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Studies directed toward the synthesis of methyllycaconitine

by

Elena V. Dneprovskaia

A dissertation submitted to the graduate faculty in

partial fulfilment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

Department: Chemistry

Major: Organic Chemistry

Major Professor: Dr. George A. Kraus

Iowa State University

Ames, Iowa

2000

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For the Major Program

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For the Graduate College

DEDICATION

To my Mother for constant support, guidance and understanding, for all sleepless nights and endless trips she shared with me, for being there for me at every moment in my life, for letting me go when she most needed me.

TABLE OF CONTENTS

GENERAL INTRODUCTION

Synthesis remains a dynamic and central area of chemistry. There are many new principles, strategies and methods of synthesis waiting to be discovered. The synthesis of new natural products and the improved synthesis of known ones will always be a major task for the synthetic chemist.

Part I introduces the basic concepts in the chemistry of cyanohydrins and provides more extensive information on the addition reactions of α-acyloxynitriles to Michael adducts.

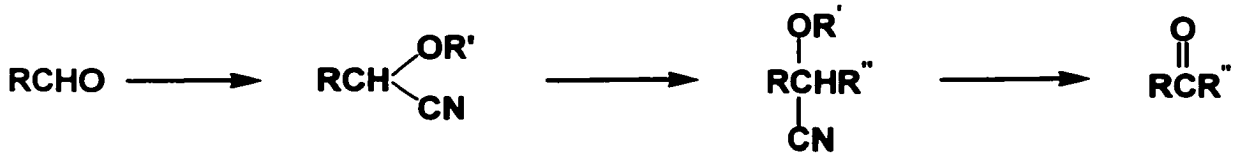
Part II is a collection of multistep syntheses accomplished over a period of five years. It outlines the general strategies for generating possible synthetic pathways to methyllycaconitine. Although emphasized as a synthetic approach to methyllycaconitine, Part II can also be regarded as the development of a general method for the construction of the skeleton of aconitine alkaloids. Systematic retrosynthetic analysis and the concurrent use of independent strategies to guide problem solving have been used to overcome difficult synthetic problems so common in the synthesis of natural products. An effort has been made to present in Part II the essentials of the synthesis in a concise form with emphasis on the logic of synthetic design and specific results, rather than on the presentation of all attempted or unsuccessful reactions.

The numbering of the compounds, schemes and references used are independent in each part. All references are listed at after the general conclusion.

PART I. A STUDY ON THE MICHAEL ADDITION REACTIONS OF α-ACYLOXYNITRILE ANIONS

INTRODUCTION

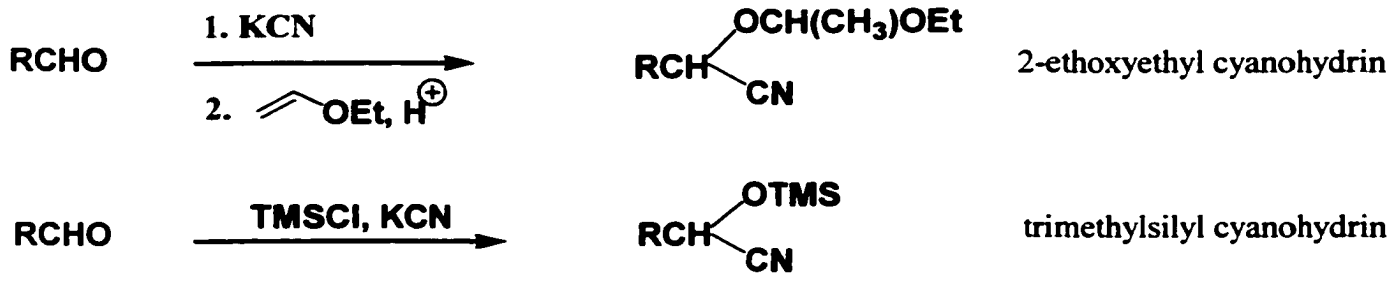
The use of masked acyl anion equivalents in the formation of carbon-carbon bonds has been found to be a powerful strategy in organic synthesis. The inversion of reactivity, which occurs when a normally electrophilic CO group is transformed into a nucleophile, provides a principally new method of connectivity in organic synthesis and broadens the possibilities for functional group manipulation. The utility of masked acyl equivalents is derived from their ability to form carbanions and from the fact that these carbanions are reactive nucleophiles towards aldehydes, alkylating agents and Michael acceptors. Among masked acyl equivalents, such as *S,S*-acetals, 1,3-dithianes, α-dialkylaminonitriles and α-alkyl- and α-aryl-*N*-acylamino acetonitriles, protected cyanohydrins have the advantage of the easy unmasking of the protected carbonyl functionality.



Scheme 1.

The 2-ethoxyethyl[1,2] and the trimethylsilyl[3] cyanohydrins are the most widely employed cyanohydrins in organic synthesis. The *O*-2-ethoxyethyl cyanohydrins are usually prepared by the reaction of an aldehyde cyanohydrin with ethyl vinyl ether under acidic conditions.[4] α-Silyloxynitriles can be prepared by a number of methods, such as cyanosilylation with trimethylsilyl cyanide under thermal conditions or under catalysis with zinc iodide,[5] or by an exchange process from the *O*-trimethylsilylated cyanohydrin of acetone[6].

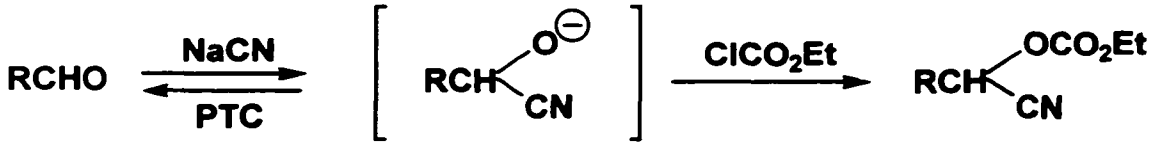
Reaction of aldehydes with trimethylsilyl chloride and potassium cyanide in acetonitrile or dimethylformamide as solvent was reported as a one-pot procedure for the preparation of α-silyloxynitriles.[7]



Scheme 2.

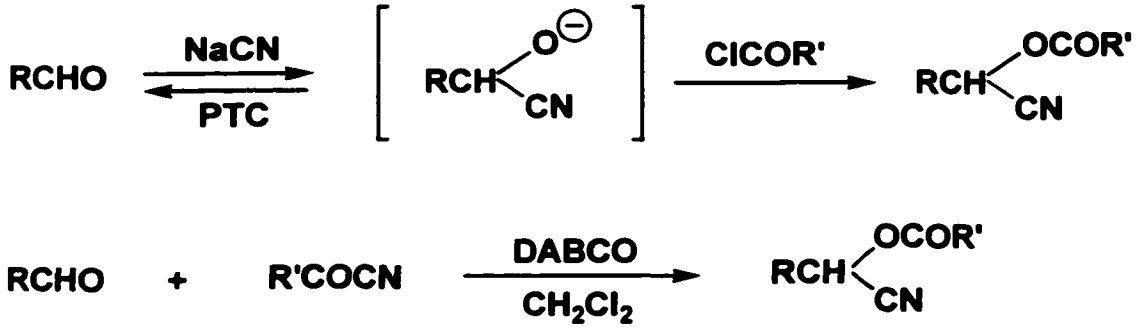
Among protected cyanohydrins, their carbonate derivatives have also been found to be useful precursors to a wide variety of ketones and to be efficient latent acyl anions in 1,4-addition reactions to Michael acceptors leading to 1,4-dicarbonyl compounds.[8] The advantages of employing cyanohydrin carbonates over other commonly used cyanohydrin derivatives are in the fact that 1) they can be easily prepared in one step in high yields under extremely mild conditions, 2) they can be formed cleanly and the crude product can be used without further purification, and 3) after hydrolysis the by-products are usually volatile and the purification of the product is facilitated. Cyanohydrin carbonates were prepared by the *in-situ* trapping of cyanohydrin anions with chloroformates under phase transfer catalysis (PTC). The procedure is usually carried out by addition of an aqueous sodium cyanide solution to a mixture of aldehyde, chloroformate and a catalytic amount of a quaternary ammonium salt in an inert organic solvent, such as toluene or methylene chloride, and subsequent separation of

the organic layer. This procedure can be employed with both aliphatic and aromatic aldehydes (Scheme 3).



Scheme 3.

In comparison with other protected cyanohydrins, cyanohydrin esters have received little attention as acyl carbanion equivalents. Chenevert *et al* have prepared cyanohydrin esters by the reaction of aldehydes with acyl chlorides using solid-liquid phase transfer catalysis with 18-crown-6 and an excess of cyanide ion.[9] Recently, Ismail *et al* have reported the DABCO-mediated coupling reaction of aldehydes with α-ketonitriles.[10] This method was found to be general for the preparation of cyanohydrin esters from α,β-unsaturated, aliphatic and aromatic derivatives (Scheme 4).



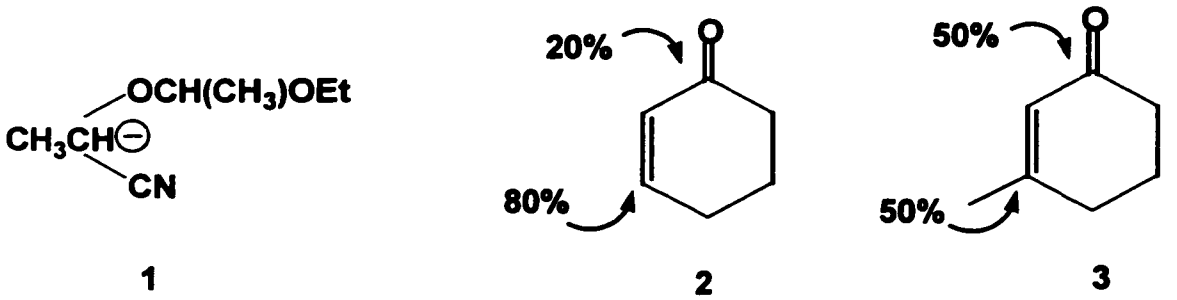
Scheme 4.

HISTORICAL

1,4-Addition of anions of protected cyanohydrins

Anions of protected cyanohydrins of aliphatic, aromatic and α,β-unsaturated aldehydes undergo 1,4-addition to cyclic and acylic Michael adducts. The synthetic utility of this reaction depends on the regioselectivity, since 1,2-addition to a carbonyl group is a competing reaction. The regioselectivity in turn was found to be dependent on the structure of the protected cyanohydrin, the Michael adduct and the reaction solvent. Conjugate addition is known to predominate with bulky anions or with enones containing a hindered carbonyl group[11], and with cyanohydrins derived from α,β-unsaturated[12] or aromatic aldehydes.[13] The use of additives, such as hexamethylphosphoric triamide or tetramethylethylenediamine, is also known to improve the ratio of 1,4- to 1,2-addition products.

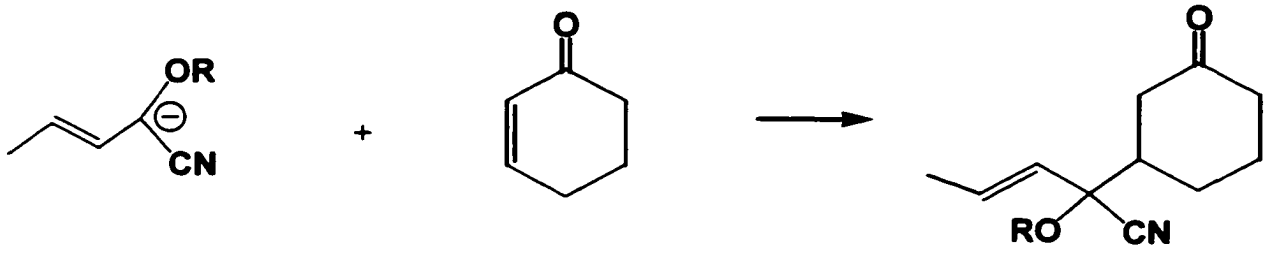
When 2-cyclohexenone was reacted with the *O*-2-ethoxyethyl cyanohydrin anion of acetaldehyde in tetrahydrofuran a 4 : 1 ratio of 1,4- to 1,2-addition products was observed.[14] The addition of HMPA improved the ratio to 9 : 1. When the same anion was reacted with a β-substituted cyclohexenone, equal amounts of 1,2- and 1,4- addition products were formed.



1 2 3

Scheme 5.

However, when 2-cyclohexenone was reacted with protected cyanohydrin anions derived from crotonaldehyde or benzaldehyde, only 1,4-addition products were isolated.[15]



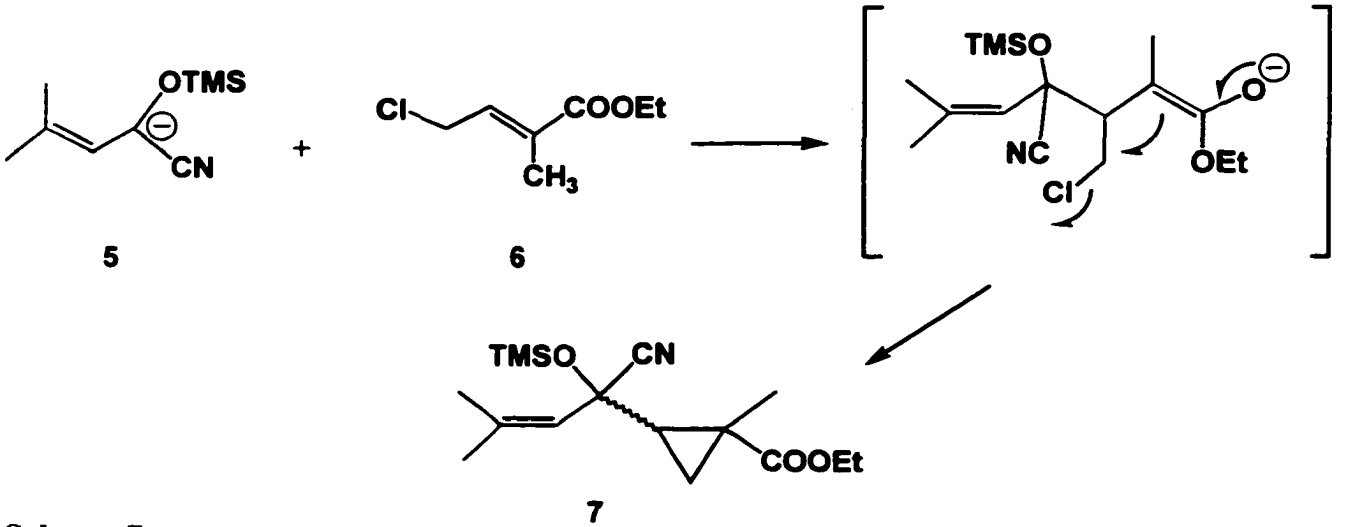
R = $Si(CH_3)_3$ 72%

R = $OCH(CH_3)OEt$ 75%

4

Scheme 6.

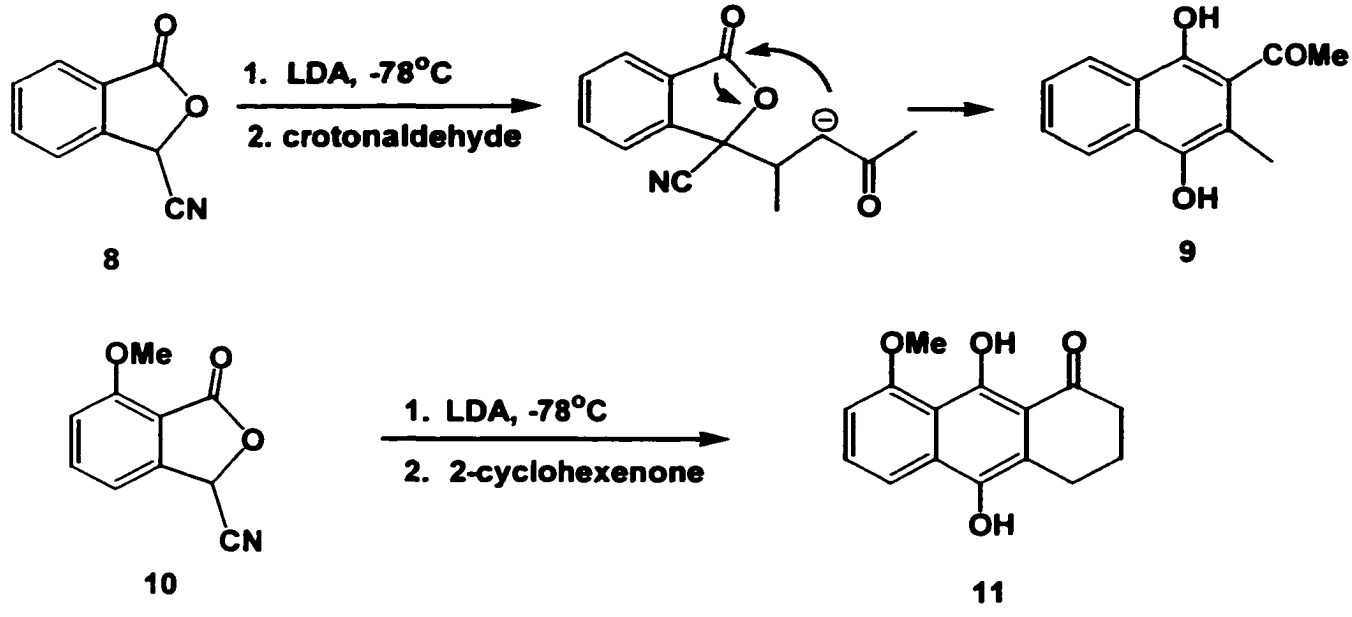
Some interesting applications of cyanohydrin 1,4-addition chemistry have involved tandem cyclization reactions. Addition of α,β-unsaturated anions to the Michael acceptor, an α,β-unsaturated ester, in which either alkylation or 1,4-addition is possible, resulted in exclusive 1,4-addition, followed by intramolecular alkylation of the intermediate ester enolate to afford cyclopropyl derivatives (Scheme 7).[16]



5 6 7

Scheme 7.

An interesting annelation route to hydroquinones, utilizing 1,4-addition of the anion of 3-cyanophthalide to α,β-unsaturated ketones as a key step, was reported by Kraus and co-workers (Scheme 7).[17] This approach was applied to the synthesis of aklavinone, the aglycone of aclacinomycin A (a member of the anthracycline antibiotics).[18]

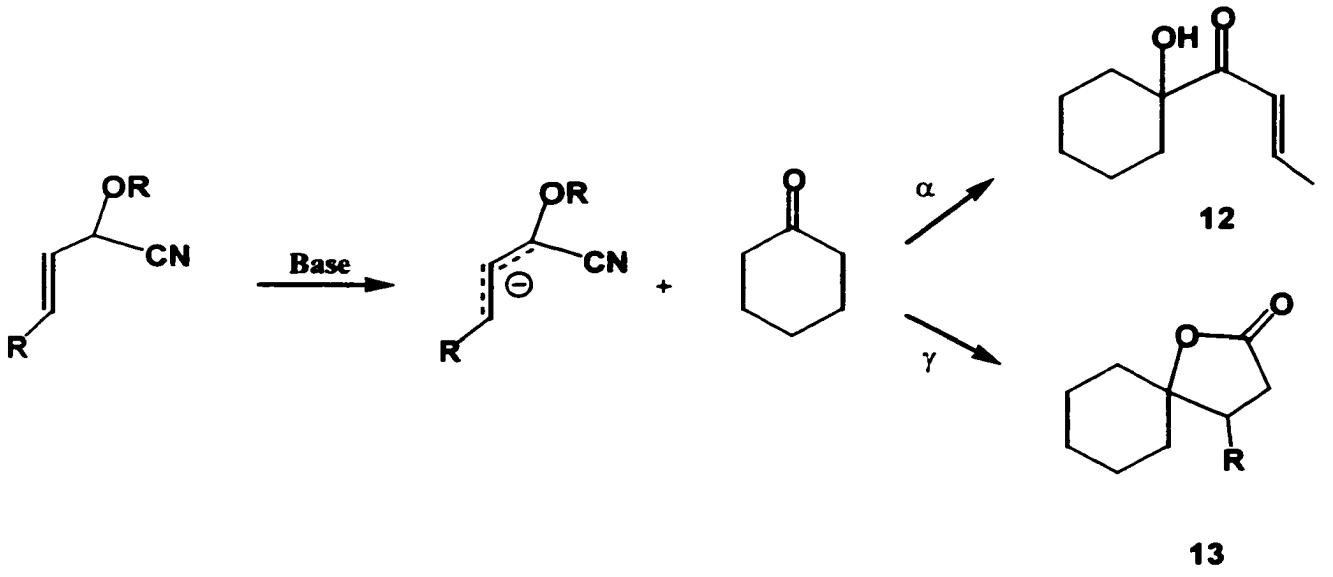


Scheme 8.

1,2-Addition reactions of anions of protected cyanohydrins

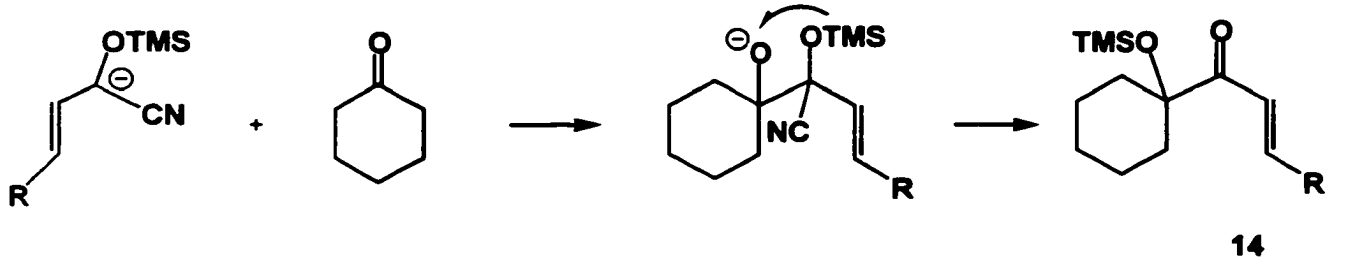
1,2-Addition of anions of protected cyanohydrins to aliphatic aldehydes, and cyclic and acyclic ketones is a commonly used method for the preparation of α-hydroxyketones. The protected cyanohydrins derived from α,β-unsaturated aldehydes, on deprotonation, form ambident anions, which can react with electrophiles at the α-position (acyl anion equivalents) or at the γ-position (homoenolate equivalents). At low temperatures (-78 °C), the anions of

cyanohydrins have been found to react with aldehydes and ketones exclusively at the α-position, while the reaction at 0 °C affords the products resulting from γ-addition (Scheme 9).[19]



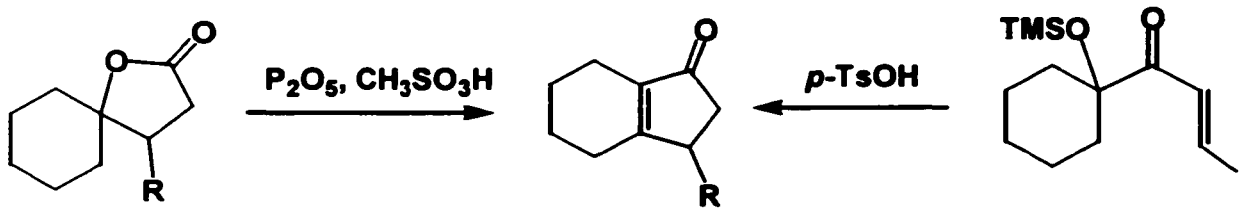
Scheme 9.

Upon reaction of the anion of *O*-trimethylsilyl cyanohydrin with aldehydes and ketones only α-addition products have been observed. The product results from entrapment of the initial kinetic adduct formed at –78 °C, since it undergoes an intramolecular 1,4-*O*-silyl rearrangement to give TMS-protected α-hydroxyketones (Scheme 10).



Scheme 10.

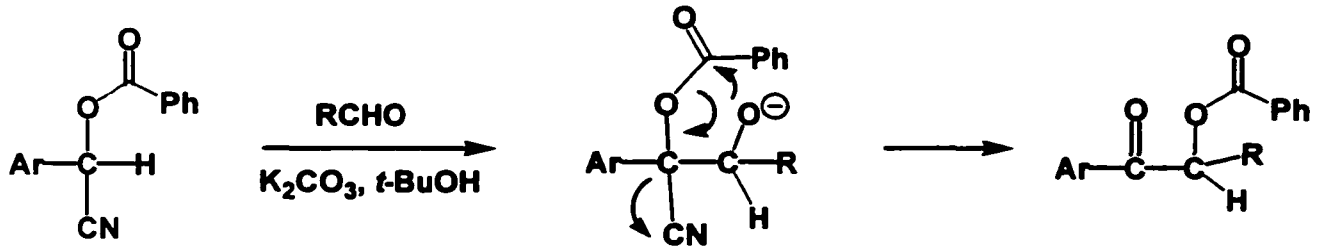
The addition reaction of cyanohydrins derived from α,β-unsaturated aldehydes to ketones leads to the formation of α-hydroxy enones, γ-lactones and α-trimethylsilyloxy enones, which are useful precursors to cyclopentenones via Nazarov cyclization and to 3-tetrahydrofuranones via 1,4-addition of an hydroxy group to enones.[20] The overall reaction sequence can be regarded as three-carbon annelation technique (Scheme 11).



13 15 14

Scheme 11.

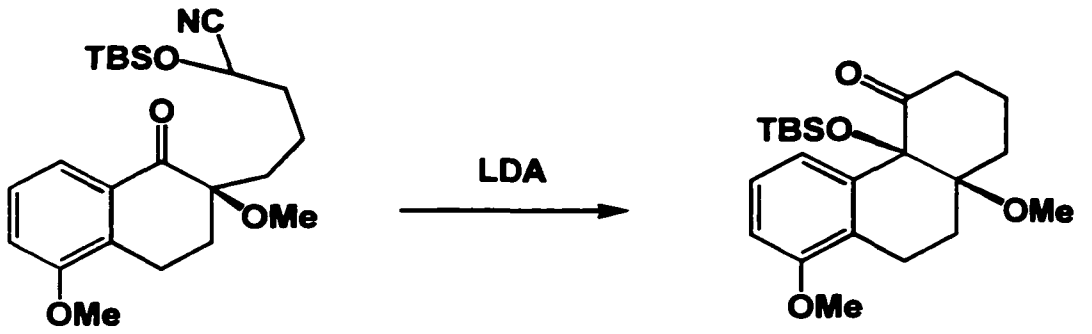
The reaction of cyanohydrin esters with aliphatic aldehydes and ketones has also been found to proceed by intramolecular 1,4-*O*-acyl rearrangement to yield α-acyloxyketones (Scheme 12).[21]



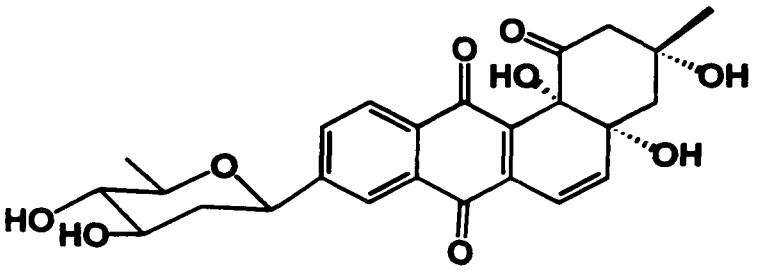
16 17

Scheme 12.

α-Hydroxyketones are valuable intermediates in organic synthesis, and this functionality is present in several natural products. The intramolecular cyclization of the anion of an *O*-*t*-butyldimethylsilyl cyanohydrin derived from aldehyde **18** has been used as a key step in the preparation of the ABC ring system, containing the α-hydroxyketone moiety, of aquayamycin, a representative of the angucycline antibiotics (Scheme 13).[22]



18 **19**

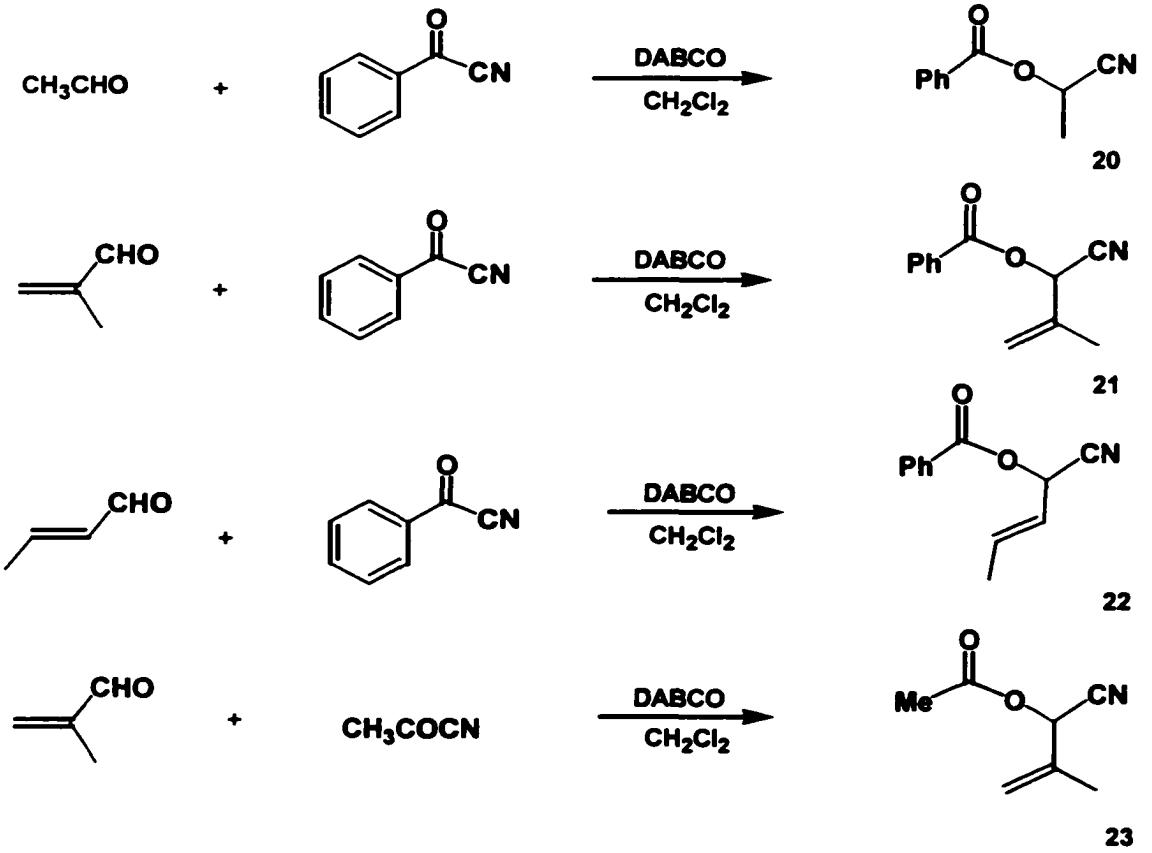


Aquayamycin

Scheme 13.

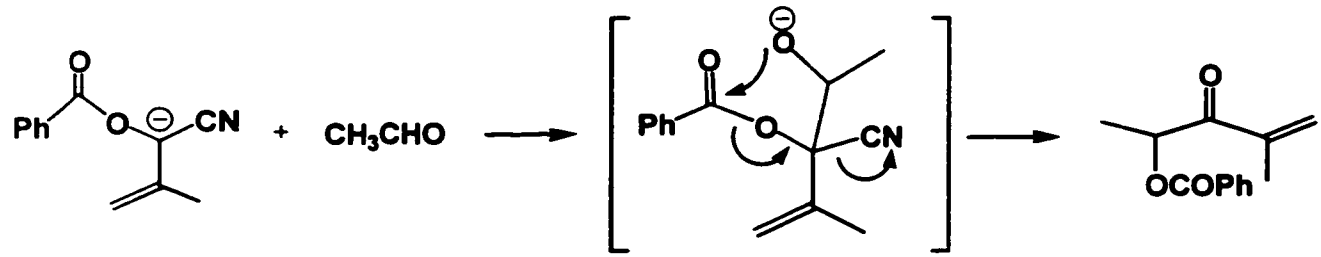
RESULTS AND DISCUSSION

In comparison with other cyanohydrin derivatives, cyanohydrin esters have received little attention as acyl carbanion equivalents. As a result, there have been no studies on the formation of anions of cyanohydrin esters and on their behaviour towards aldehydes, alkylating reagents and Michael acceptors. Recently, Hoffman and co-workers have reported the preparation of α-acyloxynitriles in one step by the DABCO-mediated reaction of acyl cyanides with aliphatic, aromatic and α,β-unsaturated aldehydes.[10] Using Hoffman's conditions, we have prepared α-acyloxynitriles **20-23** in 62%, 65%, 36% and 52% isolated yields, respectively (Scheme 14).



Scheme 14.

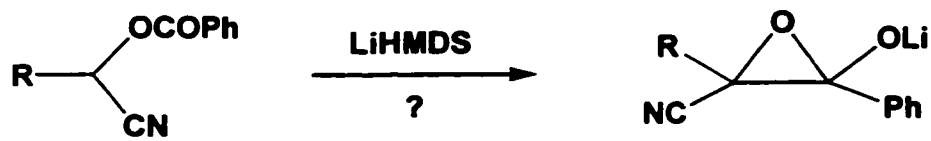
When a mixture of cyanohydrin ester and acetaldehyde was treated with lithium hexamethyldisilazane at –78 °C, the α-benzoyloxyketone **24** was isolated in 67 % yield. As previousely reported in the cases of α-silyloxynitriles[20], after 1,2-addition to the carbonyl group, the resulting intermediate underwent an intramolecular 1,4-acyl shift of the benzoyl group, followed by elimination of cyanide ion. The alkoxide of a cyanohydrin is well known to be unstable and rapidly generates ketone (Scheme 15).



21 **24**

Scheme 15.

The choice of base proved to be crucial, since the reaction with lithium diisopropylamide afforded unidentifiable reaction product mixtures. Unexpectedly, the order of the addition of the reagents was also important, because attempts to first prepare the α-benzoyloxynitrile anion and then to react it with aldehyde led to degradation of the material, possibly via the alkoxy epoxide intermediate **25** shown in Scheme 16.

