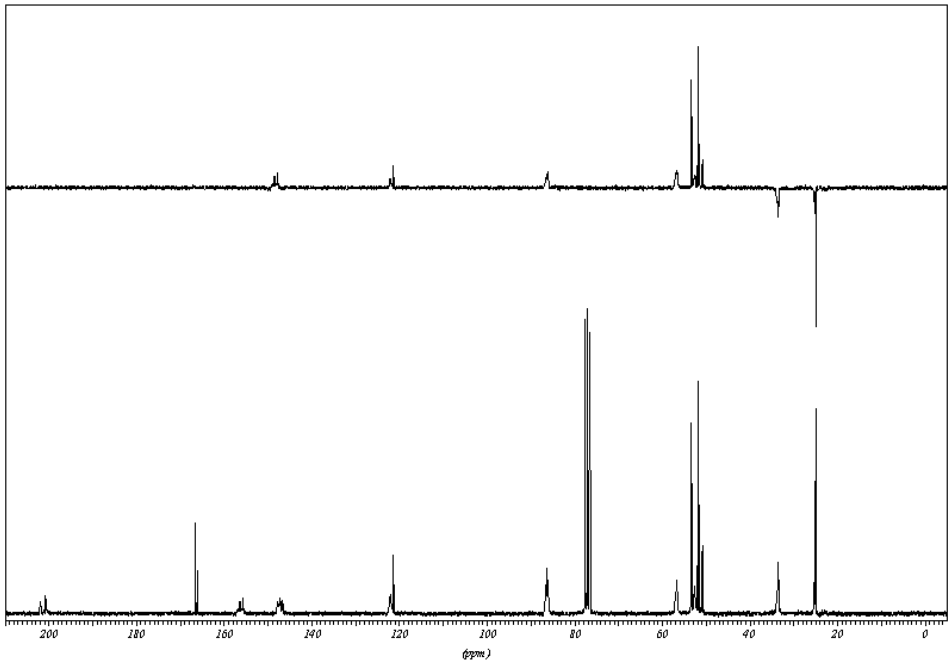


2-Methoxy-3-oxo-piperidine-1-carboxylic acid methyl ester **127**

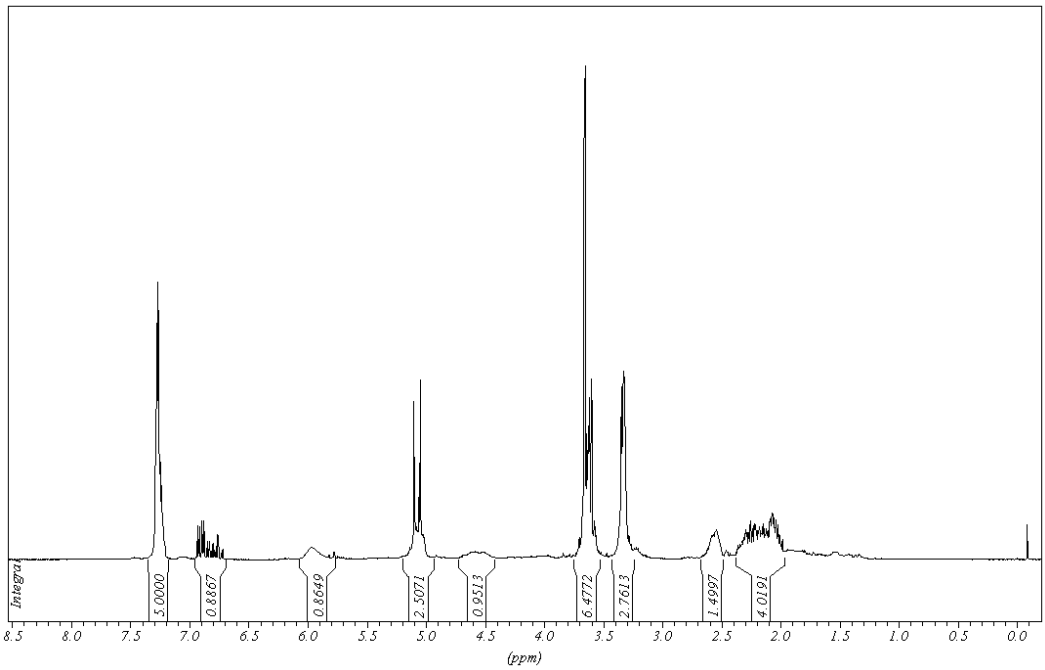


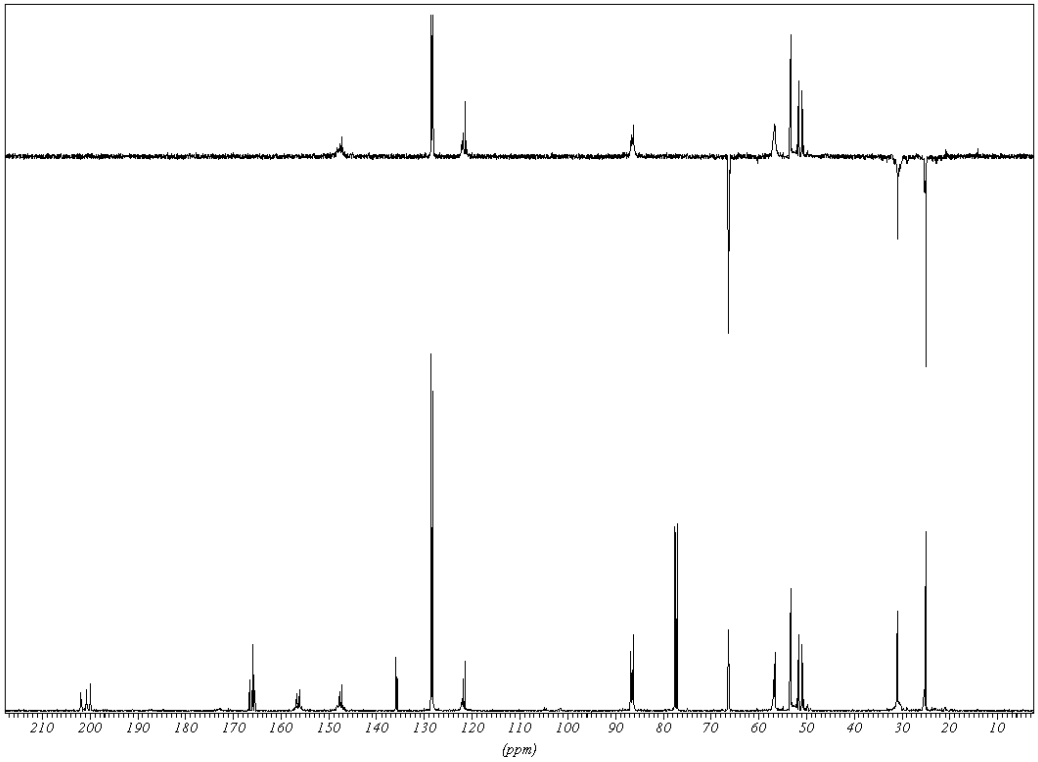
6-(Acetoxy)methyl-2-methoxy-3-oxo-piperidine-1-carboxylic acid methyl ester **128**



