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Synthetic approach towards methyllycaconitine

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NOTE TO USERS

SYNTHETIC APPROACH TOWARDS METHYLLYCACONITINE

by

Sarathy Kesavan

A dissertation submitted to the graduate faculty
in partial fulfillment of the requirements for the degree of
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This is to certify that the doctoral dissertation of

Sarathy Kesavan

has met the dissertation requirements of Iowa State University

Signature was redacted for privacy.

Major Professor

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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.

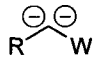
Chapter One describes the development of annulation reaction for the construction of five-, six- and seven- membered rings. Chapter Two describes a direct approach to the synthesis of methyllycaconitine, a representative of the aconitine alkaloids. The numbering of the compounds, schemes and references are independent in each section.

CHAPTER 1

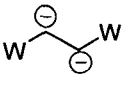
ANNULATIONS VIA DIANIONS: FORMATION OF FIVE-, SIX- AND SEVEN-MEMBERED RINGS

Introduction

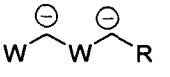
C,C-Dianions, such as those shown in Figure 1, are generated by two sequential deprotonations. They have a long and diverse history and continue to serve as important synthetic reagents.[1-6] C,C-Dianions are categorized based on the location of deprotonation. When sequential deprotonation occurs at 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.



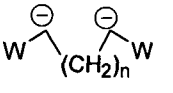
1,1-(C,C)-dianion
geminal dianion



1,2-(C,C)-dianion
vicinal dianion



1,3-(C,C)-dianion



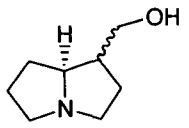
1,*n*-(C,C)-dianion
remote dianion

W = Electron withdrawing group

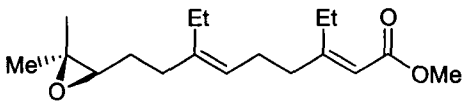
Figure 1. Examples of C,C-dianions

It is no surprise that investigators have made extensive use of these readily-accessed

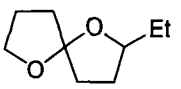
dianions in synthesis. As an introduction to their utility, a pictorial survey of some natural and unnatural products prepared using dianions is shown in Figure 2.



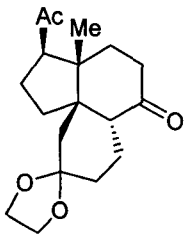
isoretronecanol



juvenile hormone O



chalcogram

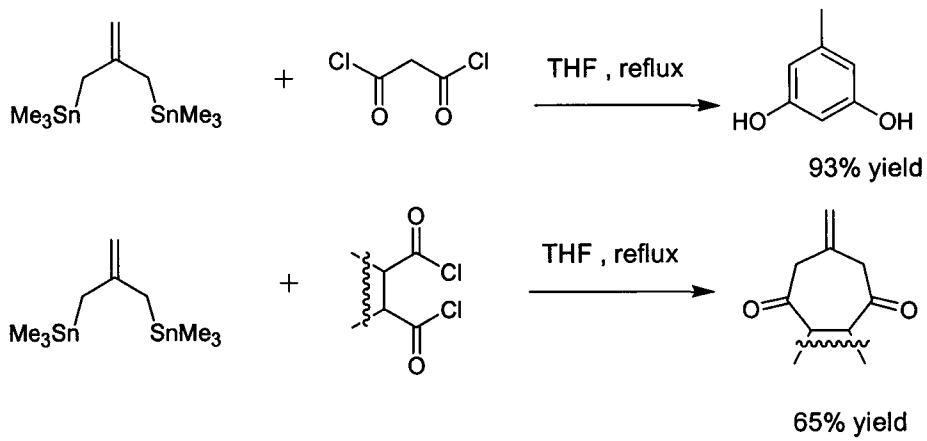


gascardic acid

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

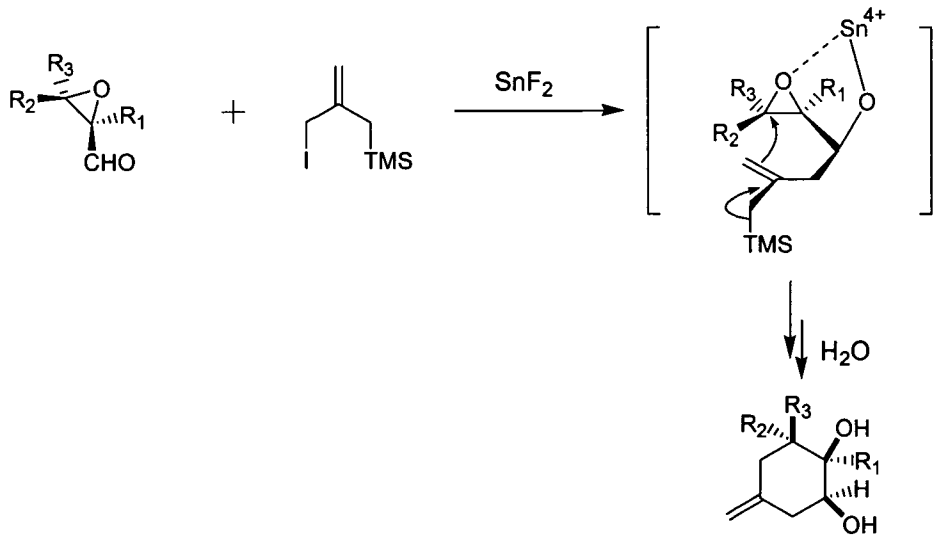
Dianion-based [3+3] Annulation

Cyclohexenes are generally prepared by Diels-Alder reactions or Robinson annulation reactions.[7] 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.[8] 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.



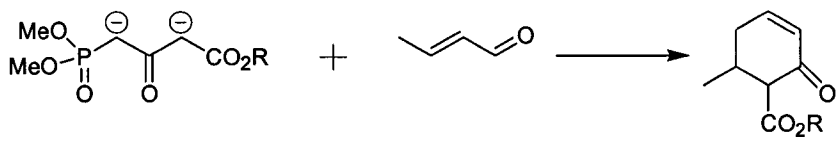
Scheme 1.

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).[9] Allyltin trihalide (generated *in situ*) addition to the carbonyl of the epoxy aldehyde occurred with good diasteroselectivity. 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.



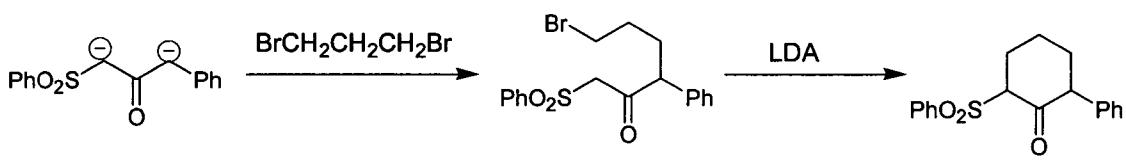
Scheme 2.

Moohoff reported an annulation using phosphorus-stabilized 1,3-(C,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.



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.

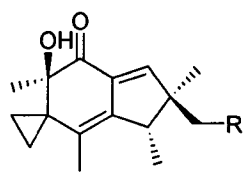


Scheme 4.

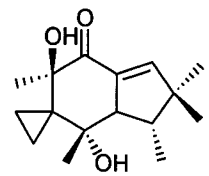
Results and Discussion

As part of a program to develop terpene-based antiviral agents,[12] we needed an efficient synthetic route to bicyclic segments present in sesquiterpenes such as illudin S.[13] The cytotoxicity and anticancer activity of illudin S has been most extensively investigated.[14] 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. [15]

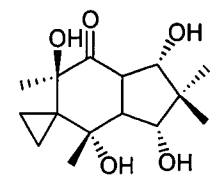
The well-documented acid lability of cyclopropyl carbinols plus the ready availability of 1,1-diacetylcyclopropane[16] led us to evaluate a [3+3] annulation route to this system. We envisioned a reaction of a 1,3-(C,C) dianion with 1,1-diacetylcyclopropane to generate the bicyclic segment of the illudins.