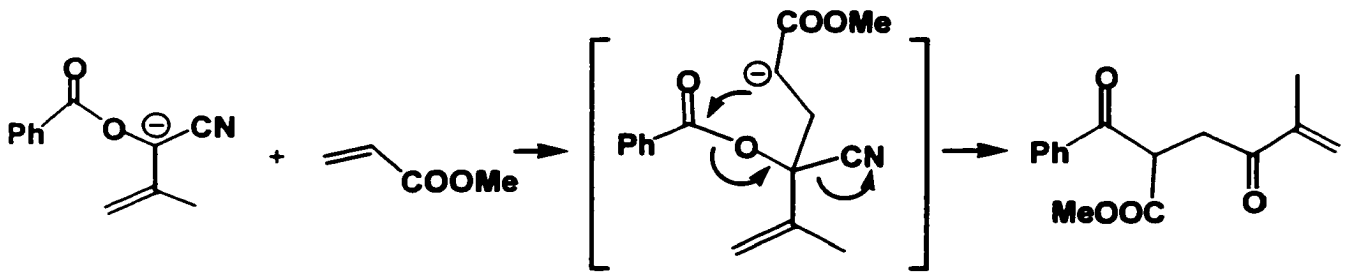


25

Scheme 16.

The instability of this anion, therefore, prevented us from studying the possible formation of the thermodynamic products resulting from γ-addition of the α,β-unsaturated nitrile to an aldehyde.

After establishing the reactivity of the α-benzyloxynitrile towards aldehydes, we next decided to study its reactivity towards Michael acceptors. When a mixture of nitrile **21** and methyl acrylate was treated with lithium hexamethyldisilazane, the product of Michael reaction again underwent an intramolecular shift of the benzoyl group, followed by elimination of cyanide ion to afford ketone **26** in 65 % yield (Scheme 17).



21 **26**

Scheme 17.

The anions of α-benzoyloxynitriles were found effective in reactions with a number of Michael acceptors. The reactions with methyl acrylate, methyl methacrylate and ethyl crotonate all produced the rearranged adducts in good to excellent yields (51-88 %). The 1,4-addition reactions of the anions to acrylonitrile and methacrylonitrile were less successful. Under these conditions, polymerization of the nitriles proceeded faster than the 1,4-addition

reaction. It was found that the competing polymerization could be partially surpressed by the addition of a small amount of hydroquinone resulting in 21-55 % yields of the products.

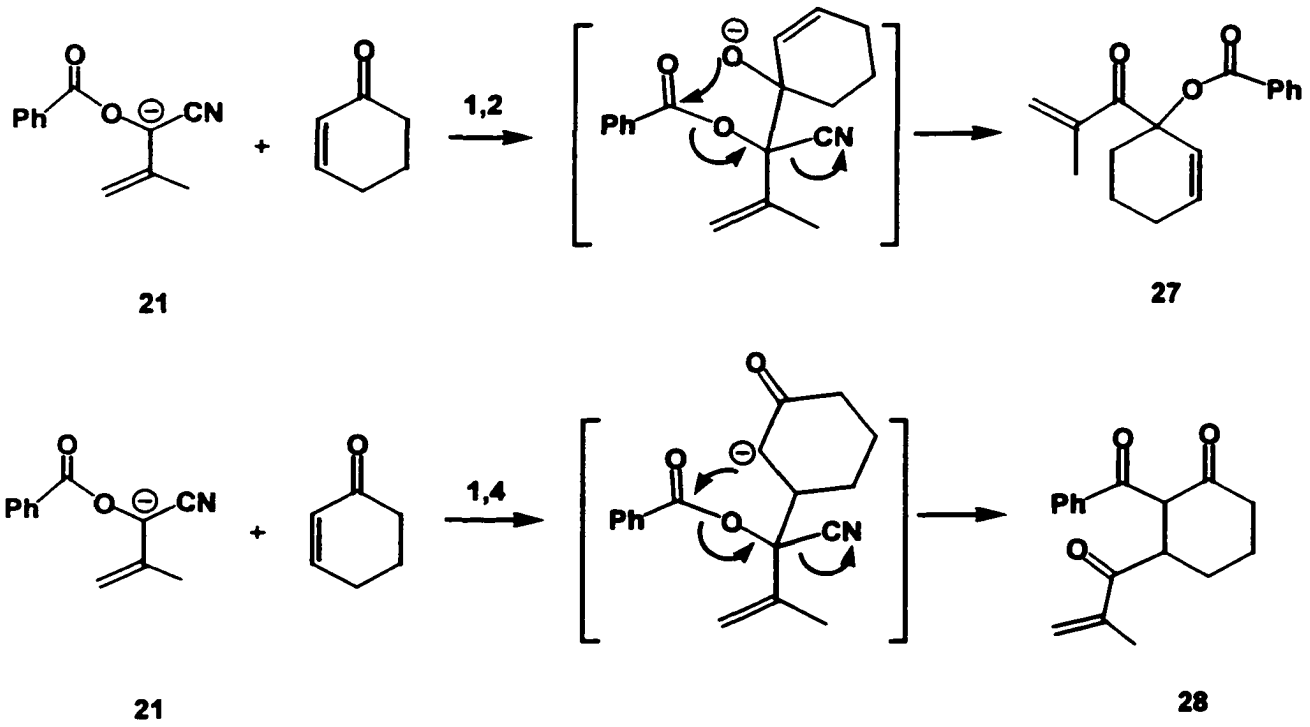
The results shown in Table 1 also indicate that Michael acceptors with β-substituents react better than Michael acceptors with α-substituent.

Table 1. Michael addition reactions of α-acyloxynitrile anions.

α-Acyloxynitrile	Adduct	Product(s)	% Yield
20	Methyl acrylate	**33**	**65**
20	Methyl methacrylate	**34**	**51**
20	Acrylonitrile	**35**	**62**
20	Methacrylonitrile	**36**	**21**
20	Ethyl crotonate	**37**	**58**
21	Methyl acrylate	**26**	**88**
21	Methyl methacrylate	**38**	**41**
21	Acrylonitrile	**39**	**55**
21	Methacrylonitrile	**40**	**26**
21	Ethyl crotonate	**41**	**57**
21	Methyl vinyl ketone	**29 + 30**	**36 + 25**
21	Cyclohexenone	**27 + 28**	**45 + 55**
22	Methyl acrylate	**42**	**85**
22	Methyl methacrylate	**43**	**48**
23	Methyl acrylate	**31**	**55**
23	Methyl methacrylate	**32**	**32**

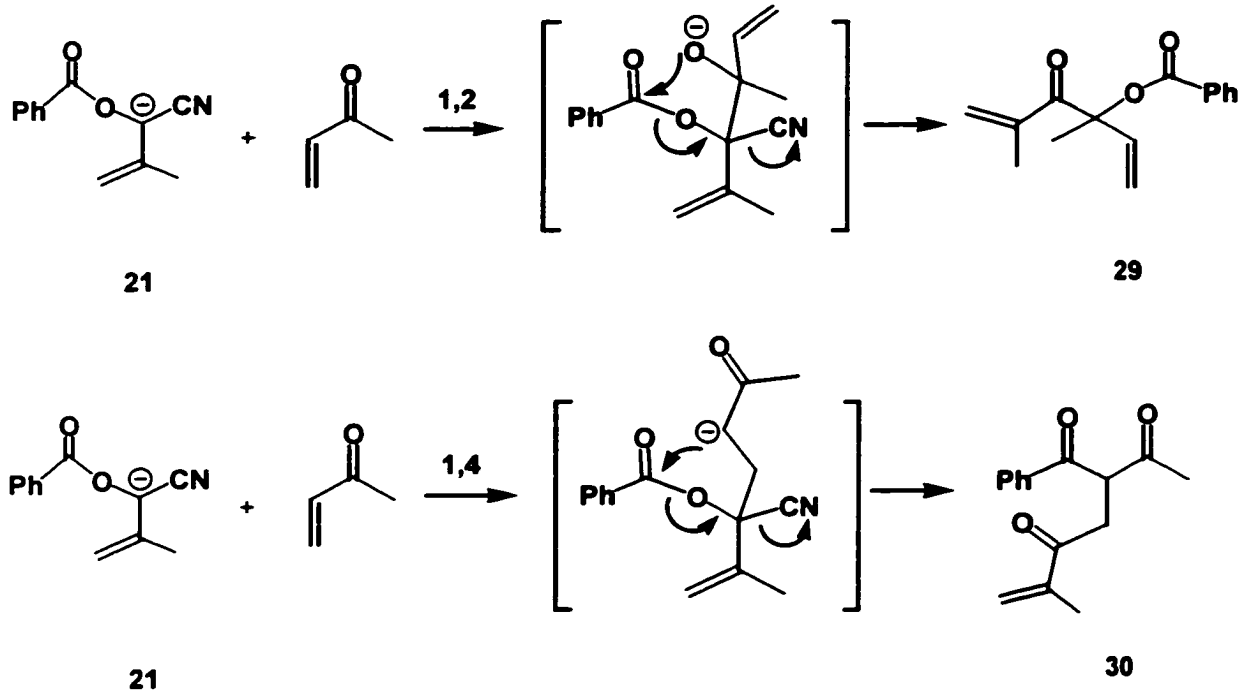
This is counter to the usual observations in Michael addition reactions, where steric factors play a significant role in the addition process. Perhaps the acyl transfer step proceeds more effectively when it produces a β-ketonitrile which can form a stable anion as in the cases of Michael acceptors without an α-substituent. However, in all cases the Michael addition reactions were always accompanied by the shift of a benzoyl group, followed by generation of the ketone.

This addition reaction was also applicable to several base-sensitive Michael acceptors, such as methyl vinyl ketone and 2-cyclohexenone. Unlike the reactions of 2-silyloxy cyanohydrins and 2-(ethoxyethyl)cyanohydrins with 2-cyclohexenone, where only 1,4-addition was observed,[11] the products of both 1,2- and 1,4-addition of the anion of **21** to 2-cyclohexenone were isolated in the ratio 1 : 1.2 (Scheme 18).



Scheme 18.

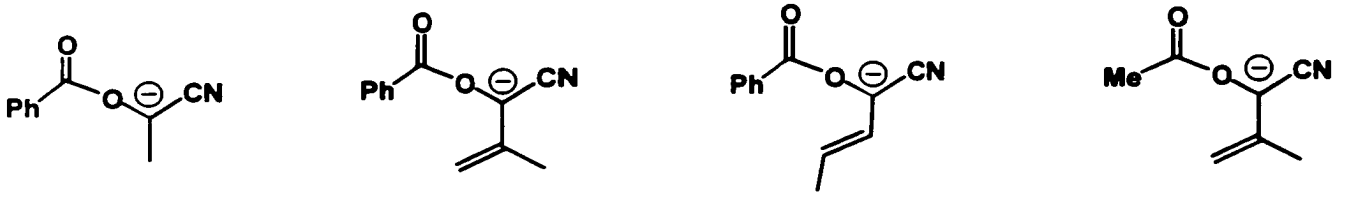
The same result was observed in the reaction with methyl vinyl ketone, where the 1,2- and 1,4-addition products were obtained in the ratio 1.44 : 1 (Scheme 19). Unlike the previous cases where the addition of HMPA only slightly affected the ratio,[13] with both methyl vinyl ketone and 2-cyclohexenone the reactions with HMPA as additive resulted in exclusive formation of the 1,4-addition products in 87% and 85% yields, respectively.



Scheme 19.

The overall outcome of the addition reactions to base-sensitive aldehydes and Michael acceptors was also found dependant on the acidity and, therefore, the structure of the α-acyloxynitrile. The stabilization of the anions of α-benzoyloxynitriles **21** and **22** by the neighbouring double bond, which is manifested by the rich red colour of the solution, results in

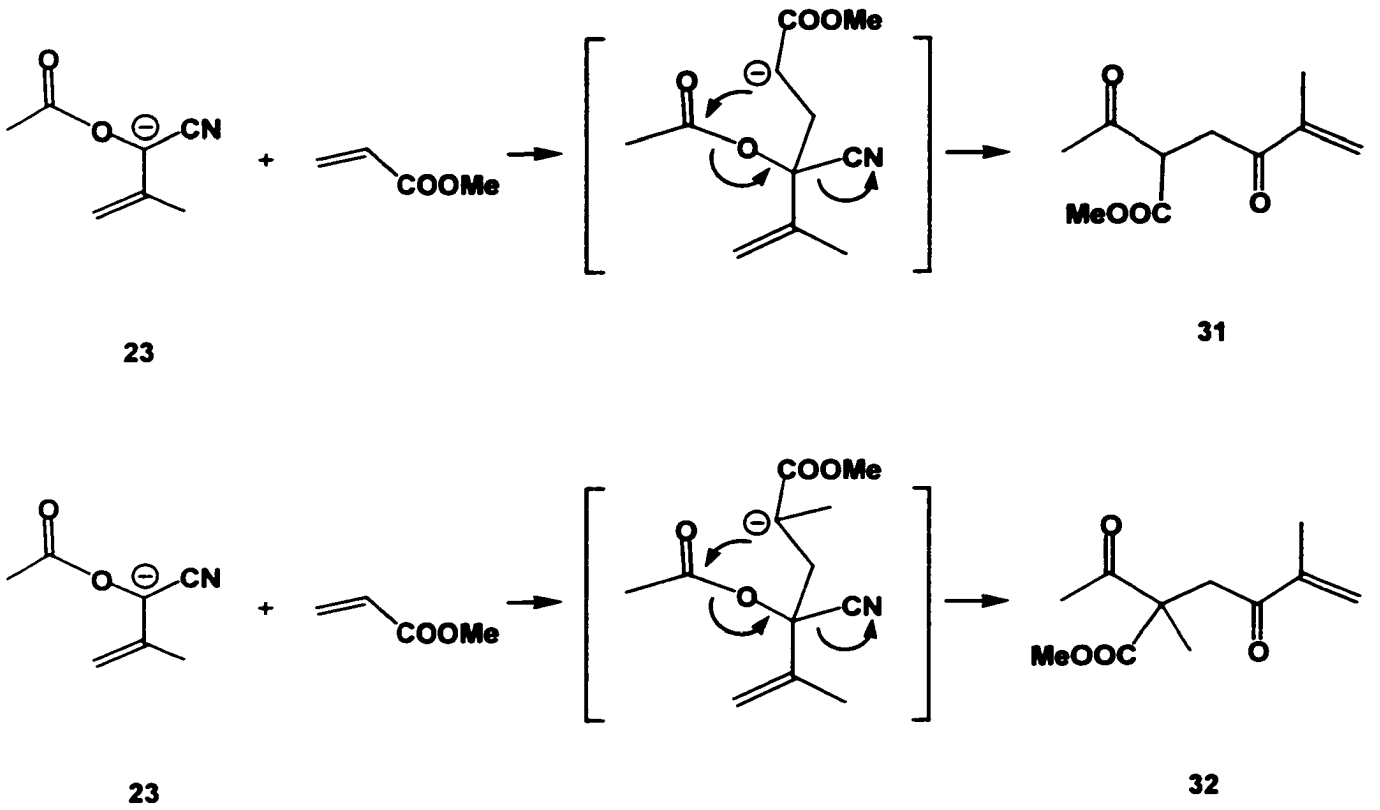
the higher acidity of these compounds compared to α-benzoyloxynitrile **20**. While **21** and **22** were selectively deprotonated in the presence of acetaldehyde and methyl vinyl ketone and, therefore successfully underwent the addition reactions, the acidity of the nitrile **20** was comparable to that of methyl vinyl ketone, resulting in the competing deprotonation of both reactants and, thus, in the formation of complex mixtures of products (Scheme 20).



20 **21** **22** **23**

Scheme 20.

The differences in the acidity were also successfully demonstrated in the selective deprotonation of the α-acetoxynitrile **23**, which can react with the base - α- to the nitrile and α- to the carbonyl group. Treatment of compound **23** with lithium hexamethyldisilazane in the presence of methyl acrylate afforded the product **31** in an excellent 82% yield (Scheme 21). Therefore, deprotonation alpha to the nitrile occurred selectively in the presence of the acetoxy group and the resulting anion underwent Michael addition to methyl acrylate, followed by the intramolecular 1,4-acyl shift and elimination of cyanide ion, to produce compound **31**. The same results were observed in the addition reaction with methyl methacrylate and the compound **32** was isolated in 78 % yield.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COOMe
COOMe
O
O
CN
MeOOC
O
23
32

Scheme 21.

CONCLUSION

Our study of the formation of anions of cyanohydrin esters and their behaviour towards aldehydes and Michael acceptors described above has demonstrated their synthetic utility as acyl carbanions. The ease of preparation of α-acyloxynitriles, their selective deprotonation and their reactions under mild reaction conditions make them convenient synthetic building blocks. The tandem Michael addition-acyl transfer-decyanation reaction gives rise to compounds, which can be valuable intermediates in organic synthesis.

EXPERIMENTAL

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. H:EA refers to hexanes: ethyl acetate solvent mixtures for thin layer chromatography (TLC) and silica gel flash chromatography (SGC). Commercially available silica gel (40 μm) was used as stationary phase. The NMR spectra were recorded at 300 MHz and the purity of all title compounds was determined to be > 95% by this method. The following symbols were used to designate peak multiplicity: s (singlet), d (doublet), t (triplet), q (quartet), ABq (AB quartet), m (multiplet).

2-Benzoyloxy-4-methylpent-4-en-3-one (24): To a solution of cyanohydrin ester **21** (0.5 g, 2.5 mmol, 1 equiv.) and acetaldehyde (0.51 g, 3.0 mmol, 1.2 equiv.) in 20 ml of anhydrous THF at –78°C was added dropwise a 1M solution of LiHMDS in anhydrous THF (2. 75 ml, 2.75 mmol, 1.1 equiv.) over 20 min. The reaction was stirred at –78°C for two hours and then allowed to warm to 0°C over 30 min. It was quenched with saturated NH_4Cl and extracted twice with ether. The organic extracts were washed with brine, dried over sodium sulfate and concentrated *in vacuo* to provide a residue which was purified by column chromatography using a 1: 3 ethyl acetate:hexanes mixture. ^1H NMR (300 MHz, $CDCl_3$) δ 1.56-1.58 (d, 3H, J = 7 Hz), 1.92-1.93 (m, 3H), 5.88-5.89 (m, 1H), 5.89-5.96 (q, 1H, J = 7 Hz), 7.41-7.46 (m, 2H), 7.53-7.58 (m, 1H), 8.05-8.08 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 17.53, 18.01, 71.30, 125.60, 128.46, 129.89, 133.32, 142.07, 166.03, 198.18.

2-Benzoyl-5-methyl-4-oxohex-5-enoic acid methyl ester (26): To a solution of cyanohydrin ester **21** (0.5 g, 2.5 mmol, 1 equiv.) and methyl acrylate (0.258 g, 0.27 ml, 3.0 mmol, 1.2 equiv.) in 10 ml of anhydrous THF at –78°C was added dropwise a 1M solution of LiHMDS in anhydrous THF (2. 8 ml, 2.8 mmol, 1.1 equiv.) over 20 min. The reaction was stirred at –78°C for two hours and then allowed to warm to 0°C over 30 min. It was quenched with saturated NH_4Cl and extracted twice with ether. The organic extracts were washed with brine, dried over sodium sulfate and concentrated *in vacuo* to provide a residue which was purified by flash chromatography on silica gel using a 1: 3 ethyl acetate: hexanes mixture. ^1H NMR (300 MHz, $CDCl_3$) δ 1.78-1.79 (m, 3H), 3.34-3.52 (m, 2H), 3.60 (s, 3H), 4.91-4.96 (dd, J = 6 Hz, 15 Hz, 1H), 5.77-5.78 (m, 1H), 6.03 (s, 1H), 7.39-7.44 (m, 2H), 7.49-7.54 (m, 1H), 7.98-8.01 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 17.5, 37.4, 48.5, 52.7, 125.9, 128.8, 128.9, 133.7, 136.0, 143.7, 169.8, 194.8, 198.4. HRMS m/z for $C_{15}H_{16}O_4$ calcd. 260.1049, found 260.1047.

1-(1-Benzoyloxycyclohex-2-enyl)-2-methylprop-2-en-1-one (27): To a solution of cyanohydrin ester **21** (0.5 g, 2.5 mmol, 1 equiv.) and 2-cyclohexenone (0.264 g, 0.27 ml, 2.75 mmol, 1.1 equiv.) in 20 ml of anhydrous THF at –78°C was added dropwise a 1M solution of LiHMDS in anhydrous THF (2.8 ml, 2.8 mmol, 1.1 equiv.) over 30 min. The reaction was stirred at –78°C for two hours and then allowed to warm to 0°C over 30 min. It was quenched with saturated NH_4Cl and extracted twice with ether. The organic extracts were washed with brine, dried over sodium sulfate and concentrated *in vacuo* to provide a residue which was purified by flash chromatography on silica gel using a 1: 3 ethyl acetate: hexanes mixture. ^1H NMR (300 MHz, $CDCl_3$) δ 1.4-2.4 (m, 6H), 1.90 (m, 3H), 5.60 (m, 1H), 6.01 (m, 1H), 6.01-6.11 (m, 1H), 6.27-6.31 (m, 1H), 7.40-7.45 (m, 2H), 7.53-7.55 (m, 1H), 8.00-8.03 (m, 2H).

^{13}C NMR ($CDCl_3$) δ 18.38, 19.49, 24.64, 32.69, 82.78, 123.21, 125.91, 128.49, 129.76, 133.23, 133.74, 141.45, 165.70, 200.16.

4-Benzoyloxy-2,4-dimethylhexa-1,5-dien-3-one (29) : To a solution of cyanohydrin ester **21** (0.5 g, 2.5 mmol, 1 equiv.) and methyl vinyl ketone (0.19 g, 0.23 ml, 2.75 mmol, 1.1 equiv.) in 20 ml of anhydrous THF at –78°C was added dropwise a 1M solution of LiHMDS in anhydrous THF (2.8 ml, 2.8 mmol, 1.1 equiv.) over 30 min. The reaction was stirred at –78°C for two hours and then allowed to warm to 0°C over 30 min. It was quenched with saturated NH_4Cl and extracted twice with ether. The organic extracts were washed with brine, dried over sodium sulfate and concentrated *in vacuo* to provide a residue which was purified by flash chromatography on silica gel using a 1: 3 ethyl acetate: hexanes mixture. ^1H NMR (300 MHz, $CDCl_3$) δ 1.77 (s, 3H), 1.87 (m, 3H), 5.27-5.30 (d, 1H, J = 11 Hz), 5.46-5.22 (d, 1H, J = 17.5 Hz), 5.50 (m, 1H), 5.90 (m, 1H), 6.21-6.30 (dd, 1H, J = 17.5, 11 Hz), 7.43-7.48 (m, 2H), 7.56-7.58 (m, 1H), 8.02-8.05 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 9.03, 24.19, 86.37, 114.95, 122.99, 128.59, 129.72, 130.29, 133.44, 138.48, 141.16, 165.45, 199.11.

3-Benzoyl-6-methylhept-6-ene-2,5-dione (30) : To a solution of cyanohydrin ester **21** (0.5 g, 2.5 mmol, 1 equiv.), methyl vinyl ketone (0.19 g, 0.23 ml, 2.75 mmol, 1.1 equiv.) and hexamethylphosphoric triamide (0.49 g, 0.48 ml, 2.75 mmol, 1.1 equiv.) in 20 ml of anhydrous THF at –78°C was added dropwise a 1M solution of LiHMDS in anhydrous THF (2.8 ml, 2.8 mmol, 1.1 equiv.) over 30 min. The reaction was stirred at –78°C for two hours and then allowed to warm to 0°C over 30 min. It was quenched with saturated NH_4Cl and extracted twice with ether. The organic extracts were washed with brine, dried over sodium sulfate and

concentrated *in vacuo* to provide a residue which was purified by flash chromatography on silica gel using a 1: 3 ethyl acetate: hexanes mixture. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.82 (s, 3H), 2.16 (s, 3H), 3.27-3.33 (dd, 1H, J = 13.6 Hz, 5 Hz), 3.44-3.50 (dd, 1H, J = 5 Hz, 13.6 Hz), 5.09-5.12 (m, 1H), 5.80 (s, 1H), 6.05 (s, 1H), 7.46-7.50 (m, 2H), 7.56-7.58 (m, 2H), 7.99-8.01 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 15.33, 17.58, 29.58, 37.12, 56.90, 65.90, 125.98, 128.91, 129.04, 133.90, 136.16, 143.75, 196.38, 198.54, 202.48. HRMS m/z for $C_{15}H_{16}O_3$ calcd. 244.10995, found 244.10975.

2-Acetyl-5-methyl-4-oxohex-5-enoic acid methyl ester (31): To a solution of cyanohydrin ester **23** (0.35 g, 2.5 mmol, 1 equiv.) and methyl acrylate (0.258 g, 0.27 ml, 3.0 mmol, 1.2 equiv.) in 20 ml of anhydrous THF at –78°C was added dropwise a 1M solution of LiHMDS in anhydrous THF (2.8 ml, 2.8 mmol, 1.1 equiv.) over 30 min. The reaction was stirred at –78°C for two hours and then allowed to warm to 0°C over 30 min. It was quenched with saturated NH_4Cl and extracted twice with ether. The organic extracts were washed with brine, dried over sodium sulfate and concentrated *in vacuo* to provide a residue which was purified by flash chromatography on silica gel using a 1: 3 ethyl acetate: hexanes mixture. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.84-1.85 (m, 3H), 2.38 (s, 3H), 3.19-3.27 (dd, 1H, J = 5.6 Hz, 18.2 Hz), 3.40-3.48 (dd, 1H, J = 8.3 Hz, 18.2 Hz), 3.74 (s, 3H), 4.05-4.09 (dd, 1H, J = 8.3 Hz), 5.82-5.83 (m, 1H), 6.06 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 17.4, 30.2, 36.5, 52.7, 53.6, 125.8, 143.6, 169.4, 198.6, 202.4. HRMS m/z for $C_{10}H_{14}O_4$ calcd. 198.2120, found 198.2115.

2-Acetyl-2,5-dimethyl-4-oxohex-5-enoic acid methyl ester (32): To a solution of cyanohydrin ester **23** (0.35 g, 2.5 mmol, 1 equiv.) and methyl methacrylate (0.50 g, 0.53 ml,

5.0 mmol, 2 equiv.) in 20 ml of anhydrous THF at –78°C was added dropwise a 1M solution of LiHMDS in anhydrous THF (2.8 ml, 2.8 mmol, 1.1 equiv.) over 30 min. The reaction was stirred at –78°C for two hours and then allowed to warm to 0°C over 30 min. It was quenched with saturated NH_4Cl and extracted twice with ether. The organic extracts were washed with brine, dried over sodium sulfate and concentrated *in vacuo* to provide a residue which was purified by flash chromatography on silica gel using a 1: 3 ethyl acetate: hexanes mixture. ^1H NMR (300 MHz, $CDCl_3$) δ 1.62 (s, 3H), 1.81-1.83 (m, 3H), 2.42 (s, 3H), 3.17-3.27 (d, 2H, J = 5.4 Hz), 3.78 (s, 3H), 5.81-5.83 (m, 1H), 6.1 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 17.4, 20.1, 32.3, 38.5, 53.7, 55.6, 126.8, 144.5, 170.2, 198.8, 202.6. HRMS m/z for $C_{10}H_{14}O_4$ calcd. 212.2120, found 212.2115.

2-Benzoyl-4-oxopentanoic acid methyl ester (33): To a solution of cyanohydrin ester **20** (0.44 g, 2.5 mmol, 1 equiv.) and methyl acrylate (0.258 g, 0.27 ml, 3.0 mmol, 1.2 equiv.) in 20 ml of anhydrous THF at –78°C was added dropwise a 1M solution of LiHMDS in anhydrous THF (2.8 ml, 2.8 mmol, 1.1 equiv.) over 30 min. The reaction was stirred at –78°C for two hours and then allowed to warm to 0°C over 30 min. It was quenched with saturated NH_4Cl and extracted twice with ether. The organic extracts were washed with brine, dried over sodium sulfate and concentrated *in vacuo* to provide a residue which was purified by flash chromatography on silica gel using a 1: 3 ethyl acetate: hexanes mixture. ^1H NMR (300 MHz, $CDCl_3$) δ 2.17 (s, 3H), 3.13-3.18 (dd, 2H, J = 7.3 Hz, 6 Hz), 3.62 (s, 3H), 4.86-4.91 (dd, 1H, J = 7.3 Hz, 6 Hz), 7.42-7.47 (m, 2H), 7.52-7.58 (m, 1H), 7.97-8.00 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 29.79, 42.20, 48.48, 52.80, 128.81, 128.91, 133.75, 135.87, 169.74, 194.58, 205.37. NRMS m/z for $C_{13}H_{14}O_4$ calcd. 234.08921, meas. 234.08917.

2-Benzoyl-2-methyl-4-oxopentanoic acid methyl ester (34): To a solution of cyanohydrin ester **20** (0.44 g, 2.5 mmol, 1 equiv.) and methyl methacrylate (0.50 g, 0.53 ml, 5.0 mmol, 2.0 equiv.) in 20 ml of anhydrous THF at –78°C was added dropwise a 1M solution of LiHMDS in anhydrous THF (2.8 ml, 2.8 mmol, 1.1 equiv.) over 30 min. The reaction was stirred at –78°C for two hours and then allowed to warm to 0°C over 30 min. It was quenched with saturated NH_4Cl and extracted twice with ether. The organic extracts were washed with brine, dried over sodium sulfate and concentrated *in vacuo* to provide a residue which was purified by flash chromatography on silica gel using a 1: 3 ethyl acetate: hexanes mixture. ^1H NMR (300 MHz, $CDCl_3$) δ 1.64 (s, 3H), 2.12 (s, 3H), 3.19-3.21 (d, 2H, J = 5.2 Hz), 3.66 (s, 3H), 7.35-7.40 (m, 2H), 7.45-7.51 (m, 1H), 7.72-7.80 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 21.72, 30.80, 49.99, 52.89, 56.07, 128.48, 132.45, 136.25, 173.41, 197.74, 205.49. NRMS m/z for $C_{14}H_{16}O_4$ calcd. 248.10486, found 248.10451.

2-Benzoyl-4-oxopentanenitrile (35): To a solution of cyanohydrin ester **20** (0.44 g, 2.5 mmol, 1 equiv.), acrylonitrile (0.16 g, 0.20 ml, 3.0 mmol, 1.2 equiv.) and hydroquinone (27 mg, 0.25 mmol, 0.1 equiv.) in 10 ml of anhydrous THF at –78°C was added dropwise a 1M solution of LiHMDS in anhydrous THF (2.8 ml, 2.8 mmol, 1.1 equiv.) over 30 min. The reaction was stirred at –78°C for two hours and then allowed to warm to 0°C over 30 min. It was quenched with saturated NH_4Cl and extracted twice with ether. The organic extracts were washed with brine, dried over sodium sulfate and concentrated *in vacuo* to provide a residue which was purified by flash chromatography on silica gel using a 1: 3 ethyl acetate: hexanes mixture. ^1H NMR (300 MHz, $CDCl_3$) δ 2.22 (s, 3H), 2.94-3.01 (dd, 1H, J = 18.2 Hz, 4.5 Hz), 3.38-3.47

(dd, 1H, J = 8.8 Hz, 18.2 Hz), 4.76-4.80 (dd, 1H, J = 4.5 Hz, 8.8 Hz), 7.41-7.51 (m, 2H), 7.59-7.65 (m, 1H), 7.97-8.01 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 29.59, 33.20, 41.49, 116.94, 129.04, 129.17, 133.91, 134.80, 189.04, 203.43. NRMS m/z for $C_{12}H_{11}O_2N$ calcd. 201.07898, found 201.07861.

2-Benzoyl-2,5-dimethyl-4-oxohex-5-enoic acid methyl ester (38): To a solution of cyanohydrin ester **21** (0.5 g, 2.5 mmol, 1 equiv.) and methyl methacrylate (0.50 g, 0.53 ml, 5.0 mmol, 2.0 equiv.) in 20 ml of anhydrous THF at –78°C was added dropwise a 1M solution of LiHMDS in anhydrous THF (2. 8 ml, 2.8 mmol, 1.1 equiv.) over 20 min. The reaction was stirred at –78°C for two hours and then allowed to warm to 0°C over 30 min. It was quenched with saturated NH_4Cl and extracted twice with ether. The organic extracts were washed with brine, dried over sodium sulfate and concentrated *in vacuo* to provide a residue which was purified by flash chromatography on silica gel using a 1: 3 ethyl acetate: hexanes mixture. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.60 (s, 3H), 1.79 (s, 3H), 3.49-3.50 (d, 1H, J = 3.8 Hz), 3.65 (s, 3H), 5.75 (m, 1H), 5.98 (s, 1H), 7.33-7.38 (m, 2H), 7.43-7.48 (m, 1H), 7.74-7.77 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 17.50, 21.72, 44.48, 52.78, 56.03, 125.39, 128.41, 132.29, 136.45, 144.62, 173.55, 297.91, 198.66.

2-Benzoyl-5-methyl-4-oxohex-5-enenitrile (39): To a solution of cyanohydrin ester **21** (0.5 g, 2.5 mmol, 1 equiv.), acrylonitrile (0.16 g, 0.20 ml, 3.0 mmol, 1.2 equiv.) and hydroquinone (27 mg, 0.25 mmol, 0.1 equiv.) in 10 ml of anhydrous THF at –78°C was added dropwise a 1M solution of LiHMDS in anhydrous THF (2.8 ml, 2.8 mmol, 1.1 equiv.) over 30 min. The reaction was stirred at –78°C for two hours and then allowed to warm to 0°C over 30 min. It

was quenched with saturated NH_4Cl and extracted twice with ether. The organic extracts were washed with brine, dried over sodium sulfate and concentrated *in vacuo* to provide a residue which was purified by flash chromatography on silica gel using a 1: 3 ethyl acetate: hexanes mixture. ^1H NMR (300 MHz, $CDCl_3$) δ 1.86-1.87 (m, 3H), 3.25-3.32 (dd, 1H, J = 4.5 Hz, 17.8 Hz), 3.75-3.84 (dd, 1H, J = 8.9 Hz, 17.8 Hz), 4.86-4.91 (dd, 1H, J = 4.5 Hz, 8.9 Hz), 5.91 (m, 1H), 6.10 (s, 1H), 7.50-7.55 (m, 2H), 7.63-7.68 (m, 1H), 8.03-8.06 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 17.45, 33.23, 36.74, 117.06, 126.73, 129.05, 129.16, 134.11, 134.73, 143.43, 189.18, 196.29.

