Synthetic approach towards methyllycaconitine

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UMI®
SYNTHETIC APPROACH TOWARDS METHYLLYACONITINE

by

Sarathy Kesavan

A dissertation submitted to the graduate faculty
in partial fulfillment of the requirements for the degree of
DOCTOR OF PHILOSOPHY

Major: Organic Chemistry

Program of Study Committee:
George A. Kraus, Major Professor
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Iowa State University
Ames, Iowa
2004
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For the Major Program
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GENERAL INTRODUCTION

Organic synthesis, with the invention of new synthetic strategies and technologies, has evolved from largely empirical approaches for the preparation of relatively simple molecules to sophisticated strategies for the construction of molecules with considerable structural and functional complexity. Organic synthesis is employed to synthesize the natural product and its analogs for the discovery of new drugs. The development of new synthetic methodologies in the course of total synthesis is imperative for the efficient synthesis of drug candidates. Apart from the practical applications, the pursuit of efficient syntheses of complex natural products is both gratifying and truly enjoyable.

Chapter One describes the development of annulation reaction for the construction of five-, six- and seven- membered rings. Chapter Two describes a direct approach to the synthesis of methyllycaconitine, a representative of the aconitine alkaloids. The numbering of the compounds, schemes and references are independent in each section.
CHAPTER 1
ANNULATIONS VIA DIANIONS: FORMATION OF FIVE-, SIX- AND SEVEN-MEMBERED RINGS

Introduction
C,C-Dianions, such as those shown in Figure 1, are generated by two sequential deprotonations. They have a long and diverse history and continue to serve as important synthetic reagents. C,C-Dianions are categorized based on the location of deprotonation. When sequential deprotonation occurs at the same carbon atom, 1,1-dianions are formed. When sequential deprotonation occurs at adjacent carbons, 1,2-dianions are formed. When sequential deprotonation occurs at carbon sites one atom apart, 1,3-dianions are formed as shown in Figure 1. The 1,3-(C,C) dianions have been most widely used in organic synthesis owing to their ready access and predictable reactivity.

![Diagram of C,C-dianions](image)

Figure 1. Examples of C,C-dianions

It is no surprise that investigators have made extensive use of these readily-accessed...
Dianions in synthesis. As an introduction to their utility, a pictorial survey of some natural and unnatural products prepared using dianions is shown in Figure 2.

![Chemical structures](image)

**Figure 2. Synthetic products resulting from the use of 1,3-(C,C)-dianions.**

**Dianion-based [3+3] Annulation**

Cyclohexenes are generally prepared by Diels-Alder reactions or Robinson annulation reactions. There are only a few examples where cyclohexenes are prepared by bringing together two three-carbon units. In all of these cases, a 1,3-(C,C) dianion acts as one of the two units. Mordini reported a novel allylic stannane reagent which functions as a dianion equivalent. Recently, 3-trimethylstannyl-2[(trimethylstannyl)methyl]propene was used as an isobutene dianion equivalent. When treated with diacyl chlorides, a cyclic product was formed through a formal [3 + n] annulation process as shown in Scheme 1.
Molander communicated an innovative approach to the synthesis of six-membered rings by use of α,β-epoxy aldehydes and iodomethyl-substituted allylic silanes (Scheme 2). Allyltin trihalide (generated in situ) addition to the carbonyl of the epoxy aldehyde occurred with good diastereoselectivity. The combination of intramolecular Lewis acid catalysis and fluoride-induced epoxide ring opening leads to formation of six-membered rings with good diastereoselectivity at three contiguous stereocenters of the newly-formed ring.
Moohoff reported an annulation using phosphorus-stabilized 1,3-\((\text{C},\text{C})\) dianions.\(^{10}\) Moohoff reacted unsaturated aldehydes with the dianion of phosphonate keto esters. This led to the formation of cyclohexenones as shown in Scheme 3.

\[ \text{MeO} \quad \text{MeO} \quad \text{MeCr} \quad \text{Me} \quad \text{O} \quad \text{CO}_2 \text{R} \quad \text{+} \quad \text{MeCr} \quad \text{Me} \quad \text{O} \quad \text{CO}_2 \text{R} \quad \rightarrow \quad \text{CO}_2 \text{R} \]

Scheme 3.

Cooke and Magnus\(^{11}\) converted 1-phenyl-3-phenylsulfonyl-2-propanone to its crimson red 1,3-dianion using two equivalents of LDA or sequential treatment with NaH and BuLi. They reacted it with 1,3-dibromopropane to give the annulated product in modest yield as shown in Scheme 4.

\[ \text{PhO}_2\text{S} \quad \text{Ph} \quad \text{O} \quad \text{Ph} \quad \text{BrCH}_2\text{CH}_2\text{Br} \quad \rightarrow \quad \text{PhO}_2\text{S} \quad \text{Ph} \quad \text{O} \quad \text{Ph} \quad \rightarrow \quad \text{LDA} \quad \rightarrow \quad \text{PhO}_2\text{S} \quad \text{Ph} \]

Scheme 4.
Results and Discussion

As part of a program to develop terpene-based antiviral agents, we needed an efficient synthetic route to bicyclic segments present in sesquiterpenes such as illudin S. The cytotoxicity and anticancer activity of illudin S has been most extensively investigated. The target of the compound is believed to be DNA. The low therapeutic index of illudin S has precluded its development as a chemotherapeutic agent. However, the semisynthetic illudin analogue, 6-(hydroxymethyl)acylfulvene (HMAF) shows outstanding activity and is now in various Phase I, II, and III clinical trials.

The well-documented acid lability of cyclopropyl carbinols plus the ready availability of 1,1-diacylcyclopropane led us to evaluate a [3+3] annulation route to this system. We envisioned a reaction of a 1,3-(C,C) dianion with 1,1-diacylcyclopropane to generate the bicyclic segment of the illudins.

\[ \text{R} = \text{H illudin M} \]
\[ \text{R} = \text{OH illudin S} \]

Figure 3. Cytotoxic sesquiterpenes
Scheme 5.

We reasoned that phosphonium salts bearing an electron-withdrawing group at the γ-position could generate the dianion. The phosphonium salts were prepared from corresponding halides as shown in Scheme 6. Having synthesized the dianion precursor, we tested our dianion annulation using 1,1-diacetylcyclopropane and phosphonium salt 2a. The results are summarized in Table 1.
Using LDA as base at -78 °C gave a modest yield of 23%. Having achieved the desired cyclization, we tried optimizing the cyclization. Ultimately, the optimized cyclization was achieved using LiTMP as base at -20 °C. The successful annulation prompted us to evaluate the annulation with a variety of 1,3-diketones as electrophiles. The results are summarized in Table 2.
Table 2: [3+3] Annulation

Table: [3+3] Annulation

<table>
<thead>
<tr>
<th>Entry</th>
<th>G</th>
<th>R</th>
<th>R1</th>
<th>R2</th>
<th>Yield % (isomer ratio)</th>
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<tr>
<td>1</td>
<td>CN</td>
<td>CH₂-CH₂</td>
<td>Me</td>
<td>Me</td>
<td>65 (3:1)</td>
</tr>
<tr>
<td>2</td>
<td>COOEt</td>
<td>CH₂-CH₂</td>
<td>Me</td>
<td>Me</td>
<td>54 (5:1)</td>
</tr>
<tr>
<td>3</td>
<td>CN</td>
<td>Me, Me</td>
<td>Me</td>
<td>Me</td>
<td>61</td>
</tr>
<tr>
<td>4</td>
<td>CN</td>
<td>CH₂-(CH₂)₂-CH₂</td>
<td>Me</td>
<td>Me</td>
<td>59</td>
</tr>
<tr>
<td>5</td>
<td>CN</td>
<td>Me, Me</td>
<td>H</td>
<td>Ph</td>
<td>53 (1:1)</td>
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<tr>
<td>6</td>
<td>COOEt</td>
<td>Me, Me</td>
<td>H</td>
<td>Ph</td>
<td>48 (1:1)</td>
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The reaction of dianions with keto aldehydes\(^\text{18}\) (entries 5 & 6) gave only one regioisomer. We believe that anion next to the electron withdrawing group is more reactive than the phosphorane and hence it reacts preferentially with the more reactive aldehyde, as shown in Scheme 7.
Having achieved [3+3] annulations, we investigated the synthesis of five-membered rings. The results of the dianion additions to 1,2-dicarbonyl compounds are depicted in Table 3. As anticipated, the yields of cyclopentenes were higher.

**Table 3: [3+2] Annulation**

<table>
<thead>
<tr>
<th>Entry</th>
<th>G</th>
<th>Base</th>
<th>R</th>
<th>Yield % (isomer ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CN</td>
<td>LiTMP</td>
<td>Me</td>
<td>61(1:1) 9</td>
</tr>
<tr>
<td>2</td>
<td>CN</td>
<td>LiTMP</td>
<td>2-furyl</td>
<td>68(1:1) 10</td>
</tr>
<tr>
<td>3</td>
<td>CN</td>
<td>LiTMP</td>
<td>Ph</td>
<td>80(1:1) 11</td>
</tr>
<tr>
<td>4</td>
<td>COOEt</td>
<td>LiTMP</td>
<td>Ph</td>
<td>65(1:1) 12</td>
</tr>
</tbody>
</table>

We also evaluated the synthesis of seven-membered rings. The results are depicted in Scheme 8. The initial adduct was oxidized using Jones reagent to give compounds 13 and 14.
Having achieved useful [3+4] annulation with modest success, we decided to change our dianion. We synthesized phosphonium salt 15 and evaluated [4+2] annulation as shown in Scheme 9. Yields were fairly modest, probably due to the instability of the dianion.

Scheme 8.

We also reacted 2b with cis-cyclopentane-1,3-dialdehyde. This reaction provided the
bicyclic adduct shown below in 38% yield.

\[
\begin{align*}
\text{CHO} & \quad \text{2b} \\
\text{CHO} & \quad \text{LITMP} \\
\end{align*}
\]

The results above demonstrate that cyclizations using dianions derived from \textit{2a} and \textit{2b} can generate five-, six- and seven-membered ring compounds. The highly functionalized ring systems produced by the dianion annulations will be useful for the synthesis of natural products. Application of this methodology in the synthesis of core-structure of Sorcodictyin-A\textsuperscript{22} is currently under progress.

[Sarcodictyin A]

Scheme 10.
Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and used without purification. Tetrahydrofuran was distilled over sodium benzophenone ketyl. Dichloromethane and benzene were distilled over calcium hydride. All experiments were performed under an argon atmosphere unless otherwise noted. Nuclear magnetic resonance measurements were performed with either a Varian 300 MHz or Bruker 400 MHz instrument. All chemical shifts are reported relative to CDCl₃ (7.26 ppm for ¹H and 77.06 ppm for ¹³C), unless otherwise noted. Coupling constants (J) are reported in Hz with abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. High resolution mass spectra were recorded on a Kratos model MS-50 spectrometer and low resolution mass spectra were performed with a Finnegan 4023 mass spectrometer. Standard grade silica gel (60 Å, 32-63 μm) was used for a flash column chromatography.

Compound 3:

To a solution of 2a (457 mg, 1.0 mmol) in 5 mL THF at -78 °C was added a solution of LiTMP generated using tetramethylpiperidine (296 mg, 2.1 mmol) and 0.8 mL of n-BuLi (2.5 M solution in hexane) in 10 mL of THF. The temperature of above solution was allowed to rise to -20 °C and stirred at -20 °C for a period of 90 min. The above solution was then cooled to -78 °C and 2,2-diacetylpropane (105 mg, 0.82 mmol) in 3 mL THF was added. The solution was warmed to 0 °C and was stirred at that temperature for an additional 1 h. The reaction was quenched with saturated ammonium chloride solution. The organic layer was extracted with ether (3 X 10 mL) and dried over MgSO₄. The crude product was chromatographed on silica gel (H:EA = 5:1 to 3:1) to afford compound 3 as mixture of
isomers. 3a: 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 5.32 (1H, bs), 2.92 (1H, dd, $J = 7.8$ Hz, $J = 4.5$ Hz), 2.50-2.60 (1H, m), 2.30-2.40 (1H, m), 1.42 (3H, m), 1.32 (3H, s), 1.00-1.10 (1H, m), 0.80-0.95 (2H, m), 0.6-0.7 (1H, m); 75 MHz $^{13}$C NMR (CDCl$_3$) $\delta$ 136.0, 120.9, 117.7, 70.3, 34.5, 28.6, 27.5, 24.2, 18.9, 8.3, 6.7. 3b: 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 5.40 (1H, bs), 2.86 (1H, t, $J = 6$ Hz), 2.50-2.52 (2H, m), 1.45 (3H, m), 1.23 (3H, s), 1.13-1.20 (1H, m), 0.78-0.90 (2H, m), 0.68-0.72 (1H, m); 75 MHz $^{13}$C NMR (CDCl$_3$) $\delta$ 136.5, 121.2, 117.5, 70.1, 38.6, 29.5, 28.2, 22.1, 18.9, 7.9, 7.4. HRMS $m/z$ for C$_{11}$H$_{15}$NO calcd 177.1151, found 117.1154.