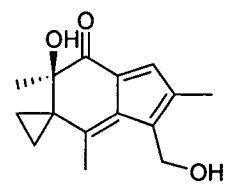
R = H illudin M
R = OH illudin S



illudin A

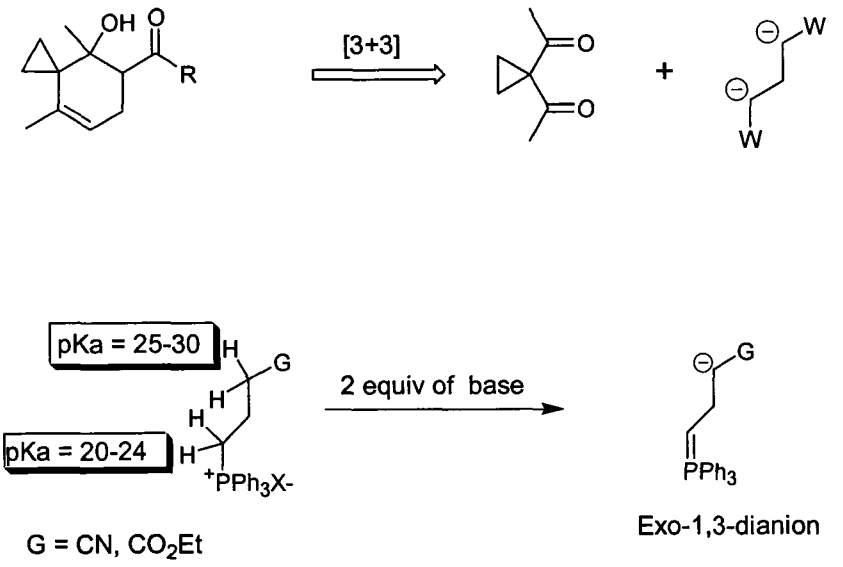


illudin B



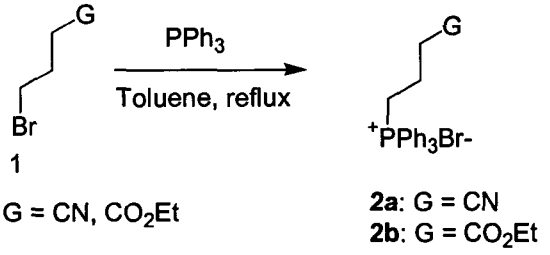
HMAF

Figure 3. Cytotoxic sesquiterpenes



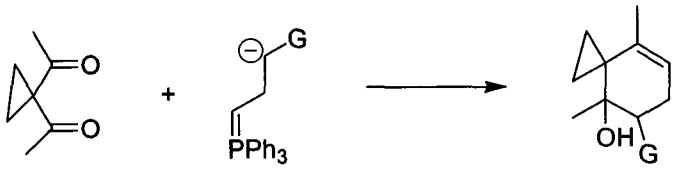
Scheme 5.

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**.[17] The results are summarized in Table 1.



Scheme 6.

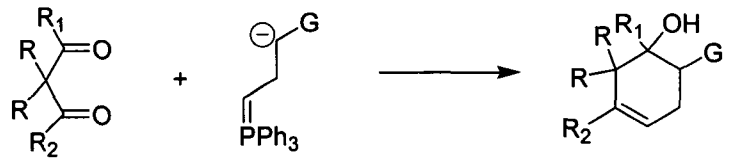
Table 1: [3+3] Annulations of 3-cyanopropyl phosphonium salts



Entry	Base	Temp (time)	Yield %
1	LDA	-78 °C	23
2	LDA, HMPA	-78 °C	27
3	LDA	-20 °C (2h)	39
4	NaHDMS	-20 °C (2h)	trace
5	LiTMP	-20 °C (2h)	65

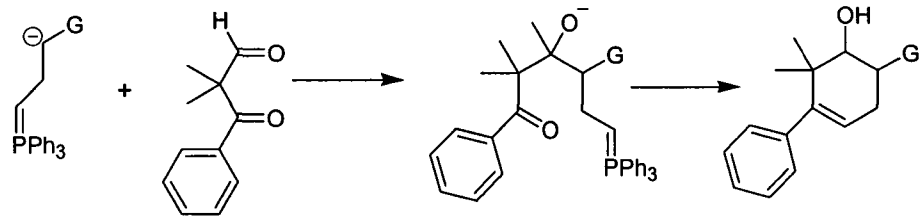
Using LDA as base at -78 °C gave a modest yield of 23%. Having achieved the desired cyclization, we tried optimizing the cyclization. Ultimately, the optimized cyclization was achieved using LiTMP as base at -20 °C. The successful annulation prompted us to evaluate the annulation with a variety of 1,3-diketones as electrophiles. The results are summarized in Table 2.

Table 2: [3+3] Annulation



Entry	G	R	R1	R2	Yield % (isomer ratio)	
1	CN	CH_2-CH_2	Me	Me	65(3:1)	**3**
2	COOEt	CH_2-CH_2	Me	Me	54 (5:1)	**4**
3	CN	Me, Me	Me	Me	61	**5**
4	CN	CH_2-$(CH_2)_2$-CH_2	Me	Me	59	**6**
5	CN	Me, Me	H	Ph	53 (1:1)	**7**
6	COOEt	Me, Me	H	Ph	48 (1:1)	**8**

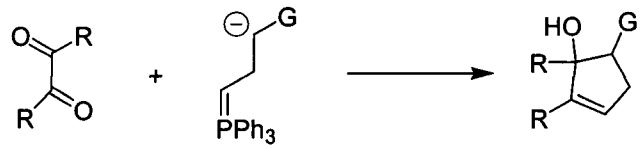
The reaction of dianions with keto aldehydes[18] (entries 5 & 6) gave only one regioisomer. We believe that anion next to the electron withdrawing group is more reactive than the phosphorane and hence it reacts preferentially with the more reactive aldehyde, as shown in Scheme 7.



Scheme 7.

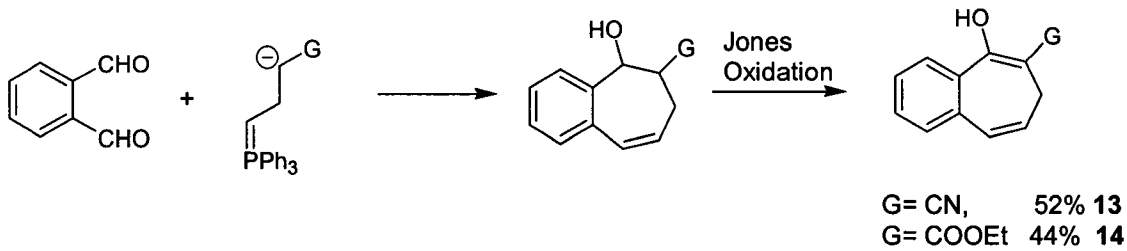
Having achieved [3+3] annulations, we investigated the synthesis of five-membered rings. The results of the dianion additions to 1,2-dicarbonyl compounds are depicted in Table 3. As anticipated, the yields of cyclopentenes were higher.

Table 3: [3+2] Annulation



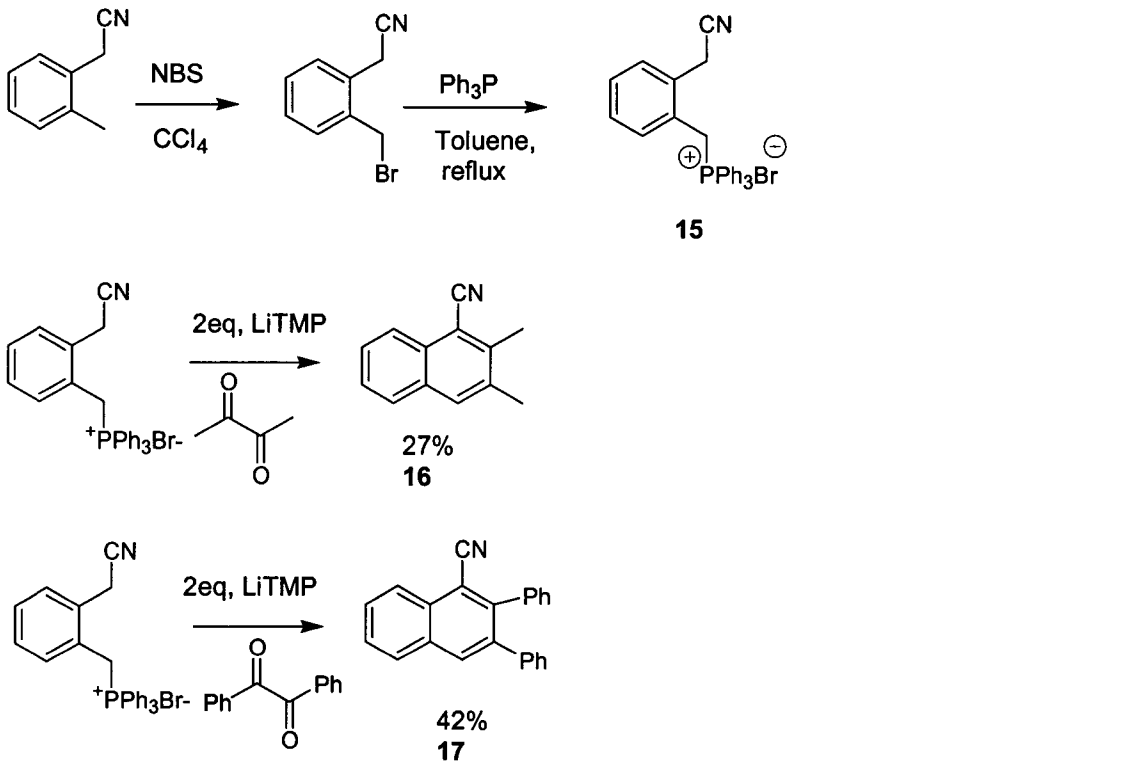
Entry	G	Base	R	Yield % (isomer ratio)
1	CN	LiTMP	Me	61(1:1) **9**
2	CN	LiTMP	2-furyl	68(1:1) **10**
3	CN	LiTMP	Ph	80(1:1) **11**
4	COOEt	LiTMP	Ph	65(1:1) **12**

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.**



Scheme 8.