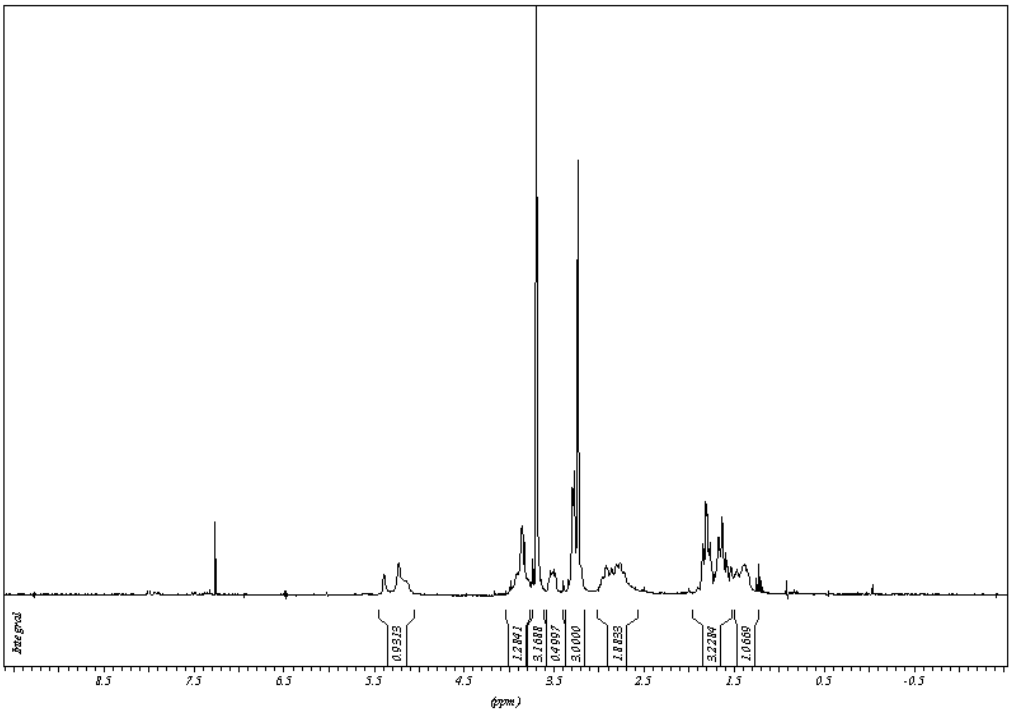


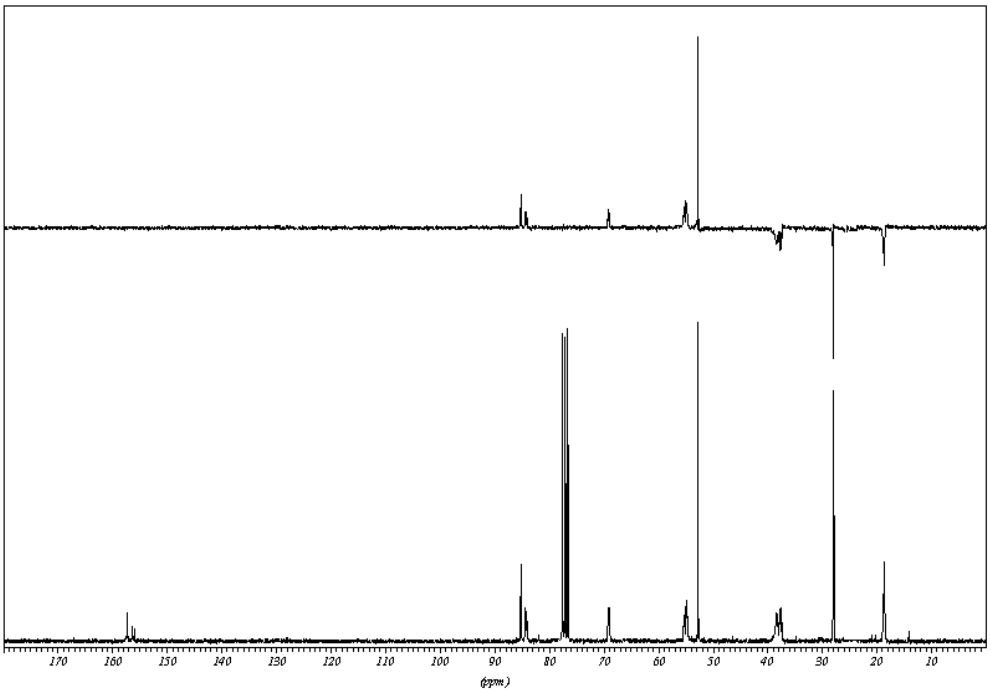
2-Methoxy-6-(2-methoxycarbonyl-vinyl)-3-oxo-piperidine-1-carboxylic acid methyl ester **129**



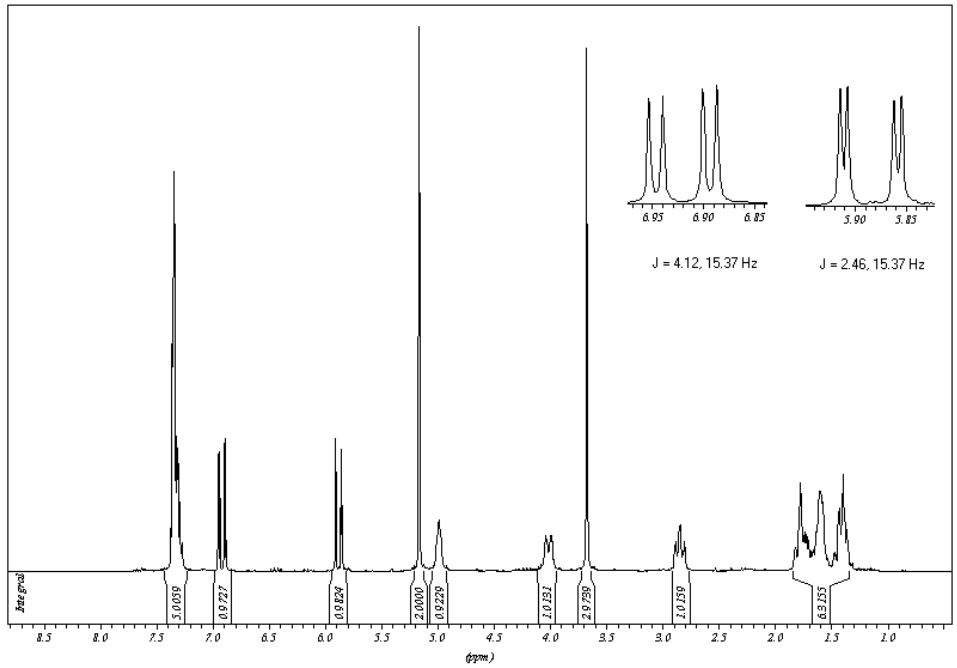


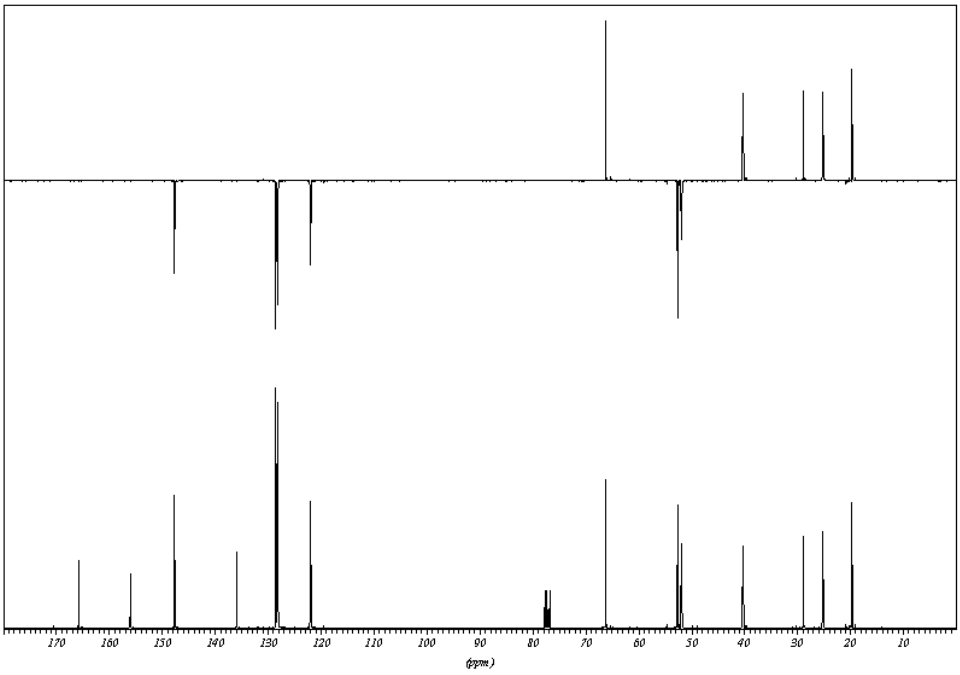
2-Methoxy-6-(2-methoxycarbonyl-vinyl)-3-oxo-piperidine-1-carboxylic acid benzyl ester **196**