**Compound 4**

To a solution of 2b (456 mg, 1.0 mmol) in 5 mL THF at -78 °C was added a solution of LiTMP generated using tetramethylpiperidine (296 mg, 2.1 mmol) and 0.8 mL of n-BuLi (2.5 M solution in hexane) in 10 mL of THF. The solution was allowed to rise to -20 °C and stirred at -20 °C for a period of 90 min. The above solution was cooled to -78 °C and 2,2-diacycylcyclopropane (105 mg, 0.82 mmol) in 3 mL THF was added. The solution was warmed to 0 °C and was stirred at that temperature for additional 1 h. The reaction was quenched with saturated ammonium chloride solution. The organic layer was extracted with ether (3 X 10 mL) and dried over MgSO$_4$. The crude product was chromatographed on silica gel (H:EA = 5:1) to afford compound 4 as mixture of isomers. 4a: 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 5.34 (1H, m), 4.17 (1H, q, $J = 7.2$ Hz), 2.77 (1H, d, $J = 11.7$ Hz), 2.33-2.41 (2H, m), 1.42 (3H, m), 1.27 (3H, t, $J = 7.2$ Hz), 1.25 (3H, s), 1.01-1.1 (1H, m), 0.80-0.90 (2H, m), 0.49-0.52 (1H, m); 75 MHz $^{13}$C NMR (CDCl$_3$) $\delta$ 174.8, 136.2, 119.0, 70.1, 60.9, 49.3, 31.4, 27.7, 21.5, 19.0, 14.8, 8.3, 6.1. 4b: 5.42 (1H, bs), 4.18 (2H, q, $J = 7.2$ Hz), 2.58-2.69 (2H, m), 2.24-2.34 (1H, m), 1.42 (3H, m), 1.30 (3H, t, $J = 7.2$ Hz), 0.82-0.94 (1H, m), 0.60-0.75 (3H,
Compound 5

To a solution of 2a (457 mg, 1 mmol) in 5 mL THF at -78 °C was added a solution of LiTMP generated using tetramethylpiperidine (296 mg, 2.1 mmol) and 0.8 mL of n-BuLi (2.5 M solution in hexane) in 10 mL THF. The solution was allowed to rise to -20 °C and stirred at -20 °C for a period of 90 min. The above solution was cooled to -78 °C and 2,2-diacetylcyclopentane (126 mg, 0.82 mmol) in 3 mL THF was added. The solution was warmed to 0 °C and stirred at that temperature for additional 1 h. The reaction was quenched with saturated ammonium chloride solution. The organic layer was extracted with ether (3 X 10 mL) and dried over MgSO4. The crude product was chromatographed on silica gel (H:EA = 5:1) to afford mixture of alcohols. 300 MHz 1H NMR (CDCl3) δ 5.04 (1H, bs), 2.99 (1H, dd, J = 11.6 Hz, J = 6 Hz), 2.23-2.78 (2H, m), 1.92-2.01 (2H, m), 1.51-1.81 (6H, m), 1.38-1.50 (3H, m), 1.27 (3H, s); 75 MHz 13C NMR (CDCl3) δ 142.5, 121.4, 115.8, 74.3, 53.9, 37.1, 36.4, 31.0, 28.8, 28.4, 27.8, 20.3, 19.8. HRMS m/z for C13H19NO calcd 205.1467, found 205.1469.

Compound 6

To a solution of 2a (457 mg, 1.0 mmol) in 5 mL THF at -78 °C was added a solution of LiTMP generated using tetramethylpiperidine (296 mg, 2.1 mmol) and 0.8 mL of n-BuLi (2.5 M solution in hexane) in 10 mL THF. The solution was allowed to rise to -20 °C and stirred at -20 °C for a period of 90 min. The above solution was cooled to -78 °C and 3,3-
dimethyl-2,4-pentanedione (105 mg, 0.82 mmol) in 3 mL of THF was added. The solution was warmed to 0 °C and was stirred at that temperature for additional 1 h. The reaction was quenched with saturated ammonium chloride solution. The organic layer was extracted with ether (3 X 10 mL) and dried over MgSO₄. The crude product was chromatographed on silica gel (H:EA = 5:1) to afford 6. 300 MHz ¹H NMR (CDCl₃) δ 5.16 (1H, bs), 3.13 (1H, dd, J =11.6 Hz, J = 6 Hz), 2.18-2.50 (2H, m), 1.64-1.64 (3H, m), 1.32 (3H, s), 1.08 (3H, s), 1.04 (3H, s); 75 MHz ¹³C NMR (CDCl₃) δ 141.72, 121.7, 116.7, 73.6, 42.5, 35.6, 28.4, 23.7, 20.6, 20.4, 19.5. HRMS m/z for C₁₁H₁₁NO calcld 179.1310, found 179.1312.

Compound 7:

To a solution of 2a (457 mg, 1 mmol) in 5 mL of THF at -78 °C was added a solution of LiTMP generated using tetramethylpiperidine (296 mg, 2.1 mmol) and 0.8 mL of n-BuLi (2.5 M solution in hexane) in 10 mL of THF. The solution was allowed to rise to -20 °C and stirred at -20 °C for a period of 90 min. The above solution was cooled to -78 °C and 2,2-dimethyl-3-oxo-3-phenylpropanaldehyde (144 mg, 0.82 mmol) in 3 mL THF was added. The solution was warmed to 0 °C and was stirred at that temperature for additional 1 h. The reaction was quenched with saturated ammonium chloride solution. The organic layer was extracted with ether (3 X 10 mL) and dried over MgSO₄. The crude product was flushed through a pad of silica to get crude mixture of 7. The mixture was dissolved in 4 mL of acetone and 0.5 mL of 2.7 M Jones reagent was added at 0 °C. After stirring at that temperature for 30 min quenched with 1 mL of isopropanol. Solvent was evaporated, dissolved in 5 mL of water and extracted with ethyl acetate (3 X 10 mL). Organic layer was dried with MgSO₄ and the crude product was chromatographed on silica gel (H:EA = 5:1) to
yield compound 7a. 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.28-7.40 (3H, m), 7.11-7.15 (2H, m), 5.61 (1H, dd, $J = 5.7$ Hz, $J = 2.4$ Hz), 4.06 (1H, dd, $J = 11.7$, $J = 6.7$ Hz), 2.71-3.03 (2H, m), 1.42 (3H, s), 1.25 (3H, s); 75 MHz $^{13}$C NMR (CDCl$_3$) $\delta$ 203, 147.9, 139.5, 129.3, 128.2, 128.1, 127.7, 122.0, 116.6, 48.8, 38.2, 30.2, 27.2, 22.8. HRMS $m/z$ for C$_{13}$H$_{15}$NO calcd 225.1157, found 225.1157.

**Compound 8:**

To a solution of 2b (457 mg, 1 mmol) in 5 mL THF at -78 °C was added a solution of LiTMP generated using tetramethylpiperidine (296 mg, 2.1 mmol) and 0.8 mL of n-BuLi (2.5 M solution in hexane) in 10 mL of THF. The solution was allowed to rise to -20 °C and stirred at -20 °C for a period of 90 min. The above solution was cooled to -78 °C and 2,2-dimethyl-3-oxo-3-phenylpropanaldehyde (144 mg, 0.82 mmol) in 3 mL THF was added. The solution was warmed to 0 °C and was stirred at that temperature for additional 1 h. The reaction was quenched with saturated ammonium chloride solution. The organic layer was extracted with ether (3 X 10 mL) and dried over MgSO$_4$. The crude product was flushed through a pad of silica to get crude mixture of 8. The mixture was dissolved in 4 mL of acetone and 0.5 mL of 2.7 M Jones reagent was added at 0 °C. After stirring at that temperature for 30 min quenched with 1 mL of isopropanol. Solvent was evaporated, dissolved in 5 mL of water and extracted with ethyl acetate (3 X 10 mL). Organic layer was dried with MgSO$_4$ and the crude product was chromatographed on silica gel (H:EA = 5:1) to yield compound 8a. 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 12.62 (1H, s), 7.25-7.30 (3H, m), 7.15-7.18 (2H, m), 5.51 (1H, t, $J = 3.6$ Hz), 4.27 (2H, q, $J = 7.2$ Hz), 3.01 (2H, d, $J = 3.6$ Hz), 1.32 (3H, t, $J = 7.2$ Hz), 1.29 (6H, s); 75 MHz $^{13}$C NMR (CDCl$_3$) $\delta$ 175.6, 172.7, 143.6, 141.4,
129.8, 127.5, 126.7, 122.3, 93.6, 60.5, 39.86, 25.7, 25.1, 14.4. HRMS m/z for C_{17}H_{20}O_{3} calcd 272.1412, found 272.1416.

**Compound 9**

To a solution of 2a (457 mg, 1 mmol) in 5 mL THF at -78 °C was added a solution of LiTMP generated using tetramethylpiperidine (296 mg, 2.1 mmol) and 0.8 mL of n-BuLi (2.5 M solution in hexane) in 10 mL of THF. The solution was allowed to rise to -20 °C and stirred at -20 °C for a period of 90 min. The above solution was cooled to -78 °C and butane-2,3-dione (70 mg, 0.82 mmol) in 3 mL THF was added. The solution was warmed to 0 °C and was stirred at that temperature for additional 1 h. The reaction was quenched with saturated ammonium chloride solution. The organic layer was extracted with ether (3 X 10 mL) and dried over MgSO₄. The crude product was chromatographed on silica gel (H:EA= 4:1) to afford 9 as mixture of alcohols. 9a: 300 MHz ¹H NMR (CDCl₃) δ 5.49 (1H, bs), 3.12 (2H, t, J = 6.7Hz), 2.49-2.78 (2H, m), 1.71-1.78 (3H, m), 1.49 (3H, s); 75 MHz ¹³C NMR (CDCl₃) δ 144.5, 125.2, 120.5, 84.4, 42.3, 33.6, 24.8, 11.9. 9b: 300 MHz ¹H NMR (CDCl₃) δ 5.39 (1H, bs), 2.98 (2H, t, J = 6.7Hz), 2.49-2.78 (2H, m), 1.71-1.78 (3H, m), 1.49 (3H, s); 75 MHz ¹³C NMR (CDCl₃) δ 143.7, 122.9, 119.9, 83.1, 41.2, 33.5, 22.8, 11.7. HRMS m/z for C₈H₁₁NO calcd 137.0841, found 137.0843.

**Compound 10**

To a solution of 2a (457 mg, 1 mmol) in 5 mL THF at -78 °C was added a solution of LiTMP generated using tetramethylpiperidine (296 mg, 2.1 mmol) and 0.8 mL of n-BuLi (2.5 M solution in hexane) in 10 mL of THF. The solution was allowed to rise to -20 °C and...
stirred at -20 °C for a period of 90 min. The above solution was cooled to -78 °C and benzil (172 mg, 0.82 mmol) in 3 mL THF was added. The solution was warmed to 0 °C and was stirred at that temperature for additional 1 h. The reaction was quenched with saturated ammonium chloride solution. The organic layer was extracted with ether (3 X 10 mL) and dried over MgSO4. The crude product was chromatographed on silica gel (H:EA= 3:1) to afford 10 as mixture of alcohols. 10a: 300 MHz 1H NMR (CDCl3) 6 7.18-7.45 (10H, m), 6.45 (1H, m), 3.38 (1H, m), 2.70-2.98 (2H, m); 75 MHz 13C NMR (CDCl3) 6 146.2, 142.5, 132.9, 129.2, 128.9, 128.6, 128.2, 127.4, 127.2, 125.4, 119.1, 87.01, 46.3, 34.2. HRMS m/z for C18H15NO calcd 261.1154, found 261.1156. 10b: 300 MHz 1H NMR (CDCl3) 6 7.18-7.45 (10H, m), 6.40 (1H, m), 3.58 (1H, m), 2.71-2.98 (2H, m); 75 MHz 13C NMR (CDCl3) 6 146.2, 143.5, 131.9, 129.1, 128.7, 128.6, 128.1, 127.4, 127.2, 125.4, 119.1, 87.01, 45.3, 33.2.

Compound 11

To a solution of 2a (457 mg, 1 mmol) in 5 mL THF was added a solution of LiTMP generated using tetramethylpiperidine (296 mg, 2.1 mmol) and 0.8 mL of n-BuLi (2.5 M solution in hexane) in 10 mL of THF. The solution was allowed to rise to -20 °C and stirred at -20 °C for a period of 90 min. The above solution was cooled to -78 °C and fluril (162 mg, 0.82 mmol) in 3 mL THF was added. The solution was warmed to 0 °C and was stirred at that temperature for additional 1 h. The reaction was quenched with saturated ammonium chloride solution. The organic layer was extracted with ether (3 X 10 mL) and dried over MgSO4. The crude product was chromatographed on silica gel (H:EA= 4:1) to afford 11 as mixture of alcohols. 11a: 300 MHz 1H NMR (CDCl3) 6 7.44 (1H, t, J = 1.5 Hz), 7.35 (1H, s), 6.39 (1H, d, J = 1.5 Hz), 6.33 (1H, d, J = 1.2Hz), 6.30 (1H, t, J = 3Hz), 3.50 (1H, t, J = 8.7
Hz), 2.84-3.00 (2H, m); 75 MHz $^{13}$C NMR (CDCl$_3$) $\delta$ 153.7, 148.1, 143.1, 142.8, 135.3, 126.7, 118.6, 111.5, 110.9, 108.1, 107.9, 83.0, 41.9, 34.4. HRMS m/z for C$_{14}$H$_{11}$NO$_3$ calcd 261.1154, found 261.1157. 11b: 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.34-7.38 (2H, m), 6.40-6.53 (1H, m), 6.34-6.40 (2H, m), 6.27-6.33 (1H, m), 5.98 (1H, t, $J = 3$ Hz), 3.64 (1H, t, $J = 8.7$ Hz), 2.98-3.02 (2H, m); 75 MHz $^{13}$C NMR (CDCl$_3$) $\delta$ 152.7, 147.1, 143.1, 142.1, 134.3, 125.7, 117.6, 111.5, 110.9, 108.1, 107.9, 83.0, 41.9, 34.4.