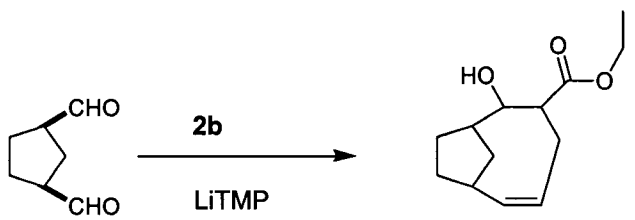
Having achieved useful [3+4] annulation with modest success, we decided to change our dianion. We synthesized phosphonium salt **15**[19] and evaluated [4+2] annulation as shown in Scheme 9. Yields were fairly modest, probably due to the instability of the dianion.



Scheme 9.

We also reacted **2b** with *cis*-cyclopentane-1,3-dialdehyde.[20] This reaction provided the

bicyclic adduct shown below in 38% yield.



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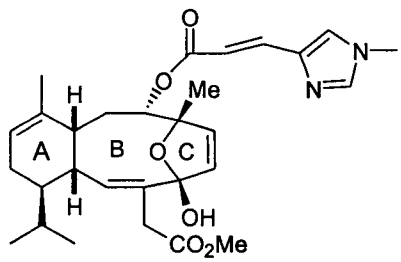
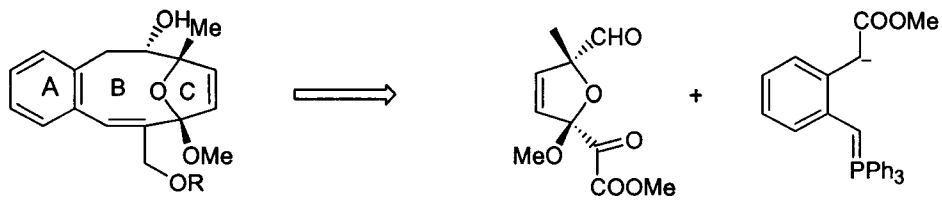
The results above demonstrate that cyclizations using dianions derived from **2a** and **2b** can generate five-, six- and seven-membered ring compounds. The highly functionalized ring systems produced by the dianion annulations will be useful for the synthesis of natural products. Application of this methodology in the synthesis of core-structure of Sorcodictyin-A[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 $CDCl_3$ (7.26 ppm for ^1H and 77.06 ppm for ^{13}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 A°, 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 $MgSO_4$. 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 ($CDCl_3$) δ 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 ($CDCl_3$) δ 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 ($CDCl_3$) δ 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 ($CDCl_3$) δ 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-diacetylcyclopropane (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 ($CDCl_3$) δ 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 ($CDCl_3$) δ 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,

m); 75 MHz ^{13}C NMR ($CDCl_3$) δ 175.0, 135.8, 119.3, 70.3, 61.4, 49.0, 31.5, 26.4, 25.0, 19.0, 14.8, 8.3, 6.3. HRMS *m/z* for $C_{13}H_{20}O_3$ calcd 224.1412, found 224.1415.

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 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-diacetylcyclopentane (126 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 mixture of alcohols. 300 MHz ^1H NMR ($CDCl_3$) 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 ^{13}C NMR ($CDCl_3$) 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 $C_{13}H_{19}NO$ 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 $MgSO_4$. The crude product was chromatographed on silica gel (H:EA = 5:1) to afford **6**. 300 MHz ^{1}H NMR ($CDCl_3$) 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 ^{13}C NMR ($CDCl_3$) 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 $C_{11}H_{17}NO$ calcd 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-phenylpropanaldehde (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 **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 $MgSO_4$ and the crude product was chromatographed on silica gel (H:EA = 5:1) to

yield compound **7a**. 300 MHz ^{1}H NMR ($CDCl_3$) δ 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 ($CDCl_3$) δ 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 $C_{15}H_{15}NO$ 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-phenylpropanaldehde (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 ($CDCl_3$) δ 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 ($CDCl_3$) δ 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 $MgSO_4$. The crude product was chromatographed on silica gel (H:EA= 4:1) to afford **9** as mixture of alcohols. **9a**: 300 MHz ^{1}H NMR ($CDCl_3$) 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 ^{13}C NMR ($CDCl_3$) δ 144.5, 125.2, 120.5, 84.4, 42.3, 33.6, 24.8, 11.9. **9b**: 300 MHz ^{1}H NMR ($CDCl_3$) 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 ^{13}C NMR ($CDCl_3$) δ 143.7, 122.9, 119.9, 83.1, 41.2, 33.5, 22.8, 11.7. HRMS *m/z* for $C_8H_{11}NO$ 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 $MgSO_4$. The crude product was chromatographed on silica gel (H:EA= 3:1) to afford **10** as mixture of alcohols. **10a**: 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.18-7.45 (10H, m), 6.45 (1H, m), 3.38 (1H, m), 2.70-2.98 (2H, m); 75 MHz ^{13}C NMR ($CDCl_3$) δ 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 $C_{18}H_{15}NO$ calcd 261.1154, found 261.1156. **10b**: 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.18-7.45 (10H, m), 6.40 (1H, m), 3.58 (1H, m), 2.71-2.98 (2H, m); 75 MHz ^{13}C NMR ($CDCl_3$) δ 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 $MgSO_4$. The crude product was chromatographed on silica gel (H:EA= 4:1) to afford **11** as mixture of alcohols. **11a**: 300 MHz ^{1}H NMR ($CDCl_3$) δ 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 ($CDCl_3$) δ 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 ^1H NMR ($CDCl_3$) δ 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 = 3Hz), 3.64 (1H, t, J = 8.7 Hz), 2.98-3.02 (2H, m); 75 MHz ^{13}C NMR ($CDCl_3$) δ 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 ^1H NMR ($CDCl_3$) δ 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 ^1H NMR ($CDCl_3$) δ 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 $MgSO_4$. 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 $MgSO_4$ and chromatographed (H:EA = 3:1) to yield compound **13**. 300 MHz ^{1}H NMR ($CDCl_3$) 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 ($CDCl_3$) 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 $C_{14}H_{14}O_3$ 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 $MgSO_4$. 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 $MgSO_4$ and chromatographed (H:EA = 3:1) to yield compound **14**. 300 MHz ^{1}H NMR ($CDCl_3$) 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 $MgSO_4$. The crude product was chromatographed on silica gel (H:EA = 6:1) to afford **16**.300 MHz ^{1}H NMR ($CDCl_3$) 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 $MgSO_4$. The crude product was chromatographed on silica gel (H:EA = 3:1) to afford **18** as

mixture of alcohols: 300 MHz ^{1}H NMR ($CDCl_3$) δ 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).

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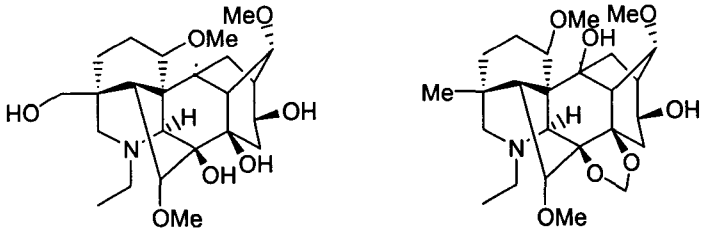
CHAPTER 2

SYNTHETIC APPROACH TOWARDS METHYLLYCACONITINE

Introduction

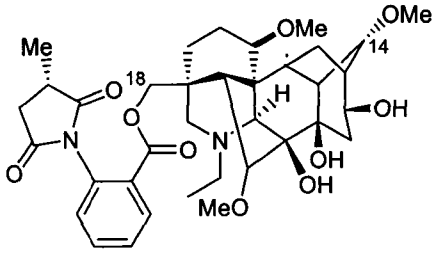
Larkspur is a toxic plant on western U.S ranges. About 5-15% of cattle poisoning on North American mountain lands are due to larkspur poisoning. Toxic alkaloids constitute 30-50% of total alkaloid content in tall larkspur.[1] Larkspur (Delphinium species) alkaloids can be divided into two structural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



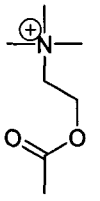
Lycoctonine (**1**) Deltaline (**2**)

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]



Methyllycaconitine (**3**)



Acetylcholine

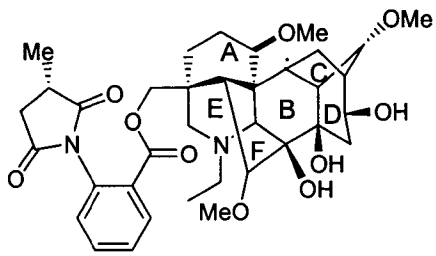
Figure 2.