2-Benzoyl-5-methyl-4-oxohex-5-enoic acid methyl ester (41): To a solution of cyanohydrin ester **22** (0.5 g, 2.5 mmol, 1 equiv.) and methyl acrylate (0.258 g, 0.27 ml, 3.0 mmol, 1.2 equiv.) in 10 ml of anhydrous THF at –78°C was added dropwise a 1M solution of LiHMDS in anhydrous THF (2. 8 ml, 2.8 mmol, 1.1 equiv.) over 20 min. The reaction was stirred at –78°C for two hours and then allowed to warm to 0°C over 30 min. It was quenched with saturated NH_4Cl and extracted twice with ether. The organic extracts were washed with brine, dried over sodium sulfate and concentrated *in vacuo* to provide a residue which was purified by flash chromatography on silica gel using a 1: 3 ethyl acetate: hexanes mixture. ^1H NMR (300 MHz, $CDCl_3$) δ 1.81-1.83 (m, 3H), 3.32-3.54 (m, 2H), 3.63 (s, 3H), 4.94-4.98 (dd, J = 6 Hz, 15 Hz, 1H), 6.08 (d, 1H, J = 15.3 Hz), 6.81-6.83 (d, 1H, J = 15.3 Hz), 7.41-7.44 (m, 2H), 7.51-7.56 (m, 1H), 7.99-8.04 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 19.7, 38.4, 49.5, 53.7, 126.9, 129.8, 130.1, 134.7, 137.0, 144.7, 170.8, 195.8, 198.4. HRMS m/z for $C_{15}H_{16}O_4$ calcd. 260.1049, found 260.1043.

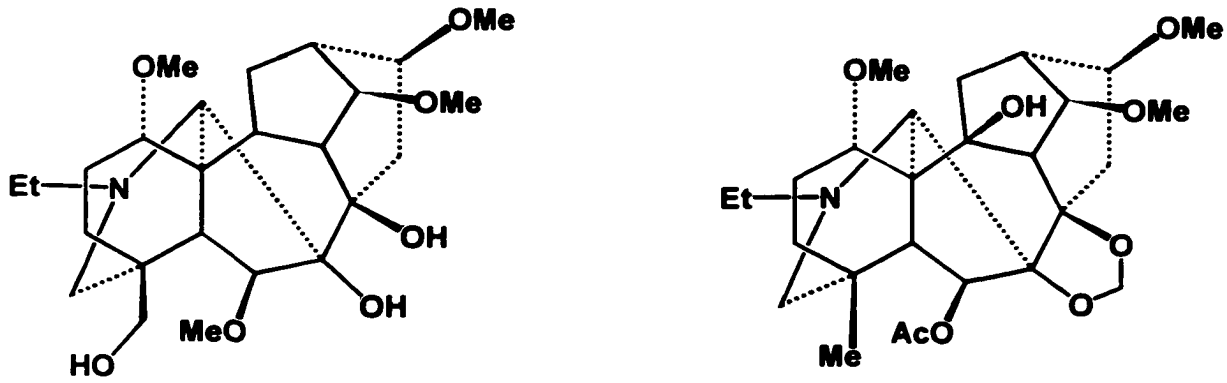
2-Benzoyl-2,5-dimethyl-4-oxohex-5-enoic acid methyl ester (42): To a solution of cyanohydrin ester **22** (0.5 g, 2.5 mmol, 1 equiv.) and methyl methacrylate (0.50 g, 0.53 ml, 5.0 mmol, 2.0 equiv.) in 20 ml of anhydrous THF at –78°C was added dropwise a 1M solution of LiHMDS in anhydrous THF (2. 8 ml, 2.8 mmol, 1.1 equiv.) over 20 min. The reaction was stirred at –78°C for two hours and then allowed to warm to 0°C over 30 min. It was quenched with saturated NH_4Cl and extracted twice with ether. The organic extracts were washed with brine, dried over sodium sulfate and concentrated *in vacuo* to provide a residue which was purified by flash chromatography on silica gel using a 1: 3 ethyl acetate: hexanes mixture. ^1H NMR (300 MHz, $CDCl_3$) δ 1.65 (s, 3H), 1.87-1.90 (m, 3H), 3.21-3.26 (m, 2H), 3.66 (s, 3H), 6.1 (d, 1H, J = 15.3 Hz), 6.82-6.85 (d, 1H, *J* = 15.3 Hz), 7.40-7.42 (m, 2H), 7.51-7.54 (m, 1H), 7.97-8.02 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 19.7, 21.4, 39.4, 49.4, 52.7, 125.9, 128.8, 129.5, 134.7, 137.0, 144.7, 170.8, 195.8, 198.4. HRMS m/z for $C_{15}H_{16}O_4$ calcd. 274.1049, found 274.1041.

PART II. STUDIES DIRECTED TOWARD THE SYNTHESIS OF METHYLLYCACONITINE

INTRODUCTION: PHARMACOLOGY

Larkspur is a serious toxic plant problem on western U.S. ranges, as larkspur poisoning sporadically kills 5-15 % of the cattle on North American mountain lands. Toxic alkaloids comprise about 20-50% of the total alkaloid concentration in tall larkspur.[1]

Larkspur (*Delphinium* species) contain numerous diterpenoid alkaloids of two structural types: lycoctonine and 7,8-methylenedioxylycoctonine (deltaline) (Figure 1).



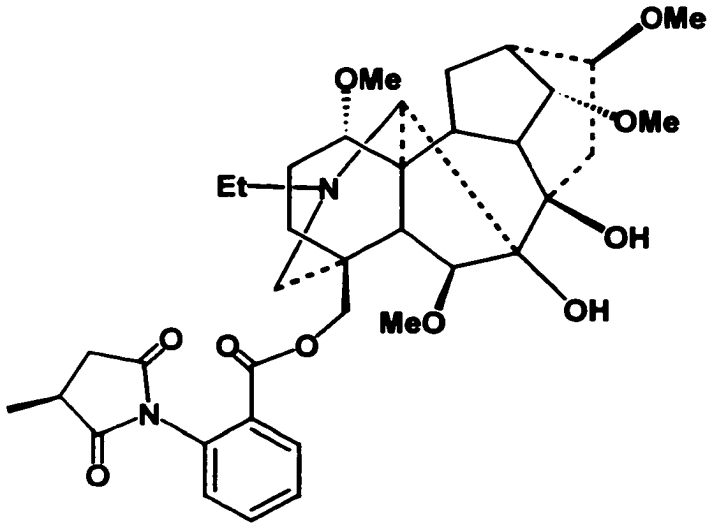
Lycoctonine **Deltaline**

Figure 1. Representative alkaloids of Delphinium species.

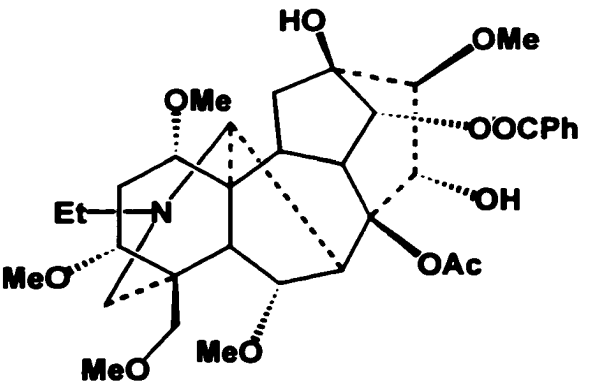
Among the lycoctonine type norditerpenoid alkaloids are three *N*-(methylsuccinimido) anthranoyl lycoctonine alkaloids which appear to be the most toxic: methyllycaconitine (MLA), 14-deacetyl nudicauline and nudicauline.[2] Intoxication results from neuromuscular paralysis, as these alkaloids reversibly bind and block nicotinic acetylcholine receptors in the

muscle and brain, thus inhibiting neurotransmission and inducing paralysis.[3] Clinical signs include labored breathing, rapid and irregular heartbeat, muscular weakness and collapse. However, in small doses MLA and several other lycoctonine esters are used in medicine as muscle relaxants during surgery.[4]

Methyllycaconitine has been reported in at least thirty different *Delphinium* species and also in *Consolida ambigua* and *Inula royaleana* and it is the principle toxic alkaloid in these species.[5] The use of *Aconitum* and *Delphinium* by various civilizations as sources of poisons and medicines starts from the year AD 77, the earliest report on the treatment of lice.[6] Despite the suggestive trivial name, methyllycaconitine has not been found in *Aconitum* species and differs from aconitine in many aspects (Figure 2).



Methyllycaconitine

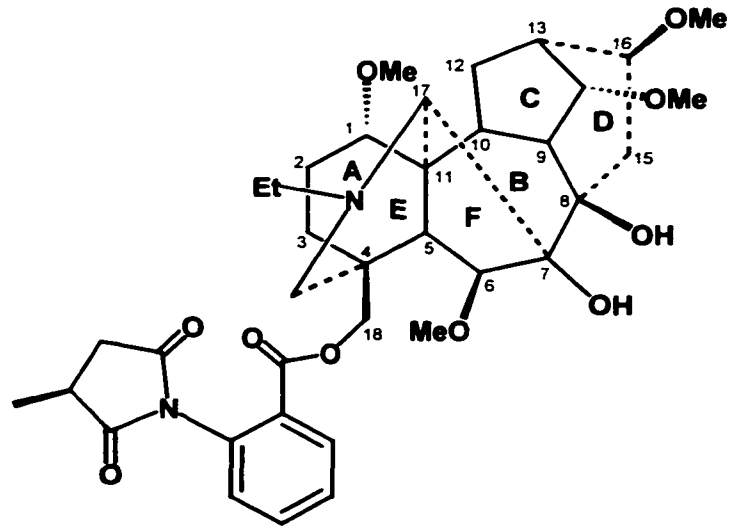


Aconitine

Figure 2. Structural differences of alkaloids of *Delphinium* and *Aconitum* species.

When employed in pharmacological studies, methyllycaconitine was found to be a novel and very potent probe for mammalian and insect nicotinic acetylcholine receptors (nAChR), displaying remarkable selectivity toward neuronal [125I]-α-bungarotoxin binding sites that correspond to α7-type nAChR in mammalian brain.[7] Combined its high activity and selectivity as nAChR antagonist have led to extensive use of MLA as a radiolabel for distinguishing nicotinic acetylcholine receptor subtypes.[8] This aspect of the selectivity of MLA has become even more important since it was suggested that these receptors might be implicated in Alzheimer's disease.[9]

Structure-activity relationship investigations have indicated that the *N*-methyl succinimidobenzoate ester at C-18 (Figure 3) affects alkaloid interactions with nACh receptors at neuromuscular junctions and the substituent at C-14 determines the potency and possibly the mechanism of nACh receptor blockade at neuromuscular synapses.[10]



Methyllycaconitine

Figure 3. Structure of methyllycaconitine.

The methyl group on the succinimido ring[11] and the ethyl group of the tertiary amine[12] were also found to be structural requirements for the selectivity and the high affinity for the α7-type nACh receptors, whereas structural modifications to the norditerpenoid core of the alkaloid might be tolerated without loss of activity or selectivity.

From molecular modeling techniques MLA and acetylcholine have been determined to be conformationally comparable and to have a template fit with the rigid nicotinic antagonist cytisine.[13] The pharmacological specificity of MLA seems to arise from the fact that the tertiary nitrogen atom of MLA and the quaternary nitrogen of acetylcholine may undergo equivalent electrostatic interaction with a receptor binding site (Figure 4).

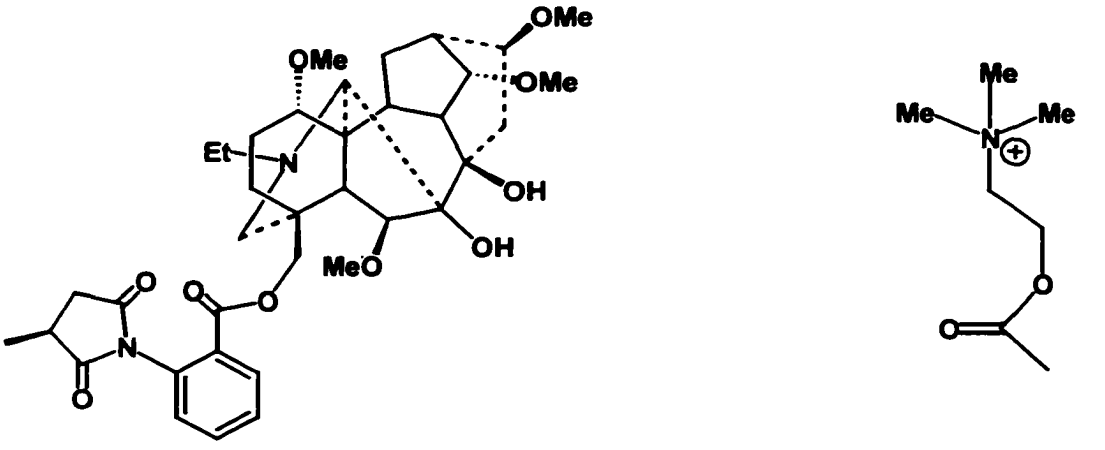


Figure 4. Structural similarities of methyllycaconitine and acetylcholine.

Because of MLA's high toxicity, not only to insects, but also to mammals, it would be impossible to use it as an agrochemical. However, it was suggested that if the inhibitory action is localised in a toxophoric section, it might be possible to find a smaller analogue that would bind to insect, but not to mammalian, nACh receptors.[14]

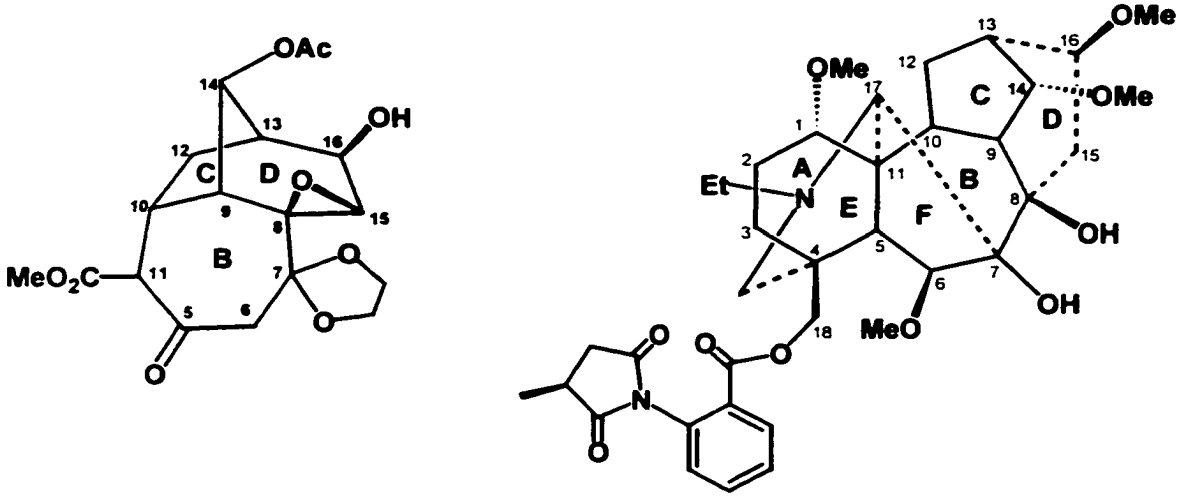
HISTORICAL

Numerous reports have been published on the isolation and characterisation of *Delphinium* and *Aconitum* alkaloids from natural sources all over the world, along with reports on their pharmacological properties. These alkaloids have been found to possess analgesic, antiarrhythmic and antiinflammatory properties[15] and several of them are proposed as lead compounds for pharmaceutical research and development. To this day, a number of MLA analogues have been prepared. However, they have been derived mainly from natural products, either directly, or from semi-synthesis.[16] The interest and the potential of this field are in sharp contrast with the fact that even an approach to the skeleton of these alkaloids remains a completely undeveloped and uncharted area. The construction of the 5,6,7-fused tricyclic moiety present in the aconitine alkaloids is a truly outstanding synthetic challenge, which still remains unresolved.

Several structurally less complex analogues of MLA have been synthesized over the past decade, but most of the synthetic efforts have been focused on the preparation of small bicyclic analogues and on establishing a structure-activity relationship to assess the structural requirements necessary for potency and selectivity. From the synthetic point of view, only three partial syntheses of MLA have been attempted, those published by van der Baan[17], Kraus[18] and Whiting[19].

One of the earliest works published on the construction of the C_{19} norditerpenoid skeleton belongs to van der Baan and co-workers.[17] They started their partial synthesis from the right-hand portion of the molecule, the BCD-carbocycle part (Figure 5). Their synthetic strategy can be divided into two main areas – the synthesis of the BCD-carbocycle with proper

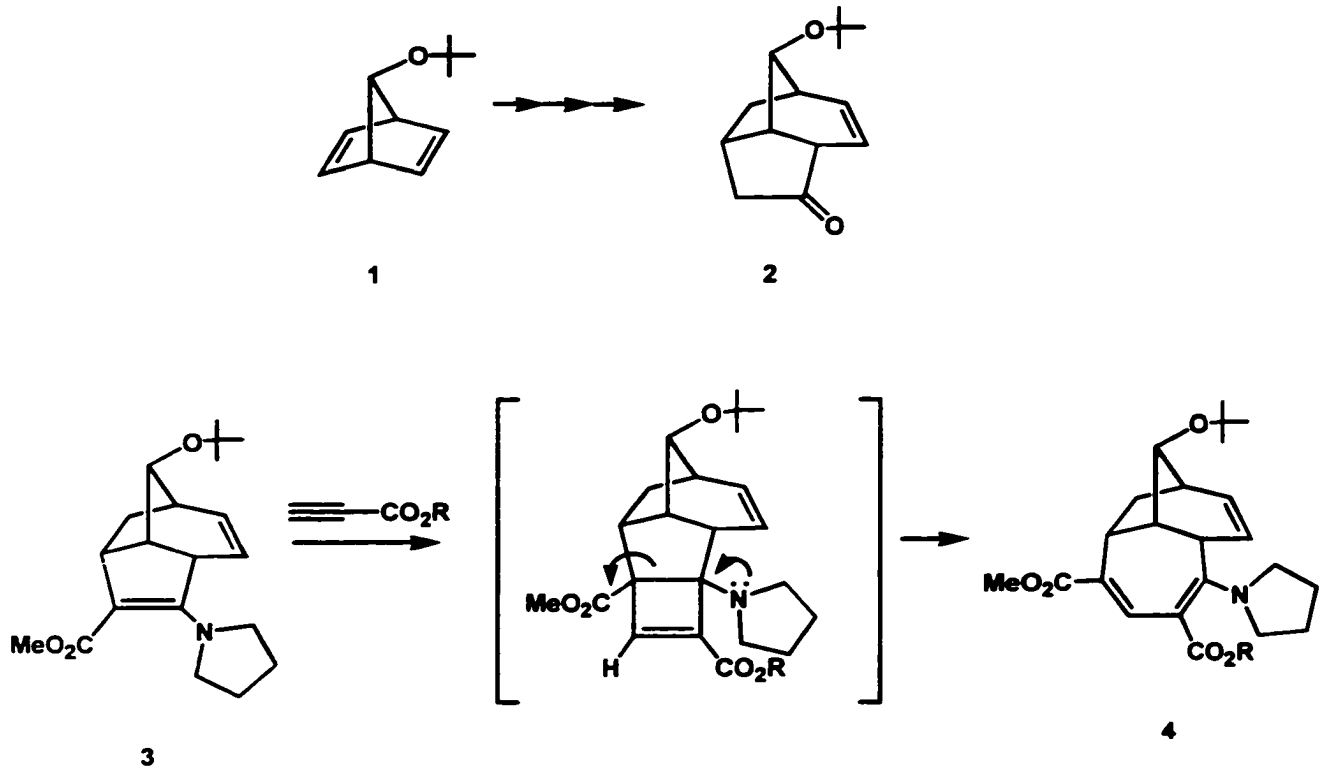
functionality and development of a general building principle for the attachment of the A- and E-rings to the existing BCD-skeleton.



BCD-Skeleton analog **Methyllycaconitine**

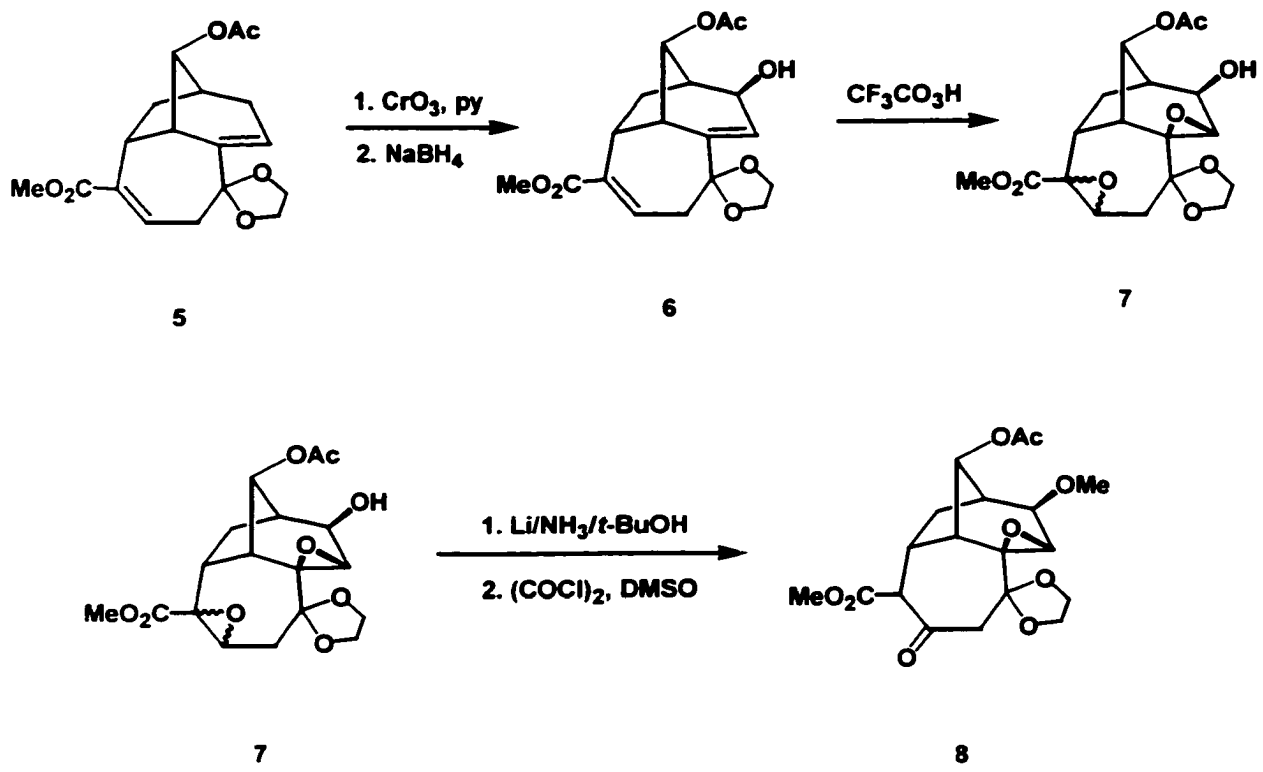
Figure 5. J.L. van der Baan's BCD-skeleton of diterpene alkaloids.

The earlier research in this group on the synthesis of substituted bicyclo[3.2.1]octane derivatives (CD-ring system) starting from 7-*t*-butoxynorbornadiene (**1**) led to an efficient synthesis of tricyclic ketone **2**,[20] which was then converted to the tricyclic 5-membered ring enamino-ester **3** (Scheme 1). The construction of the BCD-ring system was initiated by the development of a ring expansion reaction of cyclic enamino esters with propiolic esters, leading from a 5-membered ring to the 7-membered ring carbocycle **4**.



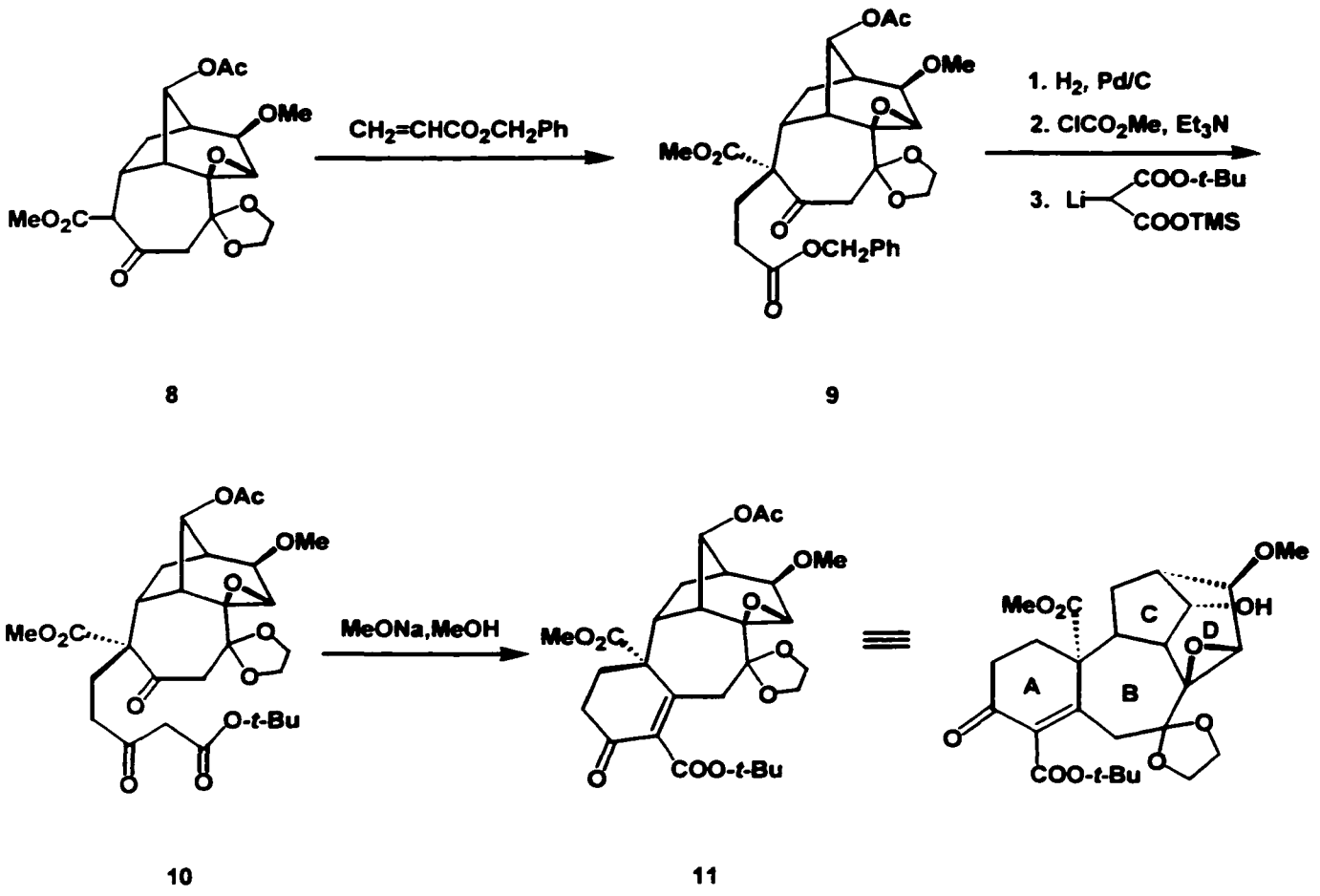
Scheme 1.

The hydroxyl group, which is present at C-16 in the majority of C_{19} diterpene alkaloids, was introduced by allylic oxidation with a chromium trioxide complex (Scheme 2). The resulting α,β-unsaturated ketone was then reduced to a mixture of exo- and endo-allylic alcohols in a 3:1 ratio. Epoxidation of both double bonds, conversion of epoxyester **7** to the corresponding β-hydroxyester, and oxidation of the latter furnished the tricyclic intermediate **8**, representing the BCD-skeleton of the diterpene alkaloids with functional groups appropriate for further elaboration of the A-, E- and F-rings.



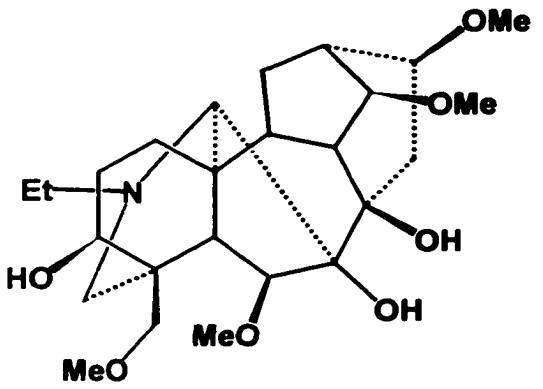
Scheme 2.

Michael addition of β-keto ester **8** to benzyl acrylate occurred in the desired exo-fashion with the endo-position being sterically hindered by the bicyclo[3.2.1]nonane system (Scheme 3). Cleavage of the benzyl group, formation of a mixed anhydride and its reaction with the lithium salt of *t*-butyltrimethylsilyl malonate gave a triacyl product, which was hydrolyzed with simultaneous decarboxylation to yield β-ketoester **10**. Treatment of the β-ketoester with sodium methoxide proceeded with cyclization to the A-ring to afford tetracyclic ABCD-ring system.

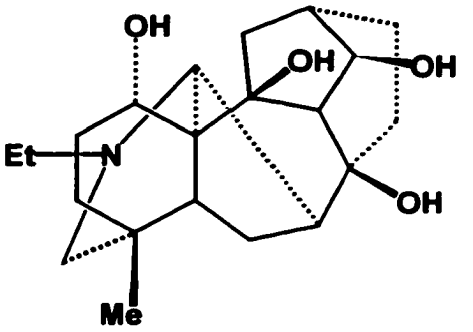


Scheme 3.

This work represents a solid synthesis of the right-hand portion of the skeleton of the C_{19}-diterpene alkaloids with all functionalities necessary for further development. This tetracyclic intermediate can be very closely associated with the simpler representatives of the C_{19}-diterpene alkaloids, such as acomonine, isodelfinine and cardiopetaline (Figure 6).



Acomonine



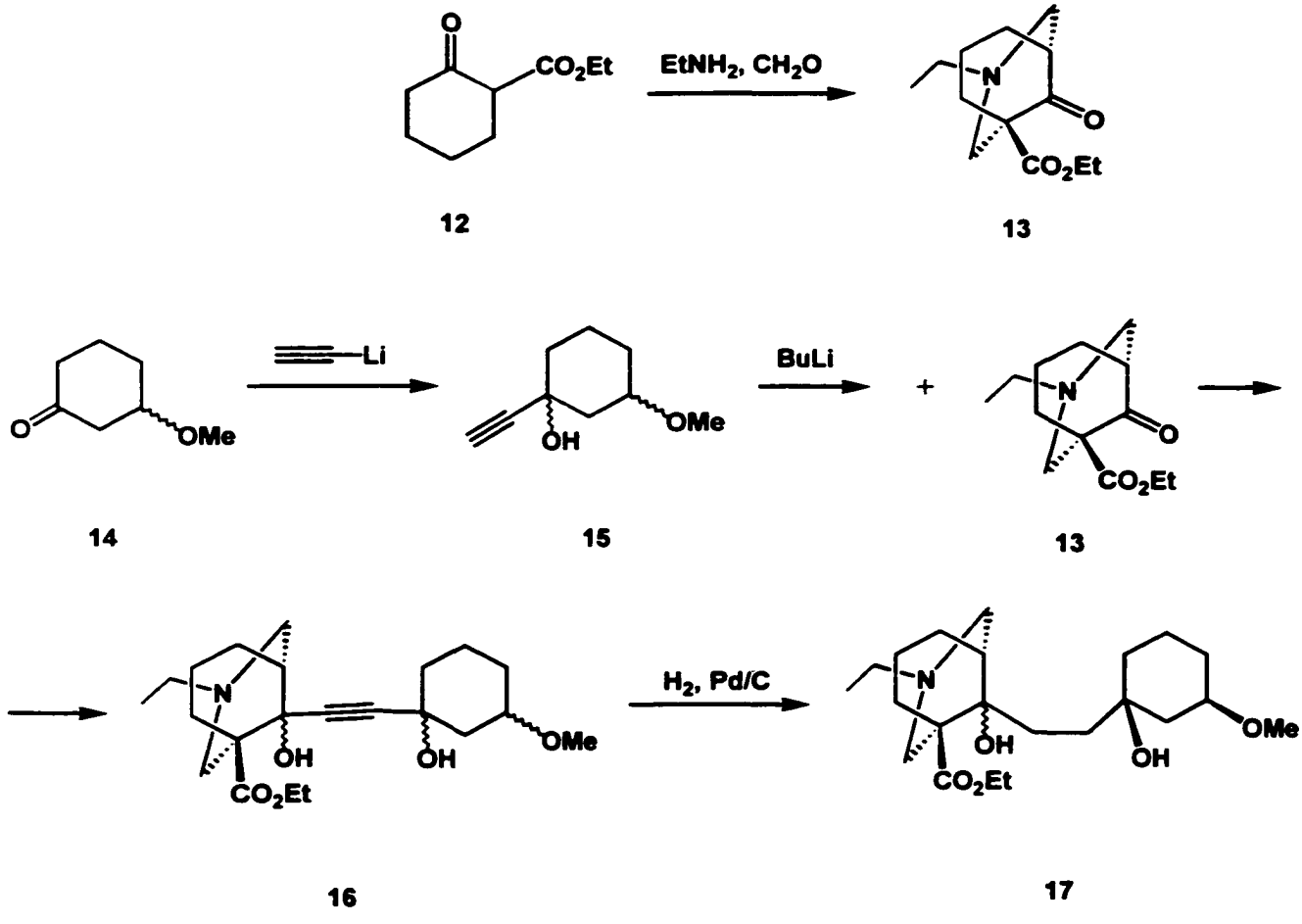
Cardiopetaline

Figure 6. Representatives of C_{19}-diterpene alkaloids.