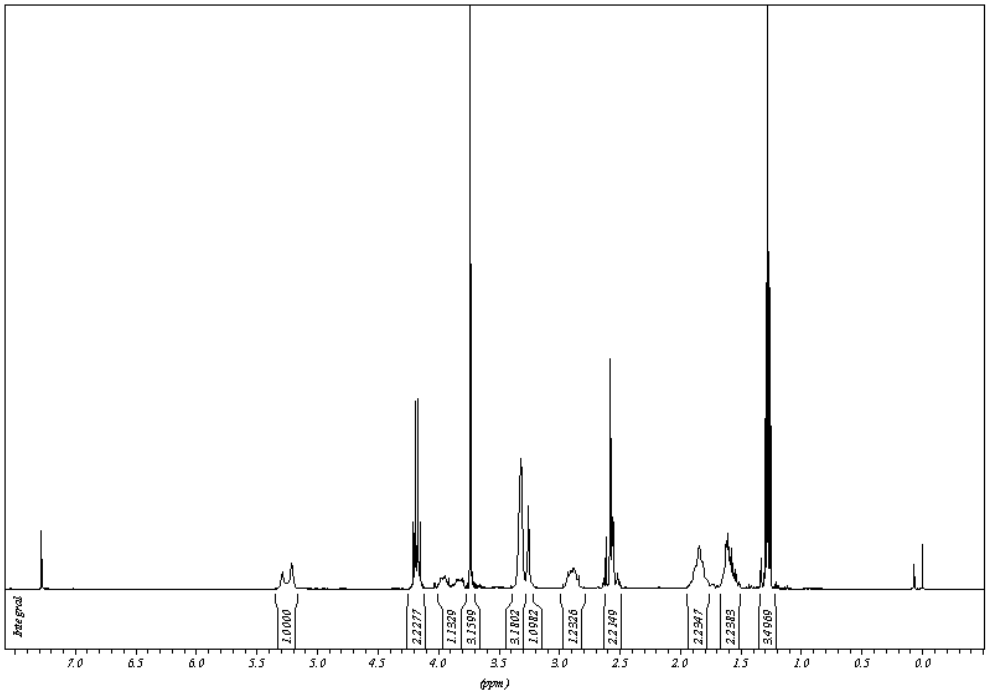


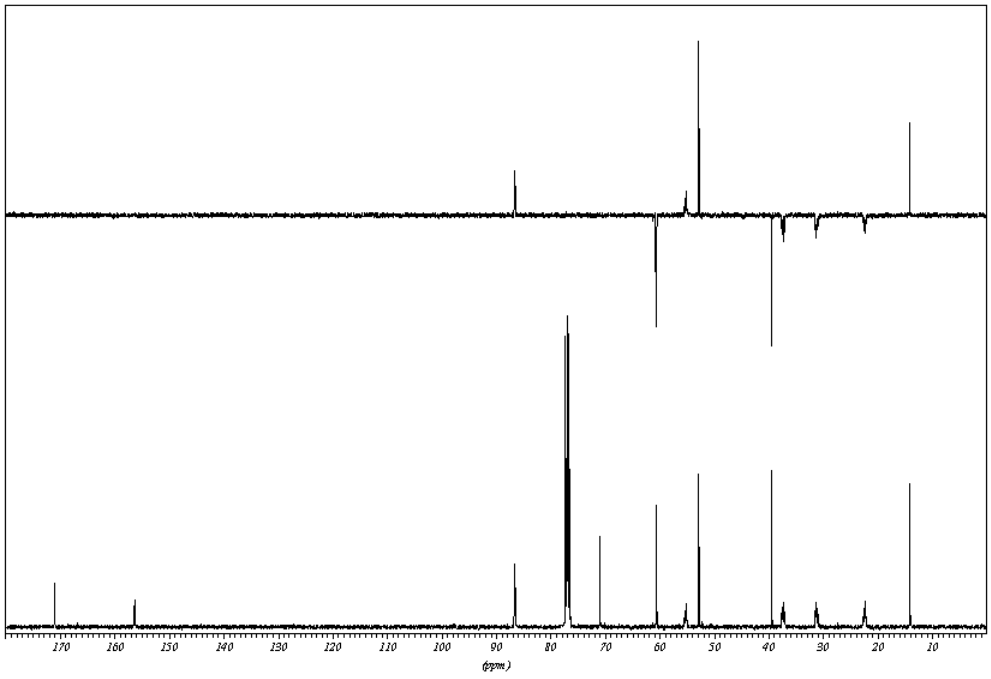
3-Hydroxy-2-methoxy-piperidine-1-carboxylic acid methyl ester **122**



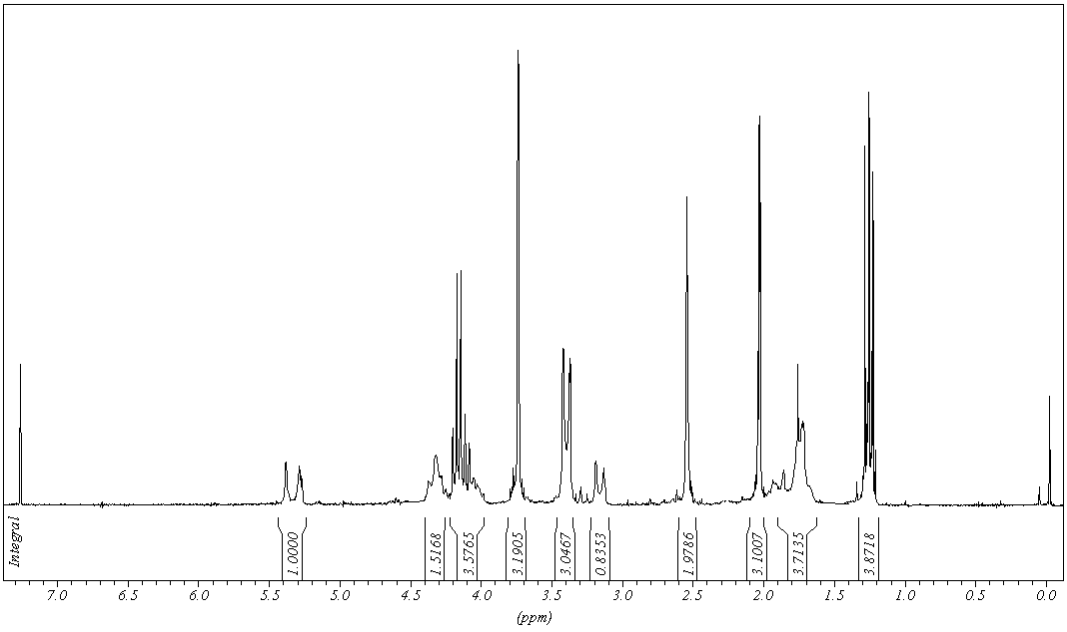


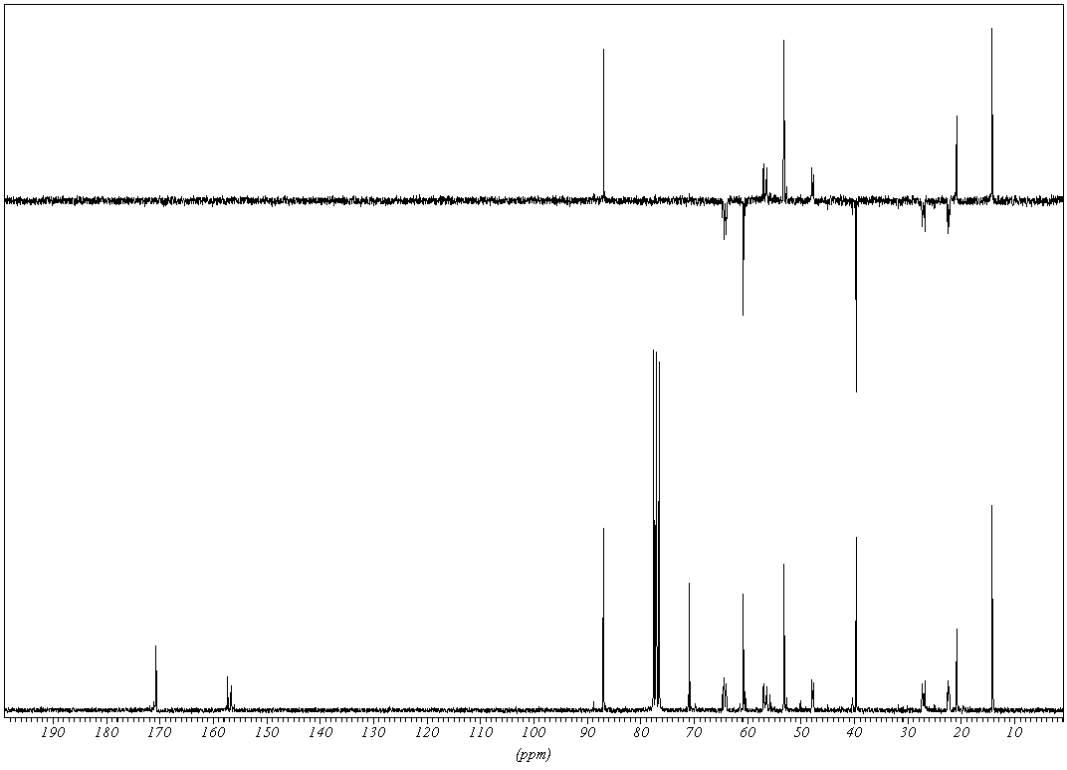
(E)-2-(2-methoxycarbonyl-vinyl)-piperidine-1-carboxylic acid benzyl ester **176**