Recently, nicotinic acetylcholine receptor chemistry and biology have gained enormous interest in the field of drug development.[4] 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.[5] 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.[6] 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.

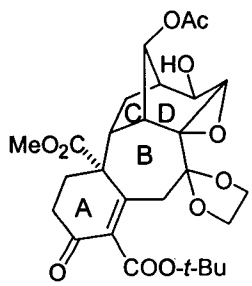
Structure-activity relationship investigations have indicated that the *N*-methyl succinimidobenznzoate ester at C-18 affects alkaloid interactions with nAChRs at neuromuscular junctions and the substituent at C-14 determines the potency and the

mechanism of nAChR blockade at neuromuscular synapses.[7] 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,[8] Whiting[9] and Kraus.[10,11] 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]



Methyllycaconitine (**3**)

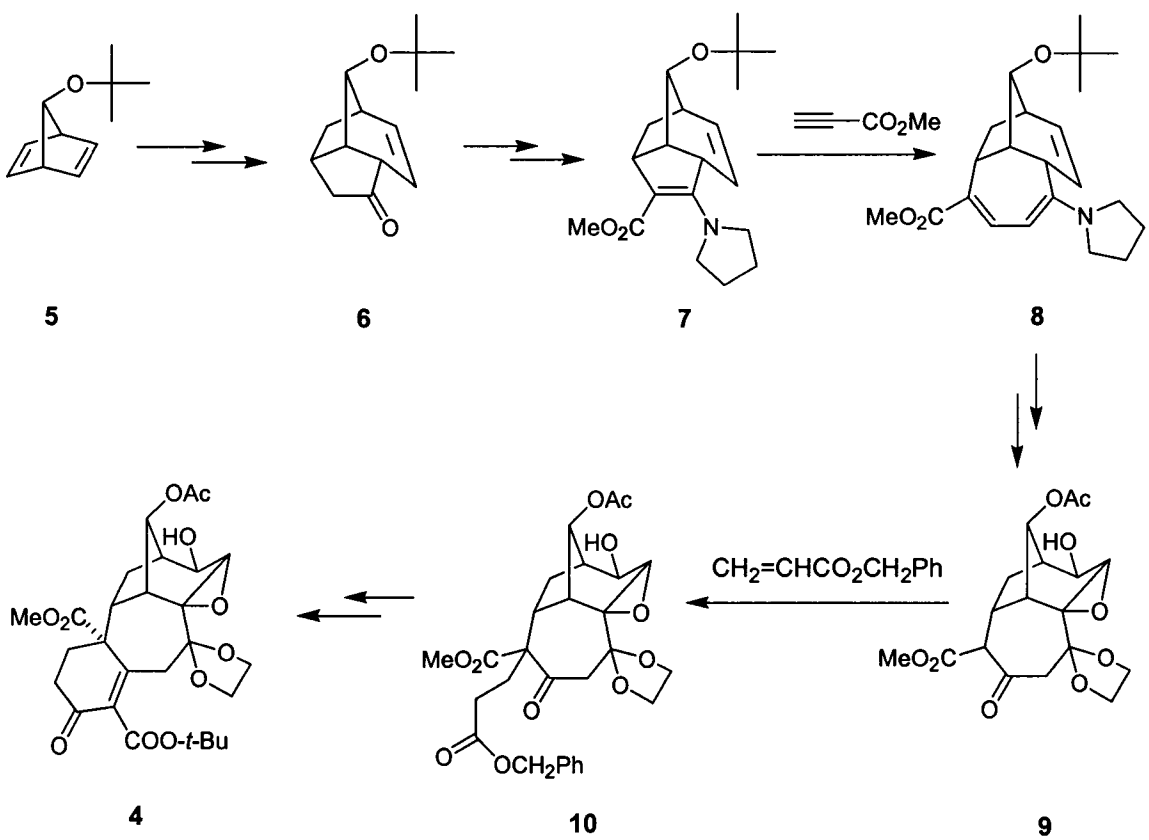


4

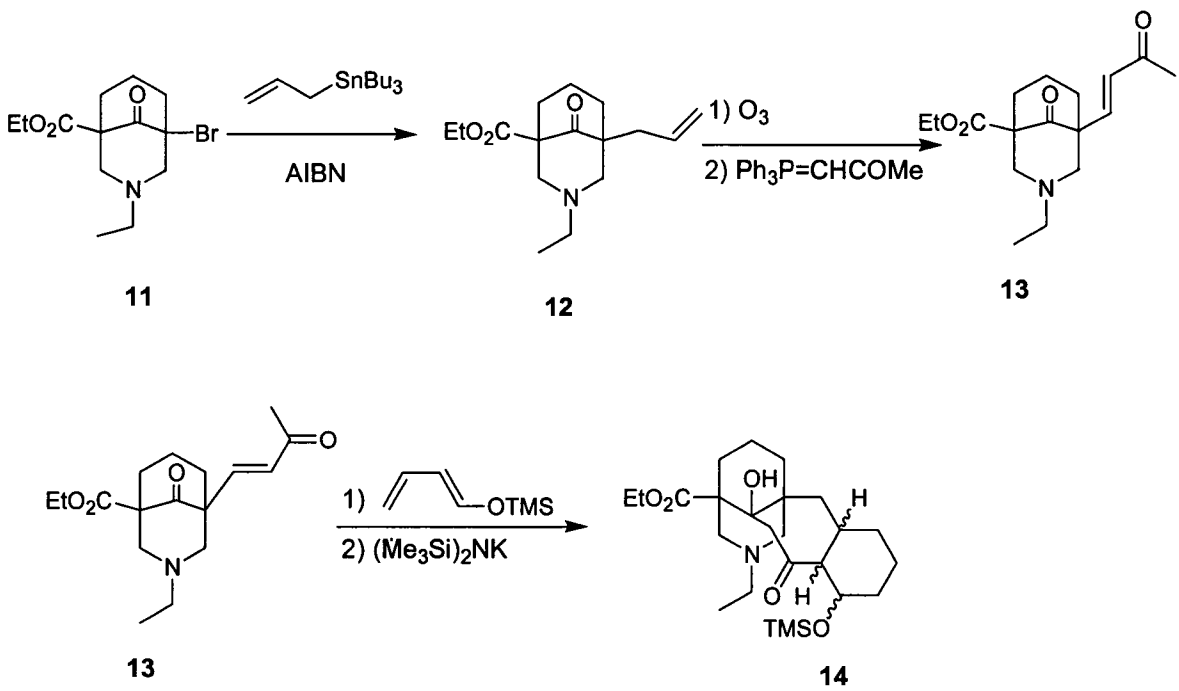
Figure 3.

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 C_{19}-diterpene alkaloids skeleton. However, their inability to make the biologically significant E and F rings decreases the synthetic value of this approach.



Scheme 1.