However, the most challenging task of the incorporation of E- and F-rings in this attempted total synthesis is still ahead and possibly may be unresolved. This is especially crucial when you bear in mind that the biological activity of these alkaloids is tied to the E-ring with the tertiary nitrogen and as it was proposed that the BCD-ring system of these alkaloids can be modified or even partially omitted without the loss of activity or selectivity.[21] In conclusion, the development of the strategy for the attachment of the A-, E-, and F-rings to the existing intermediate is crucial for this route to qualify as synthetically valuable.

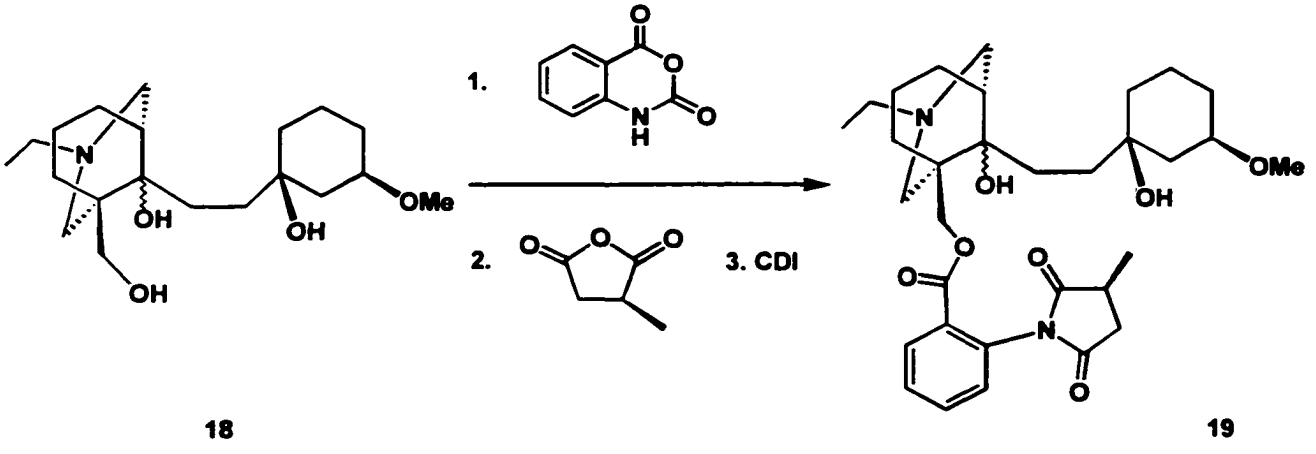
Upon closer examination one can easily see that the aconitine type alkaloids, with methyllycaconitine as one of the most complex representatives, all share a common feature, the 3-azabicyclo[3.3.1]nonane system, in their chemical structure. This structural similarity suggests this system as a common intermediate in approaches to the skeleton. The most simple 3-azabicyclo[3.3.1]nonane system is easily accessible via a double Mannich reaction to

the 2-cyclohexanone carboxylate. This approach was utilized by Blagbrough *et al* in the synthesis of substituted AE-bicyclic analogues mimicking three of the six rings found in MLA.[22] Double acetylide addition linking a monocyclic ketone to a bicyclic ketone produced a mixture of diastereomeric bishydroxy acetylenes. Reduction of the triple bond, followed by reduction of ethe ster yielded a triol, which was converted to a MLA analogue by a three-step procedure, previously developed in this group.[23]



Scheme 4.

The esterification procedure for the introduction of the methylsuccinimidobenzoate moiety onto the neopentyl-like alcohol proved to be a challenging task. All other common methods of esterification, attempted by several groups, failed due to either the steric hindrance of the neopentyl alcohol or to the formation of a stable and unreactive intermediate of 2-methylsuccinimido benzoic acid with reagents like DCC or DEAD. The procedure developed by Blagbrough *et al* involves the reaction of the neopentyl alcohol with isatoic anhydride under basic catalysis and the conversion of the resulting anthranilate ester into methylsuccinimidobenzoate ester by reaction with enantiomerically pure methylsuccinic anhydride (Scheme 5).[23] The last step proceded through the half-acid amide and the slow ring-closure step (dehydration) was accelerated by the addition of carbonyl diimidazole (CDI).

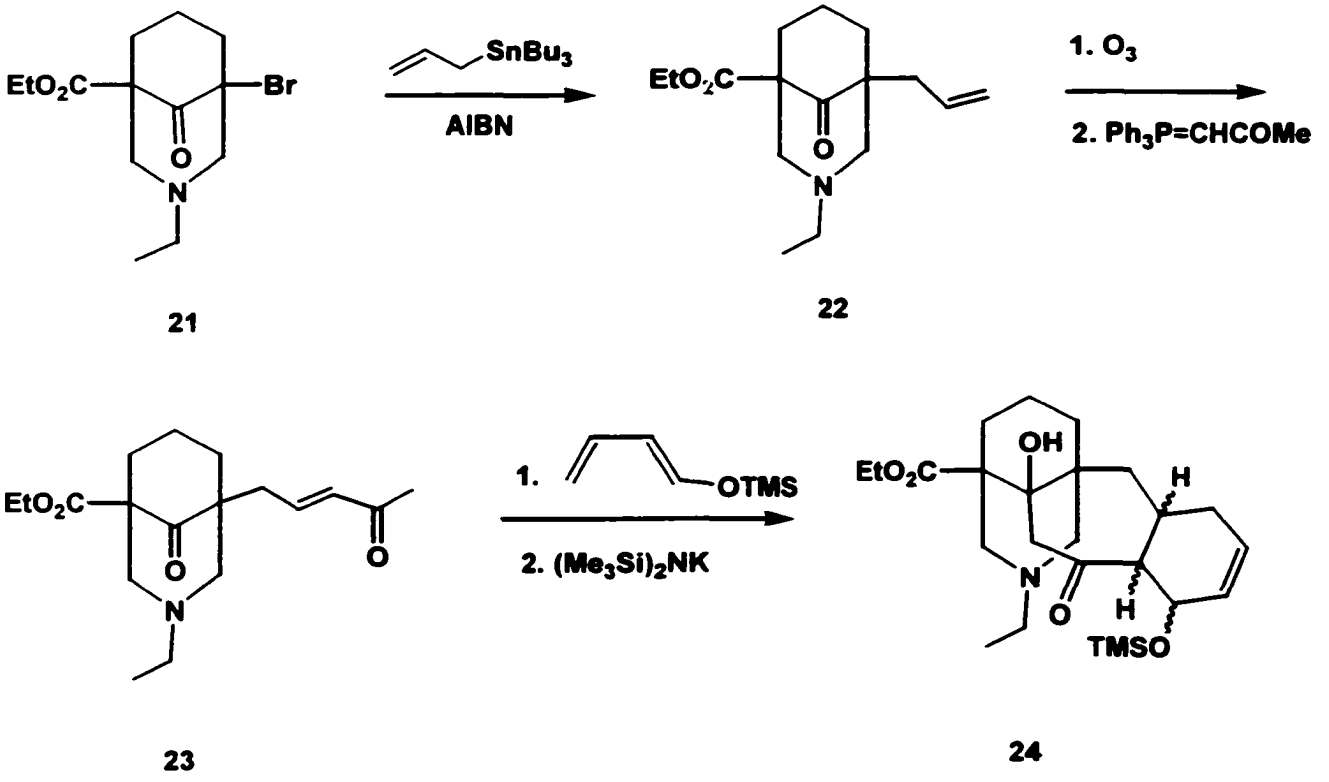


Scheme 5.

Also an important credit to Blagbrough *et al* lies in establishing the absolute configuration of the methylsuccinimide moiety as *S*,[24] since this moiety plays a significant role in the affinity and selectivity of MLA as the nicotinic receptor antagonist. However, synthetically the proposed route cannot be further developed from the AE-bicyclic analogue

toward the natural product due to the lack of functionality and, therefore, a strategy for incorporation of the 5,8,5-fused system.

The synthesis of an AEBD-tetracycle employing new methodology involving the addition reactions of bridgehead radicals to alkenyltributylstannanes and α,β-unsaturated ketones and esters has been accomplished by Kraus *et al.*[25] Initially, the bicyclic ketone **21** was reacted with allyltributyltin in the presence of AIBN to afford the alkene **22** in good yield (Scheme 6). Ozonolysis of the double bond and a Wittig reaction of the resulting aldehyde yielded enone **23**, which underwent Diels-Alder reaction with 1-trimethylsilyloxy-1,3-butadiene. Intramolecular aldol cyclization with potassium hexamethyldisilazane furnished the AEBD-ring system of the C_{19}-deterpene alkaloids.

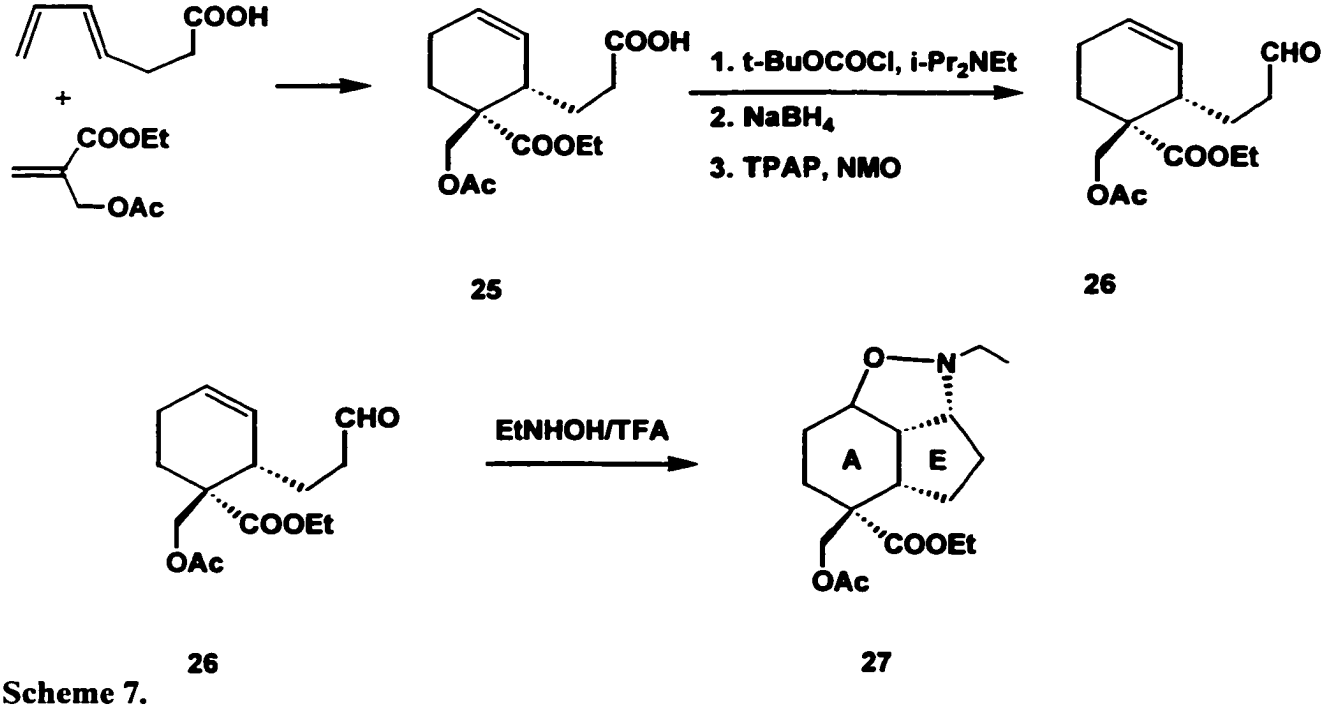


Scheme 6.

Later this approach was modified to include more complicated cases of the addition of the bridgehead radicals to the α,β-unsaturated ketones.

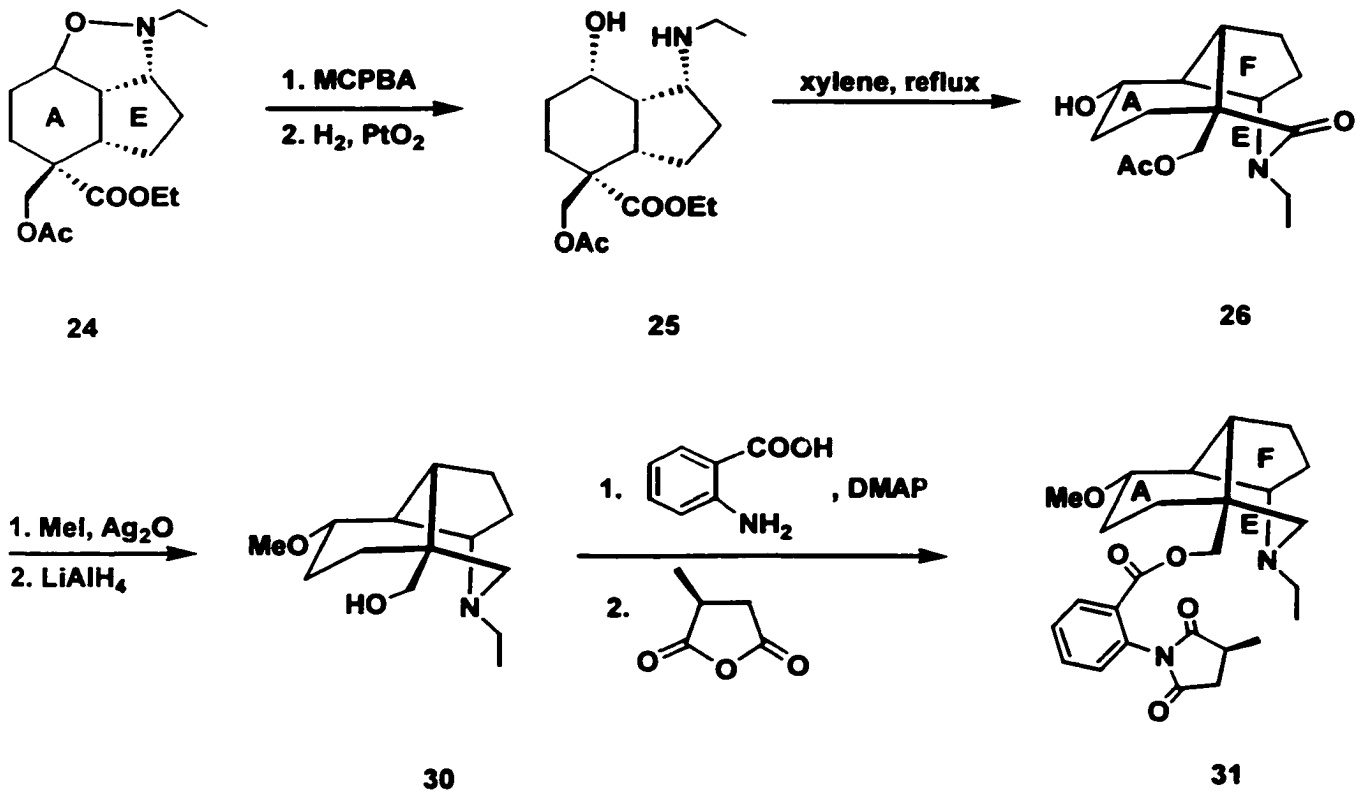
Noteworthy from the synthetic point of view is the synthesis of the AEF tricyclic fragment of MLA, achieved by Whiting and co-workers.[27] The key compound in this approach is the isoxazolidine, which contains all the stereocenters required for synthesis of the fragment. The stereocenters are set up in two key reactions - the intramolecular 1,3-dipolar addition of a nitrone functionality to the alkene and a Diels-Alder reaction.

The Diels-Alder reaction of a sodium salt of the acid with the methacrylate yielded a mixture of endo : exo products, where the ratio could not be improved beyond 3.3: 1. After separation, the endo-acid **25** was converted into aldehyde **26** by a three-step procedure involving reduction of a mixed anhydride, followed by oxidation of the resulting alcohol with TPAP and NMO (Scheme 7).



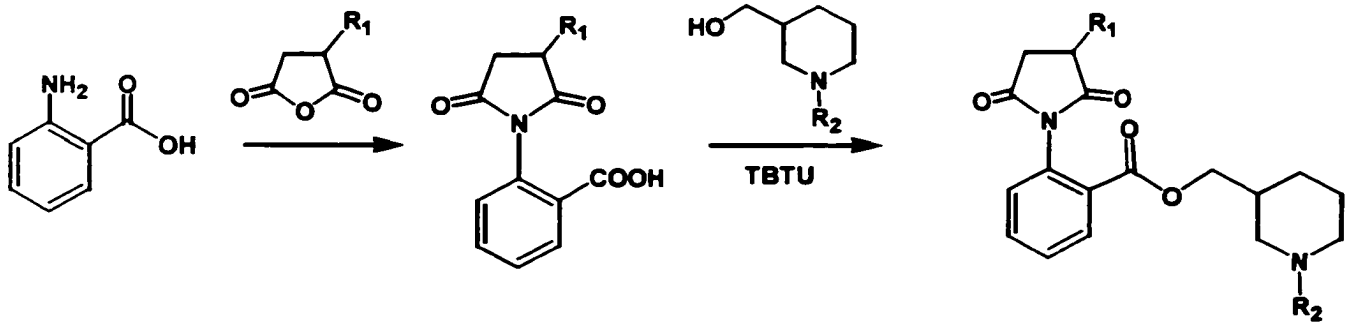
Scheme 7.

The aldehyde **26** was converted to the isoxazolidine **27** via the nitrone in a one-pot process. Treatment of the isoxazolidine **27** with MCPBA gave the N-oxide, which spontaneously ring-opened with elimination to afford a nitrone. The nitrone was reduced catalytically to amine **28**, which underwent intramolecular reaction with the ester function present in the molecule to afford the desired tricyclic system **29**. After *O*-methylation and simultaneous reduction of both the amide and ester functionalities, the obtained tricyclic neopentyl-like alcohol **30** was subjected to the esterification protocol of Blagbrough *et al*[23] to afford the AEF tricycle in 14 steps and 5% overall yield as a mixture of diastereomers.



Scheme 8.

Ring E analogues with 2-(methylsuccinimido)benzoate side chain were prepared by Bergmeier and co-workers.[26] Even these simple monocyclic compounds, when assayed for the nicotinic activity, were found to act as functional antagonists on adrenal nicotinic receptors, which means that biological activity is already partially inherited in this structure. The purpose of the study was to examine the effect of different groups on the nitrogen of the piperidine ring on the biological activity of the analogues. It was found that shortening or increasing the length of the *N*-alkyl chain or placing the oxygen in the chain resulted in no significant changes in antagonist activity. However, larger alkyl groups (e.g. *i*-Pr or $Ph(CH_2)_3$) produced more potent antagonists. The second issue they addressed was the coupling of the alcohol of the piperidine ring with 2-(methylsuccinimido)benzoic acid. They have established a new protocol for the coupling, using 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) as a coupling reagent. However, the yields for this reaction were inconsistent, ranging from 6% to 60% (Scheme 9).



32 33 34

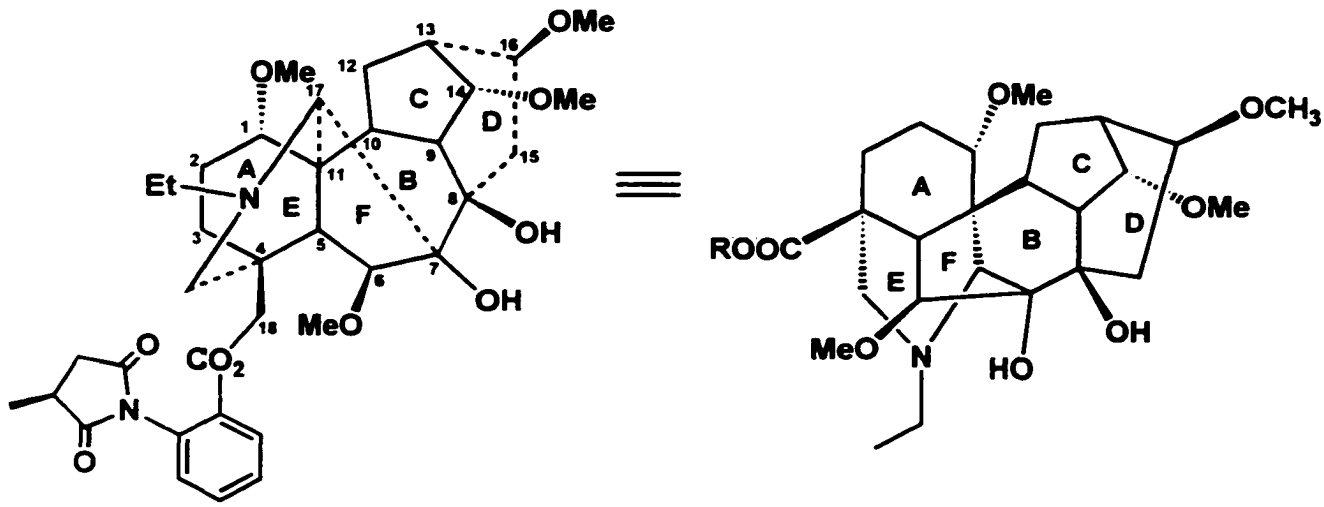
R_1= H, Me
R_2= Me, Et, *i*-Pr, *n*-Bu, EtOEt, $PhCH_2CH_2$, $Ph(CH_2)_3$

Scheme 9.

RESULTS AND DISCUSSION

FIRST RETROSYNTHETIC ANALYSIS

In our initial approach we envisioned the synthesis of an AEBC-carbocycle, possessing all necessary functionality, which would allow us to easily incorporate the E- and D-rings.

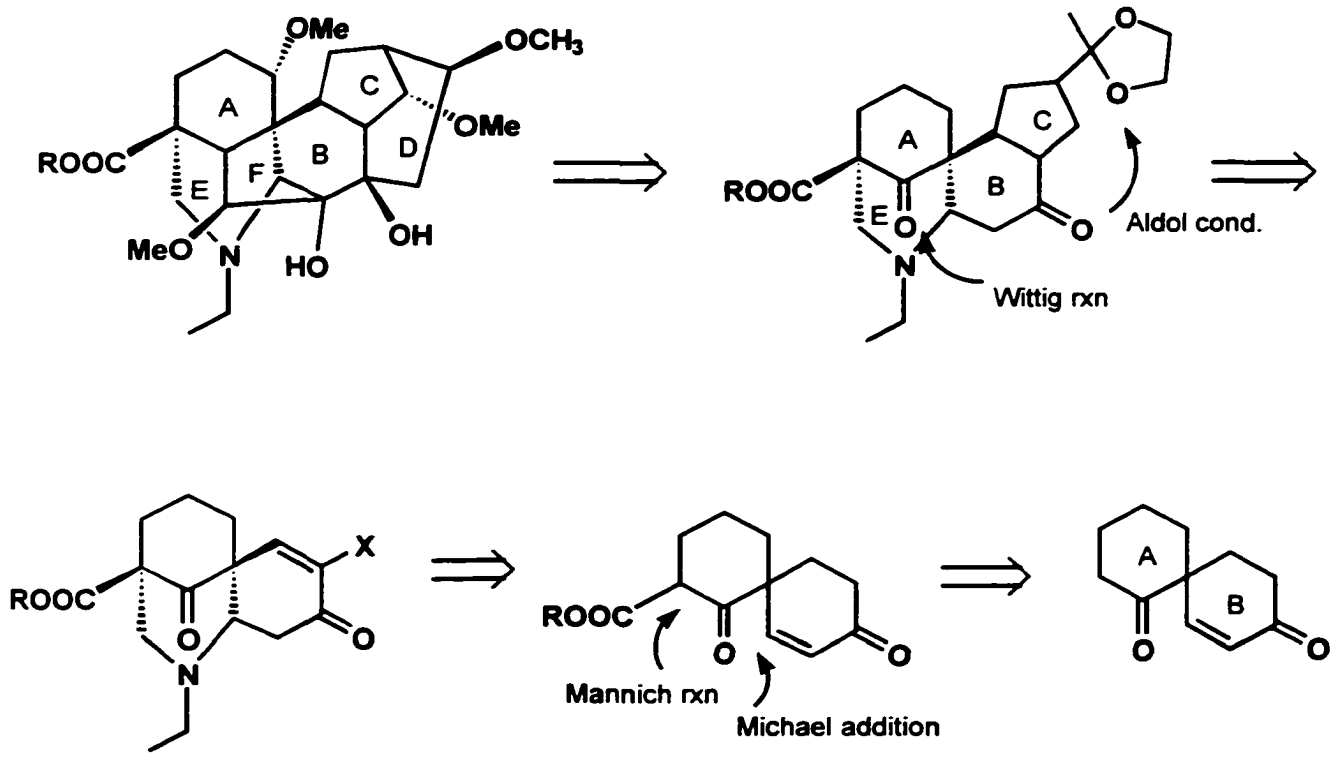


Methyllycaconitine

Figure 7.

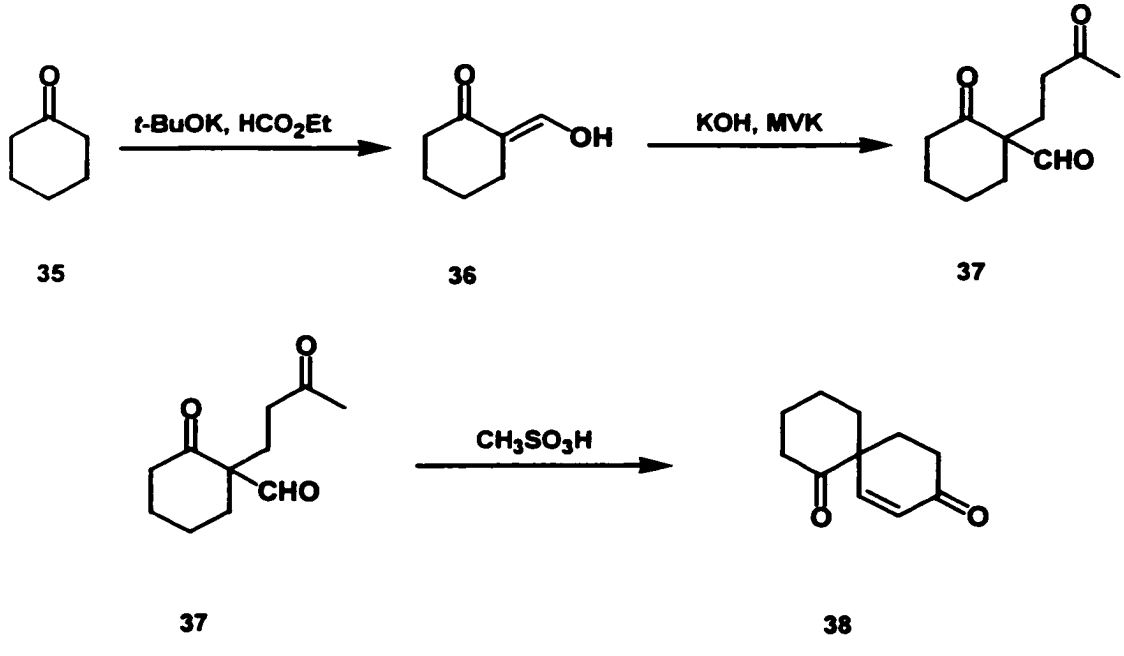
The following retrosynthetic scheme suggests three key-steps in the synthesis of the skeleton. A one-carbon extension resulting from a Wittig reaction on the carbonyl group of the 3-azabicyclo[3.3.1]nonane system would produce an aldehyde, which could undergo intramolecular aldol condensation to furnish the F-ring. After deprotection of the ketal, a second intramolecular condensation of the acetyl group with the carbonyl group of the B-ring

would result in closure of the final D-ring and, therefore, would give the desired hexacyclic skeleton of the aconitine alkaloids. The synthesis of the AEBC-carbocycle was envisioned through the addition reaction of the double bond of the tricyclic enone, which could be obtained by a tandem Mannich reaction-Michael cyclization of the spiro-keto ester. The bicyclic intermediate representing the AB-ring system in turn could be synthesized from the known spiro-diketone.



Scheme 10. Retrosynthetic analysis. Approach to the AEBC-carbocycle by a tandem Mannich reaction-Michael addition sequence.

The known[27] spirocyclic diketone **38** was obtained by a three-step procedure starting from cyclohexanone (Scheme 11). Formylation of cyclohexanone with potassium *t*-butoxide and ethyl formate yielded 2-oxocyclohexanecarbaldehyde **36**, which underwent Michael addition to methyl vinyl ketone and subsequent aldol condensation under acidic conditions to furnish the spiro-diketone **38**. When the original literature procedures, utilizing potassium hydroxide[27] or *p*-toluenesulfonic acid in benzene,[28] were employed, the final cyclization proceeded with an equal amount of a by-product, resulting from decarbonylation and aldol condensation of the two carbonyl groups. After investigating the literature of similar systems, we have found that the unwanted side reaction can be supressed by using methanesulfonic acid as the acidic catalyst,[29] thus improving the yield of the spirocompound to 85%.

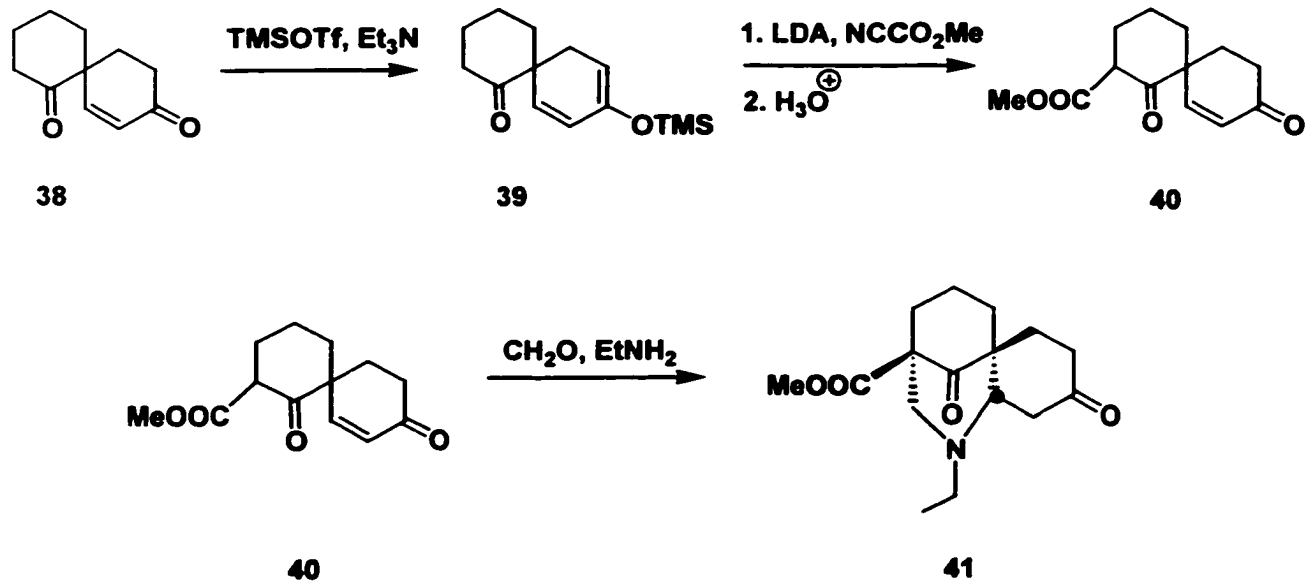


35 36 37

37 38

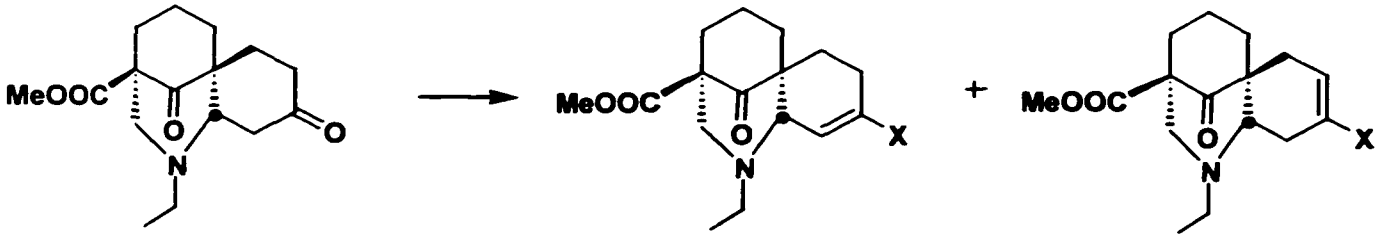
Scheme 11.

The regioselective introduction of the carboxylate group onto the A-ring required the selective protection of the unsaturated carbonyl group of the enone **38**. The selective protection of the enone was achieved with trimethylsilyl triflate and triethylamine in dry ether at $-10^{\circ}C$.[30] When the reaction was conducted at room temperature, a mixture of the mono- and bis-silylated enol ethers along with the starting material was obtained. This result clearly indicates that the reaction both kinetically and thermodynamically favours formation of the diene system **39**. Carboxylation of the A-ring with LDA and methyl cyanoformate, employing Mander's procedure[31], and acidic cleavage of the enol silyl ether set the stage for exploration of the tandem Mannich reaction-Michael addition sequence. Treatment of the compound **40** with ethylamine and formaldehyde in aqueous methanol furnished the tricyclic compound **41** as a colourless crystalline material (Scheme 12). The synthesis of the ABE-ring system was achieved in 7 steps in a good overall yield. The desired stereochemistry of the tertiary carbon adjacent to the nitrogen was confirmed by X-ray analysis of the crystalline material **41**.



Scheme 12.

With the tricyclic compound in hand, the next logical step was to explore the possibility of incorporating the F-ring into the existing system. As discussed in the retrosynthetic analysis, the Wittig reaction of the carbonyl group with methoxymethylenetriphenylphosphorane[32] would provide the required one carbon extension. After hydrolysis of methyl enol ether, the resulting aldehyde could easily undergo intramolecular aldol condensation to furnish the desired ABEF-ring system, and it would be also properly functionalized with the hydroxy group at C-6 as in the natural product. Since two carbonyl groups were present in the molecule, we differentiated the enolizable ketone from the non-enolizable one by protection of the former as the trimethylsilyl enol ether. The reaction of the tricyclic diketone **41** with lithium diisopropylamide and chlorotrimethylsilane afforded a mixture of the regioisomeric silyl enol ethers **42** in 2 : 1 ratio with the major isomer bearing a double bond close to the tertiary amine, probably due to a chelation effect.