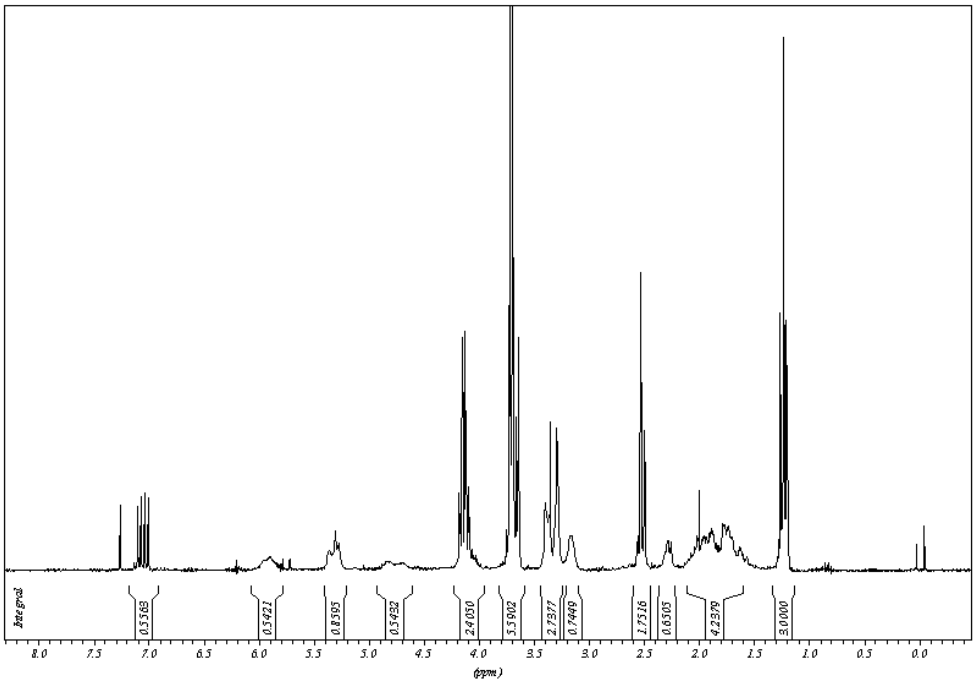


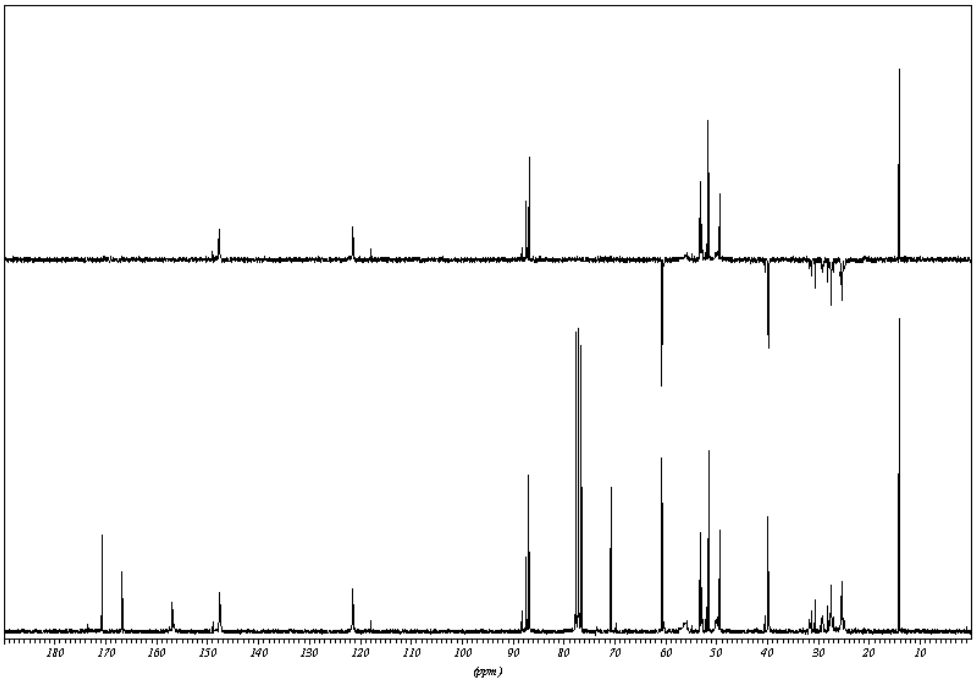
3-Hydroxy-(N-carbamate-2-methoxy-[3]-piperidyl)-propionic acid ethyl ester **138**



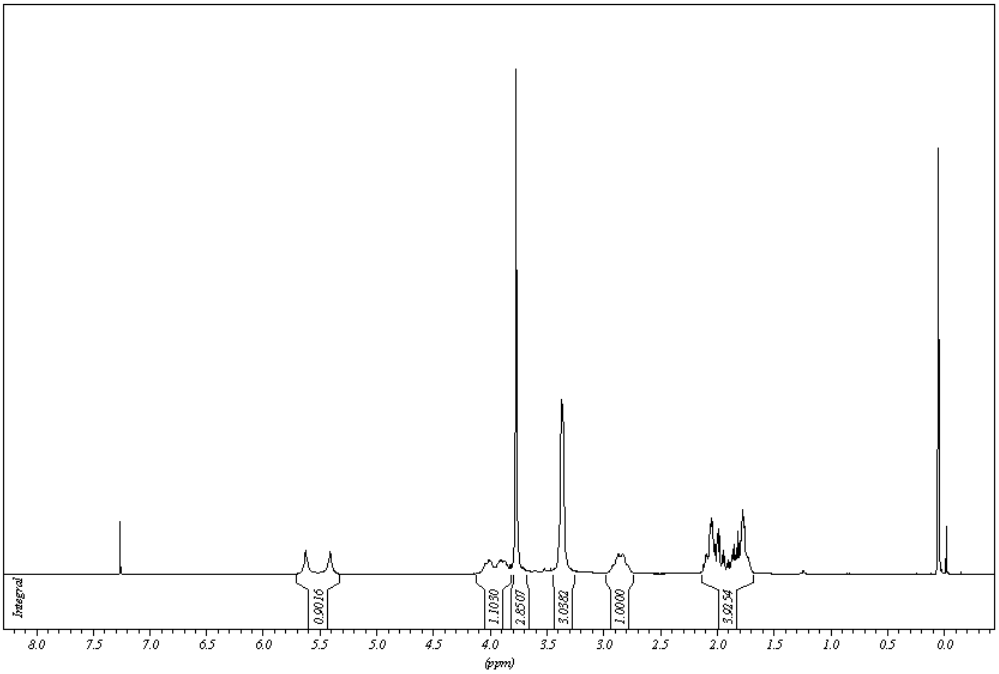


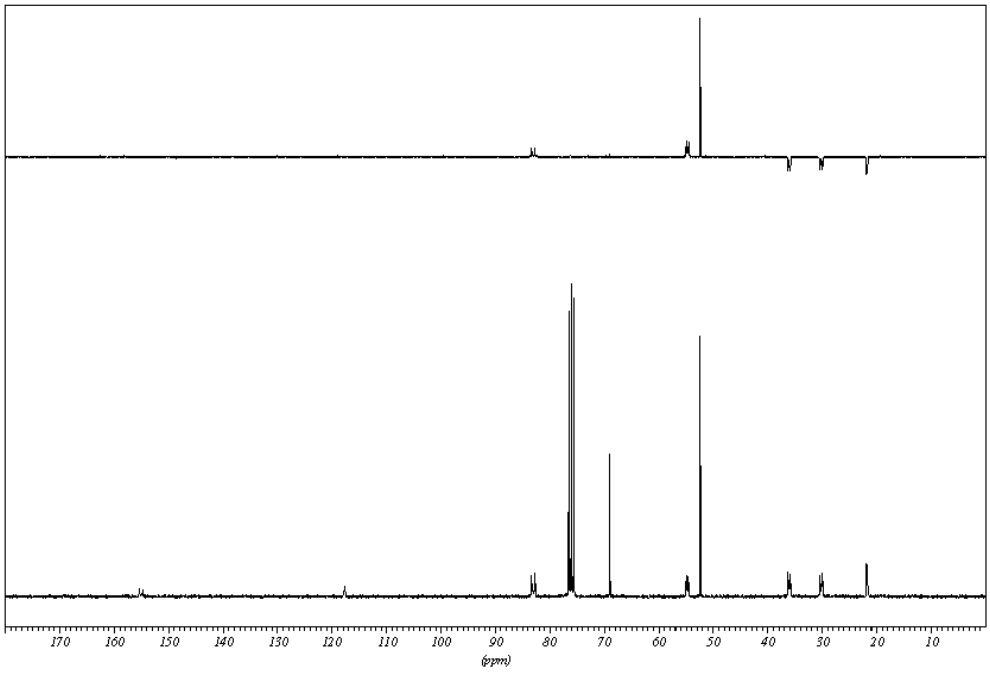
3-Hydroxy-(N-carbamate-6-(acetoxy)methyl-2-methoxy-[3]-piperidyl)-propionic acid ethyl ester **139**