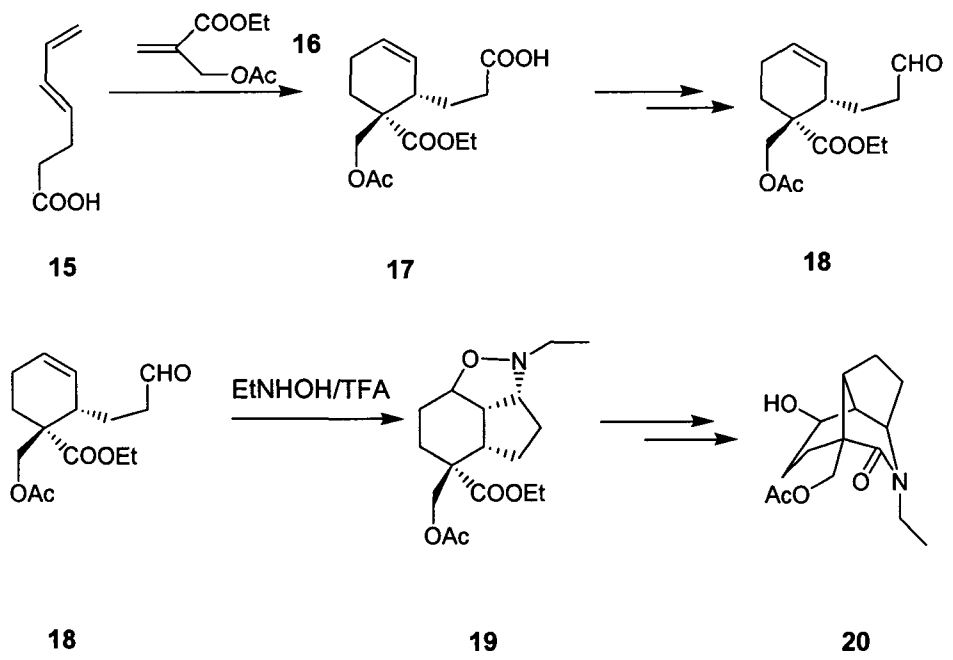


Scheme 2.

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.*[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_{19}-diterpene alkaloids.

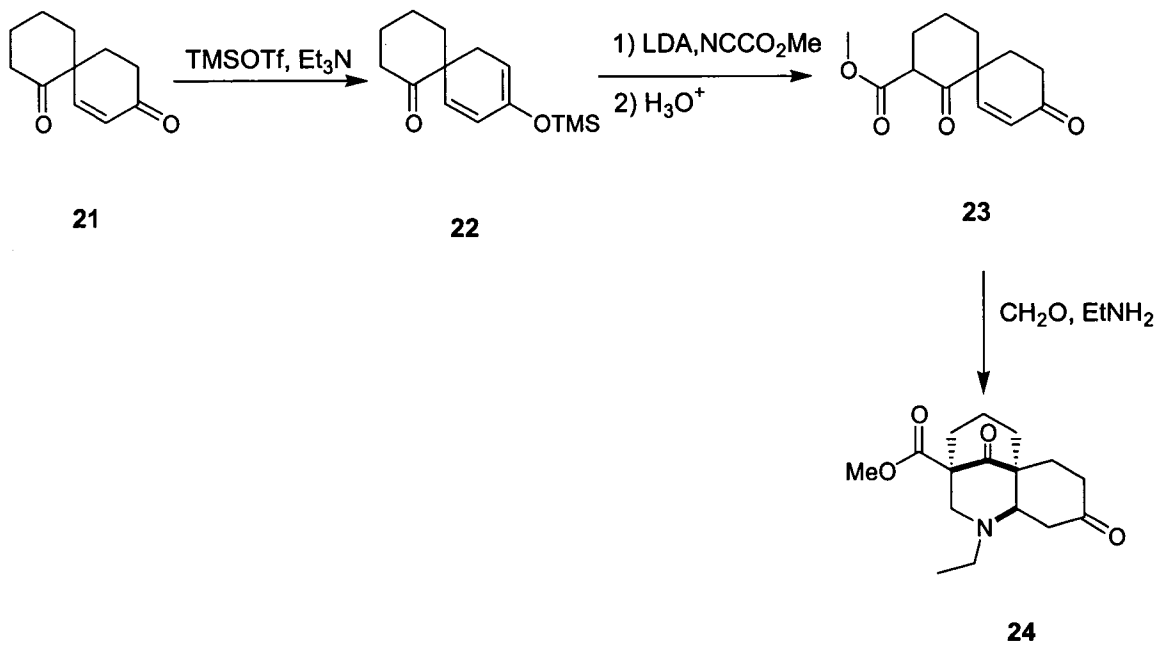
In 1998, Whitting and co-workers reported the synthesis of AEF tricyclic fragment.[9] The stereocenters of the AEF segment were set by two key reactions: the intramolecular 1,3-dipolar addition to the alkene and the Diels-Alder reaction. Diels-Alder reaction of the

sodium salt of acid **15** and acrylate **16** yielded compound **17**. Compound **17** was converted to the isoxazolidine **19** via the nitrone 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 tricylic segment to the ABEF ring system.

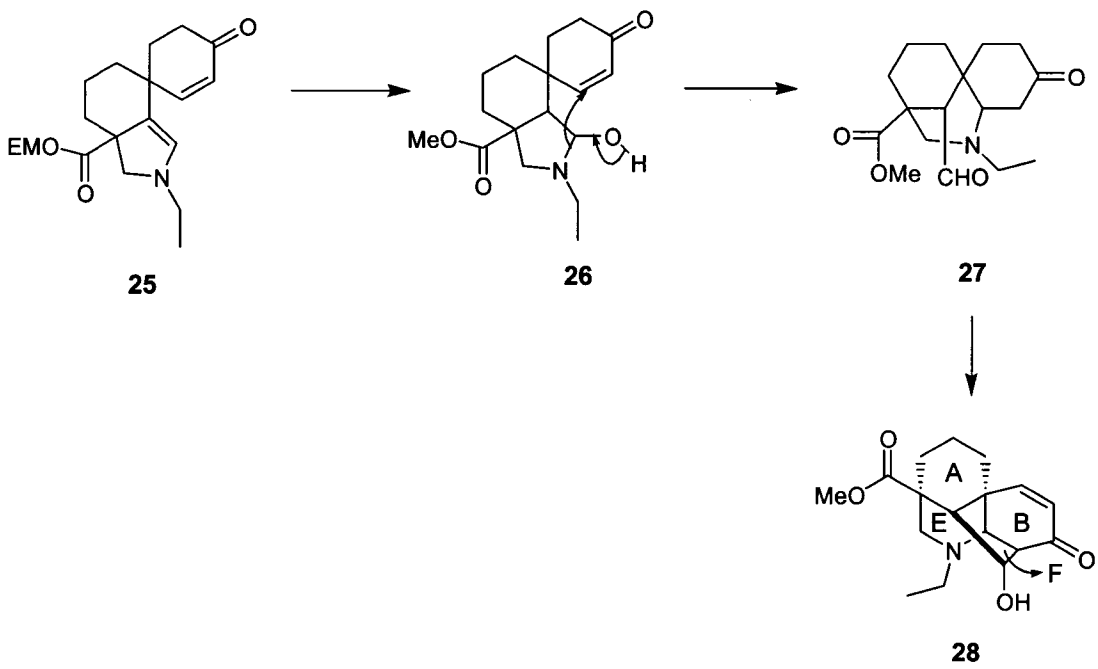


21 **22** **23** **24**

Scheme 4.