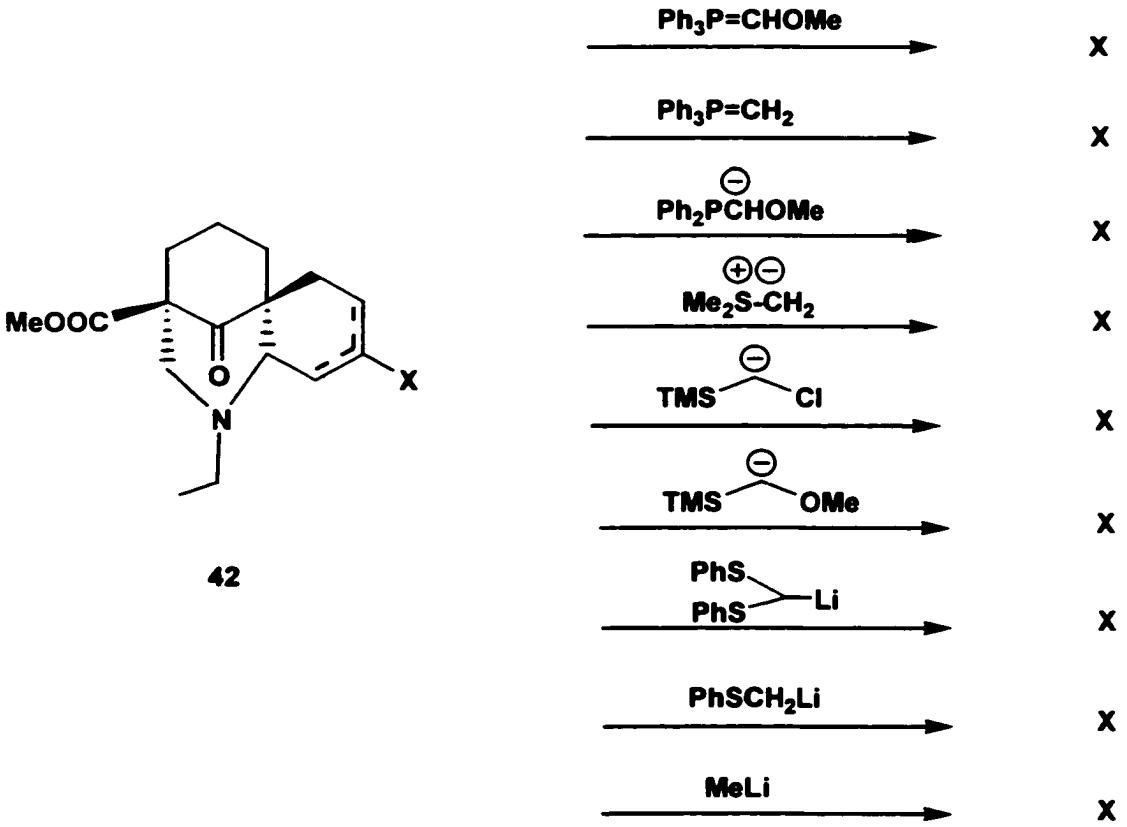
41 **42**

42a	**X = OTMS**	**2 : 1**
42b	**X = OTBS**	**1 : 1.5**
42c	**X =** 	**1 : 1**

Scheme 13.

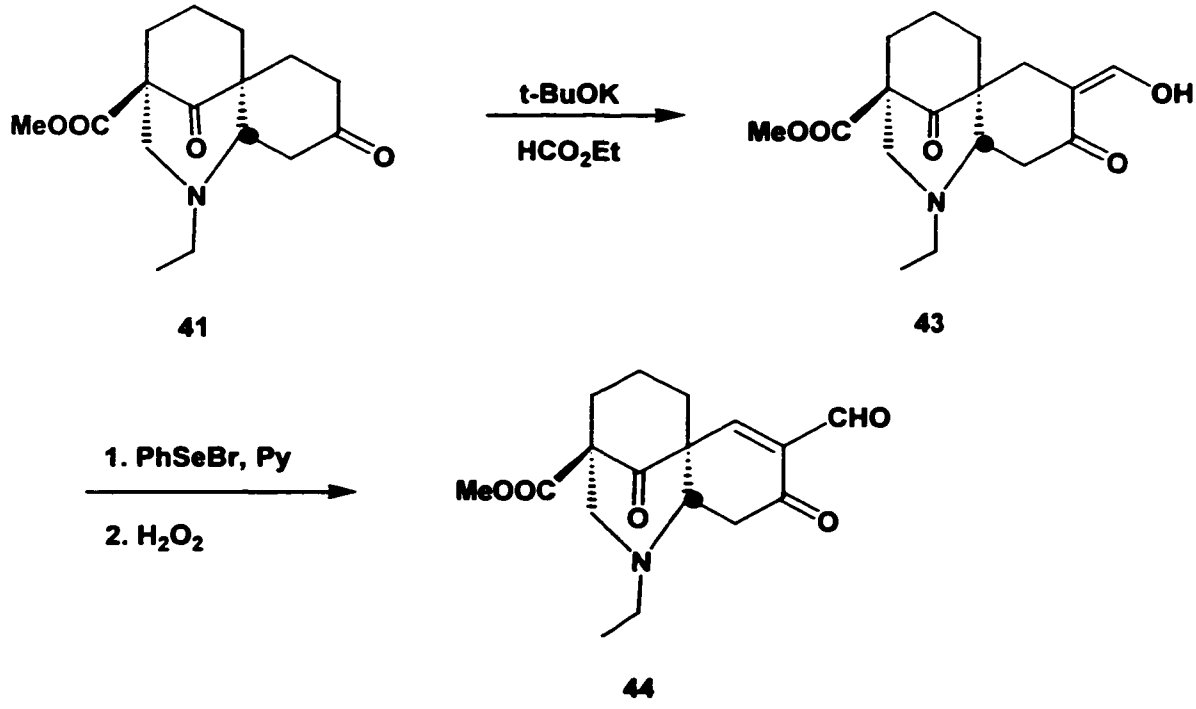
Reaction of the tricyclic diketo amine **41** with *t*-butyldimethylsilyl triflate and triethylamine afforded a mixture of the regioisomeric silyl enol ether in a 1.5 : 1 ratio with the major isomer bearing the more distant site from the amine group and so less sterically hindered for the approach of the bulky TBSOTf. Treatment of the compound **41** with pyrrolidine and PTSA in benzene produced the regioisomers **42c** in a 1 : 1 ratio.

Although use of the Wittig reaction appeared to be very smooth and straightforward, both compounds **42a** and **42b** failed to react with methoxymethylenetriphenylphosphorane[32] under a variety of conditions. Considerable efforts were invested in finding the proper conditions, which would lead to the much-desired one carbon extension (Scheme 14).



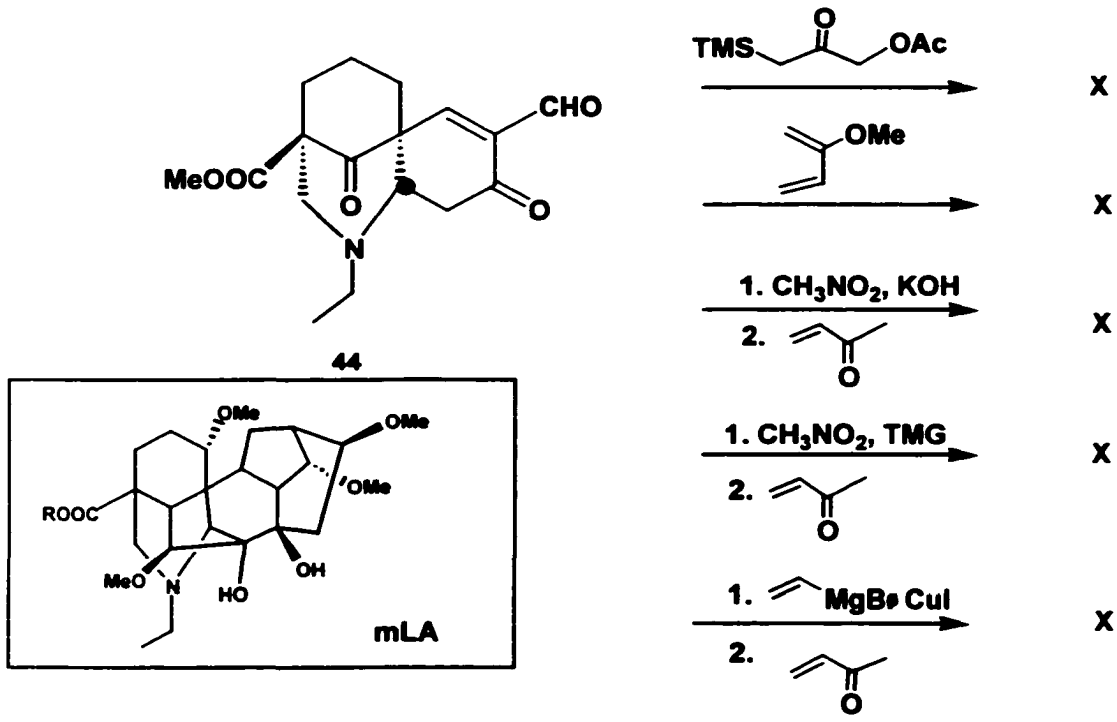
Scheme 14.

However, this carbonyl group proved to be unreactive with all chosen phosphorous and sulfur ylids, even with those which were specifically introduced for sterically hindered ketones, such as Corey's ylid.[33] The reactions with the organolithium reagents resulted in the formation of complex mixtures and disappearance of the ester group in the ^{1}H NMR spectrum. After a while, we came to the conclusion that, unfortunately, this transformation cannot be achieved. Later on, this conclusion was confirmed by Blagbrough *et al.*[34] The steric hindrance of the carbonyl group of the 3-azabicyclo[3.3.1]nonane system is much greater than it was initially thought. Since the incorporation of the F-ring was unsuccessful, we turned our attention to the formation of the C-ring by an addition reaction. With this strategy in mind, we sought to introduce the electron-deficient double bond at C9-C10 (Scheme 15).



Scheme 15.

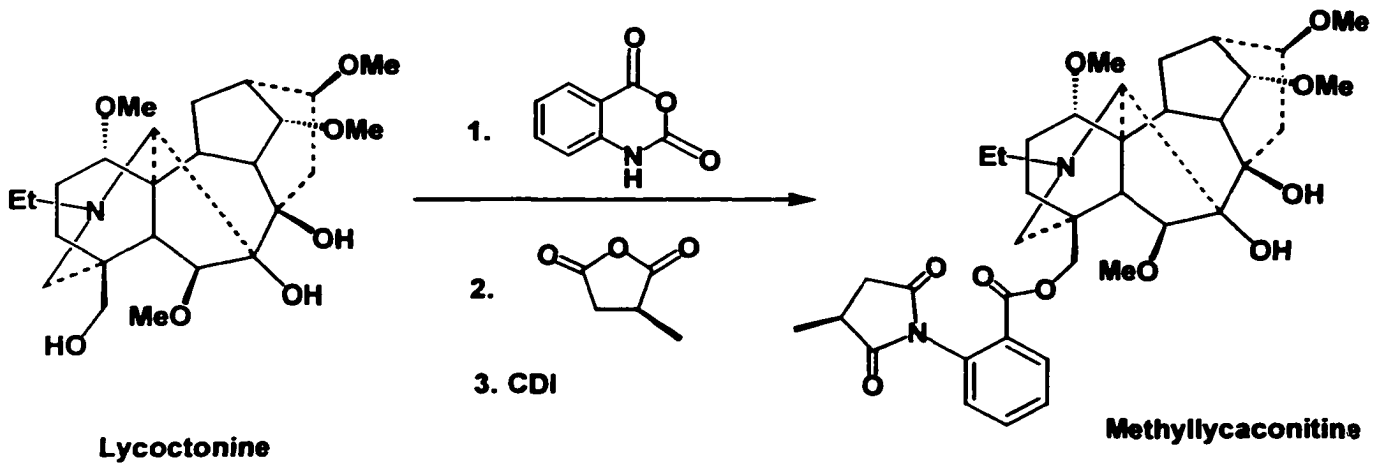
In contrast to the formation of the regioisomeric enol ethers upon treatment with LDA and TMSCl, the reaction with potassium *t*-butoxide and ethyl formate yielded just one regioisomer **43** with the hydroxymethylene group at the carbon furthest from the tertiary nitrogen. The selenium chemistry common for the introduction of the double bond[35] proceeded with the clean and quantitative formation of the desired unsaturated β-ketoaldehyde **44**. Although this double bond seemed to be quite electron-deficient and sterically unobstructed, the palladium catalyzed [3+2] addition of acetyl 2-(trimethylsilylmethyl)prop-1-en-3-ol did not result in five-membered ring formation[36] (Scheme 16). Since this cycloaddition is known to be low-yielding and dependent both on the steric hindrance and strong electron-deficiency of the double bond, the negative result in this case was not surprising.



Scheme 16.

However, the Diels-Alder reaction of **44** with 2-methoxybutadiene also failed to produce the cycloadduct. Since our cycloaddition approach was not successful, we decided to construct the fourth ring of the target molecule by two subsequent 1,4-additions. The base-catalysed addition of nitromethane or the addition of a cuprate to the double bond of β-keto aldehyde **44**, followed by trapping of the intermediate enolate with methyl vinyl ketone resulted either in the recovery of the starting material or in the formation of complex mixtures of products (Scheme 16).

In spite of its initial promise, this route became unproductive to be able to maintain our interest in it. Our attention was turned to another intriguing problem in the synthesis of methyllycaconitine. In 1994 two papers by Blagbrough *et al* on the stereochemistry of the methyl group on the succinimido ring[24] and on a new esterification protocol[23] appeared in *Tetrahedron Letters*. The introduction of a 2-methylsuccinimido benzoate ester on the C-19 neopentyl-like alcohol was achieved by a three-step procedure. First, the alcohol was reacted with isatoic anhydride, which served to introduce the anthranilate ester with the loss of one equivalent of carbon dioxide.

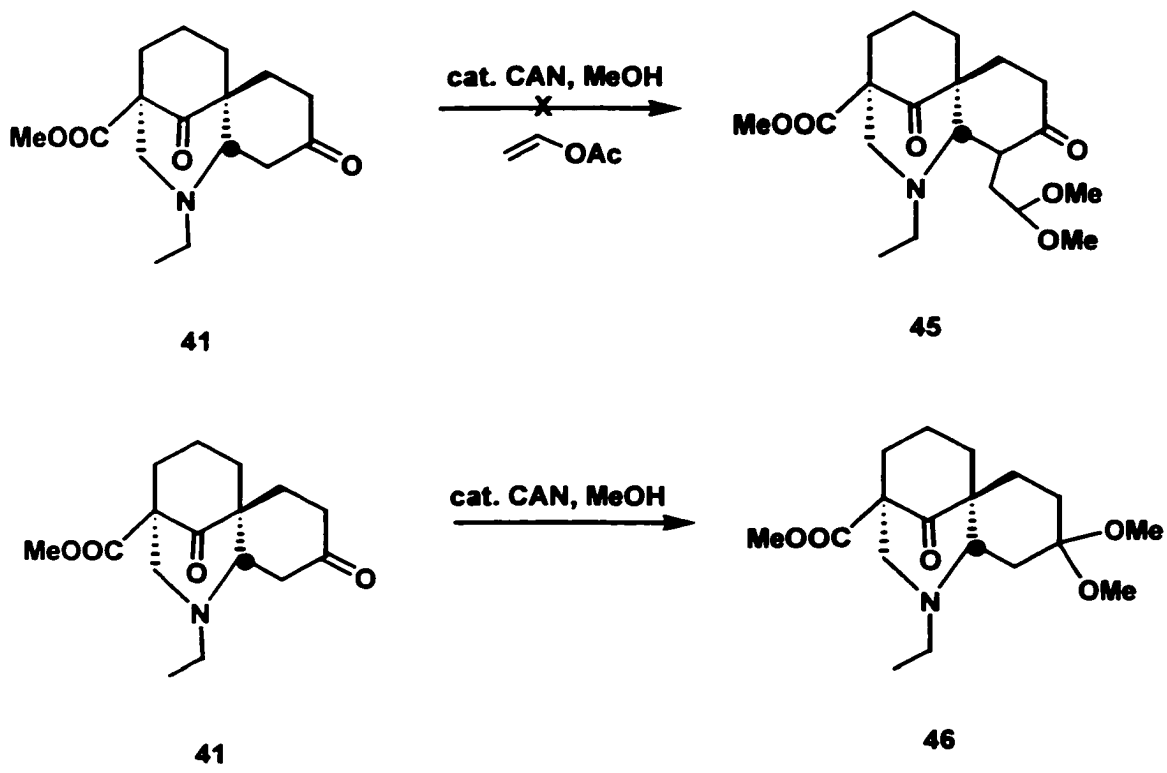


Scheme 17.

The methysuccinimide moiety was then introduced by fusion of the anthranilate with an excess of neat methylsuccinic anhydride. This reaction proceeds through the half-acid amide and the slow ring-closure step (dehydration) was accelerated by the addition of carbonyl diimidazole (CDI). When lycoctonine was subjected to this protocol, methyllycaconitine was obtained in 12 % overall yield (Scheme 17).

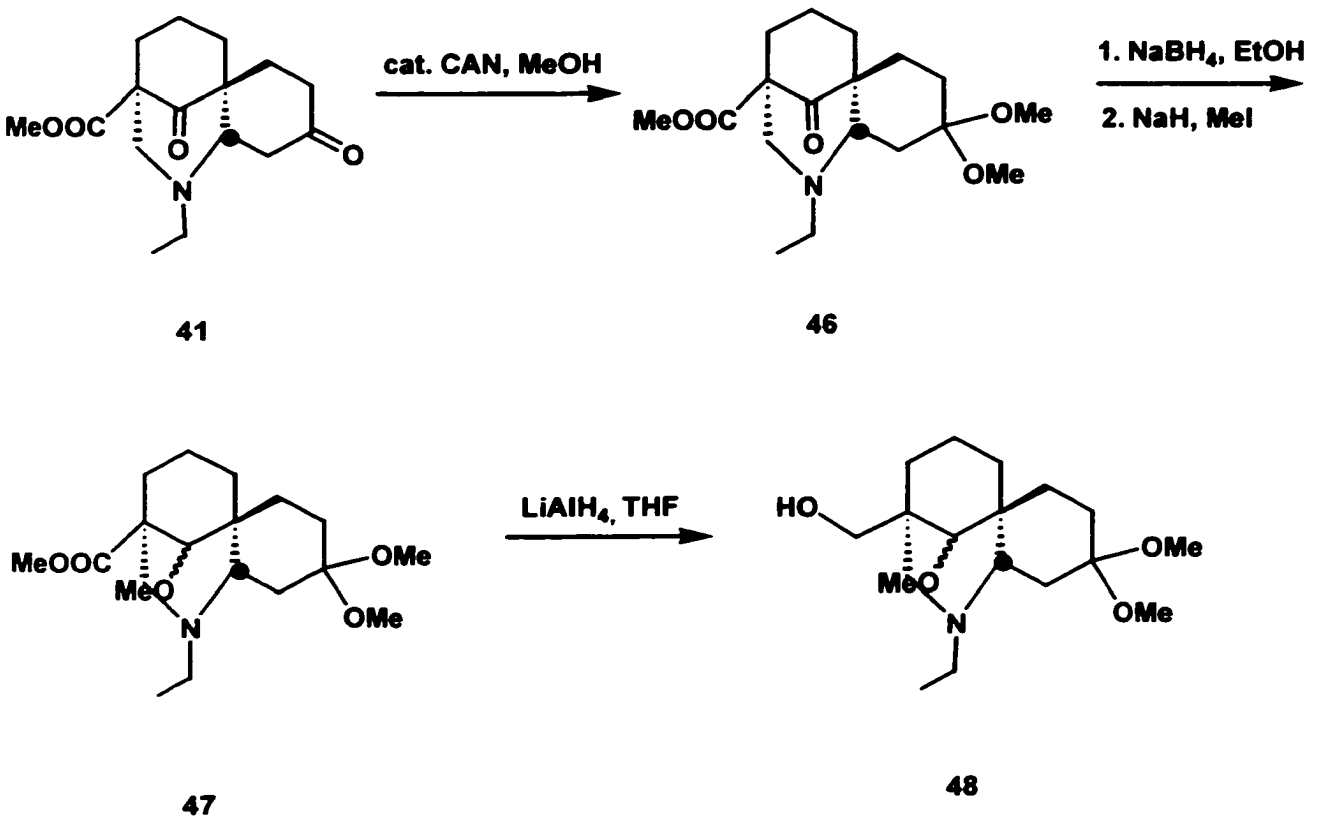
The difficulty of the appendage of this side chain on the sterically hindered neopentyl-like alcohol is obvious if it requires such unusual and harsh conditions. Though Blagbrough's protocol provides a way, the low yield of these last three steps would dramatically cut the overall yield of the synthesis of this natural product. This observation called to our attention the necessity of investigating a new, more facile method for introduction of the 2-methyl-succinimidobenzoate moiety. We felt that our tricyclic intermediate, possessing ABE-carbocycle and, thus, the steric and electronic factors present in the natural product, would be the ideal candidate for such a study.

Since the C-19 neopentyl-like alcohol would arise from the reduction of the ester group, some modifications had to be done to protect two carbonyl groups present in our tricyclic compound. In our previous studies, when attempting a one-electron oxidation of **41** alpha to the carbonyl group with the ceric ammonium nitrate in methanol with the subsequent addition of the radical-cation to the vinyl acetate,[37] we found much to our surprise that only methyl ketal **46** was formed in quantitative yield (Scheme 18). This conversion proceeded with a catalytic amount of the ceric ammonium nitrate (~0.05 equiv.) and in an amazingly short period of time (15-30 min). It seems that CAN behaved not as a one-electron oxidant, but as a Lewis acid in this reaction.



Scheme 18.

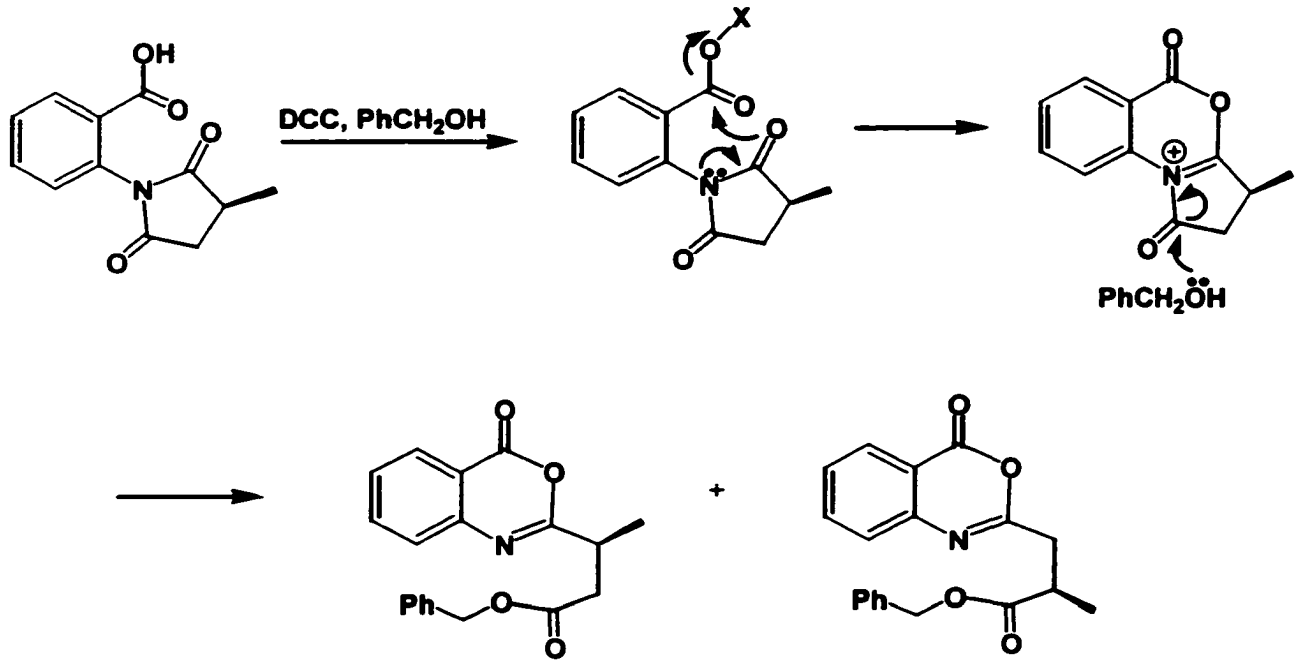
After utilising this finding to protect one carbonyl group in **41** as the methyl ketal, the second carbonyl group was reduced with sodium borohydride in ethanol, and the resulting secondary alcohol upon treatment with sodium hydride and methyl iodide was converted to the methyl ether **47**. Both the ^{1}H and ^{13}C NMR spectra showed that the reduction of the carbonyl group produced a mixture of stereoisomeric alcohols in a 1 : 1 ratio. Though at this point the diastereomeric mixture was not of concern, this result provided valuable insights on the nucleophilic additions to this sterically hindered carbonyl group. Reduction of the ester with lithium aluminum hydride in tetrahydrofuran furnished the required neopentyl alcohol **48** for our esterification studies (Scheme 19).



Scheme 19.

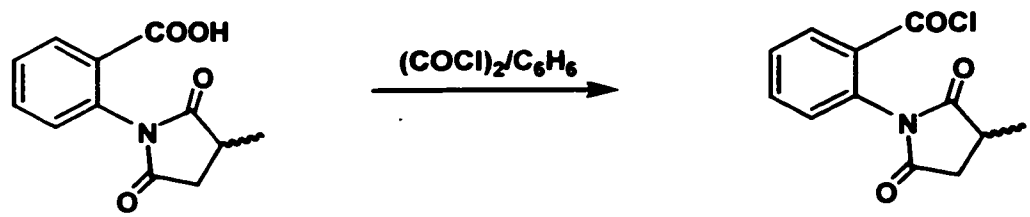
Our goal in these studies was to achieve the direct connection of the 2-methyl-succinimidobenzoic acid to the C-19 alcohol in one step and in high yield. The 2-methyl-succinimidobenzoic acid was produced in 80-90% yield by the fusion reaction of anthranilic acid with 2-methylsuccinic anhydride at low pressure.[38] Our initial attempts to couple this acid to our alcohol using the obvious dehydrating reagents like dicyclohexylcarbodiimide[39] or diethyl azodicarboxylate and triphenylphosphine (Mitsunobu's protocol)[40] failed to result in esterification. When DCC was employed, we observed formation of the intermediate

containing DCC and the 2-methylsuccinimidobenzoate moiety. This intermediate seemed to be stable and unreactive towards nucleophilic attack of alcohols. In 1998 Whiting's group, while repeating the same procedure with benzyl alcohol, reported the formation of a mixture of isomers which they proposed to be the 1,3-oxazinones (Scheme 20).[41]



Scheme 20.

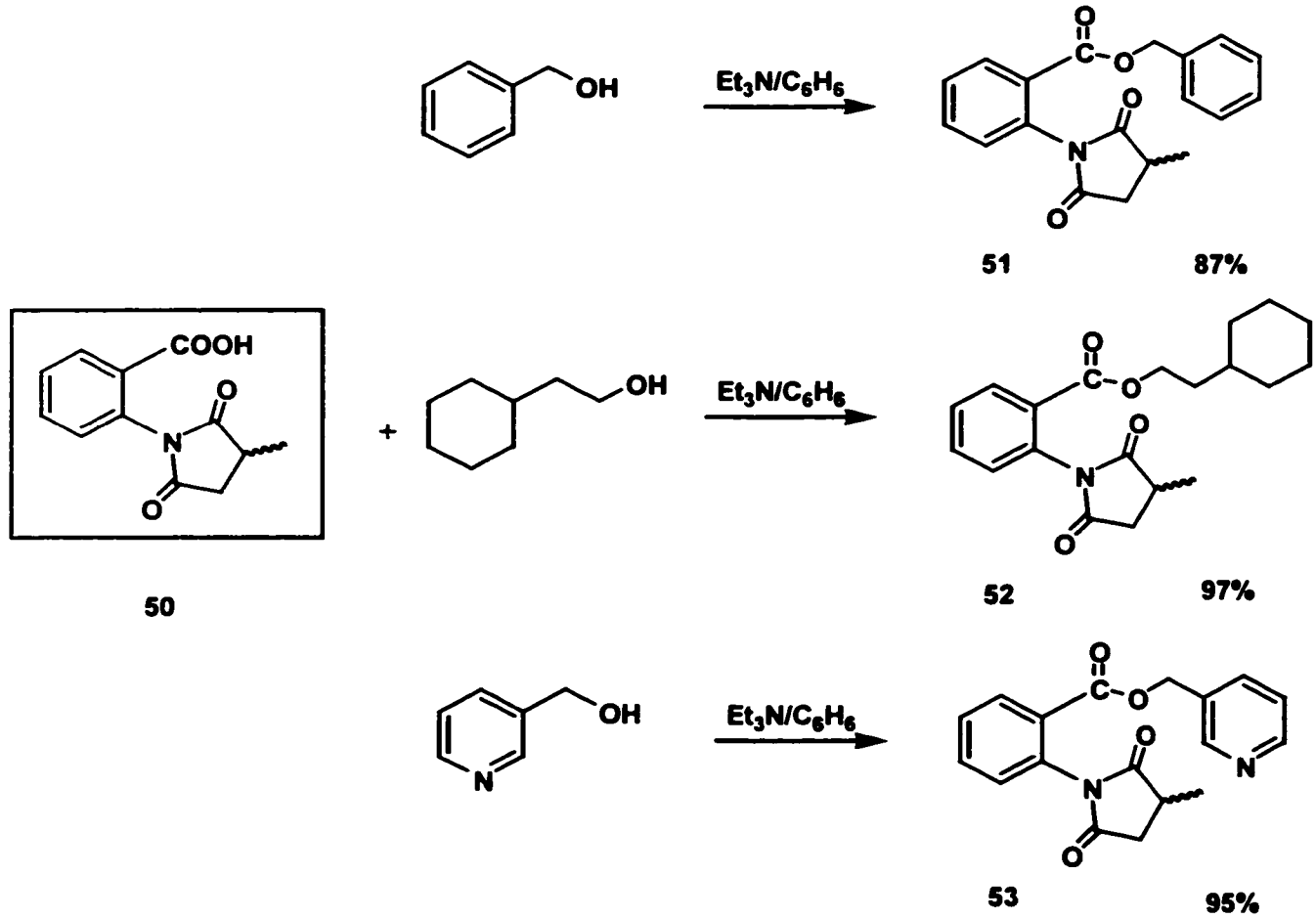
These heterocycles are presumably formed by nucleophilic attack of a carboxylic acid on the carbonyl group of the succinimido ring. Since the conventional and commonly employed methods using dehydrating agents clearly are not applicable in this case, we decided to investigate the coupling of an acid chloride with alcohols. The acid chloride of 2-methyl-succinimidobenzoic acid, formed by treatment of the latter with oxalyl chloride in benzene (Scheme 21), proved to be advantageous in two aspects - it's highly susceptible to nucleophilic attack and, being the small, reactive intermediate, it resolves the issue of steric demand of the alcohol.



49 50

Scheme 21.

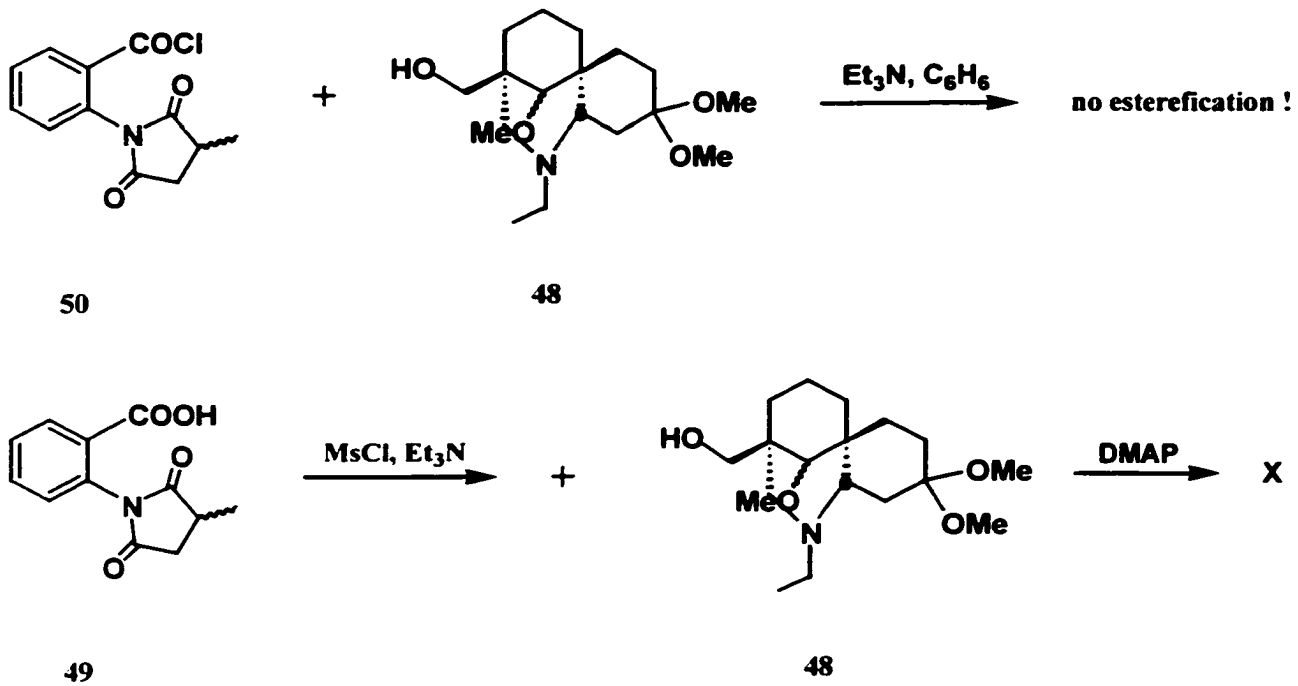
Our initial results on the coupling of this acid chloride to a number of alcohols were very encouraging, as all reactions proceeded in very high yields (87-97%) (Scheme 22).