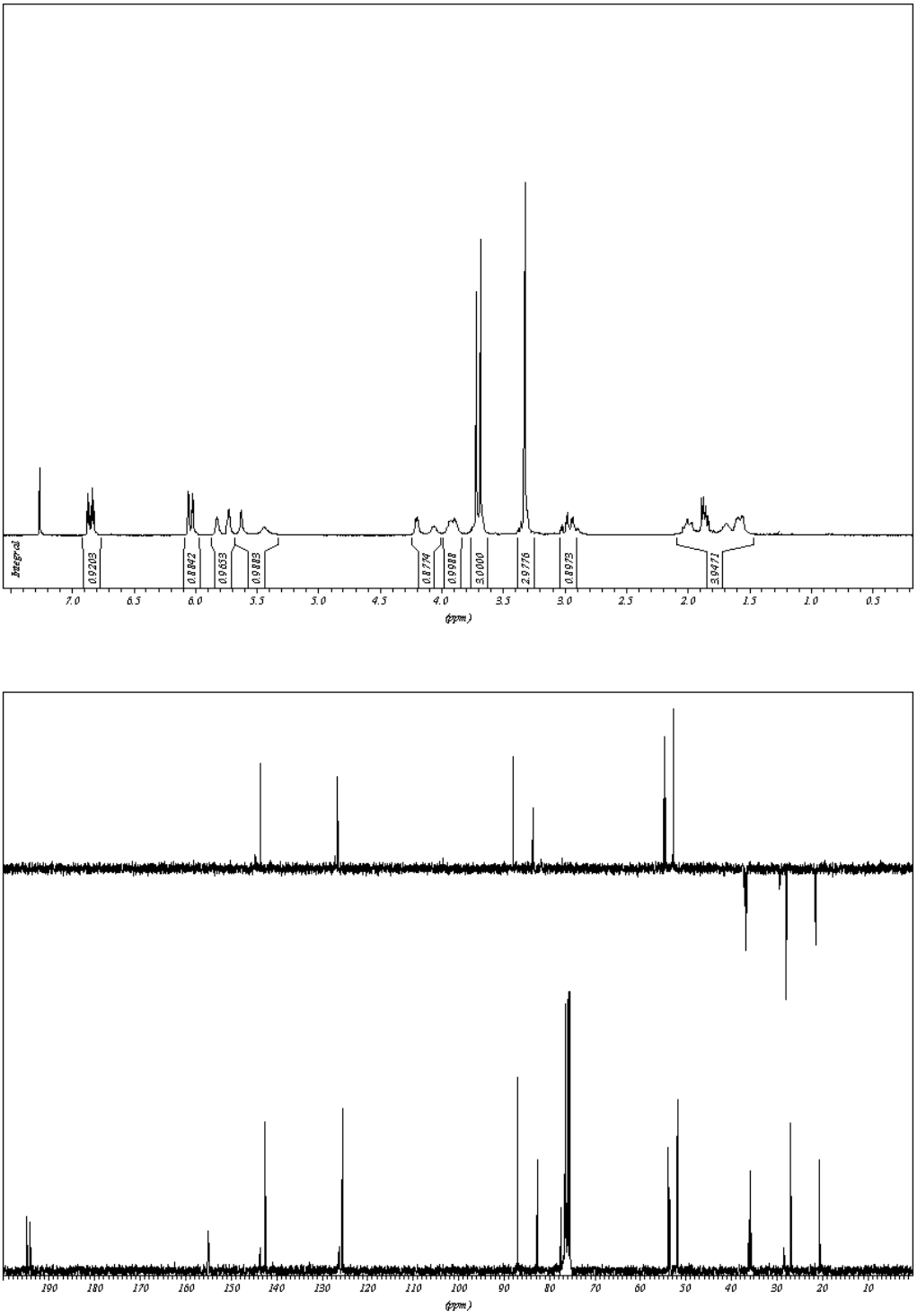


3-Hydroxy-(N-carbamate-2-methoxy-6-(2-methoxycarbonyl-vinyl)-[3]-piperidyl)-propionic acid ethyl ester **140**