Results and Discussion

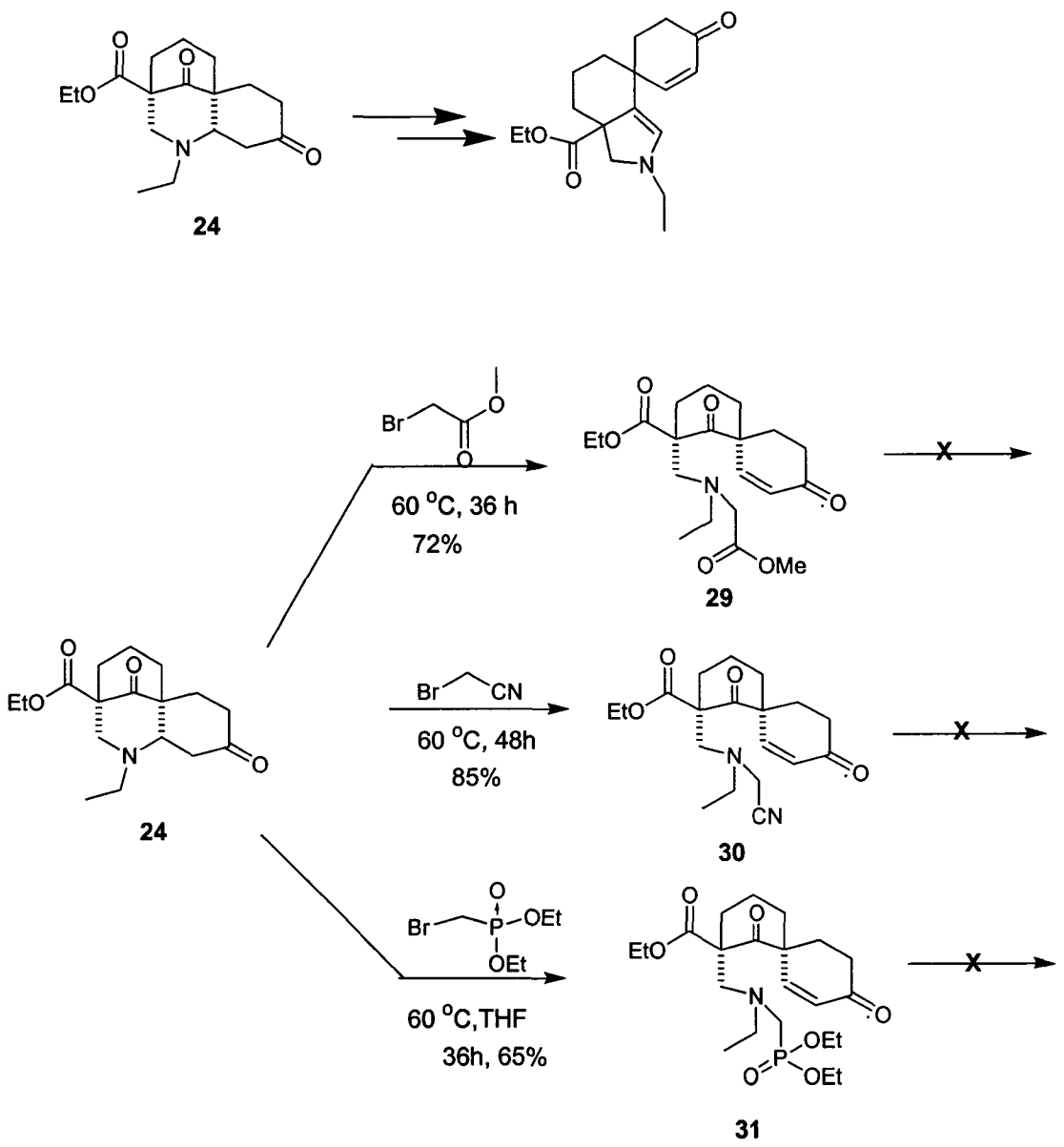
In our studies towards C_{19}-ditepenoid alkaloids, we envisioned the synthesis of an ABEF ring system possessing all necessary functionality to allow us to easily incorporate the C and D rings. Scheme **5** suggests the synthetic strategy for the ABEF ring system. The key reaction is the hydrolytic 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.



25 **26** **27** **28**

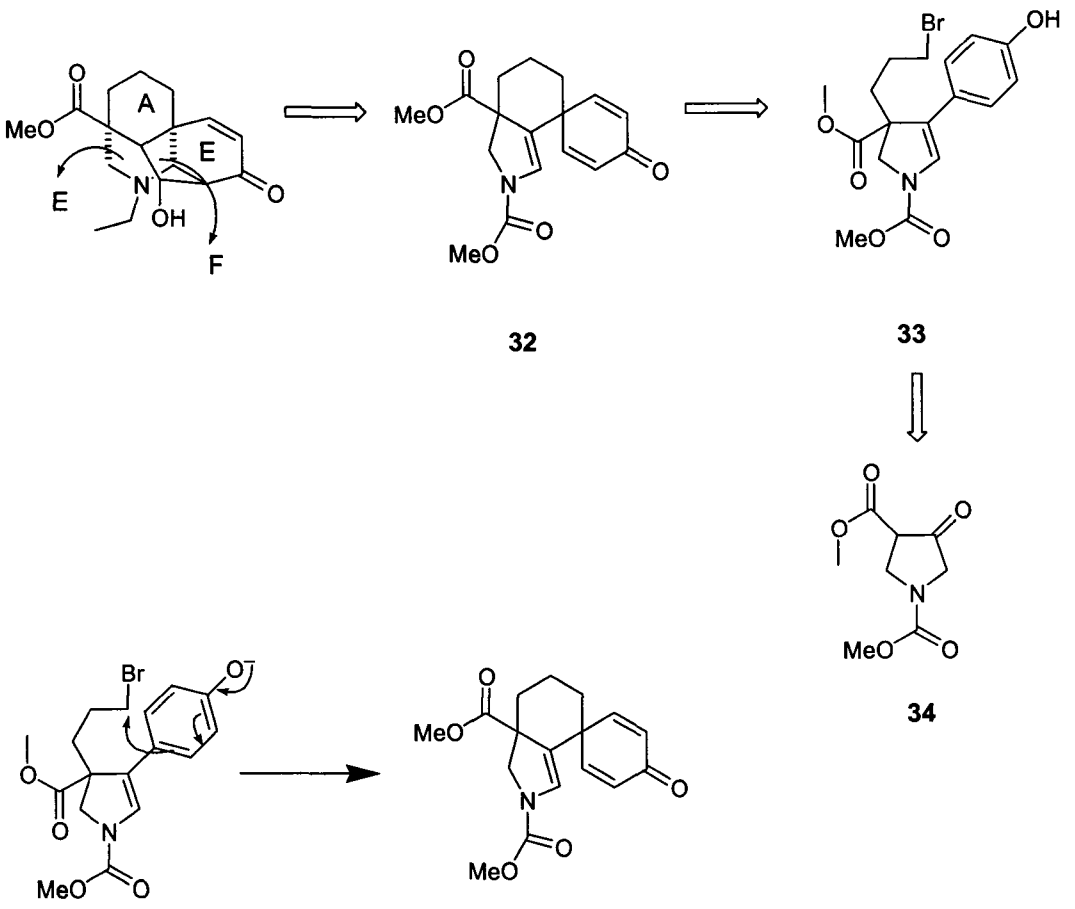
Scheme 5.

Our first approach to intermediate **25** was from compound **24** (Scheme 6).[11] 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.



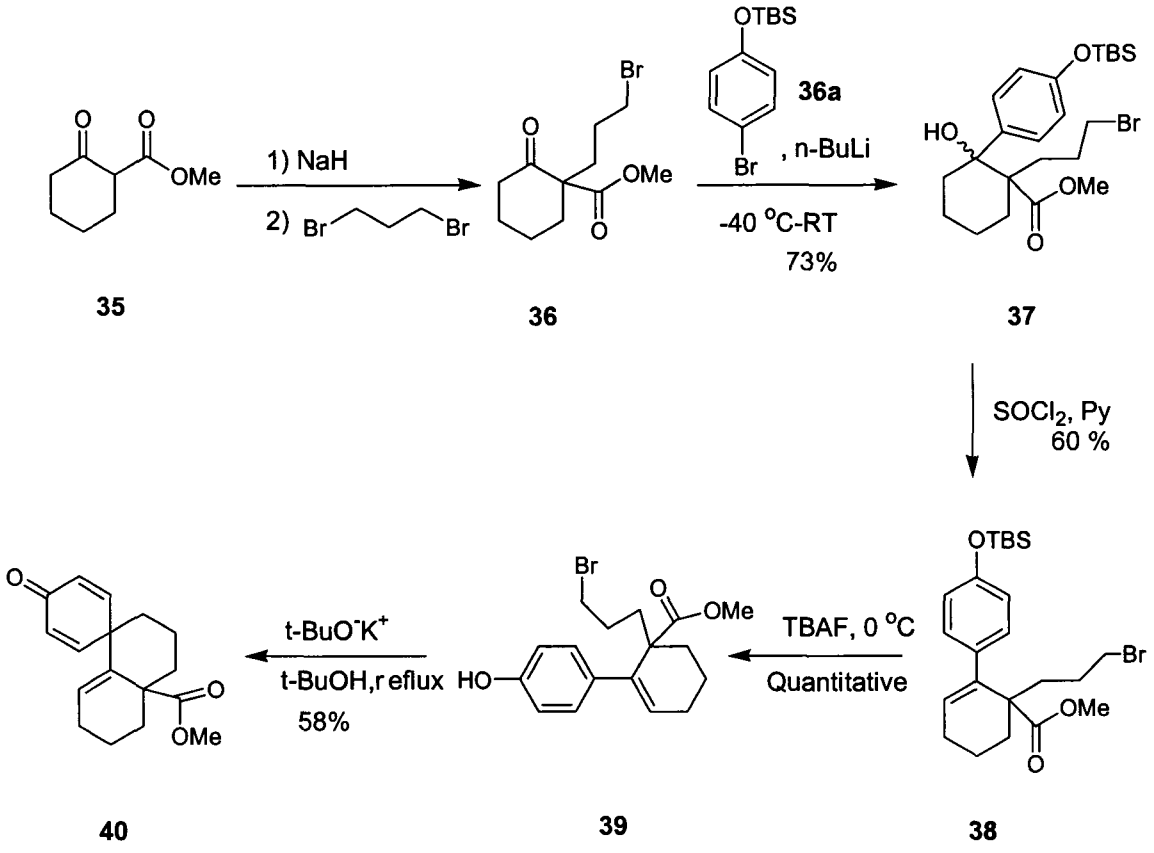
Scheme 6.