**Compound 12**

To a solution of 2b (457 mg, 1 mmol) in 5 mL THF at -78 °C was added a solution of LiTMP generated using tetramethylpiperidine (296 mg, 2.1 mmol) and 0.8 mL of n-BuLi (2.5 M solution in hexane) in 10 mL of THF. The solution was allowed to rise to -20 °C and stirred at -20 °C for a period of 90 min. The above solution was cooled to -78 °C and butane-2,3-dione (70 mg, 0.82 mmol) in 3 mL THF was added. The solution was warmed to 0 °C and was stirred at that temperature for additional 1 h. The reaction was quenched with saturated ammonium chloride solution. The organic layer was extracted with ether (3 X 10 mL) and dried over MgSO$_4$. The crude product was chromatographed on silica gel (H:EA= 4:1) to afford 12 as mixture of alcohols. 12a: 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.15-7.30 (10H, m), 6.45 (1H, m), 3.71 (2H, m), 3.57 (1H, t, $J = 8.4$ Hz), 2.98-3.10 (1H, m), 2.71-2.22 (1H, m), 0.95 (3H, t, $J = 7.2$ Hz). 12b: 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.15-7.30 (10H, m), 6.43 (1H, m), 3.61-3.78 (2H, m), 3.47 (1H, t, $J = 8.4$ Hz), 2.98-3.10 (1H, m), 2.71-2.22 (1H, m), 0.95 (3H, t, $J = 7.2$ Hz).
**Compound 13**

To a solution of 2b (456 mg, 1 mmol) in 5 mL THF at -78 °C was added a solution of LiTMP generated using tetramethylpiperidine (296 mg, 2.1 mmol) and 0.8 mL of n-BuLi (2.5 M solution in hexane) in 10 mL of THF. The solution was allowed to rise to -20 °C and stirred at -20 °C for a period of 90 min. The above solution was cooled to -78 °C and pthalaldehyde (110 mg, 0.82 mmol) in 3 mL THF was added. The solution was warmed to 0 °C and was stirred at that temperature for additional 1 h. The reaction was quenched with saturated ammonium chloride solution. The organic layer was extracted with ether (3 X 10 mL) and dried over MgSO₄. The crude product was flushed through a pad of silica to get crude mixture of alcohols. The mixture was dissolved in 4 mL of acetone and 0.5 mL of 2.7 M Jones reagent was added at 0 °C. After stirring at that temperature for 30 min quenched with 1 mL of isopropanol. Solvent was evaporated, dissolved in 5 mL of water and extracted with ethyl acetate (3 X 10 mL). Organic layer was dried with MgSO₄ and chromatographed (H:EA = 3:1) to yield compound 13. 300 MHz $^1$H NMR (CDCl₃) δ 7.98 (1H, t, J = 6 Hz), 7.23-7.43 (10H, m), 6.57 (1H, d, J = 7.5 Hz), 6.17-6.24 (1H, m), 4.28 (2H, q, J = 7.2 Hz), 2.60 (1H, d, J = 5.1 Hz), 1.34 (3H, t, J = 7.2 Hz). 75 MHz $^{13}$C NMR (CDCl₃) δ 171.8, 167.5, 137.7, 134.0, 133.2, 129.8, 129.7, 129.5, 128.7, 126.6, 102.0, 61.2, 21.6, 14.5 HRMS m/z for C₁₄H₁₄O₃ calcd 230.0943, found 230.0948.

**Compound 14**

To a solution of 2a (456 mg, 1 mmol) in 5 mL THF at -78 °C was added a solution of LiTMP generated using tetramethylpiperidine (296 mg, 2.1 mmol) and 0.8 mL of n-BuLi (2.5 M solution in hexane) in 10 mL of THF. The solution was allowed to rise to -20 °C and
stirred at -20 °C for a period of 90 min. The above solution was cooled to -78 °C and pthalaldehyde (110 mg, 0.82 mmol) in 3 mL THF was added. The solution was warmed to 0 °C and was stirred at that temperature for additional 1 h. The reaction was quenched with saturated ammonium chloride solution. The organic layer was extracted with ether (3 X 10 mL) and dried over MgSO₄. The crude product was flushed through a pad of silica to get crude mixture of alcohols. The mixture was dissolved in 4 mL of acetone and 0.5 mL of 2.7 M Jones reagent was added at 0 °C. After stirring at that temperature for 30 min quenched with 1 mL of isopropanol. Solvent was evaporated, dissolved in 5 mL of water and extracted with ethyl acetate (3 X 10 mL). Organic layer was dried with MgSO₄ and chromatographed (H:EA = 3:1) to yield compound 14. 300 MHz ¹H NMR (CDCl₃) δ 8.01 (1H, t, J = 6 Hz), 7.23-7.43 (10H, m), 6.57 (1H, d, J = 7.5 Hz), 6.17-6.24 (1H, m), 2.6 (1H, d, J = 5.1 Hz), 1.34 (3H, t, J = 7.2 Hz).

Compound 16

To a solution of 15 (458 mg, 1 mmol) in 5 mL of THF at -78 °C was added a solution of LiTMP generated using tetramethylpiperidine (296 mg, 2.1 mmol) and 0.8 mL of n-BuLi (2.5 M solution in hexane) in 10 mL of THF. The solution was allowed to rise to -20 °C and stirred at -20 °C for a period of 90 min. The above solution was cooled to -78 °C and 2,3-butanedione (70 mg, 0.82 mmol) in 3 mL of THF was added. The solution was warmed to 0 °C and was stirred at that temperature for additional 1 h. The reaction was quenched with saturated ammonium chloride solution. The organic layer was extracted with ether (3 X 10 mL) and dried over MgSO₄. The crude product was chromatographed on silica gel (H:EA = 6:1) to afford 16. 300 MHz ¹H NMR (CDCl₃) δ 8.13 (1H, d, J = 8.4 Hz), 7.51-7.77 (4H, m),
2.68 (3H, s), 2.46 (3H, s).

**Compound 17**

To a solution of 15 (458 mg, 1 mmol) in 5 mL THF at -78 °C was added a solution of LiTMP generated using tetramethylpiperidine (296 mg, 2.1 mmol) and 0.8 mL of n-BuLi (2.5 M solution in hexane) in 10 mL of THF. The solution was allowed to rise to -20 °C and stirred at -20 °C for a period of 90 min. The above solution was cooled to -78 °C and benzil (172 mg, 0.82 mmol) in 3 mL THF was added. The solution was warmed to 0 °C and was stirred at that temperature for additional 1 h. The reaction was quenched with saturated ammonium chloride solution. The organic layer was extracted with ether (3 X 10 mL) and dried over MgSO₄. The crude product was chromatographed on silica gel (H:EA = 7:1) to afford 17.

300 MHz 1H NMR (CDCl₃) δ 8.33 (1H, d, J = 8.4 Hz), 8.10 (1H, m), 7.98 (1H, d, J = 7.2 Hz), 7.51-7.77 (2H, m), 7.10-7.31 (10H, m).

**Compound 18:**

To a solution of 2b (457 mg, 1 mmol) in 5 mL THF at -78 °C was added a solution of LiTMP generated using tetramethylpiperidine (296 mg, 2.1 mmol) and 0.8 mL of n-BuLi (2.5 M solution in hexane) in 10 mL of THF. The solution was allowed to rise to -20 °C and stirred at -20 °C for a period of 90 min. The above solution was cooled to -78 °C and (105 mg, 0.82 mmol) in 3 mL THF was added. The solution was warmed to 0 °C and was stirred at that temperature for additional 1 h. The reaction was quenched with saturated ammonium chloride solution. The organic layer was extracted with ether (3 X 10 mL) and dried over MgSO₄. The crude product was chromatographed on silica gel (H:EA = 3:1) to afford 18 as
mixture of alcohols: 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 5.24-5.39 (2H, m), 4.08-4.18 (2H, m), 2.70-3.67 (1H, m), 2.23-2.73 (3H, m), 1.35-2.01 (6H, m), 1.31-1.35 (3H, m), 0.92-1.21 (2H, m).

References:


CHAPTER 2
SYNTHETIC APPROACH TOWARDS METHYLLYACONITINE

Introduction

Larkspur is a toxic plant on western U.S ranges. About 5-15% of cattle poisoning on North American mountain lands are due to larkspur poisoning. Toxic alkaloids constitute 30-50% of total alkaloid content in tall larkspur.¹ Larkspur (Delphinium species) alkaloids can be divided into two structural types, namely lycactonine and 7,8-methylenedioxylycoctonine (deltaline) as shown in Figure 1.

![Lycocctonine (1) and Deltaline (2)](image)

Figure 1. Representative alkaloids of Delphinium species.

Among the numerous alkaloids, the lycoctonine type norditerpenoid alkaloid methyllycacoctonine (MLA) appears to be most toxic. Toxicity is attributed to its ability to act as a potent inhibitor of the acetylcholine receptor (nAChR) binding, thus leading to neuromuscular paralysis.² Clinical signs include labored breathing, rapid and irregular heartbeat, muscular weakness and collapse.³
Recently, nicotinic acetylcholine receptor chemistry and biology have gained enormous interest in the field of drug development. The nAChRs are large family of ligand gated ion channels located throughout the body in the central nervous system, peripheral nervous system and at the neuromuscular junction. The family contains numerous receptor subtypes consisting of pentameric arrays made up from a variety of distinct peptide subunits. Isolation/synthesis of subtype selective agonists and antagonists could elucidate the biological roles of the subtypes and eventually lead to candidates for drug development. Pharmacological studies have shown MLA to selectively bind to the α7 subtype nAChRs in mammalian brain. The α7 subtype is amongst the most prevalent nAChR in the brain and has been implicated as playing a key role in conditions such as schizophrenia, Alzheimer’s disease and epilepsy. The combined qualities of high affinity binding, functional potency and subtype selectivity renders MLA as a primary lead for the development of new therapeutic agents targeting α7 nAChR.

Structure-activity relationship investigations have indicated that the N-methyl succinimidobenznozoate ester at C-18 affects alkaloid interactions with nAChRs at neuromuscular junctions and the substituent at C-14 determines the potency and the
mechanism of nAChR blockade at neuromuscular synapses. The methyl group on the succinimido ring and the ethyl group of the tertiary amine were also found to be structural requirements for its biological activity. The pharmacological specificity of MLA seems to arise from the fact that the tertiary nitrogen atom of MLA and quaternary nitrogen atom of acetylcholine may undergo equivalent electrostatic interaction with the receptor binding site.

Numerous Delphinium alkaloids, have been proposed as lead compounds for pharmaceutical research and development. Several structurally less complex analogs of MLA have been synthesized to establish the structural requirements necessary for biological activity. From the synthetic point of view, only a few partial syntheses of MLA have been attempted; key studies were reported by Van der Bann, Whiting and Kraus. Earliest work on norditerpenoid alkaloid by Van der Bann and coworkers led to an efficient construction of the right hand portion of the molecule, the BCDA-carbocycle part (Figure 3).7

Figure 3.

Synthesis of the ABCD ring system began with the efficient transformation of 7-tert-
butoxynorbornadiene 5 to tricyclic ketone 6, which was then converted to tricyclic enaminoester 7. The construction of the BCD ring system was accomplished by ring expansion (Scheme 1) to yield compound 8. Michael additions of β-keto ester 9 to benzyl acrylate lead to compound 10. Cleavage of the benzyl group followed by one-carbon homologation and Dieckman condensation leads to the ABCD ring system. This work represents a solid synthesis of the right-hand portion of C19-diterpene alkaloids skeleton. However, their inability to make the biologically significant E and F rings decreases the synthetic value of this approach.

Scheme 1.
Scheme 2.

The synthesis of ABDE ring system employing the addition reactions of bridgehead radicals to alkenyltributylstannanes and α,β-unsturated ketones and esters has been accomplished by Kraus et al.\textsuperscript{10} Initially, the bicyclic ketone 11 was reacted with allyltributyl in the presence of AIBN to afford the alkene 12 in good yield (Scheme 3). Ozonolysis of the double bond and a Wittig reaction of the resulting aldehyde yielded 13, which underwent Diels-Alder reaction with 1-trimethylsiloxy-1,3-butadiene. Intramolecular aldol cyclization with potassium hexamethyldisilazane furnished the ABDE ring system of the C\textsubscript{19}-diterpene alkaloids.