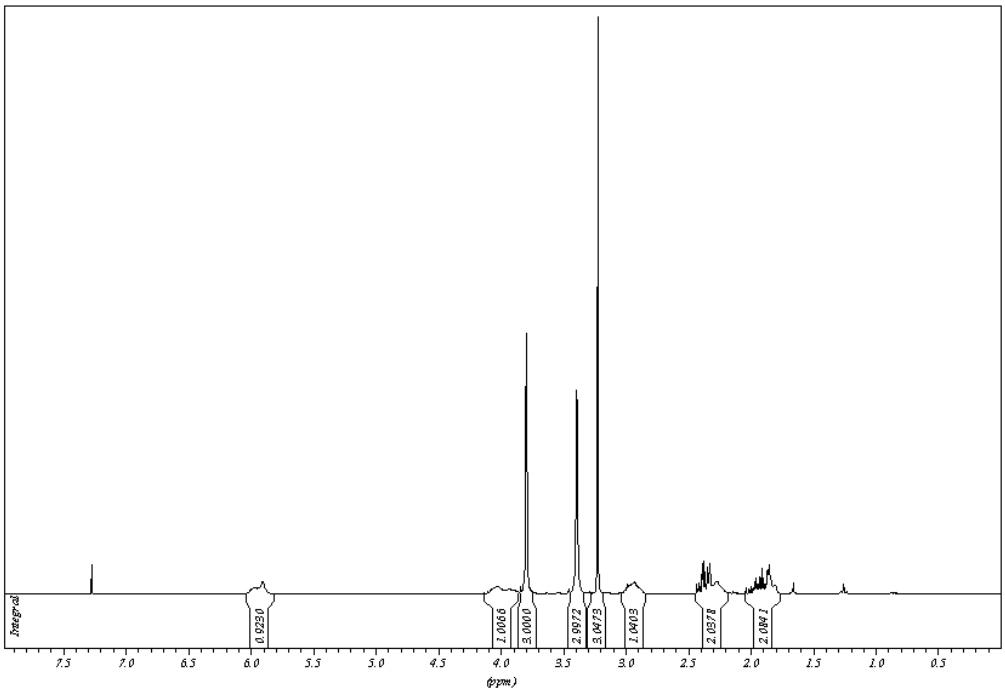


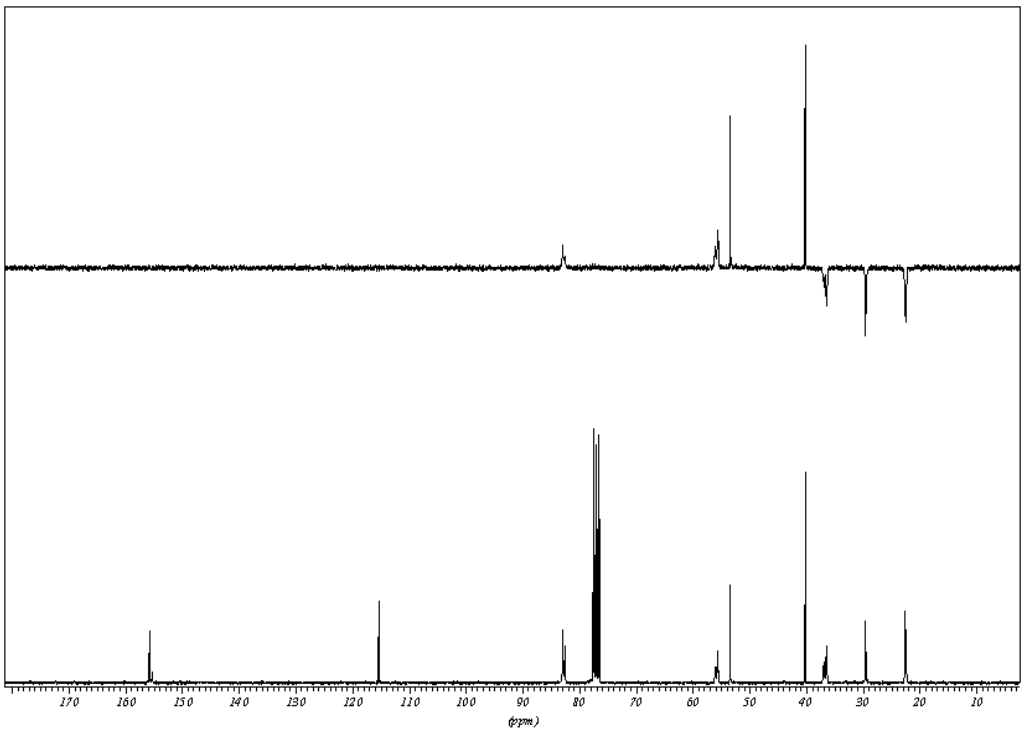


3-Cyano-3-hydroxy-2-methoxy-piperidine-1-carboxylic acid methyl ester **145**

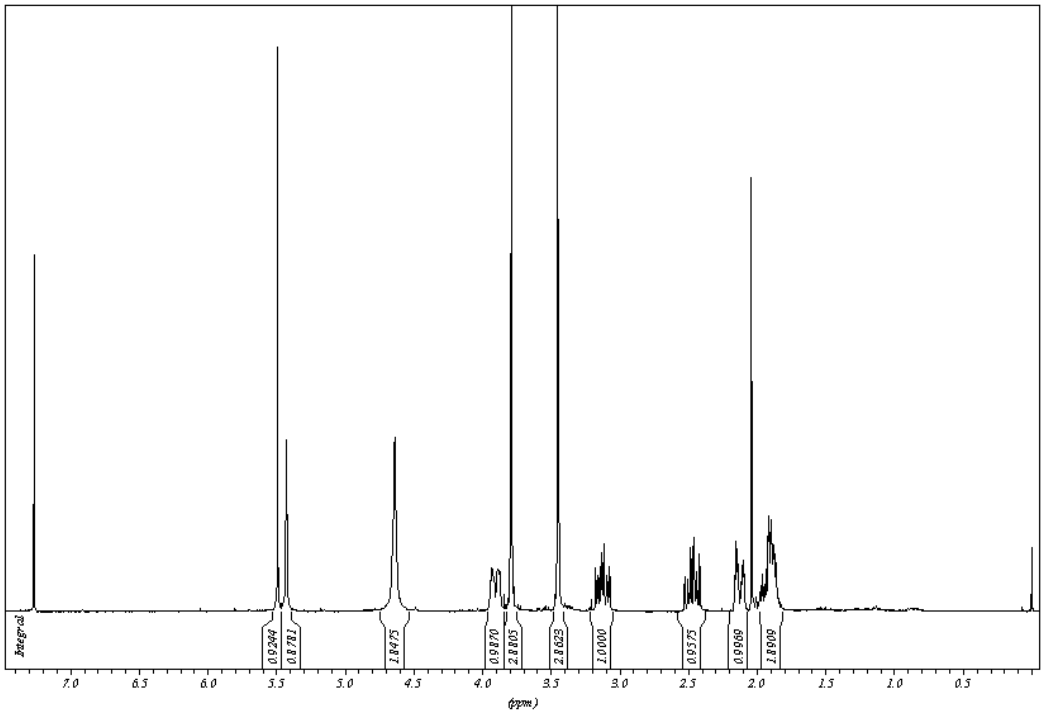


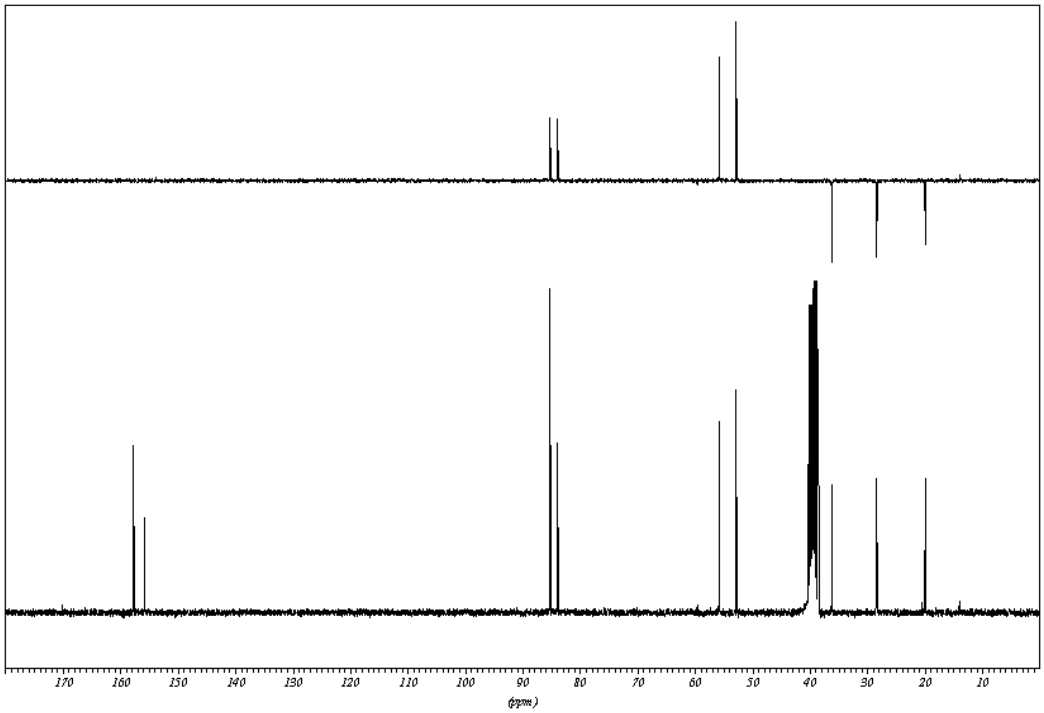
2-Hydroxy-8-methoxycarbonyl-8-aza-7-methoxy-1-oxaspiro[5.5]undec-3-en-5-one **159**