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**.



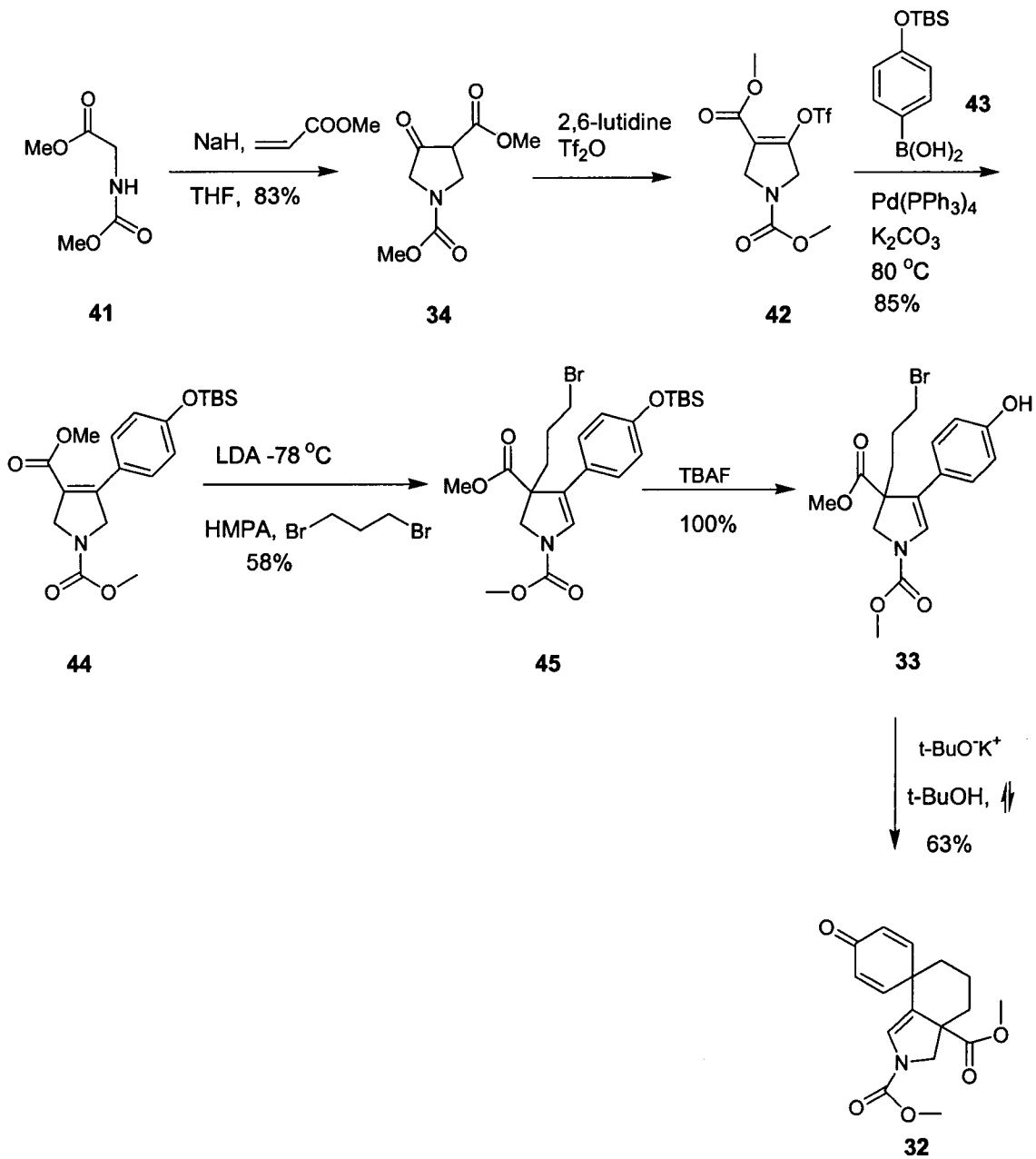
Scheme 7.

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]



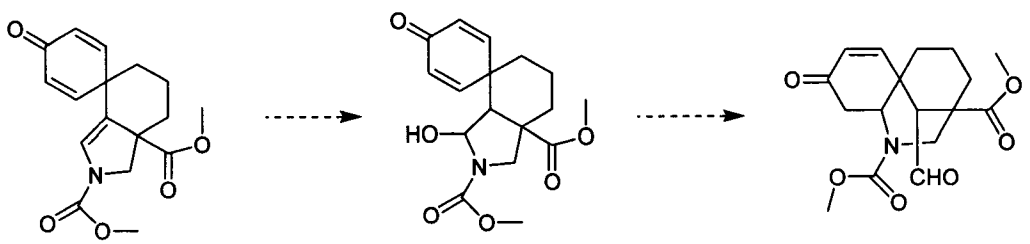
Scheme 8.

Encouraged by the above result, our synthesis toward ABEF ring system commenced from known keto ester **33**.[14] Treatment of **33** with 2,6-lutidine and triflic anhydride yielded vinyl triflate **42**. Suzuki coupling[15] of triflate **42** with boronic acid **41** yielded compound **43** in modest yield. The γ-alkylation[16] 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**.



Scheme 9.

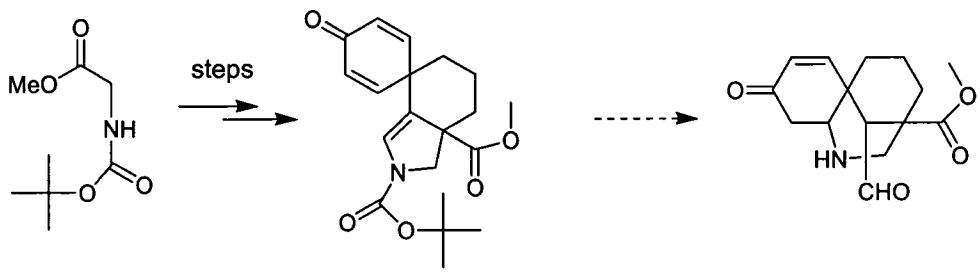
With dienone in our hand we turned our attention towards the hydrolytic skeletal rearrangement. However, many attempts to hydrolyze carbamate **32** were unsuccessful. Prolonged exposure of compound **32** to acidic conditions only led to the decomposition of **32**.



32 **46** **47**

Scheme 10.

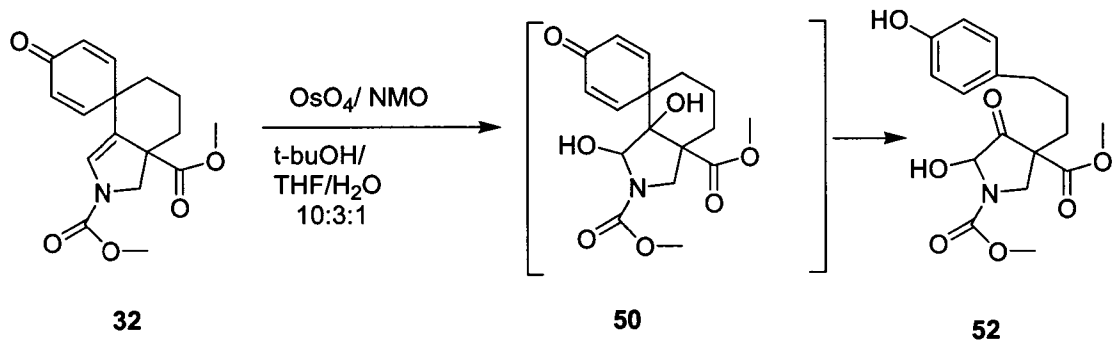
Since hydrolysis was unsuccessful, we decided to change the protecting group on nitrogen to a readily-cleavable BOC group. Thus, dienone **49** was synthesized from carbamate **48.**[13] Unfortunately, our attempts to hydrolyze enone **49** were also unsuccessful, leading to a complex mixture.



48 **49**

Scheme 11.

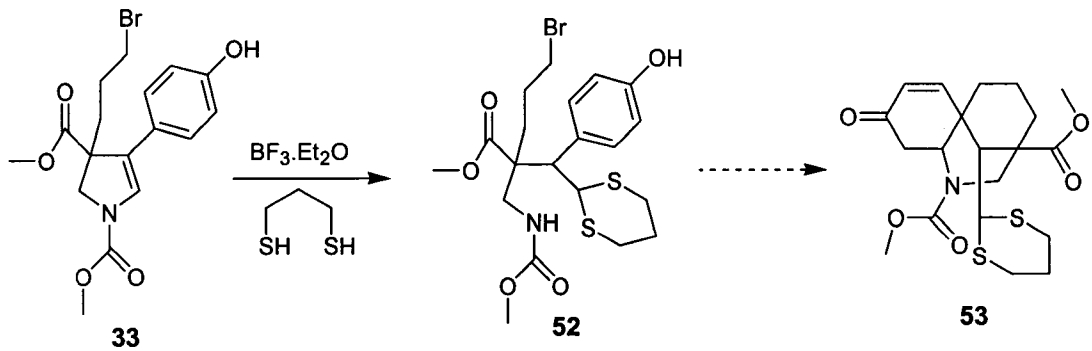
Meanwhile, dihydroxylation of enone **32** led to isolation of phenol **51**. This reaction occurs probably through diol **50** which undergoes a retro-aldol reaction to give **51**.