In 1998, Whitting and co-workers reported the synthesis of AEF tricyclic fragment.\textsuperscript{9} The stereocenters of the AEF segment were set by two key reactions: the intramolecular 1,3-dipolar addition to the alkene and the Diels-Alder reaction. Diels-Alder reaction of the
sodium salt of acid 15 and acrylate 16 yielded compound 17. Compound 17 was converted to the isoxazolidine 19 via the nitrene in a one-pot process. Cleavage of isoxazolidine liberates an amine, which underwent intermolecular reaction with ester to yield the tricyclic segment 20 as shown in Scheme 3.

Scheme 3.

In 1998, Kraus reported a direct route to ABE tricyclic segment (Scheme 4).11 His synthesis began with selective protection of enone in spirocyclic diketone 21 with trimethylsilyl triflate. Introduction of carbomethoxy group followed by hydrolysis yielded compound 22. Treatment of the compound 22 with ethylamine and formaldehyde in aqueous methanol furnished the tricyclic ABE segment. Unfortunately, unusual inertness of the carbonyl group in the one carbon bridge to a variety of nucleophiles prevented the elaboration of the tricyclic segment to the ABEF ring system.
Scheme 4.

1. TMSOTf, Et\(_3\)N

2. LDA, NCCO\(_2\)Me

3. H\(_3\)O\(^+\)

4. CH\(_2\)O, EtNH\(_2\)
Results and Discussion

In our studies towards C_{19}-ditepenoid alkaloids, we envisioned the synthesis of an ABEF ring system possessing all necessary functionality to allow us to easily incorporate the C and D rings. Scheme 5 suggests the synthetic strategy for the ABEF ring system. The key reaction is the hydrolytic skeletal rearrangement of compound 25 to aldehyde 27. Hydrolysis of the imine leads to an aminal 26, which should rearrange to aldehyde 27. An intramolecular aldol reaction could generate the required ABEF carbocycle.

Scheme 5.

Our first approach to intermediate 25 was from compound 24 (Scheme 6). Treatment of 24 with variety of halides led to the formation of enones 29-31. Attempts to facilitate intramolecular cyclization to generate the tricyclic intermediate using excess base were unsuccessful. Hence, an alternate strategy was conceived for the construction of ABEF ring system.
Scheme 6.

The ABEF ring system could be envisioned from dienone 32 through hydrolytic skeletal rearrangement. Intramolecular para-C-alkylation\(^{12}\) of phenol 33 could lead to dienone 32. Keto ester 34 could act as a precursor for phenol 33.
To test the feasibility of intramolecular cyclization, a model study was undertaken as shown in Scheme 8. Thus β-ketoester 36\(^{13}\) was reacted with the aryllithium generated from bromoether 36a to produce alcohol 37 as mixture of isomers. Dehydration of alcohol 36 using thionyl chloride and subsequent removal of silyl protection from compound 38 using TBAF yielded phenol 39. Heating phenol 39 in tert-butanol with 1.2 equivalents of potassium tert-butoxide yielded the dienone 40 through an intramolecular spirocyclization.\(^{12}\)
Encouraged by the above result, our synthesis toward ABEF ring system commenced from known keto ester 33. Treatment of 33 with 2,6-lutidine and triflic anhydride yielded vinyl triflate 42. Suzuki coupling of triflate 42 with boronic acid 41 yielded compound 43 in modest yield. The γ-alkylation of compound 43 using LDA and HMPA furnished compound 44. Treatment of compound 44 with TBAF led to the removal of the TBS protecting group yielding phenol 33. The intramolecular cyclization was achieved using potassium tert-butoxide to yield dienone 32.
With dienone in our hand we turned our attention towards the hydrolytic skeletal rearrangement. However, many attempts to hydrolyze carbamate 32 were unsuccessful. Prolonged exposure of compound 32 to acidic conditions only led to the decomposition of 32.
Scheme 10.

Since hydrolysis was unsuccessful, we decided to change the protecting group on nitrogen to a readily-cleavable BOC group. Thus, dienone 49 was synthesized from carbamate 48. Unfortunately, our attempts to hydrolyze enone 49 were also unsuccessful, leading to a complex mixture.

Scheme 11.

Meanwhile, dihydroxylation of enone 32 led to isolation of phenol 51. This reaction occurs probably through diol 50 which undergoes a retro-aldol reaction to give 51.
Scheme 12.

In order to solve the problem of hydrolysis we decided to change the order of the steps. Phenol 33 was converted to dithiane 52. Surprisingly, all of our attempts to facilitate the intramolecular cyclization only led to decomposition of starting material.

Scheme 13.

Meanwhile, we sought to synthesize phenol 54. Reductive removal of the benzyl group from 55,17 followed by treatment with BOC anhydride led to compound 56. The lithium enolate of 56 was treated with aldehyde 57 to get the aldol adduct, which was subsequently oxidized with Jones reagent to get compound 58. Treatment of compound 58 with pivaloyl chloride and triethylamine led to the isolation of compound 59. Methyl cuprate addition to compound 59 led to the formation 60 in modest yield. Efforts to convert 60 to 54 were futile.
Scheme 14.

Even though we were unable to synthesize the required ABEF ring system, our unsuccessful routes did give us some valuable insights. We learned that there is need for an early F ring construction. We need to introduce the required carbon appendages for F ring construction quite early in our synthesis. Secondly, the para-C-alkylation could be a useful tool for an efficient construction of the AB ring system and a simple substituted phenol could act as a precursor for the B ring.

Second Generation Approach

In spite of the failure of the approaches discussed previously, the knowledge gained through the previous approaches decreased the synthetic challenge considerably. Scheme 15 gives the retrosynthesis.
Scheme 15 provides us an opportunity to construct the F through an aldol reaction. The ABE segment could be constructed from BE segment through the \textit{para}-C-alkylation reaction. Finally, substituted 3-aminophenol could act as the B ring.

The synthesis began from 3-aminophenol. Protection of the amino group with BOC anhydride followed by protection of the phenol as a TBS ether gave compound 62. Regioselective \textit{ortho}-metallation\textsuperscript{18} of the aryl ring followed by treatment with excess DMF led to the production of aldehyde 63 as shown in Scheme 16. The BOC group acts as an \textit{ortho}-directing group. One of the \textit{ortho} positions is selectively blocked by bulky the TBS group, leading to selective \textit{ortho}-metallation. The silyl ether was deprotected using TBAF to yield phenol 64.
Scheme 16.

The phenol was converted to a MOM ether using methoxymethyl chloride and diisopropylethylamine to give compound 65. Heating aldehyde 65 with dimethyl malonate in presence of piperidine led to the isolation of lactam 66 in 90% yield. This reaction occurs through α-β-unsaturated diester which subsequently loses the BOC protecting group to cyclize to the lactam 66. The N-ethyl group was introduced using potassium carbonate and ethyl iodide to give compound 67 as shown in Scheme 17. The lactam 67 represents the BE segment of lycocotonine alkaloid.
With the BE segment in hand, the next goal was to synthesize the ABE ring system of lycocotonine. However, we decided to introduce the carbon units required for the F ring at this stage. The carbon units required for the construction of the F ring were introduced by way of a vinyl unit, which could be oxidatively cleaved to an aldehyde group later in the synthesis. Conjugate addition of vinylcuprate (generated from vinyl magnesium bromide and copper(I) iodide) yielded ketoester 68 in fairly modest yield. Ultimately, vinylcuprate stabilized using dimethyl sulfide as the additive (entry 4, Table 1) was chosen for the conjugate addition.

**Table 1. Conjugate addition experiments**
<table>
<thead>
<tr>
<th>Copper Source</th>
<th>Additive</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>CuI</td>
<td>None</td>
<td>43</td>
</tr>
<tr>
<td>CuCN</td>
<td>None</td>
<td>47</td>
</tr>
<tr>
<td>CuI</td>
<td>TMSCl</td>
<td>55</td>
</tr>
<tr>
<td>CuI</td>
<td>Me₂S</td>
<td>60</td>
</tr>
<tr>
<td>None</td>
<td>None</td>
<td>17</td>
</tr>
</tbody>
</table>

Synthesis of the ABE segment began by steroselectively alkylating\(^{19}\) compound 68 using NaH and 1, 3-dibromopropane to yield compound 69. The *cis*-relationship of the vinyl and ester groups was determined by 2D NOESY NMR. Treatment of compound 69 with 4 N HCl led to the isolation of phenol 70 as shown in Scheme 18.
Having achieved the synthesis of phenol 70 with the desired stereochemistry, we turned our attention towards the appendage of the A ring. However we were unable to effect the desired para-C-alkylation using standard conditions (t-BuO'K\(^+\), t-BuOH). Finally we were able to achieve the much-needed cyclization using 18-crown-6 and NaH. Heating phenol 70 in THF with the presence of NaH and crown ether led to an intramolecular cyclization leading to the formation of compound 71 in modest yield as shown in Scheme 19. Compound 71 represents the ABE segment of lycocotonine.
Scheme 19

Construction of the ABEF segment required the selective oxidation of the terminal double bond in the presence of enone as shown in Scheme 20. Unfortunately, we were unable to oxidize the terminal double bond selectively. We decided on a detour as shown in Scheme 21.

Scheme 20.

Ozonolysis of compound 69 gave an aldehyde in 92% yield. Treatment of the aldehyde with timethylorthoformate in methanol with the presence of a catalytic amount of PTSA led
to the protection of the aldehyde as a dimethyl acetal with a subsequent removal of the MOM group to liberate phenol 73 in 62% yield. Heating phenol 73 in THF in the presence of NaH and crown-ether led to an intramolecular cyclization leading to the formation of ABE segment of lycoctonine as shown in Scheme 21.

![Scheme 21](image)

Having constructed the ABE ring system (compound 74), we went towards the addition of the F ring. Surprisingly, the reduction of dienone proved difficult. Hydrogenation of the dienone led to the reduction of only the less hindered double bond. Use of reducing agents
like Zn/acetic acid\textsuperscript{20} and K-selectride\textsuperscript{21} led to the isolation of complex mixtures. Finally, we were able to reduce the enone double bond using Li/NH\textsubscript{3}\textsuperscript{22} along with concomitant reduction of the ester group to an aldehyde to yield compound 76 as shown in Scheme 22.

Scheme 22.

Having achieved our 1,4-reduction, we tried converting the tricyclic intermediate 76 to the ABEF ring system. Attempts to do an intramolecular aldol reaction under acidic conditions led to the decomposition of the ketoaldehyde. We attributed the failure of this reaction to the aldehyde group present in the molecule. Surprisingly, we were unable to oxidize the sterically hindered aldehyde. Hence, we turned our attention to a selective reduction. Hydrolysis of the methyl ester using LiOH gave acid 77 in modest yield. Li/NH\textsubscript{3}
reduction of the acid led to selective reduction of the enone to yield acid 78, which was treated with diazomethane to yield methyl ester 79 as 3:1 mixture of isomers. The major isomer was crystallized and its structure was confirmed using X-ray crystallography.

Scheme 23.

Treatment of compound 79 with 4N HCl led to the isolation of compound 80 in 58% yield plus 17% of ketoaldehyde 81 arising from the minor isomer. Compound 80 represents the ABEF carbocycle of methyllycaconitine as shown in Scheme 24.
Compound 80 was elaborated to enone 84 as shown in Scheme 25. Treatment of compound 80 with CSA and *para*-methoxybenzylacetamidate\textsuperscript{23} gave compound 82. The silyl enol ether (generated using LDA, and TMSCl) of 82 was converted to enone 83 using Pd(OAc)\textsubscript{2}.\textsuperscript{24}
Scheme 25.

The enone 84 represents the ABEF carbocycle skeleton of the aconitine alkaloids with all the functionality necessary to install the C and D rings as shown in Scheme 26. Finally, the biologically significant 2-methylsuccinimido benzoate ester on the C19 neopentyl alcohol would be introduced to yield the core structure of MLA.
Recently a novel C$_{20}$-diterpenoid alkaloid was isolated from Aconitum racemulosum.$^{25}$ To test the generality of our approach we synthesized the ABE segment of this alkaloid as shown in Scheme 27.
Alkylation of compound 68 using NaH and 1,3-dibromoethane afforded compound 85. Treatment of compound 85 with 4N HCl led to the isolation of phenol 86 which was subsequently transformed to the ABE segment of racemulosomine using NaH and 18-crown-6.
In conclusion, we developed a direct synthetic route to ABEF segment of methyllycaconitine using intramolecular anionic spiro cyclization. Construction of the ABE segment of methyllycaconitine and racemulosine through a common bicyclic intermediate was achieved. Elaboration of the ABEF segment of lycoctonine alkaloid to the pentacyclic intermediate is under progress.
Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and used without purification. Tetrahydrofuran was distilled from sodium benzophenone ketyl. Dichloromethane and benzene were distilled over calcium hydride. All experiments were performed under argon atmosphere unless otherwise noted. Nuclear magnetic resonance experiments were performed with either a Varian 300 MHz or Bruker 400 MHz instrument. All chemical shifts are reported relative to CDCl₃ (7.26 ppm for H and 77.06 ppm for C), unless otherwise noted. Coupling constants (J) are reported in Hz with abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. High resolution mass spectra were recorded on a Kratos model MS-50 spectrometer and low resolution mass spectra were performed with a Finnegan 4023 mass spectrometer. Standard grade silica gel (60 Å, 32-63 μm) was used for a flash column chromatography.