50 51 87% 52 97% 53 95%

Scheme 22.

However, when the same conditions were applied to our key compound, a complex mixture of products was obtained. The mixed anhydride approach also failed to produce the desired ester (Scheme 23).

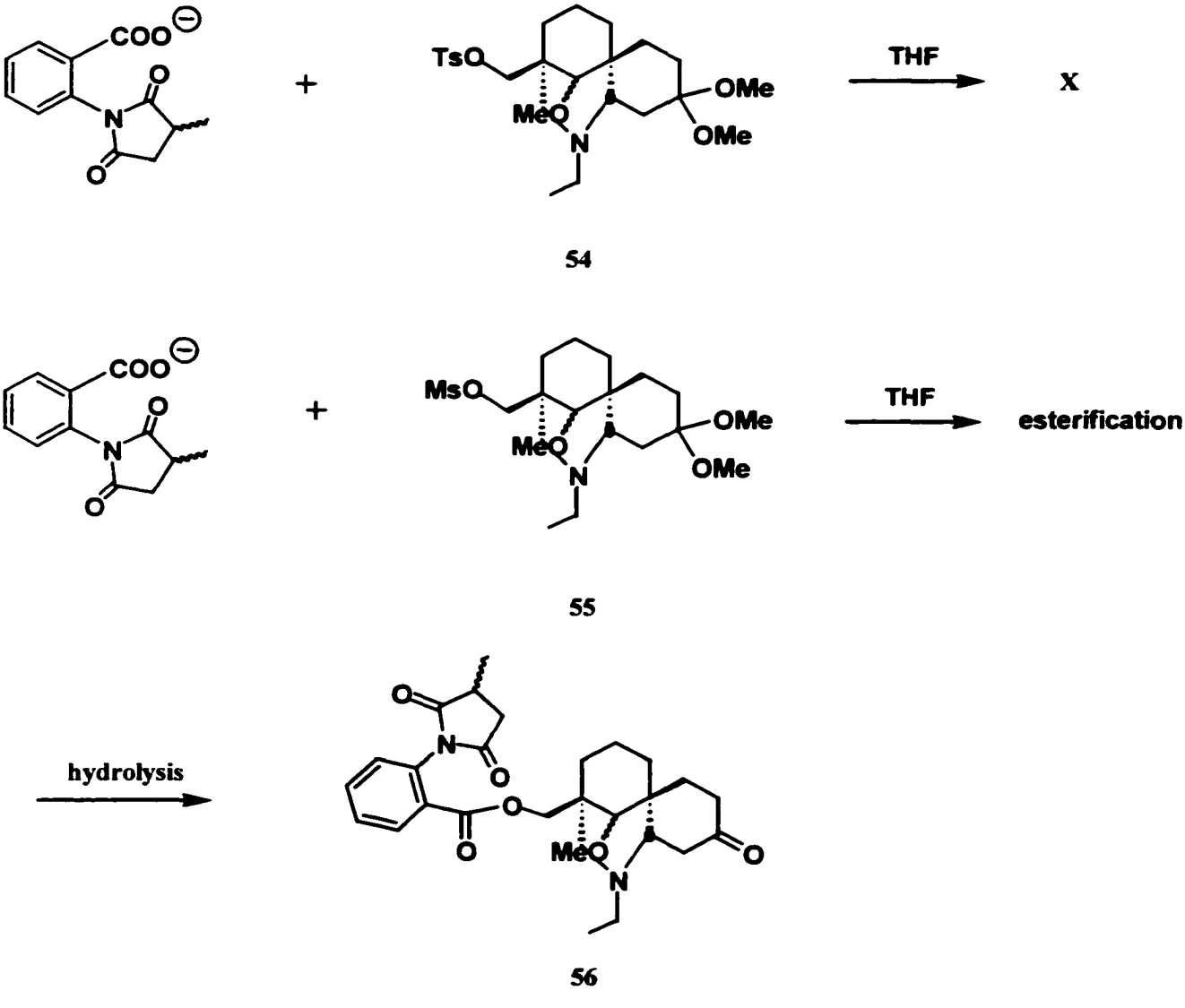


Scheme 23.

Next, we decided to investigate the possibility of nucleophilic attack of the carboxylate group on the tosylate group[42] of the tricyclic compound. When 2-methylsuccinimidobenzoic acid was treated with sodium hydride, followed by addition of the tosylate, only starting material was recovered. We felt that the negative result in this case could be due to the steric requirements of the tosylate (Scheme 24). Our logic proved to be correct. When the sodium salt of 2-methyl succinimidobenzoic acid was treated with the less sterically hindered mesylate of our key compound, the esterification occurred in good yield to give compound **56**, where

the dimethyl ketal underwent hydrolysis during the reaction. Hence, this attractive synthetic shortcut allows one to improve the overall yield of the total synthesis of methyllycaconitine and other lycoctonine alkaloids, containing this moiety.

After resolving the issue with the appendage of the side chain, we once again turned our attention to the synthesis of the hexacyclic skeleton of methyllycaconitine.



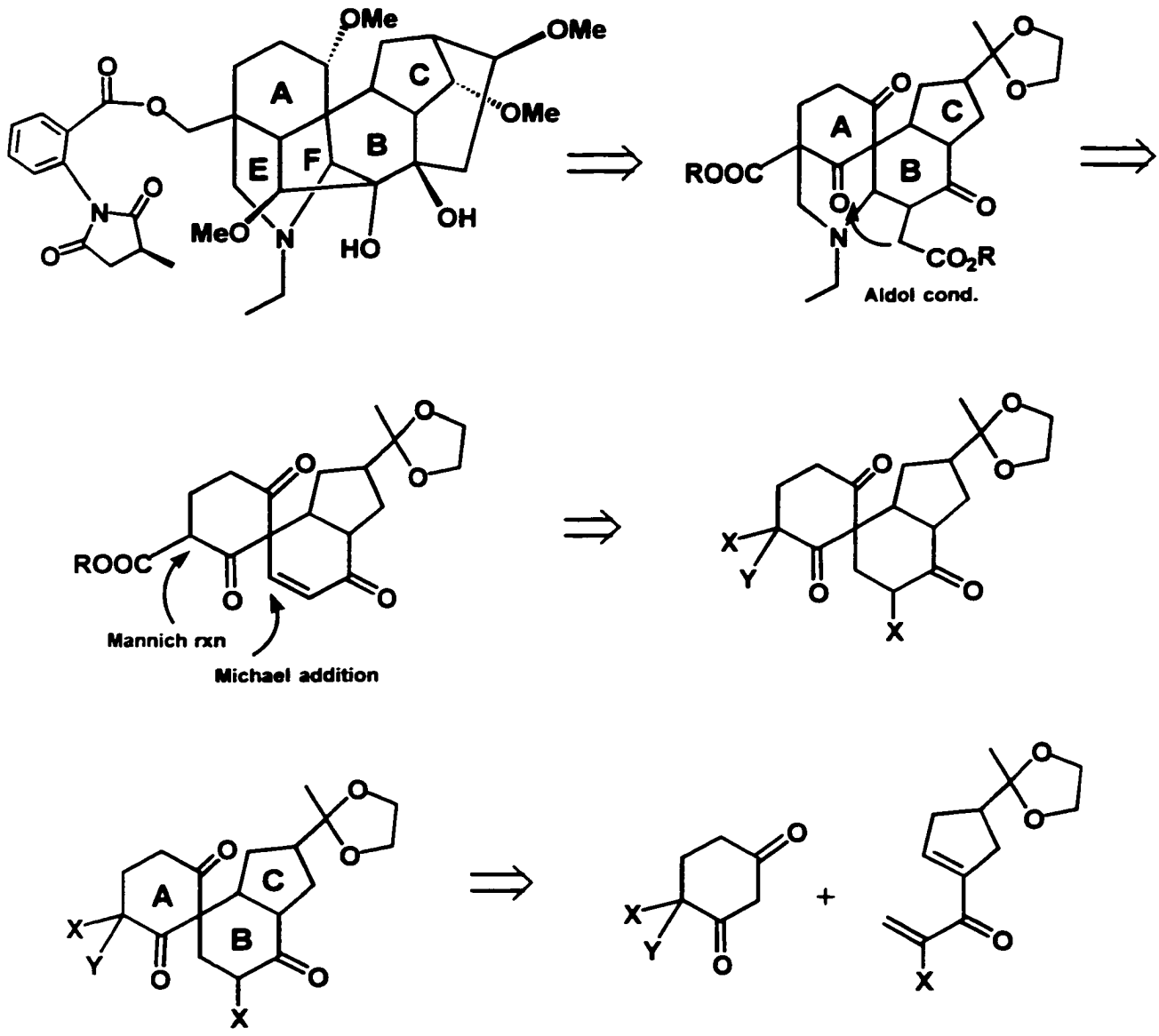
Scheme 24.

SYNTHETIC STUDIES BASED ON THE DOUBLE MICHAEL ADDITION OF CYCLOHEXANE-1,3-DIONES TO DIENONES: SECOND RETROSYNTHETIC ANALYSIS

In spite of the failure of the approach discussed previously, the wealth of knowledge about the system we were trying to synthesize was augmented considerably. Since all attempts to construct the fourth C-ring of our system using our tricyclic intermediate **41** proved to be futile, we decided to investigate a new synthetic approach in which this ring would be automatically incorporated at an earlier stage of the synthesis. The tetracyclic intermediate, possessing the E-ring with the tertiary nitrogen required for biological activity, could once again arise from the same Mannich reaction-Michael addition sequence we used in the synthesis of the tricyclic compound **41**. The construction of the ABC-carbocycle was envisioned utilizing a double Michael addition of a cyclohexane-1,3-dione to a dienone (Scheme 25).

This retrosynthetic scheme provides an opportunity to construct four out of the six rings present in the target molecule in two tandem reactions using the shortest pathway possible to envision and sets the stage for closure of the D-ring. The problem of constructing the final and the most difficult in the synthesis F-ring might be resolved by intramolecular nucleophilic attack of the β-ketoester on the carbonyl group of the A ring. (Scheme 25).

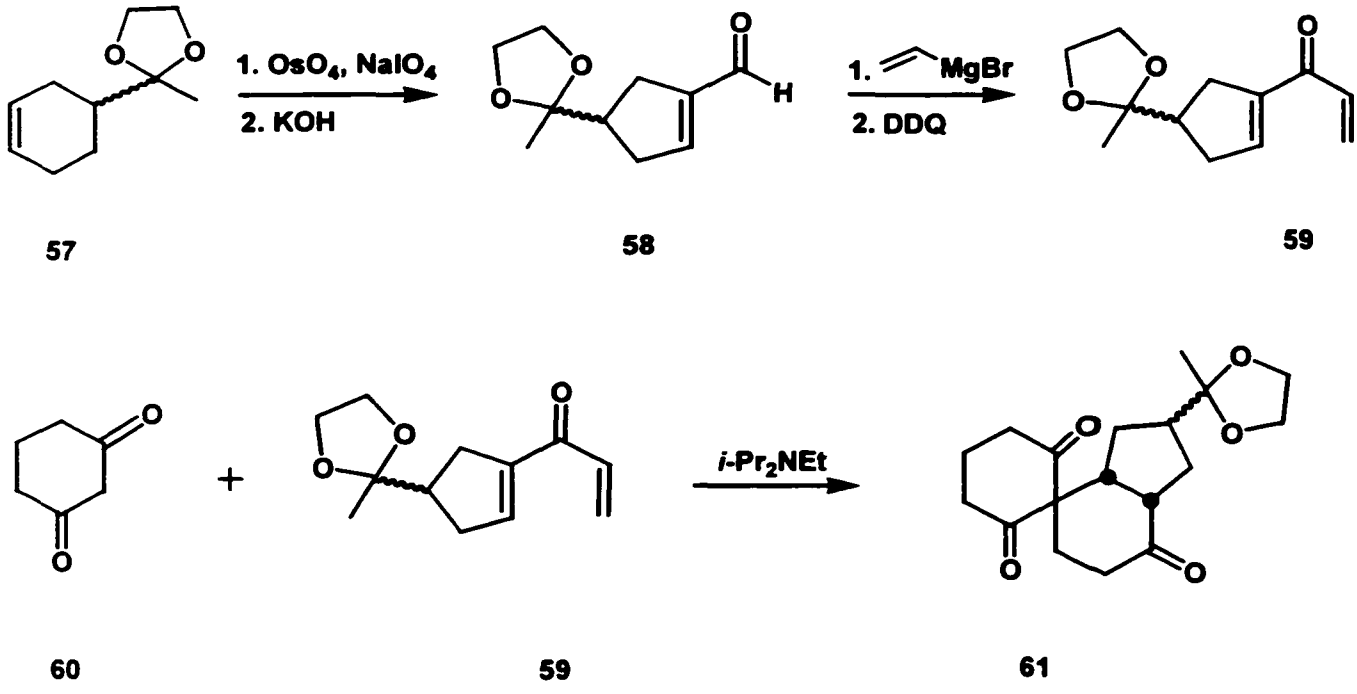
Initial experiments designed to test the double Michael addition of cyclohexane-1,3-diones to the proposed dienones as the key step in the synthesis of the ABC tricyclic fragment required the preparation of the dienones mentioned above.



Scheme 25.

The synthesis of the dienone was achieved in six steps. Diels-Alder reaction of butadiene and methyl vinyl ketone furnished 4-acetylcyclohexene, the carbonyl group of which was protected as a ketal with ethylene glycol. Cleavage of the double bond, using osmium tetraoxide and sodium periodate,[43] resulted in the formation of a dialdehyde, which was subjected to the intramolecular aldol condensation under basic conditions to afford

1-cyclopentenecarbaldehyde. Treatment of this aldehyde with vinyl magnesium bromide after hydrolysis produced bis-allylic alcohol. Attempts to oxidize this alcohol with the standard chromium complexes (CrO_3, PCC or PDC) resulted in rearrangement to a pentadienal. A literature survey of similar systems revealed only two methods available for the oxidation of this kind of bis-allylic alcohols, one method employing nickel peroxide[44] and another using activated manganese(II) oxide[45]. The oxidation with activated manganese(II) oxide required five to ten equivalents of the reagent and usually proceeded in a low yield. Nickel peroxide is very toxic and an expensive reagent and requires a cumbersome titration procedure to determine its activity. These methods were obviously unsatisfactory for a multi-step synthesis.

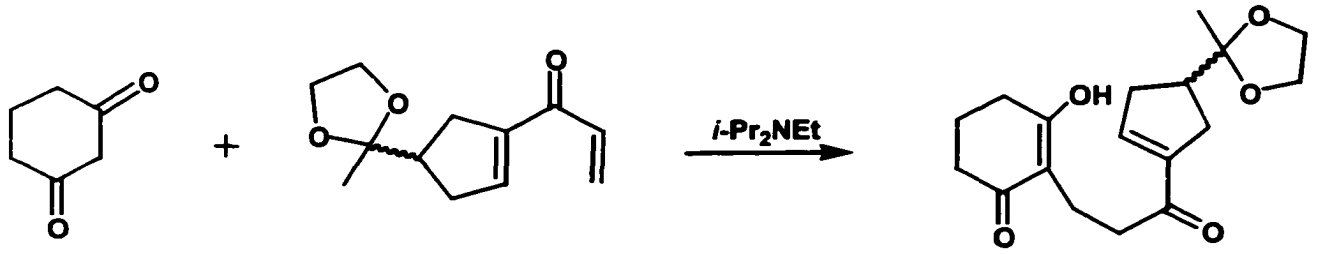


57 58 59

60 59 61

Scheme 26.

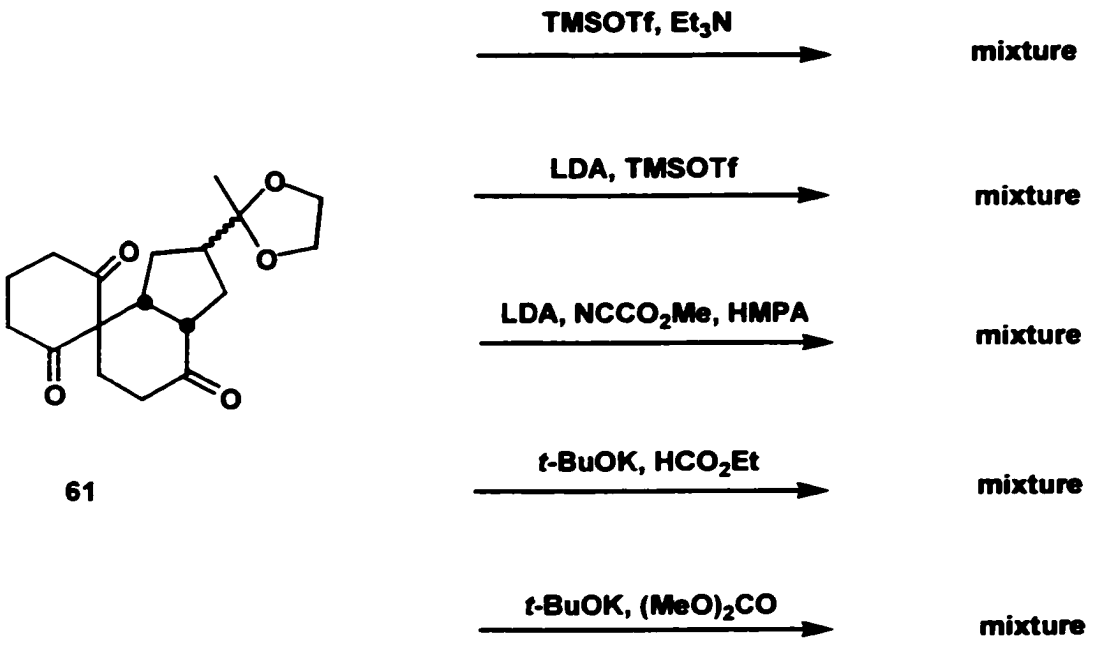
The fact that DDQ is commonly employed in the oxidation of benzylic and allylic alcohols[46] led us to investigate this oxidant in our system. Treatment of the bis-allylic alcohol with one equivalent of DDQ resulted in the clean and quantitative formation of the desired dienone **59**. When a mixture of cyclohexane-1,3-dione **60** and dienone **59** was heated for two hours at 80°C in the presence of diisopropylethylamine as base, the double Michael addition proceeded efficiently in high yield with the formation of the desired tricyclic intermediate **61**, possessing the ABC-carbocycle of the natural product. If this reaction was conducted at lower temperature or in a shorter period of time, the intermediate **62**, resulting from just one Michael addition process, was recovered along with the product (Scheme 27). Since the 1-acetyl cyclopentene is known to be a very unreactive Michael adduct, this result clearly indicates that the first step of this reaction is the addition to the acyclic double bond and that the unreactivity of the cyclic double bond is overcome only by the intramolecular process.



60 **59** **62**

Scheme 27.

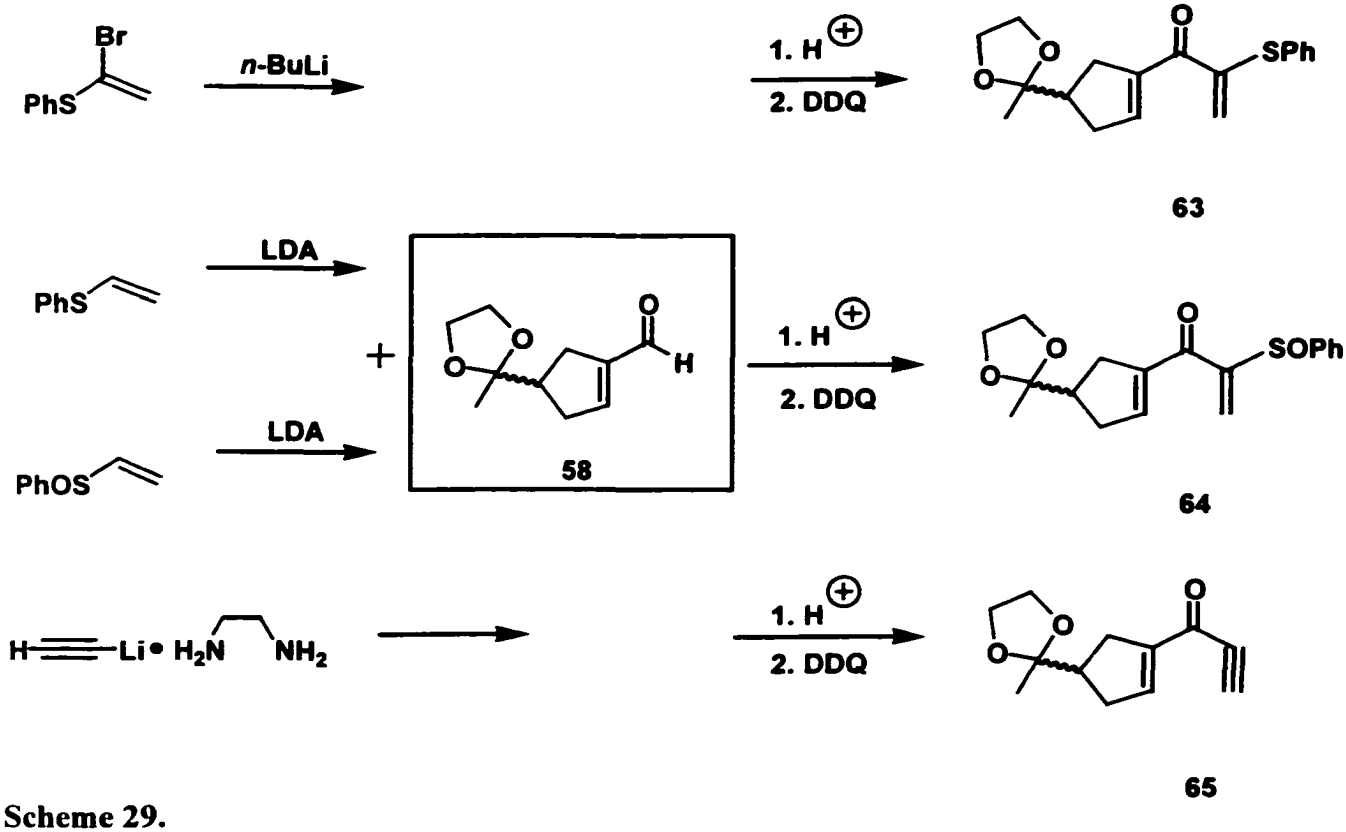
With this intermediate in hand and taking into account the steric effects of its unusual spirocyclic skeleton, we decided to investigate the possibility of selective reactions among three carbonyl groups. However, all of our attempts to affect the regioselective formation of an enolate in this system were unsuccessful (Scheme 28).



Scheme 28.

The encouraging results on the cycloaddition with the necessity to differentiate among the three carbonyl groups in the system clearly called for modifications. Since the cycloaddition reaction combines two parts of the molecule, it gives the flexibility of modifying both parts independently. The problem of differentiating the carbonyl group on the dienone can be easily resolved by introducing an electron-withdrawing group alpha to the carbonyl. This would also result in a more electron deficient double bond, thus, favourably affecting Michael addition to it. Since our retrosynthetic analysis called for the introduction of the double bond on the ABC-carbocycle for the Mannich reaction-Michael addition sequence, we decided to prepare dienones with electron-withdrawing groups, which could be easily eliminated later on in our synthesis. A reasonable choice was to utilize phenylsulfide or

phenylsulfoxide groups. Also appealing was the idea of reacting the cyclohexane-1,3-dione with a ynone, which could result in the formation of a tricyclic intermediate with an already installed double bond and, thus, provide a shortcut in our synthesis. Following the logic above, the aldehyde **58** was treated with lithiated phenyl vinyl sulfide and phenyl vinyl sulfoxide and with lithium acetylide ethylenediamine complex. The resulting alcohols were then subjected to the oxidation protocol with DDQ.

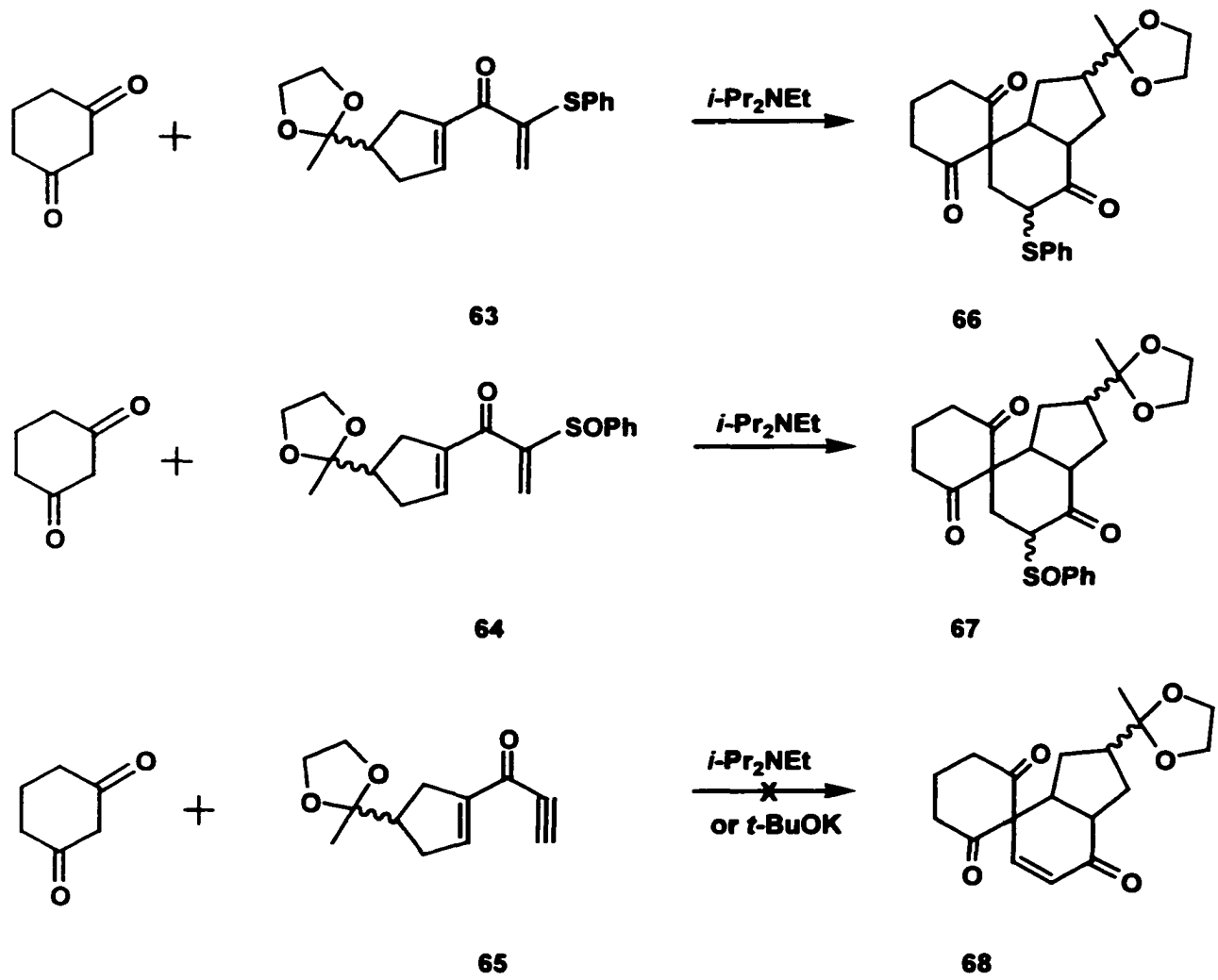


Scheme 29.

In all three cases this reaction differed from the previously conducted experiment. With phenyl sulfide as the substituent, the oxidation required six to eight hours for completion, with phenyl sulfoxide - twelve to fifteen hours and with the triple bond - up to twenty four hours for completion. Also, only in the latter case did the oxidation proceed with quantitative

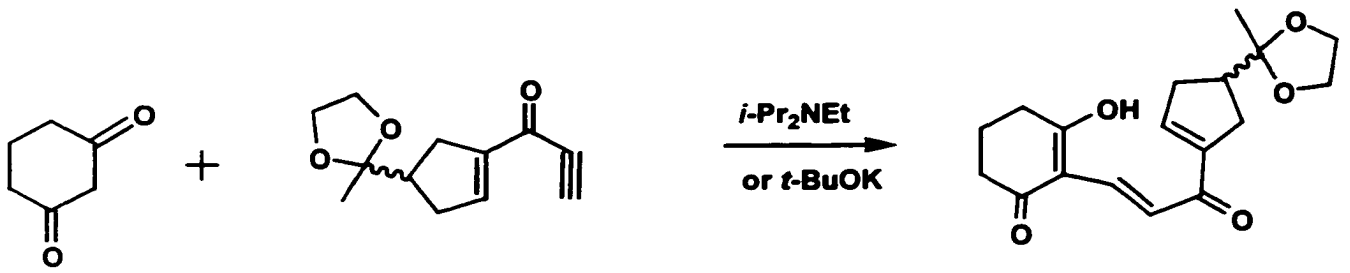
formation of the ketone, while in the case of the sulfur-containing substituents the yield of the desired ketones was lowered to 40-60 % by side reactions, presumably polymerization and sulfur oxidation, which occurred during the reaction.

However, with the modified dienones, the stage was set for further development of our synthesis. The double Michael addition of cyclohexane-1,3-dione to the dienones with the phenyl sulfide and phenyl sulfoxide substituents, afforded the tricyclic intermediates as a mixture of diastereomers in 65 and 45% yields, respectively.



Scheme 30.

The Michael addition of the cyclohexane-1,3-dione to the ynone resulted in the quantitative formation of the intermediate **69**, possessing a *trans* acyclic double bond and, thus, incapable of undergoing the second Michael addition to the cyclic double bond (Scheme 31).

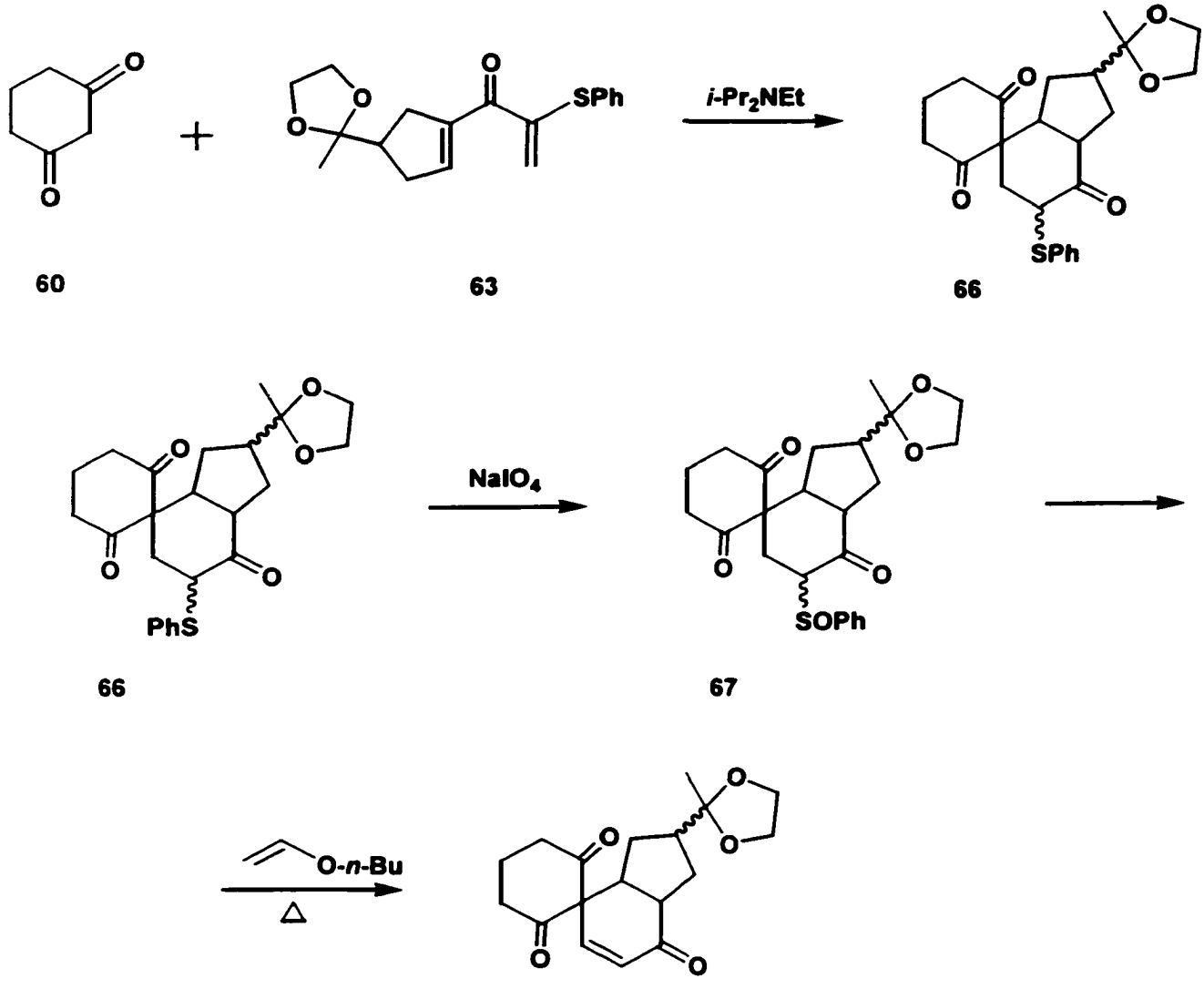


65 **69**

Scheme 31.

Since the cycloaddition reaction to the dienone with the phenyl sulfide substituent produced the most favourable results, we concentrated our synthetic efforts in this direction.

Oxidation of the sulfide to a sulfoxide was achieved with sodium periodate in aqueous dioxane.[47] A new stereogenic center was introduced at this point into the existing mixture of diastereomers and H^1 NMR spectroscopy showed six different protons alpha to the carbonyl and sulfoxide groups. Elimination of the phenyl sulfoxide group was effected cleanly by reflux in toluene with *n*-butyl vinyl ether, which facilitated the elimination process by binding phenylsulfinic acid and, thus, preventing the reverse addition reaction.