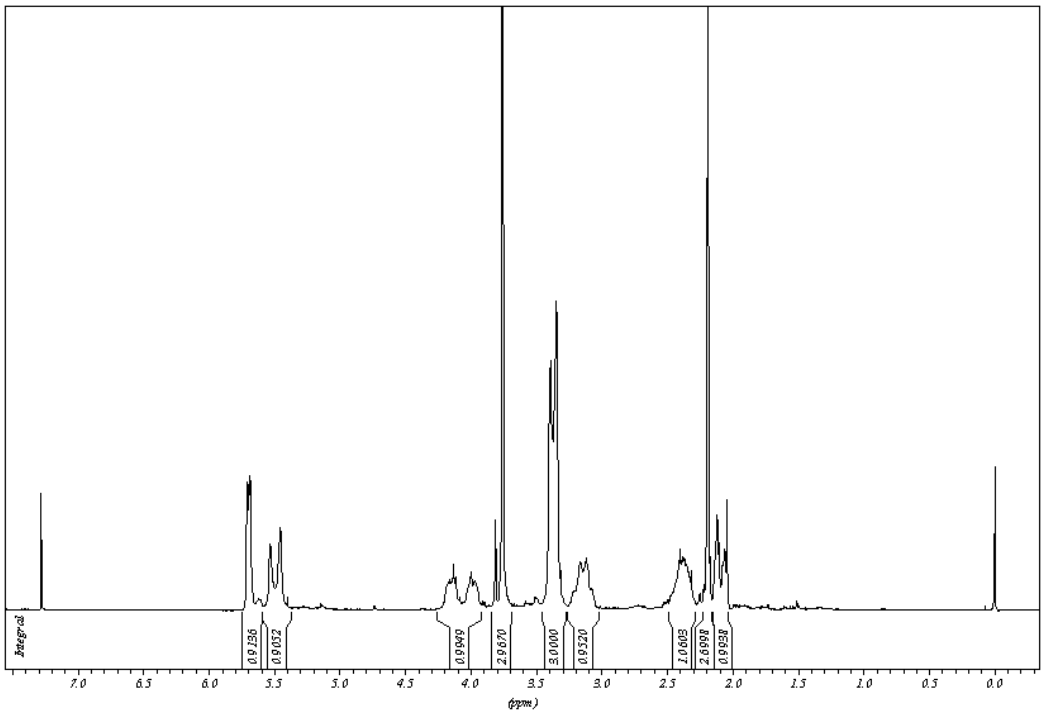


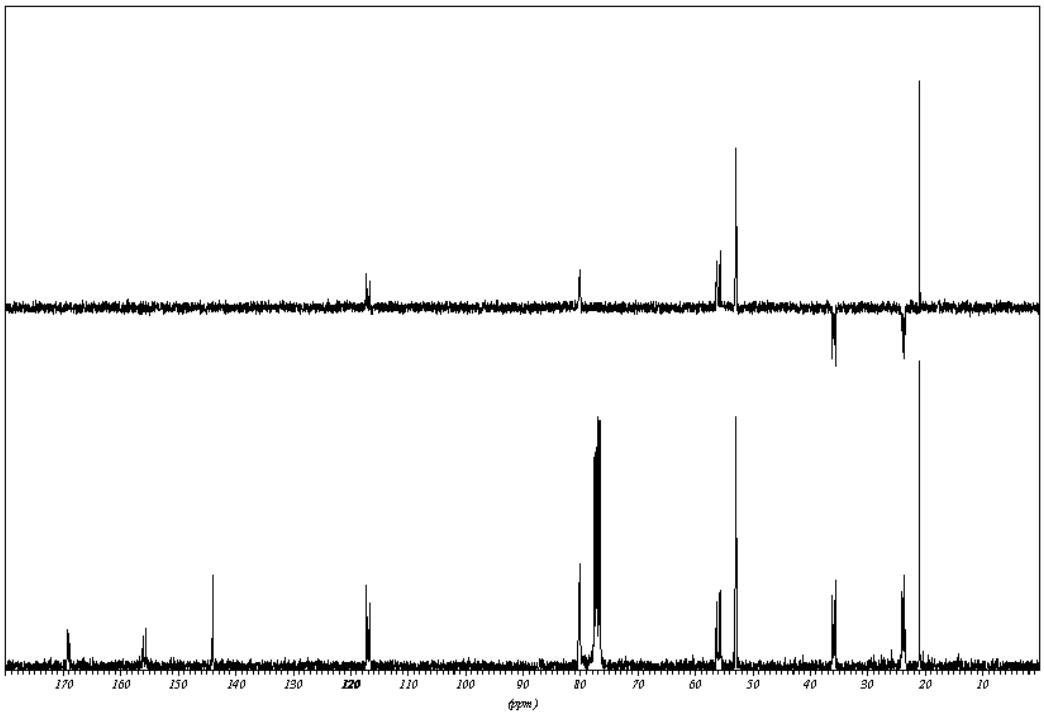
3-Cyano-3-methanesulfonyloxy-2-methoxy-piperidine-1-carboxylic acid methylester **164**



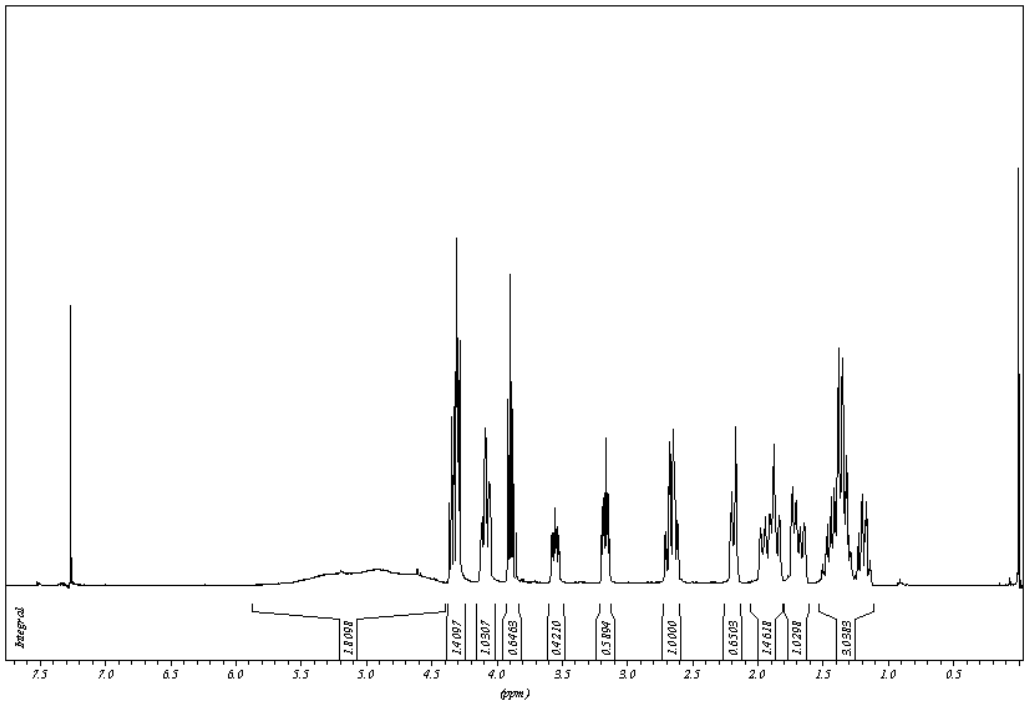


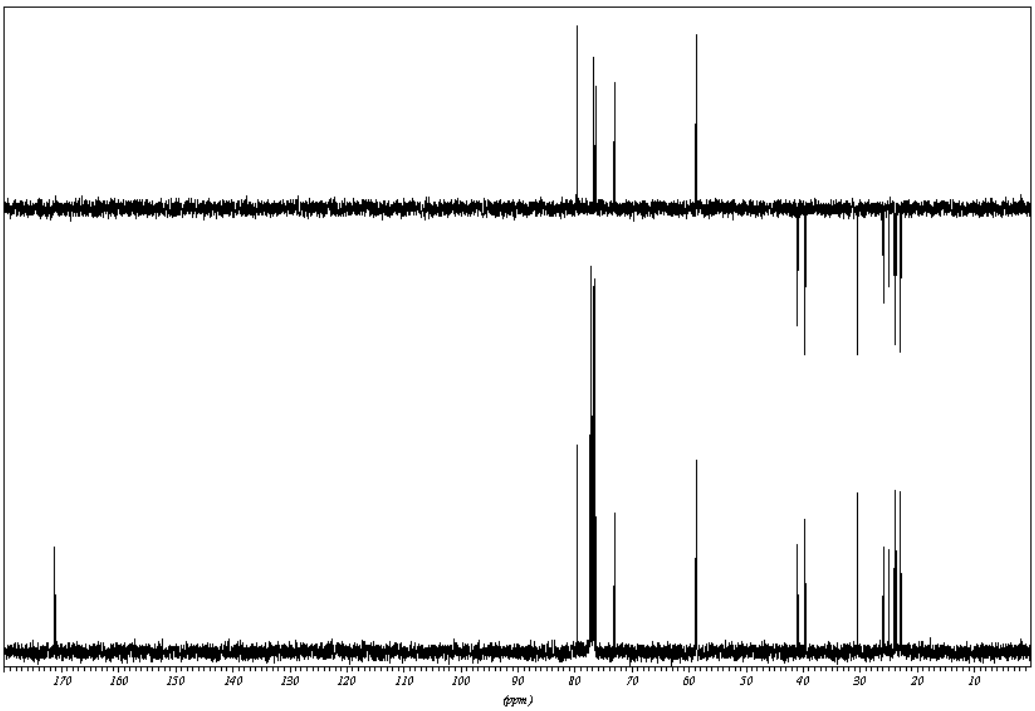
4-Amino-7-aza-7-carbamate-6-methoxy-1-oxa-2-thiaspiro[4.5]dec-3-ene 2,2-dioxide **165**