Compound 29

A mixture of 24 (100 mg, 0.326 mmol) and 1 mL 2-bromomethyl acetate were heated at 60 °C for 24 h. The mixture was concentrated in vacuo, the residue was diluted with ethyl acetate and washed with brine. The organic layer was dried over MgSO₄, filtered, and evaporated in vacuo. The residue was purified by chromatography (H:EA = 1:1) to afford compound 29 (85 mg, 69%). 300 MHz ¹H NMR (CDCl₃) δ 7.07 (1H, d, J = 10.2 Hz), 6.04 (1H, d, J = 10.2 Hz), 4.29-4.25 (2H, m), 3.83 (3H, s), 3.59 (1H, d, J = 12.3 Hz), 3.2-3.3 (2H, m), 3.04 (1H, J = 12.3 Hz), 2.6-2.7 (1H, d, J = 15 Hz), 2.3-2.5 (4H, m), 1.8-2.2 (5H, m), 1.5 (3H, t, J = 7.2Hz), 1.3 (3H, t, J = 9Hz).
Compound 30

A mixture of 24 (100 mg, 0.326 mmol) and 1 mL 2-bromoacetonitrile was heated at 60 °C for 36 h. The mixture was concentrated in vacuo, the residue was diluted with ethyl acetate and washed with brine. The organic layer was dried over MgSO₄, filtered, and evaporated in vacuo. The residue was purified by chromatography (H:EA = 1:1) to afford 30 (80 mg, 71%). 300 MHz ¹H NMR (CDCl₃) δ 6.7 (1H, d, J = 10.2 Hz), 6.08 (1H, d, J = 10.2 Hz), 4.1-4.3 (2H, m), 3.83 (3H, s), 3.61 (1H, d, J = 12.3 Hz), 3.2-3.3 (2H, m) 3.04 (1H, J = 12.3 Hz), 2.6-2.7 (1H, d, J = 15 Hz), 2.3-2.5 (4H, m), 1.8-2.2 (5H, m), 1.5 (3H, t, J = 6.9 Hz).

Compound 31

A mixture of 24 (100 mg, 0.326 mmol) and 1 mL ethylbromomethyl phosphonate were heated at 60 °C for 36 h. The mixture was concentrated in vacuo, the residue was diluted with ethyl acetate and washed with brine. The organic layer was dried over MgSO₄, filtered, and evaporated in vacuo. The residue was purified by chromatography (H:EA = 3:1) to afford 31 (97 mg, 65%). 300 MHz ¹H NMR (CDCl₃) δ 6.70 (1H, d, J = 10.2 Hz), 6.08 (1H, d, J = 10.2 Hz), 4.10-4.30 (6H, m), 3.81-3.95 (2H, m) 3.83 (3H, s), 3.61 (1H, d, J = 12.3 Hz), 3.04 (1H, J = 12.3 Hz), 2.60-2.70 (1H, d, J = 15 Hz), 2.3-2.5 (4H, m), 1.8-2.2 (5H, m), 1.50-1.65 (9H, m).

Compound 37

To a solution of ether 36 (173 mg, 0.60 mmol) in THF (10 mL) at -78 °C was added 2.42 mL of n-BuLi (2.5 M in hexanes, 0.6 mmol). After 30 min at that temperature, a solution of bromide 36a (168 mg, 0.58 mmol) in 1 mL THF was added dropwise. The reaction mixture was gradually warmed to rt and quenched with saturated NH₄Cl. The organic
solvent was evaporated in vacuo. The residue was diluted with ethyl acetate and washed with brine. The organic layer was dried over MgSO₄, filtered, and evaporated in vacuo. The residue was purified by chromatography (H:EA = 4:1) to afford 37 as mixture of isomers (255 mg, 85% yield). 300 MHz $^1$H NMR (CDCl₃) δ 7.37 (2H, d, $J = 8.7$ Hz), 7.12 (2H, d, $J = 8.7$ Hz), 3.90-4.20 (2H, m), 3.30-3.50 (2H, m), 2.10-2.40 (4H, m), 1.20-2.0 (8H, m), 1.22 (3H, t, $J = 6.9$ Hz), 0.90 (9H, s), 0.21 (6H, s).

**Compound 38**

To a solution of alcohol 37 (163 mg, 0.32 mmol) in 0.5 mL of pyridine at 0 °C was added 116 mg (0.978 mmol) of SOCl₂. After being stirred at 0 °C for 45 min 2 mL of ice cold water was poured into the reaction mixture. The organic layer was extracted with ethyl acetate (3 X 5 mL) and dried over MgSO₄, filtered, and evaporated in vacuo. The residue was purified by chromatography (H:EA = 4:1) to afford 38 (92 mg, 60%). 300 MHz $^1$H NMR (CDCl₃) δ 6.99 (2H, d, $J = 8.4$ Hz), 6.71 (2H, d, $J = 8.4$ Hz), 5.94 (1H, t, $J = 4.8$ Hz), 4.12-4.20 (2H, m), 3.07-3.11 (2H, m), 2.10-2.30 (2H, m), 1.80-2.10 (2H, m), 1.50-1.80 (6H, m), 1.24 (3H, t, $J = 7.2$ Hz), 0.96 (9H, s), 0.18 (6H, s).

**Compound 39**

To a solution of 39 (61 mg, 0.127 mmol) in THF (3 mL) at 0 °C was added 130 μL of TBAF (1M in THF). The reaction mixture was stirred at that temperature for 30 min and quenched with saturated NH₄Cl. The organic solvent was evaporated in vacuo. The residue was diluted with ethyl acetate and washed with brine. The organic layer was dried over MgSO₄, filtered, and evaporated in vacuo. The residue was purified by chromatography...
(H:EA = 2:1) to afford 39 (46 mg, quantitative yield). 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.11 (2H, d, $J = 8.7$ Hz), 6.79 (2H, d, $J = 8.7$ Hz), 6.01 (1H, t, $J = 4.8$Hz), 4.12-4.20 (2H, m), 3.00-3.11 (2H, m), 2.10-2.40 (2H, m), 1.80-2.10 (2H, m), 1.50-1.80 (6H, m), 1.25 (3H, t, $J = 7.2$ Hz).

**Compound 40**

To a solution of 39 (37 mg, 0.1 mmol) in 10 mL freshly distilled t-BuOH at room temperature was added t-BuOK (13 mg, 0.11 mmol). The above solution was refluxed under argon for 24 h. The reaction mixture was cooled to room temperature and then quenched with 1 mL of saturated NH$_4$Cl. The organic solvent was evaporated in vacuo. The residue was diluted with ethyl acetate and washed with brine. The organic layer was dried over MgSO$_4$, filtered, and evaporated in vacuo. The residue was purified by chromatography (H:EA = 2:1) to afford 40 (17 mg, 58 % yield). 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.07 (1H, d, $J = 10.2$ Hz), 6.89 (1H, d, $J = 10.2$ Hz), 6.26 (1H, d, $J = 10.2$ Hz), 6.09 (1H, d, $J = 10.2$ Hz), 5.69 (1H, t, $J = 3.6$ Hz), 4.16-4.24 (2H, m), 2.53 (1H, d, $J = 13.2$ Hz), 2.01-2.10 (3H, m), 1.63-1.74 (4H, m), 1.42-1.58 (4H, m), 1.26 (3H, t, $J = 7.2$ Hz); 75 MHz $^{13}$C NMR (CDCl$_3$) $\delta$ 186.6, 176.4, 156.4, 153.3, 135.6, 129.3, 128.1, 125.5, 61.3, 46.9, 46.4, 37.6, 36.4, 36.2, 25.9, 19.4, 18.5, 14.4.

**Compound 42**

To a suspension of KH (197 mg, 4.49 mmol) in 10 mL of THF at 0 °C was added a solution of ketoester 34 (900 mg, 4.47 mmol) in THF (45 mL). After 30 min, PhN(Tf)$_2$ (1.92 g, 5.36 mmol) was added at 0 °C in one portion. The reaction mixture was stirred at rt for 4 h. The mixture was diluted with petroleum ether and flushed through a pad of silica gel. The
filtrate was concentrated in vacuo to afford 42 (895 mg, 62% yield) 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.4 (2H, d, $J = 7.2$ Hz), 6.80 (2H, d, $J = 7.2$ Hz), 4.40-4.60 (4H, m), 3.73 (3H, s), 3.66 (3H, s).

**Compound 44**

A solution of 42 (1.51 g, 4.68 mmol) in toluene (60 mL) was treated with Pd(PPh$_3$)$_3$ (540 mg, 0.468 mmol), boronic acid 43 (1.3 g, 5.15 mmol), K$_2$CO$_3$ (970 mg, 7.02 mmol) and H$_2$O (2 mL). The reaction was boiled for 12 h at 85 °C. After cooling the reaction mixture, it was partitioned with ethyl acetate and sat. Na$_2$CO$_3$. The combined organic layers were dried over MgSO$_4$, filtered, and evaporated in vacuo. The residue was purified by chromatography (H:EA = 3:1) to afford 44 (1.55 g, 85%) as a yellow oil. 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.32 (2H, d, $J = 1.2$ Hz), 6.81 (2H, d, $J = 7.2$ Hz), 4.50-4.70 (4H, m), 3.71 (3H, s), 3.66 (3H, s), 0.94 (9H, s), 0.21 (6H, s).

**Compound 45**

To a solution of diisopropylamine (298 $\mu$L, 2.13 mmol) in THF (10 mL) was added n-BuLi (2.5 M solution in hexanes, 850 $\mu$L, 2.12 mmol) at -78 °C. After 15 min at 0 °C, the solution was taken back to -78 °C and hexamethylphosphorilic triamide (435 $\mu$L, 2.5 mmol) was added. A solution of compound 44 (750 mg, 1.97 mmol) in 20 mL of THF was slowly transferred to the mixture at -78 °C via cannula. After 30 min 1,3-dibromopropane (486 $\mu$L, 4.79 mmol) was added to reaction mixture. After being gradually warmed up to rt, the mixture was quenched with H$_2$O. The mixture was diluted with ethyl acetate and washed with brine. The organic layer was dried over MgSO$_4$, filtered, and evaporated in vacuo. The
residue was purified by chromatography (H:EA = 5:1) to give 45 (569 mg, 58%). 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.11 (2H, d, $J = 8.7$ Hz), 6.96 (1H, s), 6.74 (2H, d, $J = 8.7$ Hz), 4.10-4.20 (2H, m), 3.82 (3H, s), 3.72 (3H, s), 3.31 (2H, t, $J = 6.6$ Hz), 1.71-2.08 (4H, m), 0.96 (9H, s), 0.18 (6H, s).

**Compound 33:**

To a solution of 45 (400 mg, 0.97 mmol) in THF (3 mL) at 0 °C was added 1 mL of TBAF (1M in THF). The reaction mixture was stirred at that temperature for 30 min and quenched with saturated NH$_4$Cl. The organic solvent was evaporated in vacuo. The residue was diluted with ethyl acetate and washed with brine. The organic layer was dried over MgSO$_4$, filtered, and evaporated in vacuo. The residue was purified by chromatography (H:EA = 2:1) to afford 33 (385 mg, Quantitative yield). 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.15 (2H, d, $J = 8.7$ Hz), 6.96 (1H, s), 6.75 (2H, d, $J = 8.7$ Hz), 4.18-4.21 (1H, m), 3.82 (3H, s), 3.79-3.83 (1H, m), 3.72 (3H, s), 3.31 (2H, t, $J = 6.6$ Hz), 2.03-2.13 (2H, m), 1.82-1.88 (1H, m), 1.78-1.82 (1H, m).

**Compound 32:**

To a solution of 33 (370 mg, 0.92 mmol) in 90 mL freshly distilled t-BuOH at rt was added t-BuOK (130mg, 1.1 mmol). The above solution was refluxed under argon for 24 h. The reaction mixture was cooled to room temperature and then quenched with 1 mL of saturated NH$_4$Cl. The organic solvent was evaporated in vacuo. The residue was diluted with ethyl acetate and washed with brine. The organic layer was dried over MgSO$_4$, filtered, and evaporated in vacuo. The residue was purified by chromatography (H:EA = 2:1) to afford 32
(180 mg, 63%). 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 6.93 (1H, d, $J = 10.2$ Hz), 6.82 (1H, d, $J = 9.9$ Hz), 6.42 (1H, s), 6.37 (1H, d, $J = 9.9$ Hz), 6.17 (1H, d, $J = 10.2$ Hz), 4.07-4.15 (1H, m), 3.73 (6H, s), 3.55-3.59 (1H, m), 2.65-2.71 (1H, m), 1.76-1.91 (2H, m), 1.64-1.69 (2H, m), 1.42-1.49 (1H, m); 75 MHz $^{13}$C NMR (CDCl$_3$) $\delta$ 186.8, 172.3, 155.1, 153.8, 153.2, 130.6, 127.8, 126.9, 58.3, 52.8, 52.1, 51.5, 50.3, 37.3, 32.8, 19.5. HRMS $m/z$ for C$_{17}$H$_{19}$NO$_5$ calcd 317.1342, found 317.1311.