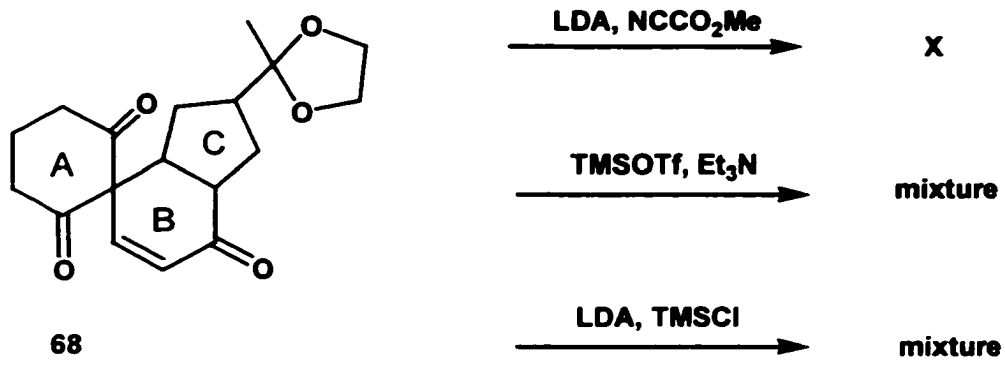


60 63 66

66 67 68

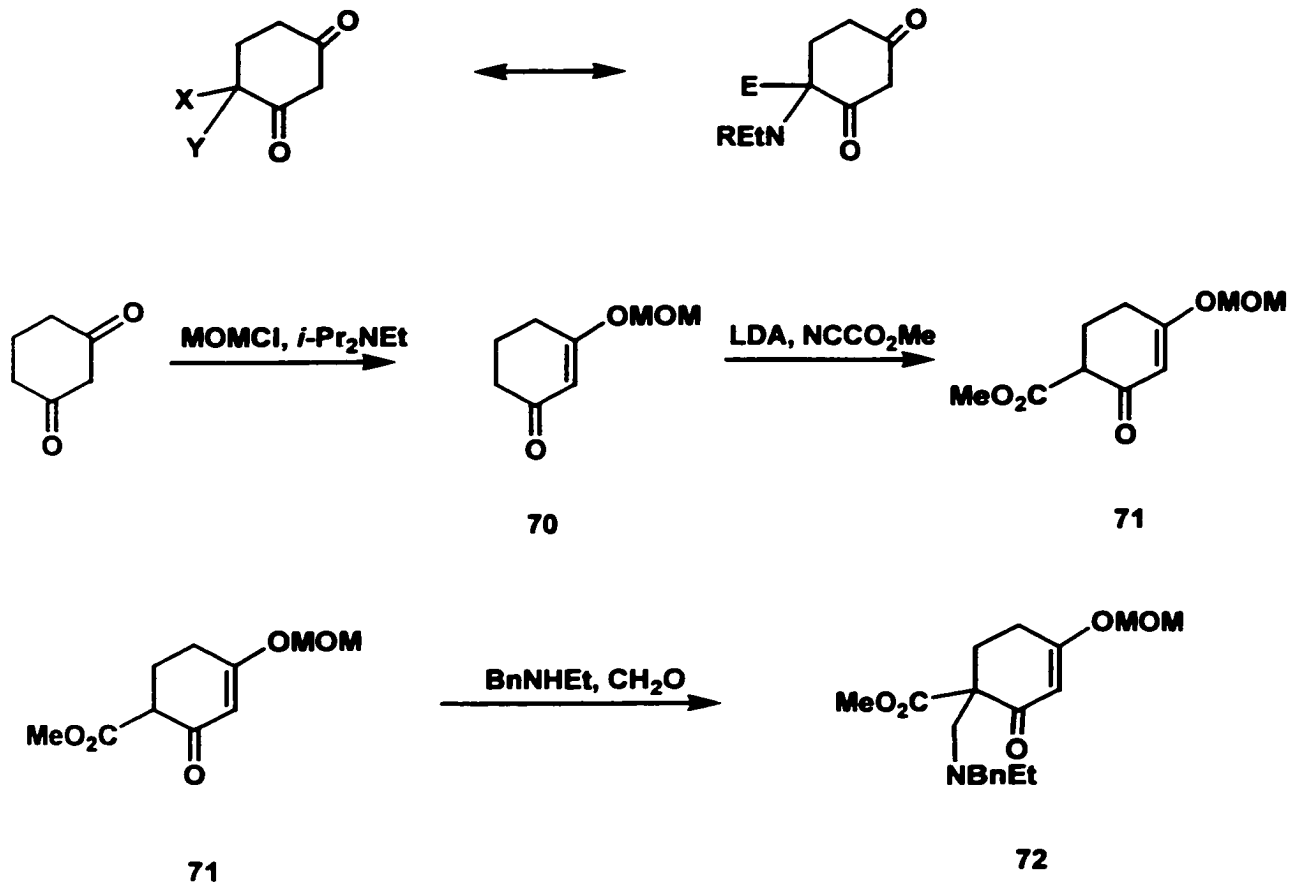
Scheme 32.

Having successfully established a protocol for installation of the double bond into the B-ring of the tricyclic intermediate, we next attempted to introduce the carboxylate group alpha to the carbonyl on the A-ring of compound **68**. However, formation of the enolate was not regioselective, resulting in a complex mixture of the products (Scheme 33).



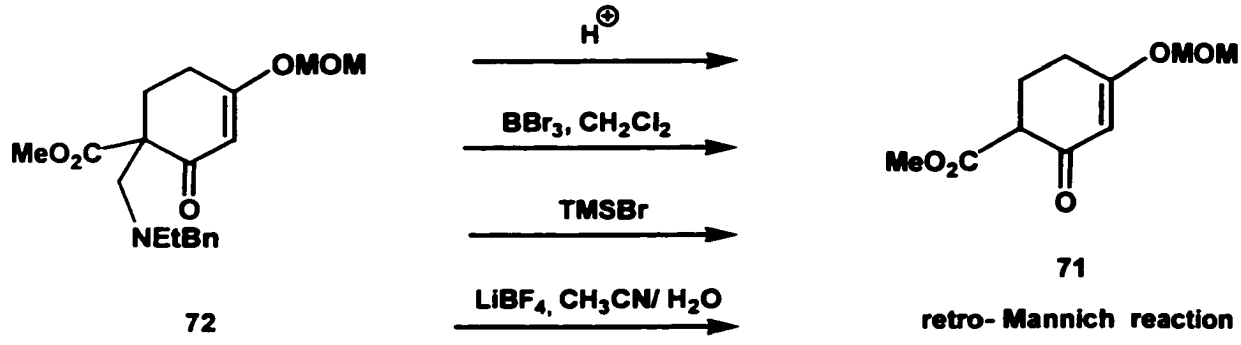
Scheme 33.

As mentioned above, the beauty of this approach lies in the countless ways one can modify both the dione and dienone. The problem with carboxylation we encountered at this point called for modifications on the cyclohexane-1,3-dione unit. The possibility of introducing both ester and ethylaminomethylene groups on the cyclohexane-1,3-dione before the cycloaddition process was extremely appealing, since elimination of the phenyl sulfoxide substituent would be accompanied by simultaneous Michael addition of the secondary amine to the new enone, resulting in closure of the E-ring. Thus, cyclohexane-1,3-dione was treated with methoxymethyl chloride and diisopropylethylamine, followed by lithium diisopropylamide and methyl cyanoformate to furnish compound **71**. The reaction of this β-ketoester with benzylethylamine and formaldehyde afforded the Mannich adduct **72**. Recovery of the cyclohexane-1,3-dione for the double Michael addition required the deprotection of the MOM-enol ether.



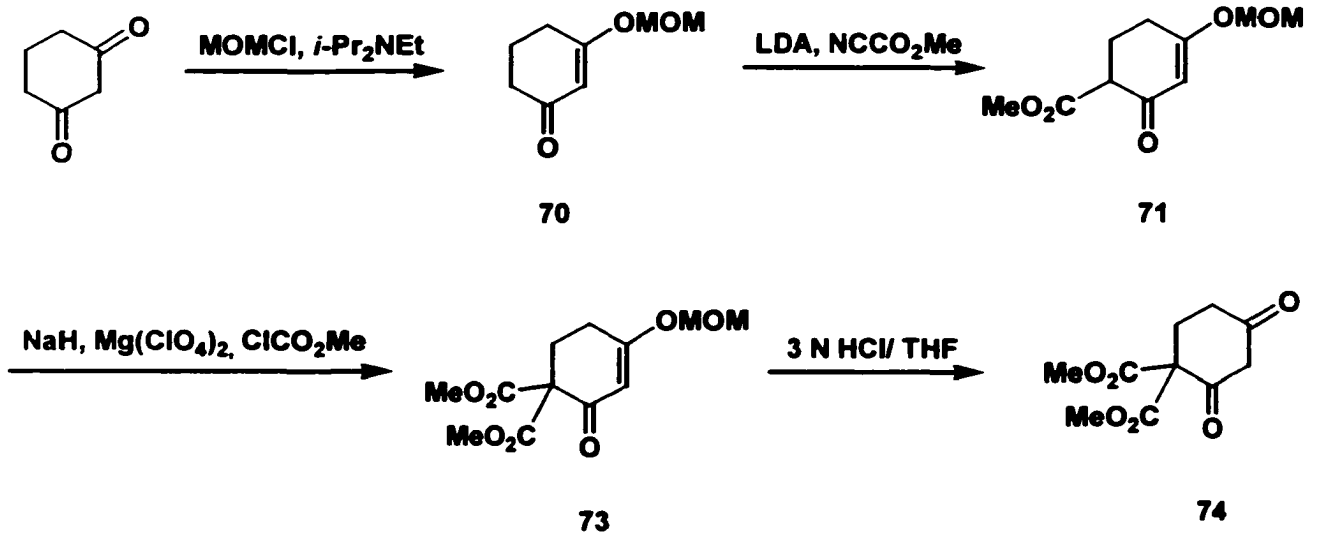
Scheme 34.

However, all attempts to remove the MOM group (Scheme 35) resulted in the retro-Mannich reaction and complete recovery of **71**.



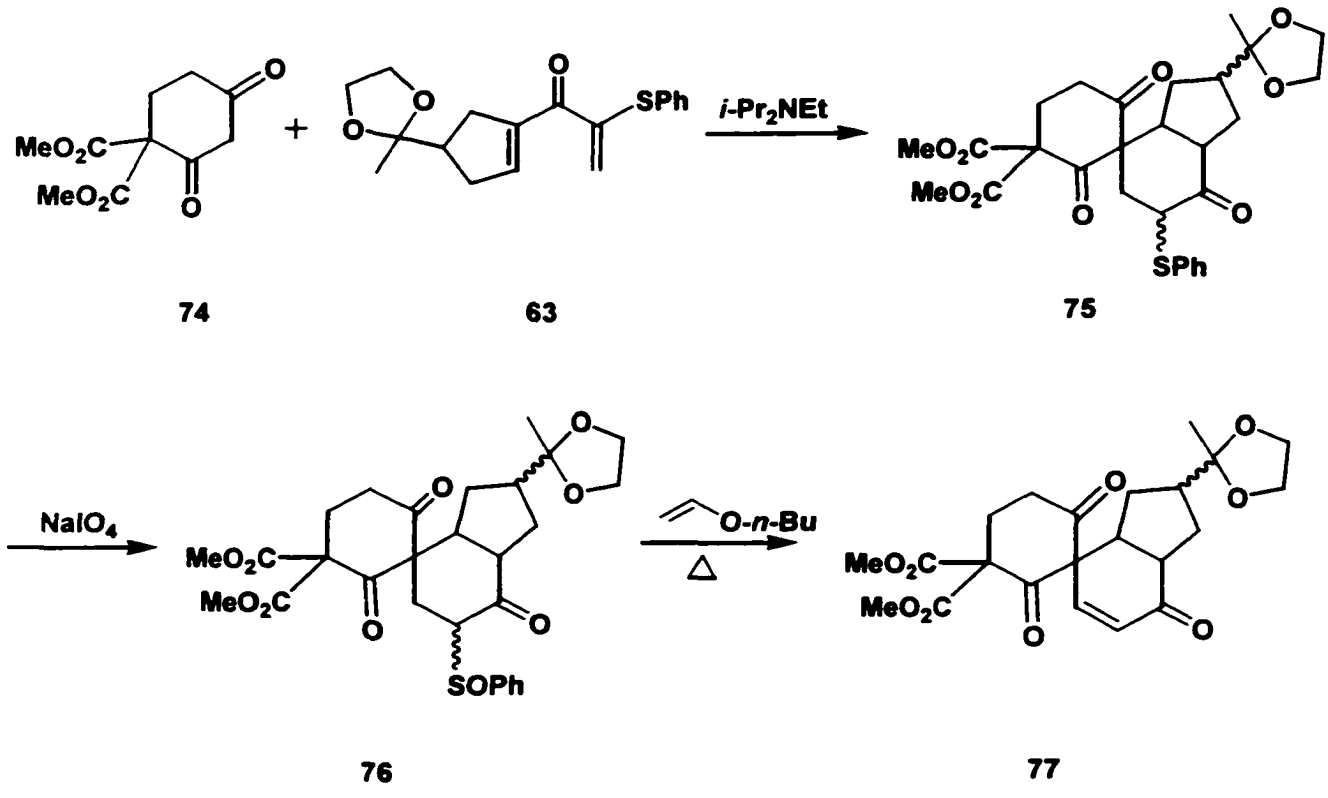
Scheme 35.

Since introduction of the ethylaminomethylene group was unsuccessful, we decided to install a second carboxylate group. The presence of two identical ester groups on a cyclohexane-1,3-dione could benefit our scheme in two ways. First, it would cut down the number of diastereomers, since only the axial ester group would react later on with the ethylamino group to produce amide. Second, the formed amide could be easily reduced to the tertiary amine and the other ester group would be carried through the synthesis and then reduced to the neopentyl alcohol for introduction of the 2-methylsuccinimidobenzoate moiety. Thus, upon treatment with sodium hydride, magnesium perchlorate and methyl chloroformate ketoester **71** was converted to diester ketone **73** in an excellent yield (Scheme 35). Conversion of sodium enolate to magnesium enolate by the means of magnesium perchlorate was necessary to favour C-alkylation over O-alkylation,[48] which always competes in these systems. Deprotection of MOM-enol ether under acidic conditions produced dimethyl 2,4-dioxocyclohexane dicarboxylate **74**.



Scheme 36.

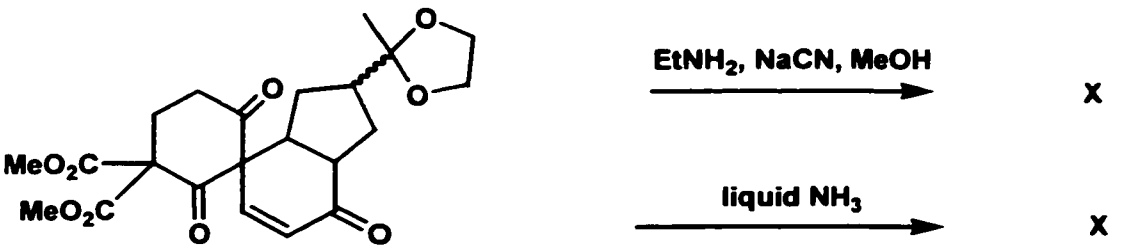
Reaction of the dione **74** with the dienone **63** under our usual conditions proceeded unusually slowly compared to cyclohexane-1,3-dione and afforded a by-product along with the desired tricyclic compound. The unidentified by-product seemed to result from ring cleavage of the cyclohexane-1,3-dione and migration of the ester group. Oxidation of the phenylsulfide of the tricyclic intermediate **75** with sodium periodate, followed by thermolysis of the phenylsulfoxide furnished the enone **77** (Scheme 37).



Scheme 37.

As discussed above, the reaction of the tricyclic enone **77** with primary amines and ammonia could proceed in two steps with the Michael addition of the primary amine to the enone, followed by selective aminolysis of the axial ester group, resulting in stereoselective

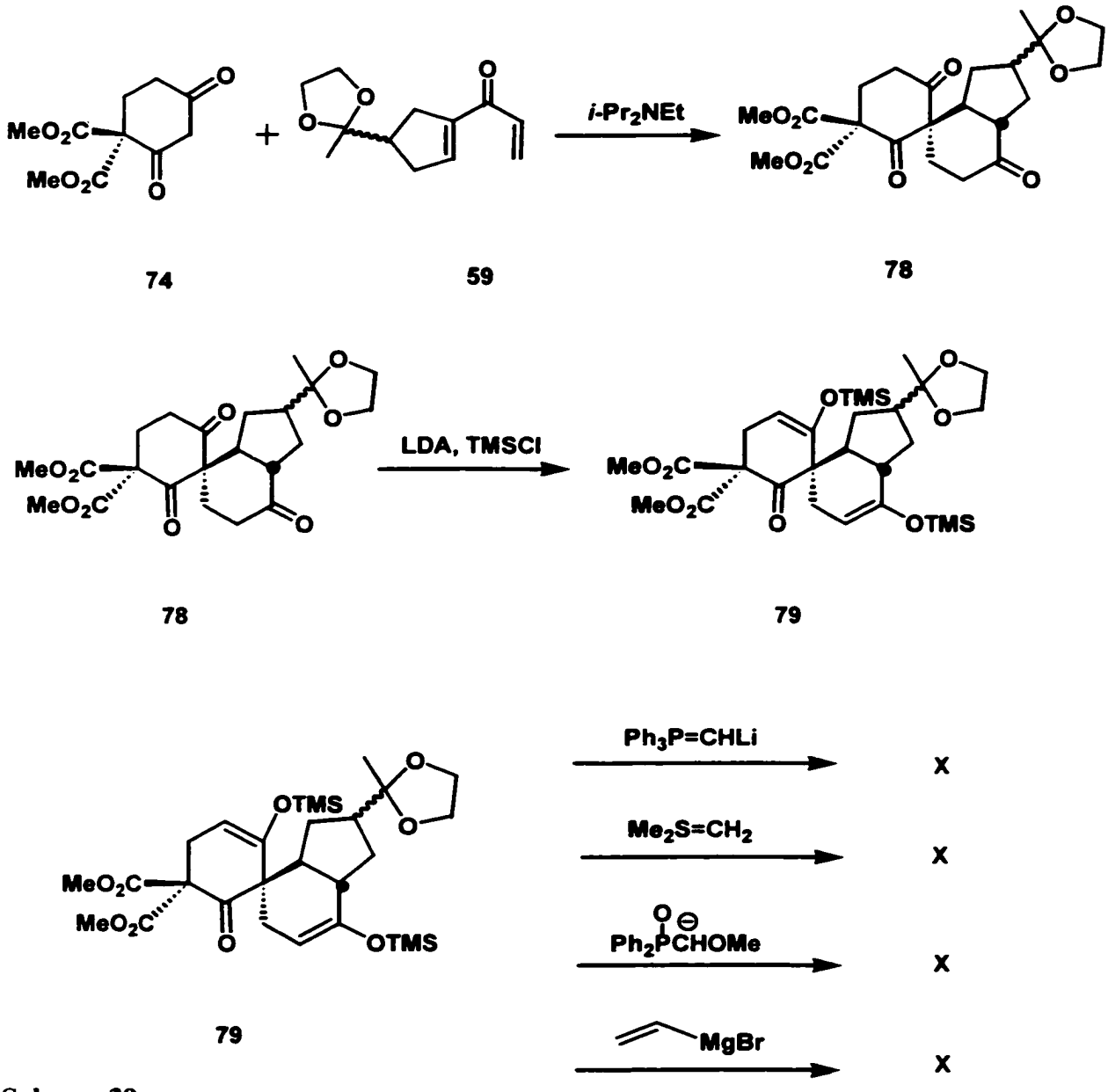
intramolecular closure of the E-ring. To our disappointment, treatment of the tricyclic diester-enone 77 with liquid ammonia or ethylamine in the presence of sodium cyanide in methanol[49] produced complex mixtures of products, from which the desired tetracyclic compound could not be isolated (Scheme 38).



77

Scheme 38.

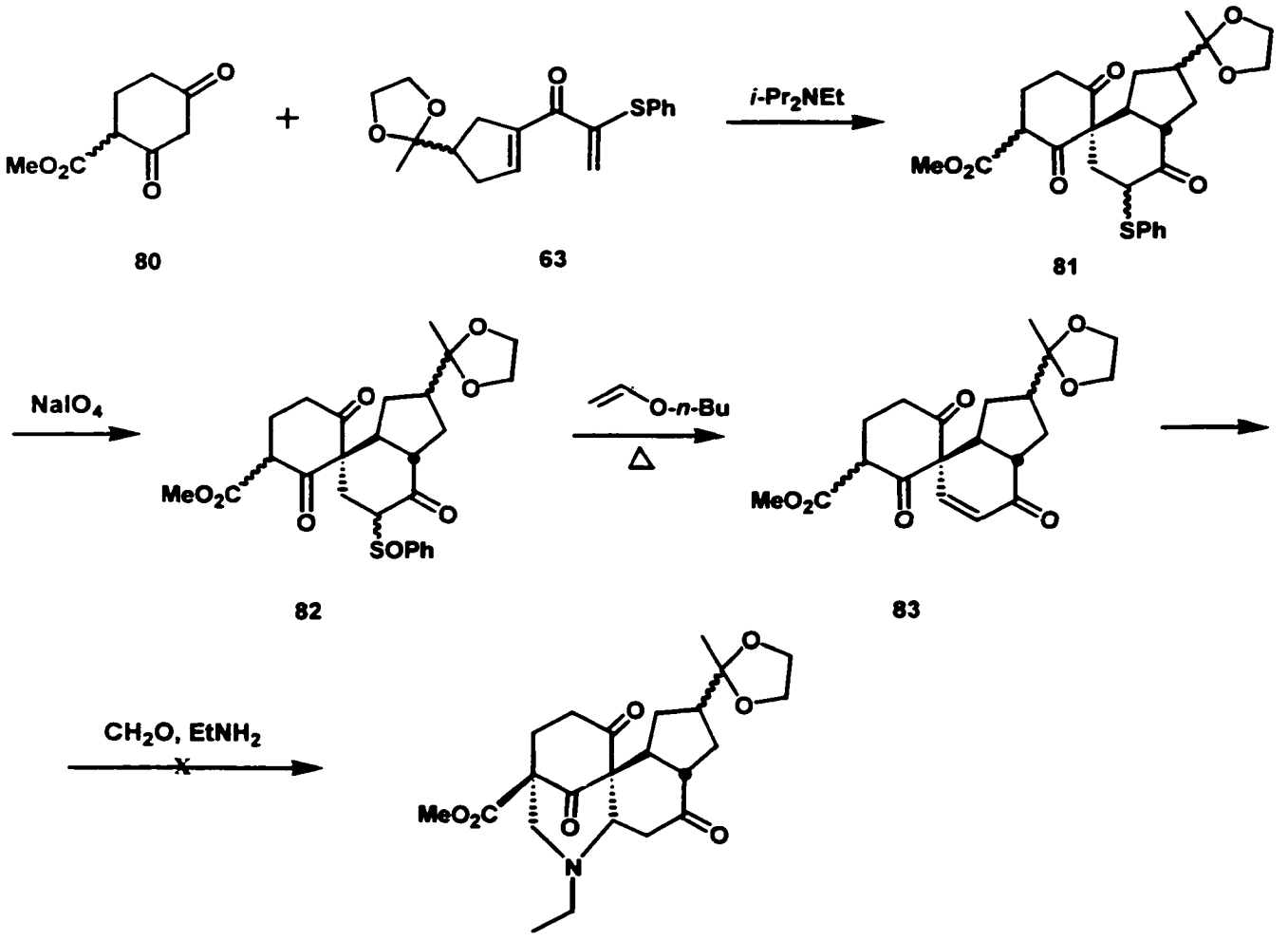
With this tricyclic intermediate in hand, we once again turned our attention to incorporation of the F-ring. As previously discussed, the F-ring could be formed by a two step sequence – a Wittig reaction with one carbon extension and an intramolecular aldol condensation of the resulting aldehyde. The carbonyl group of the 3-azacyclo[3.3.1]nonane system present in our previously synthesized ABE-intermediate proved to be too sterically hindered and, thus, unreactive towards Wittig reagents. However, we reasoned that this carbonyl group would be more sterically accessible before closure to the 3-azabicyclo-[3.3.1]nonane system corresponding to the AE-carbocycle, and could hopefully undergo the Wittig reaction to achieve the required one carbon extension. This reasoning was briefly examined with our ABC-carbocycle. Taking advantage of the presence of the non-enolizable carbonyl group, the two other enolizable carbonyl groups were protected as the trimethylsilyl enol ethers.



Scheme 39.

Remarkably, neither phosphonium ylids[50], sulfur ylids[51] nor Grinard reagents were effective in this reaction with the carbonyl group of the A-ring (Scheme 39). The stability of this carbonyl group towards nucleophilic attack is very unusual.

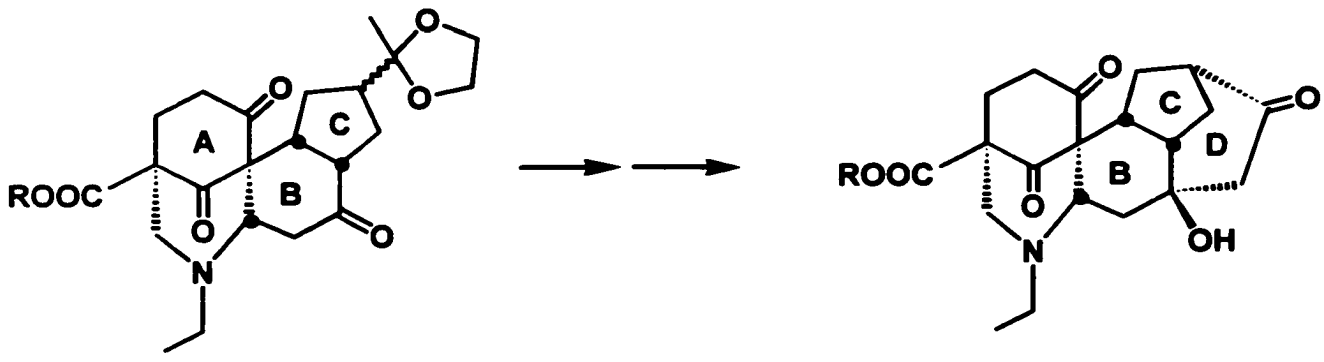
Since the tricyclic intermediate containing two equivalent ester groups did not produce positive leads, incorporation of the F-ring was once again proposed through the tandem Mannich reaction-Michael addition sequence, as this methodology proved to be successful in the closure of the F-ring in the first approach. The methyl 2,4-dioxocyclohexane carboxylate **80**, easily obtainable by reaction of dimethyl malonate with methyl vinyl ketone, followed by Dieckman condensation,[52] may lead to a very concise synthesis of a ABCE-carbocycle. After cycloaddition, the acidic α-proton of the β-keto-ester should ensure the effective Mannich reaction-intramolecular Michael addition sequence.



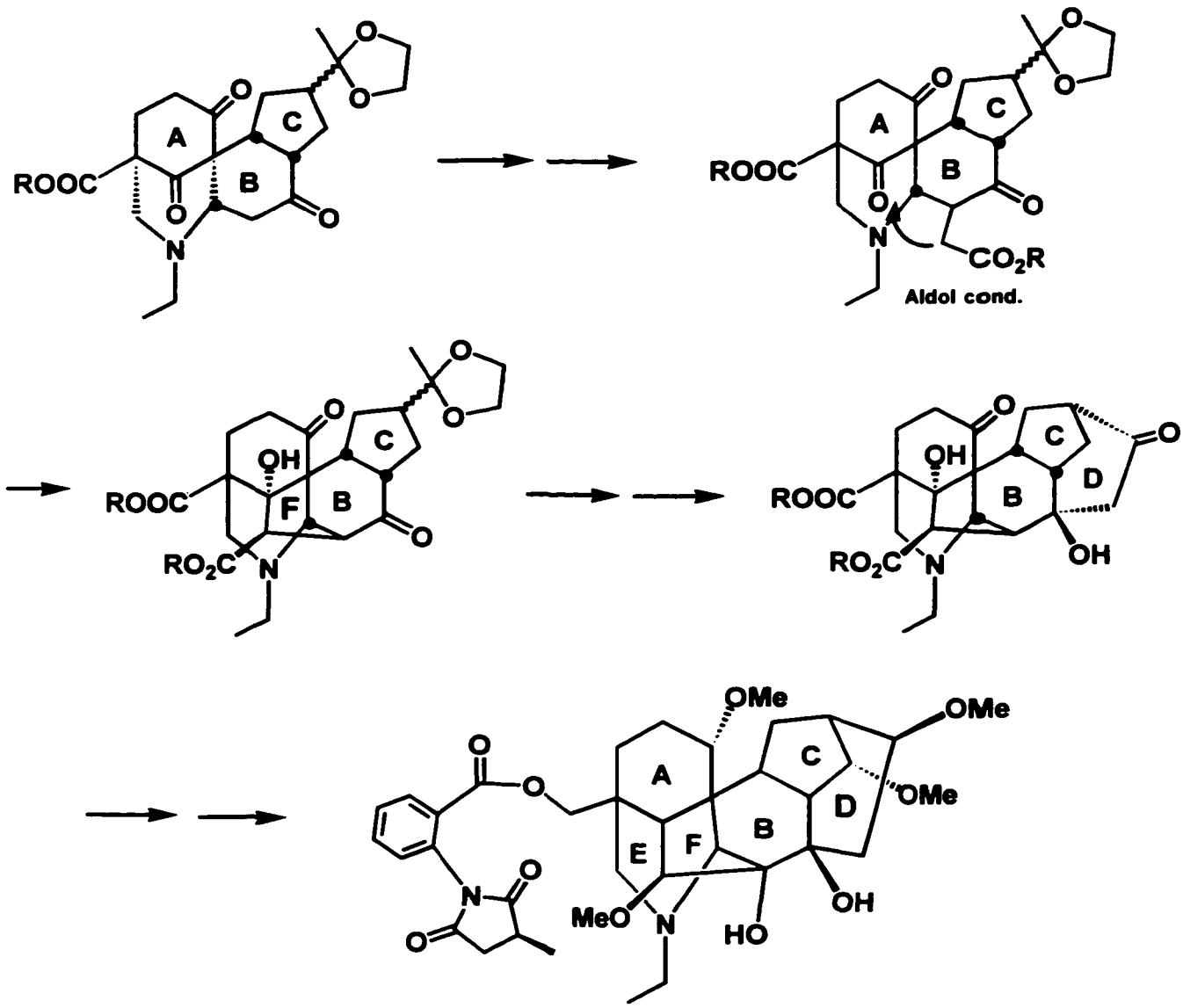
Scheme 40.

Our goal of achieving a very effective synthesis seemed indeed within our reach, warranted by the success of this methodology and strategically chosen reaction partners. Following the previously established pathway, the dione **80** was reacted with dienone **63** (Scheme 40). The phenyl sulfide group of the resulting tricyclic intermediate **81** was oxidized to the phenyl sulfoxide **82** and the latter underwent thermal elimination of phenylsulfinic acid in the presence of *n*-butyl vinyl ether to give the desired enone **83**. To our great disappointment, when the enone **83** was subjected to the same Mannich reaction-Michael addition cyclization conditions, which was used on the similar compound **40** in the conversion to **41**, a complex mixture of unidentifiable products was obtained. This confusing result can only be explained by the presence of the multiple reactive sites in the molecule **83**.

Although the desired cyclization was not achieved on this particular molecule, it definitely should be achievable on a modified analogue. The unlimited flexibility of the route presented in this dissertation allows the rapid and facile elaboration of the ABCE-carbocycle skeleton of the aconitine alkaloids with all functionality necessary to install the D-ring in two easy steps - deprotection of the ketal and aldol condensation (Scheme 41), and possibly to introduce the most difficult in the synthesis F-ring by an intramolecular aldol condensation (Scheme 42).



Scheme 41.



Scheme 42.

Even at the present stage, considerable progress has been made in this direction. Given the fact that only a few approaches have been reported towards the total synthesis of the aconitine alkaloids, this work can be stated as a pioneering and interesting research in the chemistry of the aconitine alkaloids. However, the total synthesis of a natural product of such complexity as methyllycaconitine will probably remain a life-time task for any organic chemist.

CONCLUSION

A synthesis of tricyclic fragment of methyllycaconitine starting with spirocyclic diketone was achieved utilizing tandem Michael addition-Mannich reaction sequence. A convenient alternative for the introduction of the methylsuccinimidobenzoate ester side chain onto small molecule analogues of methyllycaconitine was developed. It was demonstrated that double Michael addition of cyclohexadiones to functionalized dienones allows to obtain tricyclic fragment and may offer a convenient route to the tetracyclic analogue of methyllycaconitine by the tandem Mannich reaction-Michael addition sequence.

EXPERIMENTAL

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. H: EA refers to hexanes: ethyl acetate solvent mixtures for thin layer chromatography (TLC) and silica gel flash chromatography (SGC). Commercially available silica gel (40 μm) was used as a stationary phase. The NMR spectra were recorded at 300 MHz and the purity of all title compounds were determined to be > 95% by this method. The following symbols were used to designate peak multiplicity: s (singlet), d (doublet), t (triplet), q (quartet), ABq (AB quartet), m (multiplet), bs (broad singlet).