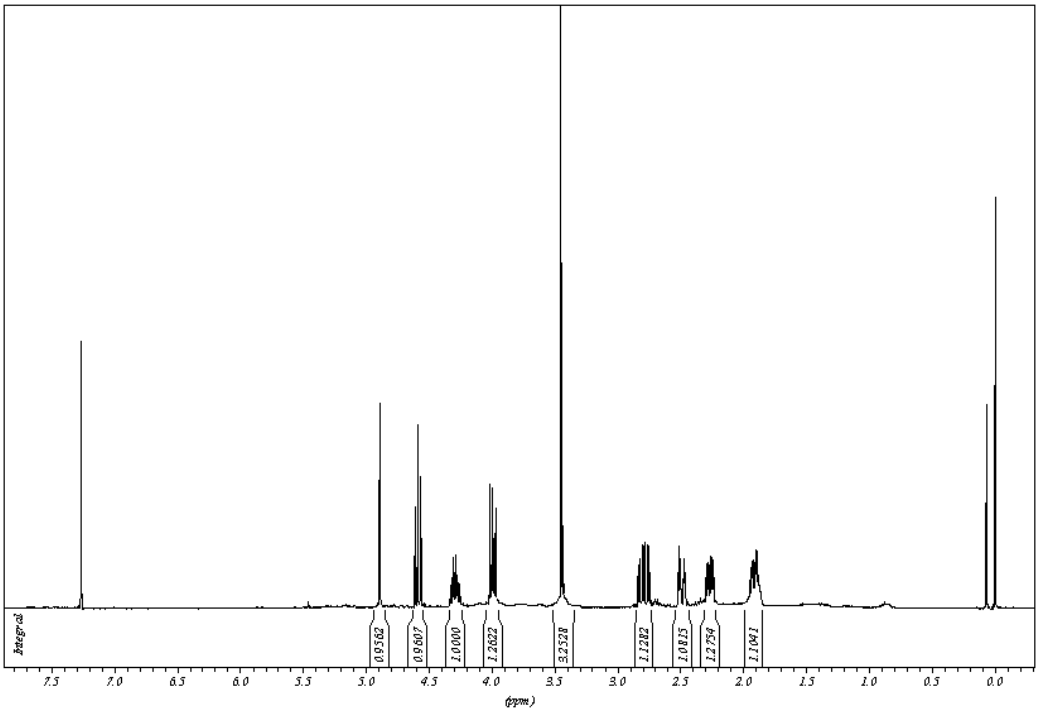


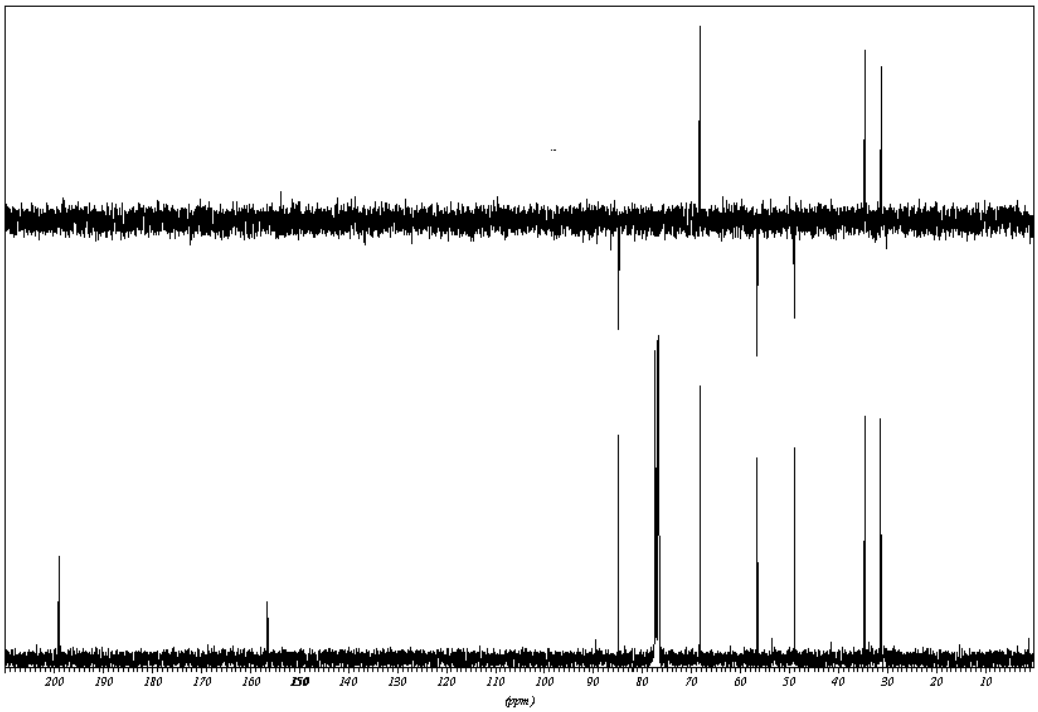
3-Acetoxy-2-methoxy-5,6-dihydro-1(2H)-pyridinecarboxylic acid methyl ester **172**



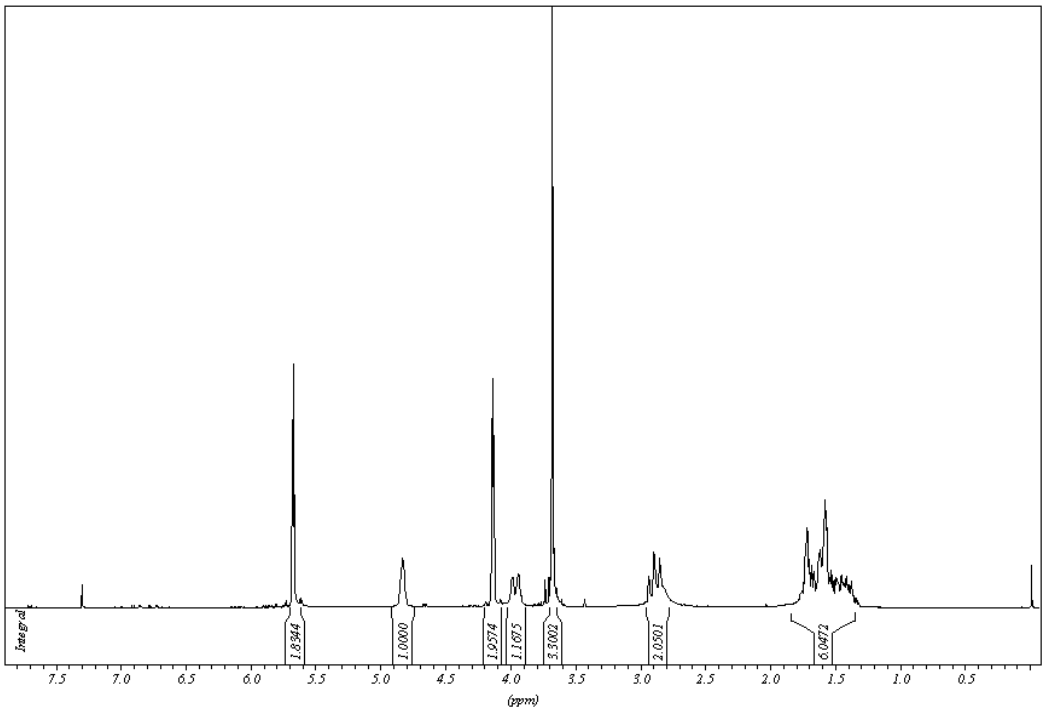


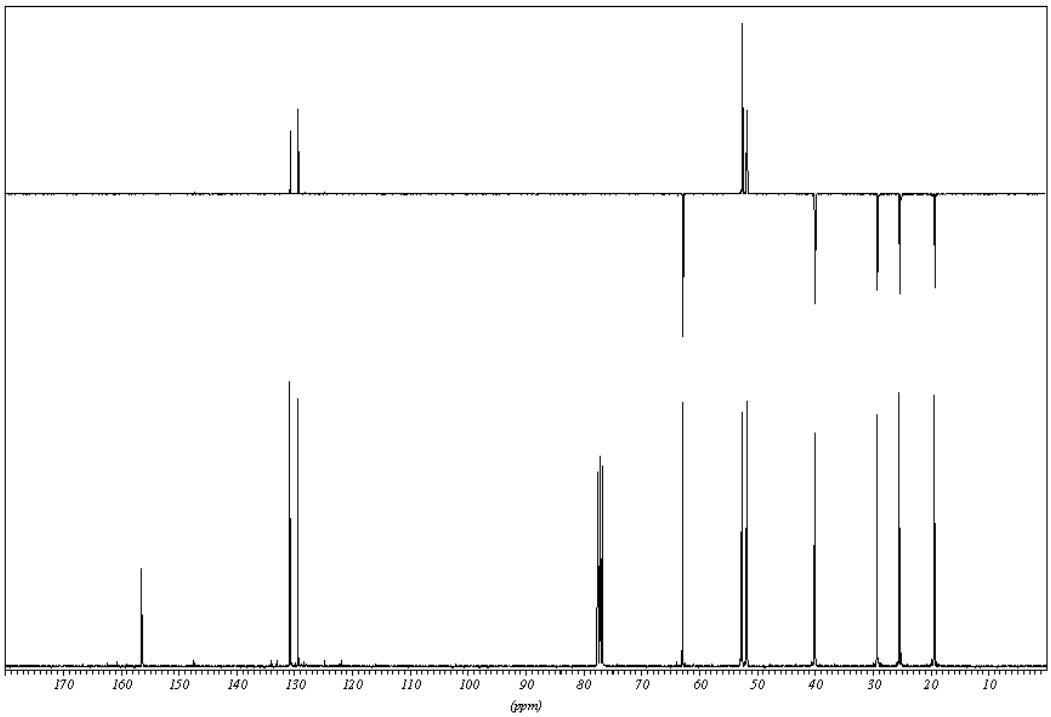
1,2-Dihydroxyhexahydroindolizidine-3-on **184**





5-Methoxy-tetrahydro-oxazolo[3,4-a]pyridin-3,6-dione ***188***





3-[1-(Methoxycarbonyl)-2-piperidyl]-2-propen-1-ol **191**

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