**Compound 49**

300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 6.91 (1H, d, $J = 10.2$ Hz), 6.72 (1H, d, $J = 9.9$ Hz), 6.45 (1H, s), 6.31 (1H, d, $J = 9.9$ Hz), 6.05 (1H, d, $J = 10.2$ Hz), 4.07-4.15 (1H, m), 3.73 (3H, s), 3.55-3.59 (1H, m), 2.65-2.71 (1H, m), 1.76-1.91 (2H, m), 1.64-1.69 (2H, m), 1.42-1.49 (1H, m), 1.23 (9H, s).

**Compound 51**

To a solution 32 (15 mg, 0.047 mmol) in $t$-BuOH/THF/H$_2$O (1 mL/0.5 mL/0.3 mL) was added 7 mg (0.052 mmol) of NMO and 0.26 mL of OsO$_4$ (0.005 mmol) solution (5 mg/mL). The mixture was stirred at room temperature for 3 h and quenched with saturated NH$_4$Cl. Diluted with ethyl acetate and the organic layer washed with brine. The organic layer was dried over MgSO$_4$, filtered, and evaporated in vacuo. The residue was purified by chromatography (H:EA = 2:1) to afford 51 (10 mg, 60% yield). 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 6.97 (2H, d, $J = 8.4$ Hz), 6.73 (2H, d, $J = 8.4$ Hz), 5.22 (1H, bs), 4.13-4.20 (1H, m), 3.79 (3H, s), 3.65 (3H, m), 3.62-3.68 (1H, m), 2.52 (2H, t, $J = 7.2$ Hz), 1.40-1.81 (4H, m).
Compound 52

To a solution of compound 32 (28 mg, 0.088 mmol) in 3 mL CH₂Cl₂ was added 12.3 µL BF₃·Et₂O and 9.7 µL propane-1,3-dithiol at 0 °C. The reaction was raised to room temperature and stirred at that temperature for 16 h, quenched with saturated NH₄Cl, diluted with ethyl acetate and the organic layer washed with brine. The organic layer was dried over MgSO₄, filtered, and evaporated in vacuo. The residue was purified by chromatography (H:EA = 3:1) to afford 52 (19 mg, 45%) as a mixture of isomers. 300 MHz ¹H NMR (CDCl₃) δ 7.05 (2H, d, J = 8.4 Hz), 6.85 (2H, d, J = 8.4 Hz), 5.22 (1H, m), 4.13-4.20 (1H, m), 3.80-4.01 (4H, m) 3.79 (3H, s), 3.62-3.68 (2H, m), 3.32 (2H, m), 1.40-1.80 (6H, m).

Compound 58

To a solution of diisopropylamine (461 µL, 3.3 mmol) in THF (15 mL) was added n-BuLi (2.5 M solution in hexanes, 1.3 mL, 3.2 mmol) at -78 °C. After 15 min at 0 °C, the solution was cooled to -78 °C and a solution of compound 55 (690 mg, 3 mmol) in 5 mL THF was added slowly to the mixture. After 20 min, a solution of 57 (792 mg, 3.6 mmol) in THF (2 mL) was slowly added to this mixture at -78 °C and the mixture was allowed to raise to room temperature and quenched with saturated NH₄Cl. The organic solvent was evaporated in vacuo. The residue was diluted with ethyl acetate and washed with brine. The organic layer was dried over MgSO₄, filtered, and evaporated in vacuo. The crude mixture was dissolved in acetone (10 mL) and 2.0 mL of Jones reagent was added to the reaction mixture at 0 °C. After stirring at that temperature for 45 min, 2 mL isopropanol was added to quench the reaction. The organic solvent was evaporated and the residue was diluted with saturated ammonium chloride. The aqueous layer was extracted with ethyl acetate. The organic layer
was dried over MgSO₄, filtered, and evaporated in vacuo. The residue was purified by chromatography (H:EA = 4:1) to afford 58 (1.19g, 89 % yield). 300 MHz ¹H NMR (CDCl₃) δ 7.97 (2H, d, J = 8.4 Hz), 6.87 (2H, d, J = 8.4 Hz), 3.74-3.80 (2H, m), 3.66 (3H, s), 3.67-3.72 (1H, m), 3.12-3.29 (2H, m), 1.43 (9H, s), 1.10-1.20 (3H, m), 0.91 (9H, m), 0.22 (6H, s).

Compound 59

To a solution of compound 58 (640 mg, 1.42 mmol), in 5 mL HMPA was added 575 mg (5.68 mmol) triethylamine and 667 mg (5.53 mmol) pivaloyl chloride. The above mixture was allowed to stir at rt for 24 h. The reaction mixture was poured into half saturated NaCl solution, extracted with ethyl acetate. The organic layer was dried over MgSO₄, filtered, and evaporated in vacuo. The residue was purified by chromatography (H:EA = 4:1) to afford 59 (580 mg, 81%). 300 MHz ¹H NMR (CDCl₃) δ 7.36 (2H, d, J = 8.4 Hz), 7.05 (2H, d, J = 8.4 Hz), 4.18-4.28 (2H, m), 3.54 (3H, s), 3.27-3.34 (2H, m), 1.45 (9H, s), 1.33 (9H, s), 1.21 (9H, s), 1.10 (3H, t, J = 7.2 Hz).

Compound 60

To a suspension of CuI (96.55 mg, 0.506 mmol) in 3 mL THF at -78 °C was added 0.75 mL MeLi (1.4 M in THF). The mixture was brought up to 0 °C and stirred at that temperature for 15 min. The above mixture was taken back to -78 °C and a solution of 59 (203 mg, 0.41 mmol) in 5 mL of THF was cannulated to the reaction mixture. After stirring at -78 °C for 1 h, the temperature was gradually raised to 0 °C. The reaction was quenched with saturated NH₄Cl and extracted with ethyl acetate. The organic layer was dried over MgSO₄, filtered, and evaporated in vacuo. The residue was purified by chromatography (H:EA = 3:1) to afford
Compound 62

To a solution of 3-aminophenol (12.0 g, 110 mmol) in 250 mL t-BuOH was added di-t-butyldicarbonate (24 g, 110 mmol). The above mixture was heated at 80 °C for 23 h. The solvent was evaporated and the residue was dissolved in 300 mL of CH₂Cl₂. The organic layer was washed with brine, dried and evaporated to give protected phenol which was taken directly to the next step. The crude mixture was dissolved in 200 mL of DMF. Imidazole (10.02 g, 165 mmol) and TBSCl (16.85 g, 110 mmol) was added and the reaction mixture was stirred at room temperature for 12 h. The mixture was poured into half saturated NaCl solution, extracted with ethyl ether. The organic layer was dried over MgSO₄, filtered, and evaporated in vacuo. The residue was purified by chromatography (H:EA = 2:1) to afford 62 (32.6 g, 92%). 400 MHz ¹H NMR (CDCl₃) δ 7.12 (1H, t, J = 8 Hz), 6.88 (1H, d, J = 8 Hz), 6.85 (1H, s), 6.49 (1H, d, J = 8 Hz), 6.39 (1H, s), 1.49 (9H, s), 0.95 (9H, s), 0.18 (6H, s).

Compound 63

To a solution of 62 (10 g, 31 mmol) in 300 mL ethyl ether was degassed for 20 min and cooled to -78 °C. To the above solution 46 mL t-BuLi (1.7 M solution in pentane) was added and the mixture was gradually warmed to 0 °C. The mixture was quenched with saturated NH₄Cl and mixture was
poured into 100 mL of water and extracted with ether. The combined ether extracts was washed with brine, dried and evaporated under reduced pressure to give 63, 400 MHz $^1$H NMR (CDCl$_3$) $\delta$ 10.45 (1H, s), 9.66 (1H, s), 7.93 (1H, s), 7.39 (1H, d, $J = 8.4$ Hz), 6.70 (1H, d, $J = 8.4$ Hz), 1.49 (9H, s), 0.96 (9H, s), 0.19 (6H, s).

**Compound 64**

The crude mixture of 63 was dissolved in 100 mL of THF. 30 mL of TBAF (1M solution in THF) was added at 0 °C. After stirring at that temperature for 30 min the reaction was quenched with saturated NH$_4$Cl. The mixture was poured into 60 mL of water and extracted with ethyl acetate. The combined organic extracts was washed with brine, dried and evaporated under reduced pressure. The crude product was purified by chromatography (H:EA = 2:1) to give 64 (4.92 g, 69 % yield over two steps). 400 MHz $^1$H NMR (CDCl$_3$) $\delta$ 10.66 (1H, s), 9.69 (1H, s), 7.94 (1H, s), 7.70 (1H, s), 7.49 (1H, d, $J = 8.4$ Hz), 6.61 (1H, d, $J = 8.4$ Hz), 1.52 (9H, s); 75 MHz $^{13}$C NMR (CDCl$_3$) $\delta$ 193.3, 163.5, 153.8, 143.9, 139.2, 115.6, 110.3, 104.8, 81.9, 28.5.

**Compound 65**

To a solution of 64 (5.00 g, 21.5 mmol) in 300 mL CH$_2$Cl$_2$ was added 11.3 mL of diisopropylethylamine (64.5 mmol). The mixture was cooled to 0 °C and 3.26 mL MOMCl was added slowly. The mixture was warmed to room temperature and stirred at that temperature for 8 h. The mixture was diluted with 100 mL CH$_2$Cl$_2$ and the organic layer was washed with saturated NaHCO$_3$ and brine. The organic extracts were dried over MgSO$_4$, filtered, and evaporated in vacuo. The residue was purified by chromatography (H:EA = 5:1) to afford 65.
(5.13 g, 85% yield). 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 10.52 (1H, s), 9.66 (1H, s), 8.06 (1H, s), 7.46 (1H, d, $J = 8.4$ Hz), 6.69 (1H, d, $J = 8.4$ Hz), 5.19 (2H, s), 3.44 (3H, s), 1.52 (9H, s); 100 MHz $^{13}$C NMR (CDCl$_3$) $\delta$ 193.4, 163.5, 153, 144.1, 138.45, 116.4, 109.64, 105.1, 94.2, 81.2, 56.7, 28.4.

**Compound 66**

To a solution of 65 (4.00 g, 14.2 mmol) in 25 mL methanol was added dimethylmalonate (5.63 g, 42.6 mmol) and piperidine (604 mg, 7.1 mmol). The mixture was refluxed for 24 h. The reaction mixture was cooled to room temperature and the organic solvents were evaporated to give solid residue. The solid residue was washed with hexane/ethyl ether (3:1) mixture and filtered to get pure 66 as a white solid (3.89 g, 90% yield). 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 8.41 (1H, s), 7.75 (1H, d, $J = 8.4$ Hz), 7.10 (1H, s), 6.94 (1H, s), 5.36 (2H, s), 3.80 (3H, s), 3.45 (3H, s).

**Compound 67**

To a solution of compound 66 (3.6 g, 13 mmol) in 250 mL of acetone was added K$_2$CO$_3$ (10 g, 104 mmol) and ethyl iodide (6.84 g, 39 mmol). After being refluxed under argon for 15 h, the mixture was filtered and organic solvent was evaporated in vacuo. The residue was diluted with ethyl acetate and washed with brine. The organic layer was dried over MgSO$_4$, filtered, and evaporated in vacuo. The residue was purified by chromatography (EA:CH$_2$Cl$_2$ = 1:1) to afford 67 (3.21 g, 85%). 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 8.41 (1H, s), 7.71 (1H, d, $J = 8.4$ Hz), 7.02 (1H, s), 6.94 (1H, s), 5.36 (2H, s), 4.27 (2H, q, $J = 7.2$ Hz), 3.80 (3H, s), 3.45 (3H, s), 1.21 (3H, t, $J = 7.2$ Hz).
Compound 68

To a suspension of CuI (2.29 g, 12 mmol) in 25 mL of THF at -78 °C was added 3 mL of dimethyl sulfide and 24 mL of vinylmagnesium bromide (1 M solution in THF). The mixture was brought up to 0 °C and stirred at that temperature for 15 min. The above mixture was taken back to -78 °C and a solution of 67 (1.85 g, 6 mmol) in 75 mL of THF was cannulated to the reaction mixture. After stirring at -78 °C for 1 h, the temperature was gradually raised to 0 °C. The reaction was quenched with saturated NH₄Cl and extracted with ethyl acetate. The organic layer was dried over MgSO₄, filtered, and evaporated in vacuo. The residue was purified by chromatography (H:EA = 5:1) to afford 68 (1.19 g, 60 % yield). 300 MHz ¹H NMR (CDCl₃) δ 7.11 (1H, d, J = 8.4 Hz), 6.71-6.79 (2H, m), 5.78 (1H, dt, J = 12 Hz, J = 8Hz), 5.21 (1H, d, J = 8 Hz), 5.18 (2H, m), 5.06 (1H, d, J = 12 Hz), 3.88-4.09 (3H, m), 3.68 (3H, s), 3.52 (1H, d, J = 7.4 Hz), 3.49 (3H, s), 1.26 (3H, t, J = 7.2 Hz); 100 MHz ¹³C NMR (CDCl₃) δ 169.0, 164.9, 157.5, 138.9, 136.2, 128.9, 119.0, 118.2, 109.9, 94.5, 55.95, 53.4, 52.2, 42.7, 37.6, 12.3.