9-Trimethylsilanyloxy-spiro[5.5]undeca-7,9-dien-1-one (39): Trimethylsilyl triflate (1.2 ml, 1.37 g, 6.18 mmol) was added slowly via a syringe to a solution of ketone **38** (1.0 g, 5.62 mmol) and triethylamine (0.68 g, 6.74 mmol) in dry ethyl ether at –10°C under argon. Upon addition, the end of the needle was kept below the surface of the solution to prevent hydrolysis of the TMSTf. The mixture was stirred at – 10°C for six hours, during which a dark brown oil precipitated out of the light yellow solution. The solution was decanted from the residue and the solvent was removed *in vacuo* to afford the product as a yellow oil. ^{1}H NMR spectroscopy showed 95% conversion to the trimethylsilyl enol ether and 5% of the starting material. Since any attempts to separate the compounds via distillation led to decomposition of the material due to the high boiling point, this mixture was used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.17 (s, 9H), 1.63-1.88 (m, 6H), 2.16-2.23 (dd,

1H, J = 5.46 Hz, 17 Hz), 2.34-2.36 (m, 1H), 2.47-2.52 (m, 1H), 2.64-2.71 (dd, 1H, J = 3.9 Hz, 17 Hz), 4.78 (m, 1H), 5.71-5.75 (dd, 1H, J = 2 Hz, 10 Hz), 5.90-5.93 (d, 1H, J = 10 Hz).

1,9-Dioxo-spiro[5,5]undec-7-ene-2-carboxylic acid methyl ester (40): A solution of freshly prepared lithium diisopropylamide (2.4 mmol) in dry THF was added via a syringe to a solution of the enol silyl ether **39** (0.5 g, 2.0 mmol) in dry THF at –78°C under argon. The reaction mixture was allowed to warm up to 0°C over a period of one hour and stirred at 0°C for an additional hour. Then it was cooled back to –78°C and hexamethylphosphoric triamide (0.2 ml, 2.0 mmol) was added, followed by methyl cyanoformate (0.2 g, 0.2 ml, 2.4 mmol). The resulting mixture was stirred at –78°C for one hour, allowed to warm up to 0°C over 20 min, quenched with saturated ammonium chloride and extracted repeatedly with ethyl ether. The organic layer was dried over sodium sulfate and the solvent was removed *in vacuo*. The residue was redissolved in THF and treated with an aqueous 3M solution of hydrochloric acid for ten minutes. The obtained mixture was again extracted with ethyl ether and the organic layer was washed with brine and dried over sodium sulfate. The solvent was removed *in vacuo* and the resulting dark-red residue was purified by flash chromatography on silica gel using 1: 1 Hex: EA mixture as eluent to afford 0.41 g (86%) of the product **40** and 14% of the compound **39**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47-1.49 (d, 1H, J = 5.13 Hz), 1.55- 2.1 (m, 5H), 2.20-2.35 (m, 3H), 2.43-2.50 (m, 2H), 2.55-2.61 (m, 1H), 3.71 (s, 3H), 6.0-6.03 (d, 1H, J = 6 Hz), 6.68-6.70 (d, 1H, J = 6 Hz).

7-Ethyl-4,13-dioxo-7-aza-tricyclo[7.3.1.0^{1,6}]tridecane-9-carboxylic acid methyl ester (41): To a solution of the compound **40** (0.8 g, 3.38 mmol) in 20 ml of methanol was added a 37%

aqueous solution of formaldehyde (0.30 g, 3.38 mmol), followed by a 70% aqueous solution of ethylamine (0.22 g, 3.38 mmol). The resulting mixture was stirred at room temperature for six hours, concentrated and the residue was redissolved in methylene chloride and washed twice with brine. The organic layer was dried over sodium sulfate, concentrated and the resulting yellow oil was purified by flash chromatography on silica gel (Hex: EA = 1: 1) to afford 0.55 g (89%) of a white crystalline material, which was recrystallized from hexane. ^{1}H NMR ($CDCl_3$) δ 1.10-1.20 (t, 3H, J = 6Hz), 1.22-1.27 (dt, 1H, J = 3 Hz, 12 Hz), 1.53-1.64 (m, 1H), 1.82-1.90 (m, 1H), 2.08-2.20 (m, 2H), 2.30-2.40 (m, 4H), 2.47-2.57 (m, 3H), 2.78-2.89 (dt, 1H, J = 3Hz, 6Hz), 2.93-3.15 (m, 1H), 3.11-3.14 (d, 1H, J = 9Hz), 3.42-3.45 (d, 1H, J = 9 Hz), 3.40-3.48 (m, 1H), 3.77 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 13.11, 20.53, 31.72, 36.50, 38.22, 38.47, 42.86, 46.64, 50.68, 52.28, 54.78, 59.11, 68.39, 171.14, 210.50, 212.39. IR (neat) 1256, 1704, 1706, 1739 cm^{-1}. X-Ray is on the p. 98.

7-Ethyl-13-oxo-4-trimethylsilanyloxy-7-aza-tricyclo[7.3.1.0^{1,6}]tridec-4-ene-9-carboxylic acid methyl ester and 7-ethyl-13-oxo-4-trimethylsilanyloxy-7-aza-tricyclo[7.3.1.0^{1,6}]-tridec-3-ene-9-carboxylic acid methyl ester (42a): To a solution of the compound **40** (2 g, 6.85 mmol) in dry THF at – 78°C under argon was added a freshly prepared solution of lithium diisopropylamide (7.53 mmol) in dry THF, followed by trimethylsilyl chloride (0.82 g, 0.96 ml, 7.53 mmol). The mixture was stirred at –78°C for 30 min, then allowed to warm up to room temperature where it was quenched with an aqueous saturated solution of ammonium chloride. The resulting solution was extracted with ether and the combined ether extracts were washed with an aqueous solution of sodium bicarbonate, brine and dried over sodium sulfate. The solvent was removed *in vacuo* to afford a light-yellow oil, which was determined by ^{1}H

NMR spectroscopy to be a 2:1 mixture of regioisomers. ^{1}H NMR ($CDCl_3$) **42a:** δ 4.71-4.73 (m, 1H) and 4.88 (bs, 1H) **42b:** 4.71-4.72 (m,1H) and 4.87 (bs, 1H) **42c:** 3.89 (bs, 1H), 4.02 (bs, 1H).

7-Ethyl-3-formyl-4,13-dioxo-7-aza-tricyclo[7.3.1.0^{1,6}]tridecane-9-carboxylic acid methyl ester (43): To a solution of the ketone **41** (1.0 g, 3.42 mmol) and ethyl formate (0.51 g, 6.85 mmol) in dry THF at room temperature under argon was added a 1M solution of potassium *t*-butoxide in dry THF (3.42 mmol, 3.42 ml). The resulting solution was stirred under argon for 12 hours, then water was added and the mixture was extracted twice with ethyl ether. The ether extracts were discarded, the aqueous layer was acidified with dilute hydrochloric acid and extracted four times with ethyl ether. The ether extracts were combined, dried over sodium sulfate and concentrated *in vacuo* to afford the product as a yellow oil, which was unstable (1.1 g, quantitative yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10-1.16 (t, 3H, J = 6 Hz), 1.52-1.60 (m, 1H), 1.78-1.88 (m, 1H), 1.89-1.92 (d, 1H, J = 12 Hz), 2.14-2.25 (m, 2H), 2.34-2.36 (d, 2H, J = 6 Hz), 2.40-2.65 (m, 3H), 2.78-2.81 (d, 1H, J = 12 Hz), 2.87-3.10 (m, 1H), 3.08-3.11 (d, 1H, J = 9 Hz), 3.47-3.54 (m, 2H), 3.70 (s, 3H), 8.67 (s, 1H), 13.96 (bs, 1H).

7-Ethyl-3-formyl-4,13-dioxo-7-aza-tricyclo[7.3.1.0^{1,6}]tridec-2-ene-9-carboxylic acid methyl ester (44): To a solution of ketoaldehyde **43** (0.6 g, 1.87 mmol) in dry methylene chloride was added pyridine (0.3 g, 0.3 ml, 3.75 mmol), followed by phenylselenium bromide (0.53 g, 2.25 mmol). The mixture was stirred at room temperature for 30 min, then washed with a saturated solution of ammonium chloride. The organic layer was cooled to –10°C on an ice-acetone bath and a 30% solution of hydrogen peroxide (2 ml) was added dropwise to the

cold solution. The mixture was stirred for 30 min, separated from aqueous layer, washed with saturated sodium bicarbonate, dried over sodium sulfate and concentrated *in vacuo* to afford the product in quantitative yield.

7-Ethyl-4,4-dimethoxy-13-oxo-7-aza-tricyclo[7.3.1.0^{1,6}]tridecane-9-carboxylic acid methyl ester (46): To a solution of the tricyclic ketone **41** (0.6 g, 1.87 mmol) in methanol was added ceric ammonium nitrate(0.201g, 0.374 mmol, 0.2 equiv). The mixture was stirred for 30 min, after which the TLC plate indicated the absence of starting material. The solution was concentrated *in vacuo*, redissolved in hexane and flash chromatographed through a pad of silica gel (5 cm). Hexane was evaporated to afford the compound **46** as a slightly yellow oil in quantitative yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98-1.12 (dt, 1H, J = 3 Hz, 12 Hz), 1.09-1.14 (t, 3H, J = 6 Hz), 1.15-1.24 (t, 3H, J = 12 Hz), 1.45-1.53 (m, 1H), 1.55-2.15 (m, 6H), 2.18-2.26 (m, 1H), 2.4-2.68 (m, 3H), 2.88-3.02 (m, 1H), 3.00-3.04 (d, 1H, J = 12 Hz), 3.10 (s, 3H), 3.15 (s, 3H), 3.19-3.25 (dd, 1H, J = 3 Hz, 12 Hz), 3.36-3.40 (dd, 1H, J = 3 Hz, 12 Hz), 3.72 (s, 3H).

2-(3-Methyl-2,5-dioxo-pyrrolidin-1-yl)-benzoic acid 7-ethyl-4,4,13-trimethoxy-7-aza-tricyclo[7.1.0.^{1,6}]tridec-9-ylmethyl ester (56): To a solution of the alcohol **48** (1.0 g, 3.06 mmol) in dry THF at 0°C was added methanesulfonyl chloride (0.527 g, 0.36 ml, 4.60 mmol), followed by triethylamine (0.93 g, 1.28 ml, 9.20 mmol). The mixture was allowed to warm up to room temperature and a solution of 2-methylsuccinimidobenzoic acid (0.86 g, 3.68 mmol) in 5 ml of dry THF was added to this mixture. The resulting solution was stirred at room temperature for three hours, diluted with dichloromethane and washed with brine. Then it was

dried over sodium sulfate, concentrated *in vacuo* and the residue was purified by column chromatography on silica gel with pure EA as eluent. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99-1.06 (t, J = 6 Hz, 3H), 1.3-2.0 (m, 10H), 2.23-2.30 (m, 1H), 2.30-2.55 (m, 3H), 2.60-2.80 (m, 3H), 2.85-3.03 (m, 1H), 3.07 (s, 1H), 3.38-3.5 (m, 2H), 3.46 (s, 3H), 3.91 (d, J = 9 Hz, 1H), 4.13 (d, J = 9 Hz, 1H), 7.21 (m, 1H), 7.44 (m, 1H), 7.59 (m, 1H), 8.1 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 12.63, 16.36, 20.33, 33.91, 35.19, 36.56, 36.72, 36.89, 37.12, 38.10, 38.94, 40.98, 47.27, 48.26, 61.53, 63.07, 88.83, 129.21, 129.32, 132.31, 132.74, 132.91, 133.02, 176.81, 180.22, 180.92, 214.56. MS m/e (NH3/CI) 497.1 (M+1), 383.0, 263.9, 251.0, 234.0, 216.0.

4-(2-Methyl-[1,3]dioxolan-2-yl)-cyclopent-1-enecarbaldehyde (58): The alkene **57** (10 g, 0.06 mol) was dissolved in 600 ml of a 1: 1 mixture of THF/ H_2O. A solution of freshly prepared osmium tetraoxide in *t*-butanol (5 mg/ml, 15 ml, 0.3 mmol) was added, followed by sodium periodate (38.1 g, 0.18 mol). The resulting mixture was stirred for eight hours and the white precipitate formed was filtered and washed repeatedly with dichloromethane. The clear solution was extracted four times (100 ml of each portion) with dichloromethane and the combined organic extracts were washed with brine and dried over sodium sulfate. The solvent was removed *in vacuo* to give a yellow viscous oil, which was purified by chromatography on silica gel (Hex: EA = 1: 1). The resulting dialdehyde was dissolved in 200 ml solution of THF: H_2O = 1: 1, and 20 ml of a 3M solution of sodium hydroxide was added. The mixture was stirred for one hour. Then 100 ml of brine was added and the solution was extracted four times with ethyl ether (50 ml each portion). The combined ether extracts were washed with brine, dried over sodium sulfate and passed through a short pad of silica gel (5 cm). The solvent was removed *in vacuo* to afford the product as a colorless, viscous oil. ^{1}H NMR (300

MHz, $CDCl_3$) δ 1.25 (s, 3H), 1.98-2.03 (m, 1H), 2.88-2.98 (m, 1H), 3.22-3.25 (m, 1H), 3.88-3.96 (m, 4H), 6.95 (m, 1H), 9.71 (s, 1H). ^{13}C NMR ($CDCl_3$) 22.37, 27.44, 32.75, 49.95, 64.77, 64.88, 112.05, 146.91, 154.66, 189.78.

1-[4-(2-Methyl-[1,3]dioxolan-2-yl)-cyclopent-1-enyl]-propenone (59): To a solution of aldehyde **58** (0.9 g, 5 mmol) in 15 ml of dry THF was added a 1M solution of vinyl magnesium bromide in THF (5.5 ml, 5.5 mmol) by a syringe. The mixture was stirred at room temperature for three hours, then quenched with diluted hydrochloric acid and extracted with ethyl ether. The combined ether extracts were washed with brine, dried over sodium sulfate, flashed through a short pad of silica gel (3 cm) and concentrated in vacuo. The yellow residue was redissolved in dry methylene chloride, cooled to 0°C and DDQ (1.24 g, 5.5 mmol) was added to this solution in portions. The resulting mixture was stirred for 3 hours, the yellow precipitate formed was filtered off, the resulting solution was washed repeatedly with saturated sodium bicarbonate, dried over sodium sulfate and concentrated *in vacuo* to afford the crude product, which was purified by flash chromatography (Hex: EA = 5: 1). ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (s, 3H), 2.03-2.11 (m, 2H), 2.40-2.51 (m, 1H), 2.61-2.78 (m, 2H), 3.74-4.04 (m, 4H), 5.74-5.78 (dd, 1H, J = 3 Hz, 9Hz), 6.24-6.29 (dd, 1H, J = 3 Hz, 15 Hz), 6.70-6.79 (dd, 1H, J = 9 Hz, 15 Hz), 6.72 (m, 1H).

8-(2-Methyl-1,3-dioxolan-2-yl)-2', 6', 5-trioxo-spiro[bicyclo[4.3.0]octane-2-1'-cyclohexane] (61): To a solution of cyclohexane-1,3-dione (3.92 g, 0.035 mol) in 100 ml of ethyl acetate was added the dienone **59** (3.6 g, 0.0175 mol) , followed by diisopropylethylamine (2.26 g, 0.0175 mol). The resulting mixture was refluxed for three

hours when the TLC plate indicated the absence of starting material. The solution was concentrated *in vacuo*, and the bright-red residue was purified by flash chromatography (Hex: EA = 3: 1) to afford a light-yellow oil, which slowly solidified. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04-1.12 (m, 1H), 1.23 (s, 3H), 1.48-1.50 (m, 2H), 1.62-1.78 (m, 1H), 1.79-1.88 (m, 1H), 2.02-2.20 (m, 2H), 2.22-2.31 (dt, 1H, J = 6 Hz, 12 Hz), 2.36-2.41 (dm, 1H, J = 12 Hz), 2.55-2.65 (m, 3H), 2.75-2.82 (m, 1H), 2.91-3.20 (m, 4H), 3.88-4.0 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 18.30, 22.01, 22.92, 24.70, 27.54, 37.02, 37.59, 37.81, 43.67, 48.83, 51.59, 64.55, 64.58, 67.81, 111.35, 206.46, 209.33, 209.70. HRMS m/z for $C_{18}H_{24}O_5$ calcd. 320.162375, found 320.162367.

1-[3-(2-Methyl-1,3-dioxolan-2-yl)-cyclopent-1-enyl]-2-phenylsulfonyl-prop-2-en-1-ol (63a): To a solution of freshly prepared lithium diisopropylamide (46.7 mmol) in dry THF at –78°C under argon was added phenyl vinyl sulfide (6.36 g, 46.7 mmol, 6.1 ml) by a syringe, followed by the dropwise addition of HMPA (8.37 g, 46.7 mmol). The mixture was stirred for twenty minutes, then the solution of the aldehyde **58** (8.5 g, 46.7 mmol) in 100 ml of dry THF was added via a canula. Then the dry-ice bath was removed and the mixture was allowed to warm up to room temperature over thirty minutes, where it was quenched with saturated ammonium chloride and extracted three times with dichloromethane (50 ml each portion). The organic extracts were combined, washed with brine and dried over sodium sulfate. The solvent was removed *in vacuo* and the residue was purified by chromatography on silica gel (Hex: EA = 4: 1) to give 9.96 g (68%) of the product as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (s, 3H), 1.85-1.93 (m, 1H), 2.02-2.15 (m, 1H), 2.28-2.47 (m, 1H), 2.76-2.79 (m, 1H), 3.41-3.42 (d, J = 5.5, 1H), 3.85-3.98 (m, 4H), 4.95-4.96 (m, 1H), 5.02 (s, 1H), 5.56-5.57

(m, 1H), 5.95-5.96 (m, 1H), 7.29-7.38 (m, 3H), 7.40-7.48 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 20.10, 27.49, 31.33, 53.89, 64.26, 64.76, 73.25, 112.72, 114.84, 127.90, 129.23, 131.40, 133.28, 133.37, 143.83, 147.24.

1-[3-(2-Methyl-1,3-dioxolan-2-yl)-cyclopent-1-enyl]-2-phenylsulfonyl-prop-2-en-1-one (63): To a solution of alcohol **63a** (0.7 g, 2.20 mmol) in 50 ml of dry dichloromethane at room temperature under argon was added 2,3-dichloro-5,6-dicyanoquinone (0.5 g, 2.20 mmol). The mixture was stirred at room temperature for six hours, then filtered and washed repeatedly with saturated sodium bicarbonate, dried over sodium sulfate and passed through a short pad of silica gel. Solvent was removed *in vacuo* to give 0.46 g (66%) of the product as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (s, 3H), 1.95-2.18 (m, 2H), 2.35-2.49 (m, 1H), 2.51-2.68 (m, 1H), 3.52-3.61 (m, 1H), 3.87-3.89 (m, 4H), 5.36 (s, 1H), 5.97 (s, 1H), 6.47-6.48 (m, 1H), 7.30-7.41 (m, 3H), 7.45-7.51 (m, 1H)

8-(2-Methyl-1,3-dioxolan-2-yl)-4-phenylsulfanyl-2', 6', 5-trioxo-spiro[bicyclo[4.3.0]octane 2-1'-cyclohexane] (66): To a solution of cyclohexane-1,3-dione (1.12 g, 10 mmol) in 50 ml of ethyl acetate was added the dienone **63** (2.84 g, 9 mmol), followed by diisopropylethyl-amine (2.6 g, 29 mmol). The resulting mixture was refluxed for eight hours when the TLC plate indicated the absence of starting material. The solution was concentrated in vacuo, and the bright-red residue was purified by flash chromatography (Hex: EA = 1: 1) to afford a yellow oil, which slowly solidified. ^1H NMR (300 MHz, $CDCl_3$) δ 0.98-1.02 (m, 1H), 1.24 (s, 3H), 1.21-1.48 (m, 2H), 1.57-1.74 (m, 1H), 1.83-1.97 (m, 1H), 2.04-2.13 (m, 1H), 2.38-2.41 (m, 2H), 2.50-2.63 (m, 2H), 2.67-2.83 (m, 2H), 3.01-3.13 (m, 2H), 3.23-3.35 (m, 1H),

3.82-3.98 (m, 4H), 4.87-4.98 (dt, J = 10 Hz, <0.1 Hz, 1H), 7.22-7.38 (m, 3H), 7.47-7.51 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 18.17, 22.06, 24.43, 27.32, 31.73, 37.03, 37.87, 43.51, 49.75, 52.43, 53.63, 64.65, 68.53, 111.26, 126.73, 128.98, 131.23, 133.98, 205.17, 209.53. HRMS m/z for $C_{24}H_{28}O_5S$ calcd. 428.165745, found 428.165631.

8-(2-Methyl-1,3-dioxalan-2-yl)-4-benzenesulfinyl-2', 6', 5-trioxo-spiro[bicyclo[4.3.0] octane-2-1'-cyclohexane] (67): To a solution of compound **67** (2.0 g, 4.67 mmol) in 100 ml of dioxane: water = 1: 1 was added sodium periodate (2.0 g, 9.34 mmol). The mixture was stirred at room temperature until no starting materal appeared on the TLC plate (~six hours). Then it was extracted with dichloromethane, the organic extracts were combined, washed with brine, and dried over sodium sulfate. The solvent was removed *in vacuo* to give 2.0 g (quantitative yield) of the product as a yellow foam. The ^1H NMR ($CDCl_3$) spectrum showed the product to be a mixture of two diastereomers in the 1:2 ratio. HRMS m/z for $C_{24}H_{28}O_6S$ calcd. 443.88607, found 443.88603.

8-(2-Methyl-1,3-dioxolan-2-yl)-2', 6', 5-trioxo-spiro[bicyclo[4.3.0]oct-3-ene-2-1'-cyclohexane] (68): To a solution of sulfoxide **67** (0.3 g, 0.67 mmol) in 20 ml of carbon tetrachloride was added 0.3 ml of *n*-butyl vinyl ether. The mixture was refluxed for twelve hours, then the solvent was removed *in vacuo* and the residue was purified by chromatography on silica gel (Hex: EA = 1: 1) to give the product as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (s, 3H), 1.48-1.53 (m, 2H), 1.72-1.83 (m, 2H), 2.18-2.28 (m, 1H), 2.38-3.12 (m, 8H), 3.78-4.01 (m, 4H), 6.26-6.30 (d, J = 10 Hz, 1H), 6.64-6.69 (dd, J = 2.2 Hz, 10 Hz, 1H). HRMS m/z for $C_{18}H_{22}O_5$ cacld. 318.146725, found 318.146714.

4-Methoxymethoxy-2-oxocyclohex-3-enecarboxylic acid methyl ester (73): To a solution of lithium diisopropylamide (6.0 mmol) in 20 ml of dry THF at –78°C under argon was added a solution of **70** (0.85 g, 5.47 mmol) in 20 ml of dry THF via a canula. The solution was stirred at –78°C for one hour, then HMPA (1.0 g, 5.5 mmol) was added, followed by methyl cyanoformate (0.51 g, 0.48 ml, 6.0 mmol). The mixture was stirred at –78°C for two hours, warmed up to 0°C over twenty minutes and quenched with saturated ammonium chloride, extracted with ethyl ether. The ether extracts were combined, washed with brine, dried over sodium sulfate and concentrated. The residue was purified by flash chromatography on silica gel (Hex: EA = 1: 1) to give 1.1 g (87%) of **71.** The compound **71** (1.1 g, 5.22 mmol) was dissolved in 20 ml of dry THF and added dropwise to a suspension of sodium hydride (0.24 g, 6.0 mmol) in anhydrous THF. After ten minutes solid magnesium perchlorate (1.33 g, 6.0 mmol) was added to this mixture, followed in ten minutes by methyl chloroformate (0.56 g, 6.0 mmol). The solution was stirred at room temperature for four hours, quenched with 5% hydrochloric acid and extracted with ethyl ether. The combined ether extracts were washed with brine, dried over sodium sulfate and concentrated. The residue was purified by flash chromatography on silica gel (Hex: EA = 1: 1) to give 1.57 g (97%) of the product **73** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.41-2.46 (t, J = 6 Hz, 2H), 2.57-2.61 (t, J = 6 Hz, 2H), 3.43 (s, 3H), 3.77 (s, 6H), 5.04 (s, 2H), 5.53 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 25.60, 27.72, 53.0, 56.96, 65.09, 94.43, 103.55, 167.93, 174.67, 189.93.

2,4-Dioxo-cyclohexane-1,1-dicarboxylic acid dimethyl ester (100% enolic form) (74): To a solution of the compound **73** (5.44 g, 0.02 mol) in 100 ml of methanol was added 100 ml of

3M hydrochloric acid, and the mixture was refluxed for six hours. Then it was cooled to room temperature and extracted repeatedly with dichloromethane. The combined organic extracts were washed with brine, dried over sodium sulfate and concentrated *in vacuo* to afford a dark-brown residue, which was purified by flash chromatography on silica gel (Hex: EA = 1: 1) to give the product **74** (3.42 g) in 75 % yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.44-2.48 (t, J = 5.8 Hz, 2H), 2.55-2.61 (m, 2H), 3.79 (s, 6H), 5.51 (s, 1H), 14.5 (bs, OH). ^{13}C NMR ($CDCl_3$) δ 16.52, 24.07, 27.17, 53.50 (two carbons), 65.09, 111.88, 163.07, 167.69 (two carbons), 188.87.

8-(2-Methyl-1,3-dioxolan-2-yl)-2', 6', 5-trioxo-spiro[bicyclo[4.3.0]octane-2-1'-cyclohexane]-3',3'-dicarboxylic acid dimethyl ester (78): To a solution of 2,4-dioxo-cyclohexane-1,1-dicarboxylic acid dimethyl ester (4.00 g, 17.5 mmol) in 150 ml of ethyl acetate was added the dienone **59** (3.6 g, 0.0175 mol), followed by diisopropylethylamine (2.26 g, 0.0175 mol). The resulting mixture was refluxed for eight hours when the TLC plate indicated the absence of starting material. The solution was concentrated *in vacuo*, and the bright-red residue was purified by flash chromatography (Hex: EA = 3: 1) to afford a yellow oil, which slowly solidified. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (s, 3H), 1.38-1.46 (m, 1H), 1.73-1.88 (m, 1H), 1.98-2.08 (m, 1H), 2.32-2.88 (m, 10H), 3.02-3.18 (m, 2H), 3.78 (s, 3H), 3.86 (s, 3H), 3.92-3.98 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 22.28, 23.82, 24.70, 25.01, 28.38, 34.23, 36.89, 44.01, 46.55, 51.40, 53.59, 63.23, 64.47, 64.77, 67.99, 111.25, 166.98, 167.28, 202.72, 205.08, 209.51. HRMS m/z for $C_{22}H_{28}O_9$ calcd. 436.173335, found 436.173326.

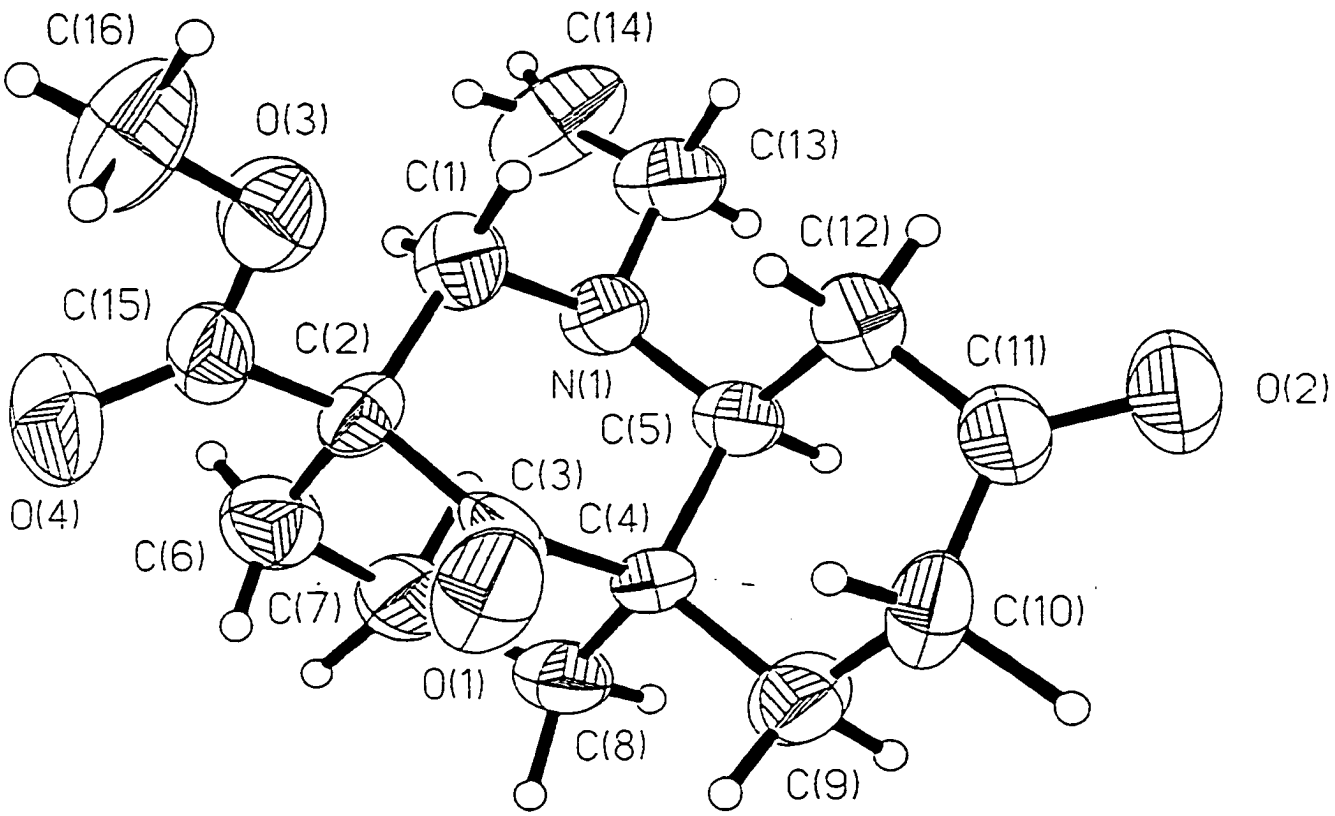
8-(2-Methyl-1,3-dioxolan-2-yl)-4-phenylsulfanyl-2', 6', 5-trioxo-spiro[bicyclo [4.3.0]octane-2-1'-cyclohexane]-3'-carboxylic acid methyl ester (81): To a solution of 2,4-

dioxo-cyclohexanecarboxylic acid methyl ester (0.74 g, 4.4 mmol) in 20 ml of ethyl acetate was added the dienone **63** (0.7 g, 2.2 mmol) , followed by diisopropylethylamine (0.56 g, 4.4 mmol). The resulting mixture was refluxed for six hours when the TLC plate indicated the absence of the starting material. The solution was concentrated *in vacuo*, and the bright-red residue was purified by flash chromatography (Hex: EA = 1: 2) to afford 0.55 g (56%) of a light-yellow foam as a mixture of four diastereomers. ^{1}H NMR δ 1.20, 1.22, 1.23, 1.24 (s, 3H, methyl of the ketal group), 3.74, 3.76, 3.79, 3.81 (s, 3H, CO_2**Me**), 4.77, 4.88, 4.51, 5.13, 4.20 (m, 1H, C**H**-SPh).

8-(2-Methyl-1,3-dioxolan-2-yl)-2', 6', 5-trioxo-spiro[bicyclo [4.3.0]oct-3-ene-2-1'-cyclohexane]-3'-carboxylic acid methyl ester (83): To a solution of compound **81** (0.82 g, 1.68 mmol) in 20 ml of dioxane: water = 1: 1 was added sodium periodate (0.72 g, 3.36 mmol). The mixture was stirred at room temperature until no starting materal appeared on the TLC plate (~six hours). Then the solution was extracted with dichloromethane, the organic extracts were combined, washed with brine and dried over sodium sulfate. The solvent was removed *in vacuo* to give 0.83 g (quantitative yield) of the product **82** as a yellow foam. ^{1}H NMR ($CDCl_3$) spectrum showed the product to be a mixture of two diastereomers in a 1: 2 ratio. To a solution of sulfoxide **82** (0.83 g, 1.68 mmol) in 20 ml of carbon tetrachloride was added 0.6 ml of *n*-butyl vinyl ether. The mixture was refluxed for twelve hours, then the solvent was removed *in vacuo* and the residue was purified by chromatography on silica gel (Hex: EA = 1: 1) to give the product as a yellow oil. ^{1}H NMR δ 1.15-1.31 (m, 2H), 1.30 (s, 3H), 1.32-1.48 (m, 1H), 1.71-1.83 (m, 1H), 2.38-5.92 (m, 7H), 3.80 (s, 3H), 3.88-4.01 (m, 4H), 6.23-6.27 (d, J = 10.2 Hz, 1H), 6.48-6.52 (dd, J = 2 Hz, 10.2 Hz). ^{13}C NMR ($CDCl_3$) δ 21.26,

22.89, 24.70, 25.12, 36.89, 44.08, 46.65, 51.40, 53.59, 63.23, 64.37, 64.79, 68.03, 111.25, 126.12, 138.04, 167.13, 202.67, 205.16, 209.51. HRMS m/z for $C_{20}H_{24}O_7$ calcd. 376.152205, found 376.152198.

APPENDIX. X-RAY STRUCTURE OF COMPOUND 41



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GENERAL CONCLUSION

A direct approach and perhaps the shortest pathway possible to the synthesis of methyllycaconitine, a representative of the aconitine alkaloids, has been developed. A tricyclic intermediate, possessing the ABE-carbocycle skeleton and 2-methylsuccinimido-benzoate ester important for biological activity, has been synthesised as a result of the research described in this dissertation. A new, more efficient method for the introduction of the 2-methylsuccinimido benzoate side chain onto the skeleton of the aconitine alkaloids has been introduced. Also an advanced tricyclic intermediate, possessing ABC-carbocycle skeleton and all necessary functionality for further development of a total synthesis has been obtained.

AFTERWORD

A student who begins his endeavour in organic chemistry soon learns that the syntheses of natural products published in scientific journals only appear easy and straightforward. In reality they rarely turn out the way they were initially planned. One can plan a reasonable and rational "paper" synthesis only to go to the lab and discover that the reactions do not work the way they should. Synthetic dead-ends, blind alleys and difficulties are the constant roommates in the life of a synthetic chemist. Behind every little achievement are a lot of time, efforts and frustration.

However, patience and the ability to overcome problems are also rewarded by the distinctive moments of enthusiasm and delight that can only be felt in organic chemistry. Organic synthesis is the one of few fields that allows so much flexibility and imagination, requires so much patience and gives so much satisfaction.

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