Compound 69

To a suspension of NaH (90 mg, 3.6 mmol) in 5 mL of THF was added a solution of compound 68 (1.01 g, 3.05 mmol) in 25 mL of THF at 0 °C. After stirring for 20 min, HMPA (530 µL, 3.06 mmol) and 1,3-dibromopropane (1.81 g, 9 mmol) was added. The mixture was refluxed for 16 h the reaction was quenched with saturated NH₄Cl. The mixture was poured into 10 mL of water and extracted with ethyl acetate. The combined organic extracts was washed with brine, dried and evaporated under reduced pressure. The crude product was
purified by chromatography (H:EA = 4:1) to give 69 (1.02 g, 79%). 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 6.99 (1H, d, $J = 8.4$ Hz), 6.66-6.72 (2H, m), 6.13 (1H, dt, $J = 12$ Hz, $J = 8$Hz), 5.38 (1H, d, $J = 8$ Hz), 5.21 (1H, d, $J = 12$Hz), 5.14 (2H, s) 4.02-4.18 (1H, m), 3.78-3.89 (1H, m), 3.49 (3H, s), 3.42 (1H, d, $J = 7.4$ Hz), 3.35 (3H, s), 3.38-3.48 (2H, m), 2.01-2.19 (2H, m), 1.84-1.93 (2H, m), 1.26 (3H, t, $J = 7.2$ Hz).

**Compound 70**

To a solution of 69 (450 mg, 1.03 mmol) in 10 mL of ethyl acetate at 0 °C was added 1 mL of 4 N HCl. The reaction mixture was stirred at that temperature for 30 min. Diluted with ethyl acetate (10 mL) and washed with 10% NaHCO$_3$ solution and brine. The organic layer was dried over MgSO$_4$, filtered, and evaporated in vacuo. The residue was purified by chromatography (H:EA = 2:1) to afford 70 (400 mg, Quantitative yield). 300 MHz $^1$H NMR (CDCl$_3$) $\delta$ 6.97 (1H, d, $J = 8.4$ Hz), 6.60 (1H, s), 6.52 (1H, d, $J = 8.4$ Hz), 6.15 (1H, dt, $J = 12$ Hz, $J = 8$Hz), 5.41 (1H, d, $J = 8$ Hz), 5.25 (1H, d, $J = 12$Hz), 4.08-4.18 (1H, m), 3.81-3.92 (1H, m), 3.51 (3H, s), 3.47 (1H, d, $J = 7.4$ Hz), 3.41-3.52 (2H, m), 2.01-2.19 (2H, m), 1.84-1.93 (2H, m), 1.26 (3H, t, $J = 7.2$ Hz); 100 MHz $^{13}$C NMR (CDCl$_3$) $\delta$ 170.65, 167.4, 157.3, 139.0, 134.2, 127.8, 120.2, 109.7, 103.6, 94.6, 56.1, 52.1, 47.3, 38.4, 33.6, 31.6, 27.6, 12.1

**Compound 71**

To a suspension of NaH (29 mg, 1.2 mmol) in 5 mL of THF was added a solution of compound 70 (390 mg, 1.00 mmol) in 10 mL of THF at 0 °C. After stirring for 20 min, 18-crown-6 (270 mg, 1.02 mmol) and 80 mL of THF was added and the reaction mixture was
refluxed for 24 h under argon. The reaction mixture was cooled to room temperature and then quenched with 1 mL of saturated NH₄Cl. The organic solvent was evaporated in vacuo. The residue was diluted with ethyl acetate and washed with brine. The organic layer was dried over MgSO₄, filtered, and evaporated in vacuo. The residue was purified by chromatography (H:EA = 1:1) to afford 71 as white solid (130 mg, 42% yield). 300 MHz ¹H NMR (CDCl₃) δ 6.47 (1H, d, J = 9.9 Hz), 6.17 (1H, d, J = 9.9 Hz), 5.91 (1H, s), 5.43 (1H, m), 5.02-5.09 (2H, m), 3.93-4.01 (2H, m), 3.65 (3H, s), 2.57 (1H, d, J = 10.2 Hz), 2.11-2.28 (2H, m), 1.81-1.98 (2H, m), 1.51-1.71 (2H, m), 1.23 (3H, t, J = 7.2 Hz); 100 MHz ¹³C NMR (CDCl₃) 186.7, 170.7, 167.4, 157.6, 151.3, 134.1, 127.7, 119.4, 108.9, 56.2, 53.2, 52.2, 42.9, 38.6, 38.0, 33.3, 18.9, 12.1. HRMS m/z for C₁₇H₁₉NO₅ calc 315.1471, found 315.1478.

**Compound 72**

To a solution of compound 69 (440 mg, 1.01 mmol) in 25 mL CH₂Cl₂/Methanol (5/1) at -78 °C, ozone was bubbled till the disappearance of starting material in TLC. Argon was bubbled to remove excess ozone, and 170 mg of Me₂S was added to the mixture. The reaction mixture was gradually brought up to room temperature and was stirred at that temperature for additional 4 h. The mixture was diluted with 20 mL of CH₂Cl₂ and washed with brine. The organic layer was dried over MgSO₄, filtered, and evaporated in vacuo. The residue was purified by chromatography (H:EA = 2:1) to afford 72 (400 mg, 92% yield). 400 MHz ¹H NMR (CDCl₃) δ 9.54 (1H, d, J = 4.8 Hz), 7.08 (1H, d, J = 8.4 Hz), 6.76 (1H, d, J = 8.4 Hz), 6.73 (1H, s), 5.16 (2H, s), 3.89-3.98 (2H, m), 3.79 (3H, s), 3.58 (1H, d, J = 4.8 Hz), 3.25 (2H, t, J = 6 Hz), 2.01-2.19 (2H, m), 1.84-1.93 (2H, m), 1.26 (3H, t, J = 7.2 Hz).
Compound 73

To a solution of compound 72 (350 mg, 0.9 mmol) in 10 mL of methanol was added trimethylorthoformate (385 mg, 3.6 mmol) and PTSA (35 mg, 0.18 mmol). The reaction mixture was stirred under argon for 24 h. The solvent was concentrated and the residue was dissolved in 50 mL of ethyl acetate. The organic layer was washed with 10% NaHCO₃ and brine. The organic layer was dried, concentrated and purified by column chromatography (H:EA = 1:1) to give 73 (275 mg, 69%) as white solid. 300 MHz ¹H NMR (CDCl₃) δ 6.97 (1H, d, J = 8.4 Hz), 6.60 (1H, s), 6.52 (1H, d, J = 8.4 Hz), 4.14 (1H, d, J = 4.4 Hz), 4.08-4.18 (1H, m), 3.81-3.92 (1H, m), 3.51 (3H, s), 3.23 (6H, s), 3.47 (1H, d, J = 7.4 Hz), 3.41-3.52 (2H, m), 2.44 (1H, d, J = 4.4 Hz), 2.01-2.19 (2H, m), 1.84-1.93 (2H, m), 1.26 (3H, t, J = 7.2 Hz).

Compound 74

To a suspension of NaH (29 mg, 1.2 mmol) in 5 mL of THF was added a solution of compound 73 (450 mg, 1.00 mmol) in 10 mL of THF at 0 °C. After stirring for 20 min, 18-crown-6 (270 mg, 1.02 mmol) and 80 mL of THF was added and the reaction mixture was refluxed for 24 h under argon. The reaction mixture was cooled to room temperature and then quenched with 1 mL of saturated NH₄Cl. The organic solvent was evaporated in vacuo. The residue was diluted with ethyl acetate and washed with brine. The organic layer was dried over MgSO₄, filtered, and evaporated in vacuo. The residue was purified by chromatography (EA:CH₂Cl₂ = 1:2) to afford 74 (265 mg, 72% yield). 400 MHz ¹H NMR (CDCl₃) δ 6.71 (1H, d, J = 9.9 Hz), 6.17 (1H, d, J = 9.9 Hz), 5.81 (1H, s), 4.14 (1H, d, J = 4.4 Hz), 3.98-4.19 (1H, m), 3.82-3.91 (1H, m) 3.73 (3H, s), 3.24 (6H, s) 2.44 (1H, d, J = 4.4 Hz), 2.11-2.28 (2H, m),
1.91-1.98 (1H, m), 1.78-1.89 (1H, m) 1.51-1.71 (2H, m), 1.23 (3H, t, J = 7.2 Hz); 100 MHz

$^{13}$C NMR (CDCl$_3$) $\delta$ 170.6, 167.5, 157.4, 139.0, 134.3, 127.8, 120.2, 120.1, 109.7, 103.6, 94.6, 56.1, 56.0, 52.1, 47.3, 38.4, 33.5, 31.6, 27.7, 12.1.

**Compound 75**

To a solution of 74 (265 mg, 0.72 mmol) in ethyl acetate was carefully added 10% Pd/C (76 mg, 0.07 mmol) at rt. After being stirred under H$_2$ balloon pressure at rt for 3 h, the mixture was filtered through celite and rinsed with ethyl acetate. The filtrate was evaporated in vacuo to give 75 (265 mg, 100%). 400 MHz $^1$H NMR (CDCl$_3$) $\delta$ 5.51 (1H, s), 4.29 (1H, d, $J = 4.4$ Hz), 3.98-4.19 (2H, m), 3.63 (3H, s), 3.24 (6H, s) 2.52-2.61 (2H, m), 2.38-2.43 (1H, m), 2.10-2.29 (4H, m), 1.51-1.81 (4H, m), 1.23 (3H, t, $J = 7.2$ Hz); 100 MHz $^{13}$C NMR (CDCl$_3$) $\delta$ 198.1, 171.65, 167.9, 161.6, 106.3, 57.3, 55.8, 53.2, 52.5, 51.2, 37.9, 37.3, 37.0, 36.1, 33.2, 32.4, 19.5, 11.9.

**Compound 75**

Liquid ammonia (10 mL) was collected in a three-neck flask at -78 °C containing compound 74 (50 mg, 0.13 mmol) and $t$-BuOH (48 mg, 0.65 mmol) in 2 mL of THF. Freshly cut lithium metal (9 mg, 1.3 mmol) was added to get a deep blue solution and mixture was stirred at that temperature for 30 min. Quenched with NH$_4$Cl and the solution turned colorless. The mixture was warmed to room temperature and ammonia was evaporated. The residue was diluted with water and extracted with ethyl acetate, dried and purified by chromatography (EA:CH$_2$Cl$_2$ = 1:1) to yield 76 (18 mg, 45%) as 3:1 mixture of isomers.

Major isomer: 400 MHz $^1$H NMR (CDCl$_3$) $\delta$ 10.04 (1H, s), 4.69 (1H, d, $J = 4.4$ Hz),
3.60-3.70 (2H, m), 3.43 (3H, s), 3.33-3.37 (1H, m), 3.24 (3H, s) 2.41-2.82 (4H, m), 2.38-2.43 (1H, m), 2.10-2.29 (2H, m), 1.51-1.81 (4H, m), 1.23 (3H, t, \( J = 7.2 \) Hz); 100 MHz \( ^{13}C \) NMR (CDCl\(_3\)) \( \delta \) 210.0, 201.1, 171.7, 104.3, 59.2, 56.5, 55.0, 53.4, 52.7, 43.1, 42.3, 36.7, 35.5, 35.2, 33.0, 32.5, 19.5, 13.8.

Minor isomer: 400 MHz \( ^1H \) NMR (CDCl\(_3\)) \( \delta \) 9.96 (1H, s), 4.49 (1H, d, \( J = 4.4 \) Hz), 3.61-3.70 (2H, m), 3.43 (3H, s), 3.33-3.37 (1H, m), 3.24 (3H, s) 2.41-2.82 (4H, m), 2.38-2.43 (1H, m), 2.10-2.29 (2H, m), 1.5-1.8 (4H, m), 1.19 (3H, t, \( J = 7.2 \) Hz); 100 MHz \( ^{13}C \) NMR (CDCl\(_3\)) \( \delta \) 207.7, 200.8, 171.5, 104.2, 56.7, 56.4, 53.8, 53.2, 51.2, 42.5, 40.7, 36.5, 35.3, 33.9, 32.8, 30.6, 19.2, 12.7.

**Compound 77**

To a solution of compound 74 (200 mg, 0.54 mmol) in 10 mL of MeOH was added LiOH (65 mg, 2.6 mmol) at room temperature. After stirring for 4 h the solvent was concentrated and the residue was dissolved in 5 mL water and then carefully acidified to pH 2 with 20% aqueous HCl. The suspension was immediately extracted with ethyl acetate (5 X 10 mL) and the combined organic extracts are dried over MgSO\(_4\) and evaporated under vacuo to yield 77 (111 mg, 59%). 400 MHz \( ^1H \) NMR (CDCl\(_3\)) \( \delta \) 5.51 (1H, s), 4.29 (1H, d, \( J = 4.4 \) Hz), 3.98-4.19 (2H, m), 3.24 (6H, s), 2.52-2.61 (2H, m), 2.38-2.43 (1H, m), 2.10-2.29 (4H, m), 1.51-1.81 (4H, m), 1.23 (3H, t, \( J = 7.2 \) Hz).

**Compound 78**

Liquid ammonia (10 mL) was collected in a three-neck flask at -78 °C containing compound 77 (111 mg, 0.32 mmol) and \( t \)-BuOH (118 mg, 1.6 mmol) in 2 mL of THF.
Freshly cut lithium metal (22.4 mg, 3.2 mmol) was added to get a deep blue solution and mixture was stirred at that temperature for 30 min, quenched with NH₄Cl and the solution turned colorless. The mixture was warmed to room temperature and ammonia was evaporated. The residue was diluted with 5 mL of water and then carefully acidified to pH 2 with 20% aqueous HCl. The suspension was immediately extracted with ethyl acetate (5 X 10 mL) and the combined organic extracts are dried over MgSO₄ and evaporated under vacuo to yield 78 as 3:1 mixture of isomers.

Major isomer: 400 MHz ¹H NMR (CDCl₃) δ 4.69 (1H, d, J = 4.4 Hz), 3.6-3.7 (2H, m), 3.43 (3H, s), 3.33-3.37 (1H, m), 3.24 (3H, s) 2.41-2.82 (4H, m), 2.38-2.43 (1H, m), 2.10-2.29 (2H, m), 1.51-1.80 (4H, m), 1.23 (3H, t, J = 7.2 Hz).

Minor Isomer: 400 MHz ¹H NMR (CDCl₃) δ 4.49 (1H, d, J = 4.4 Hz), 3.61-3.70 (2H, m), 3.43 (3H, s), 3.33-3.37 (1H, m), 3.24 (3H, s) 2.41-2.82 (4H, m), 2.38-2.43 (1H, m), 2.10-2.29 (2H, m), 1.50-1.81 (4H, m), 1.19 (3H, t, J = 7.2 Hz).

**Compound 79**

To a solution of compound 78 in 10 mL of ethyl acetate was treated with freshly prepared CH₂N₂ (solution in ether) at 0 °C. After stirring at that temperature for 20 min the organic solvent was evaporated in vacuo. The residue was diluted with ethyl acetate and washed with brine. The organic layer was dried over MgSO₄, filtered, and evaporated in vacuo. The residue was purified by chromatography (EA:CH₂Cl₂ = 1:2) to afford 79 (58 mg, 49% for two steps) as 3:1 mixture of isomers.

Major isomer: 400 MHz ¹H NMR (CDCl₃) δ 4.35 (1H, d, J = 4.4 Hz), 3.75 (3H, s), 3.60-3.70 (2H, m), 3.43 (3H, s), 3.33-3.37 (1H, m), 3.24 (3H, s) 2.41-2.82 (4H, m), 2.38-2.43 (1H,
m), 2.10-2.29 (2H, m), 1.51-1.80 (4H, m), 1.23 (3H, t, $J = 7.2$ Hz).

Minor Isomer: 400 MHz $^1$H NMR (CDCl$_3$) $\delta$ 4.29 (1H, d, $J = 4.4$ Hz), 3.75 (3H, s), 3.60-3.70 (2H, m), 3.46 (3H, s), 3.33-3.37 (1H, m), 3.21 (3H, s) 2.41-2.82 (4H, m), 2.38-2.43 (1H, m), 2.10-2.29 (4H, m), 1.51-1.80 (4H, m), 1.23 (3H, t, $J = 7.2$ Hz).

**Compound 80**

To a solution of ester 79 (50 mg, 0.13mmol) in 2 mL of THF at 0 °C was added 0.5 mL of 4 N HCl. The reaction mixture was stirred at that temperature for 4 h, diluted with ethyl acetate (10 mL) and washed with 10% NaHCO$_3$ solution and brine. The organic layer was dried over MgSO$_4$, filtered, and evaporated in vacuo. The residue was purified by chromatography (EA:CH$_2$Cl$_2$ = 1:2) to afford 80 (23 mg, 57%) as white powder and compound 81 (7 mg, 17%).

**Compound 80**: 400 MHz $^1$H NMR (CDCl$_3$) $\delta$ 4.83 (1H, dd, $J = 7.2$ Hz, 4.0 Hz), 3.90- 4.00 (1H, m), 3.80 (3H, s), 3.39 (1H, d, $J = 2.8$ Hz), 3.08 (1H, d, $J = 7.6$ Hz), 2.70-2.84 (2H, m), 2.42 (1H, d, $J = 4$Hz), 2.27-2.33 (2H, m), 2.17 (1H, d, $J = 2.8$ Hz), 1.90-2.04 (2H, m), 1.70-1.90 (4H, m), 1.20 (3H, t, $J = 7.2$ Hz); 75 MHz $^{13}$C NMR (CDCl$_3$) $\delta$ 209.6, 172.7, 166.6, 75.2, 68.7, 62.2, 57.4, 55.6, 53.0, 41.7, 41.4, 35.9, 34.89, 33.8, 33.4, 20.1, 12.8; HRMS m/z for C$_{17}$H$_{22}$O$_4$N calcd 321.15762, found 321.15810.

**Compound 81**

400 MHz $^1$H NMR (CDCl$_3$) $\delta$9.59 (1H, d, $J = 4.4$ Hz), 3.75 (3H, s), 3.60-3.70 (2H, m), 3.33-3.37 (1H, m), 2.41-2.82 (4H, m), 2.38 (1H, d, $J = 4.4$ Hz), 2.10-2.29 (4H, m), 1.50-1.80 (4H, m), 1.23 (3H, t, $J = 7.2$ Hz).
Compound 82

To a solution of compound 80 (15 mg, 0.045 mmol) in 3 mL of CH$_2$Cl$_2$ was added acetamidate (26 mg, 0.09 mmol) and 5 mg of CSA. The reaction mixture was stirred at room temperature for 24 h. The organic solvent was evaporated in vacuo. The residue was diluted with ethyl acetate and washed with brine. The organic layer was dried over MgSO$_4$, filtered, and evaporated in vacuo. The residue was purified by chromatography (H:EA = 1:1) to afford Compound 82 (15 mg, 85%). 400 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.11 (2H, d, $J$ = 8.4 Hz), 6.82 (2H, d, $J$ = 8.4 Hz), 4.65 (1H, dd, $J$ = 7.2 Hz), 4.25 (2H, s), 3.90- 4.00 (1H, m), 3.80 (3H, s), 3.65 (3H, s), 3.39 (1H, d, $J$= 2.8 Hz), 3.08 (1H, d, $J$ = 7.6 Hz), 2.70-2.84 (2H, m), 2.42 (1H, d, $J$ = 4Hz), 2.27-2.33 (2H, m), 2.17 (1H,d, $J$ = 2.8 Hz), 1.90-2.04 (2H, m), 1.70-1.90 (4H,m), 1.20 (3H, t, $J$ = 7.2 Hz).

Compound 84

To a solution of compound 82 (15 mg, 0.04 mmol) was added freshly prepared LDA (0.4 mL, 0.1 M solution) at -78°C. After stirring for 30 min TMSCl (11 mg, 0.1 mmol) was added and reaction mixture was allowed to stir at that temperature for 30 min, the mixture was quenched with H$_2$O. The mixture was diluted with ethyl acetate and washed with brine. The organic layer was dried over MgSO$_4$, filtered, and evaporated in vacuo to get crude 83 and taken directly to next step. To a solution of 83 in 1 mL of CH$_3$CN was added 5 mg of Pd(OAc)$_2$. The mixture was stirred at room temperature for 8 h. The organic solvent was evaporated in vacuo. The residue was diluted with ethyl acetate and washed with brine. The organic layer was dried over MgSO$_4$, filtered, and evaporated in vacuo. The residue was purified by chromatography (EA:CH$_2$Cl$_2$ = 1:2) to afford to yield 84 (10 mg, 65 %). 400


MHZ 'H NMR (CDCl₃) δ 7.11 (2H, d, J = 8.4 Hz), 6.77 (2H, d, J = 8.4 Hz), 6.75 (1H, d, J = 9.6 Hz), 6.10 (1H, d, J = 9.6 Hz), 4.18 (1H, d, J = 7.2 Hz), 4.32 (2H, s), 3.90- 4.00 (1H, m), 3.80 (3H, s), 3.65 (3H, s), 3.39 (1H, d, J = 2.8 Hz), 3.08 (1H, d, J = 7.6 Hz), 2.70-2.84 (2H, m), 2.42 (1H, d, J = 4 Hz), 2.27-2.33 (2H, m), 2.17 (1H, d, J = 2.8 Hz), 1.71-1.90 (4H, m), 1.22 (3H, t, J = 7.2 Hz).

**Compound 85**

To a suspension of NaH (30 mg, 1.2 mmol) in 5 mL of THF was added a solution of compound 68 (311 mg, 1.05 mmol) in 25 mL of THF at 0 °C. After stirring for 20 min, HMPA (176 µL, 1.02 mmol) and 1,3-dibromopropane (600 mg, 3 mmol) was added. The mixture was refluxed for 16 h the reaction was quenched with saturated NH₄Cl. The mixture was poured into 10 mL of water and extracted with ethyl acetate. The combined organic extracts was washed with brine, dried and evaporated under reduced pressure. The crude product was washed with brine, dried and evaporated under reduced pressure. The crude product was purified by chromatography (H:EA = 4:1) to give 85 (310 mg, 79%). 300 MHz 'H NMR (CDCl₃) δ 6.99 (1H, d, J = 8.4 Hz), 6.66-6.72 (2H, m), 6.28 (1H, dt, J = 12 Hz, J = 8Hz), 5.38 (1H, d, J = 8 Hz), 5.21 (1H, d, J = 12Hz), 5.14 (2H, s) 4.02-4.18 (1H, m), 3.78-3.89 (1H, m), 3.49 (3H, s), 3.42 (1H, d, J = 7.4 Hz), 3.35 (3H, s), 3.38-3.48 (2H, m), 2.01-2.19 (1H, m), 1.84-1.93 (1H, m), 1.26 (3H, t, J = 7.2 Hz).

**Compound 86**

To a solution of 69 (300 mg, 0.68 mmol) in 10 mL of ethyl acetate at 0 °C was added 1 mL of 4 N HCl. The reaction mixture was stirred at that temperature for 30 min, diluted with ethyl acetate (10 mL) and washed with 10% NaHCO₃ solution and brine. The organic layer
was dried over MgSO\textsubscript{4}, filtered, and evaporated in \textit{vacuo}. The residue was purified by chromatography (H:EA = 1:1) to afford 70 (270 mg, quantitative yield). 300 MHz \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \( \delta \) 6.99 (1H, d, \( J = 8.4 \) Hz), 6.66-6.72 (2H, m), 6.28 (1H, dt, \( J = 12 \) Hz, \( J = 8 \) Hz), 5.38 (1H, d, \( J = 8 \) Hz), 5.21 (1H, d, \( J = 12 \) Hz), 4.02-4.18 (1H, m), 3.78-3.89 (1H, m), 3.49 (3H, s), 3.42 (1H, d, \( J = 7.4 \) Hz), 3.38-3.48 (2H, m), 2.01-2.19 (1H, m), 1.84-1.93 (1H, m), 1.26 (3H, t, \( J = 7.2 \) Hz).

**Compound 87**

To a suspension of NaH (20 mg, 0.81 mmol) in 5 mL of THF were added a solution of compound 70 (270 mg, 0.68 mmol) in 10 mL at 0 °C. After stirring for 20 min, 18-crown-6 (200 mg, 0.81 mmol) and 60 mL of THF was added and the reaction mixture was refluxed for 24 h under argon. The reaction mixture was cooled to room temperature and then quenched with 1 mL of saturated NH\textsubscript{4}Cl. The organic solvent was evaporated in \textit{vacuo}. The residue was diluted with ethyl acetate and washed with brine. The organic layer was dried over MgSO\textsubscript{4}, filtered, and evaporated in \textit{vacuo}. The residue was purified by chromatography (H: EA = 1:1) to afford 87 as white solid (180 mg, 79% yield). 300 MHz \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \( \delta \) 6.93 (1H, d, \( J = 8.4 \) Hz), 6.57 (1H, s), 6.50 (1H, d, \( J = 8.4 \) Hz), 6.15 (1H, dt, \( J = 12 \) Hz, \( J = 8 \) Hz), 5.41 (1H, d, \( J = 8 \) Hz), 5.25 (1H, d, \( J = 12 \) Hz), 4.08-4.18 (1H, m), 3.81-3.92 (1H, m), 3.51 (3H, s), 3.47 (1H, d, \( J = 7.4 \) Hz), 2.01-2.19 (2H, m), 1.84-1.93 (2H, m), 1.26 (3H, t, \( J = 7.2 \) Hz).
References


GENERAL CONCLUSIONS

In this dissertation, we have investigated direct and concise strategies for natural products. Chapter 1 described the development of efficient annulation reaction. Phosphonium salts bearing an electron-withdrawing groups at gamma position as synthons for $[3+3]$, $[3+2]$ and $[3+4]$ annulations. Reactions of dianions generated from phosphonium salts with bis-electrophiles yielded five, six and seven membered rings.

Chapter 2 described a direct approach to the synthesis of methyllycaconitine, a representative of the aconitine alkaloids, has been developed. A tetracyclic intermediate, possessing the ABEF-carbocycle skeleton has been synthesized as a result of the research described in this dissertation. Construction of ABE segment of methyllycaconitine and racemulosine through a common bicyclic intermediate was also achieved.
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