32 **50** **52**

Scheme 12.

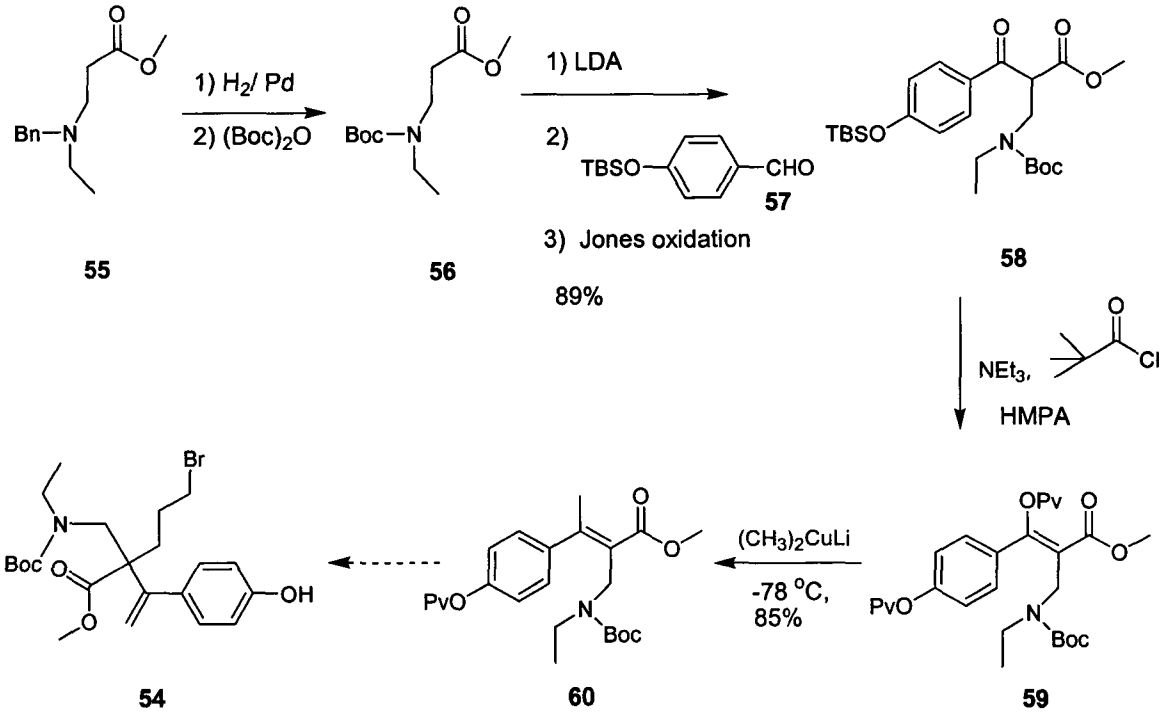
In order to solve the problem of hydrolysis we decided to change the order of the steps. Phenol **33** was converted to dithiane **52**. Surprisingly, all of our attempts to facilitate the intramolecular cyclization only led to decomposition of starting material.



33 **52** **53**

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.

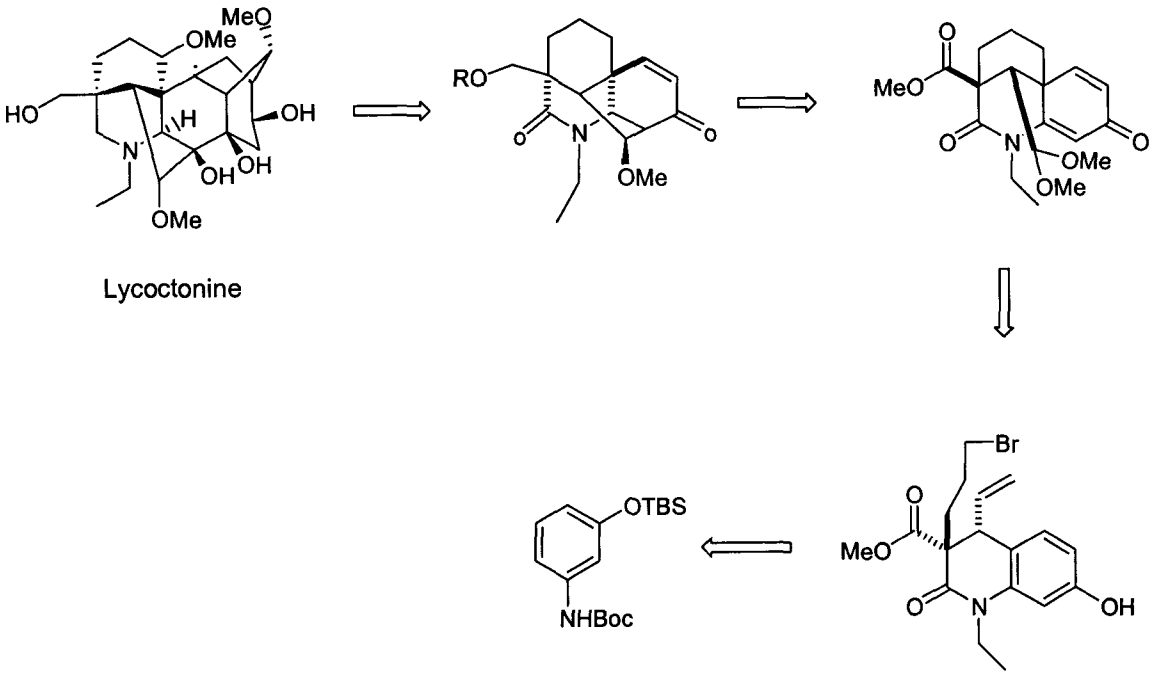


Scheme 14.

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

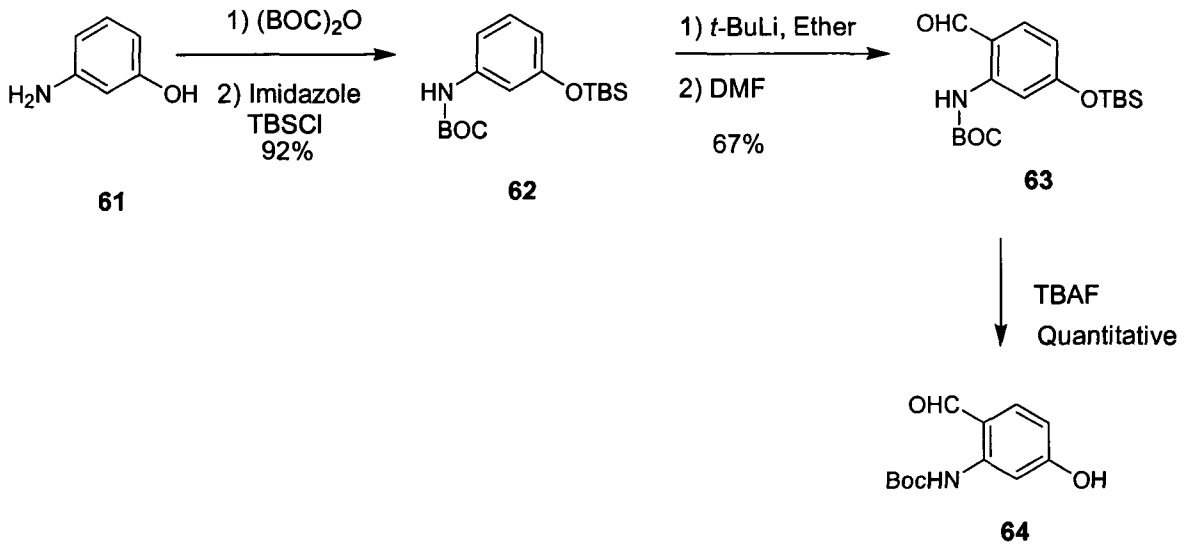
In spite of the failure of the approaches discussed previously, the knowledge gained through the previous approaches decreased the synthetic challenge considerably. Scheme 15 gives the retrosynthesis.



Scheme 15.

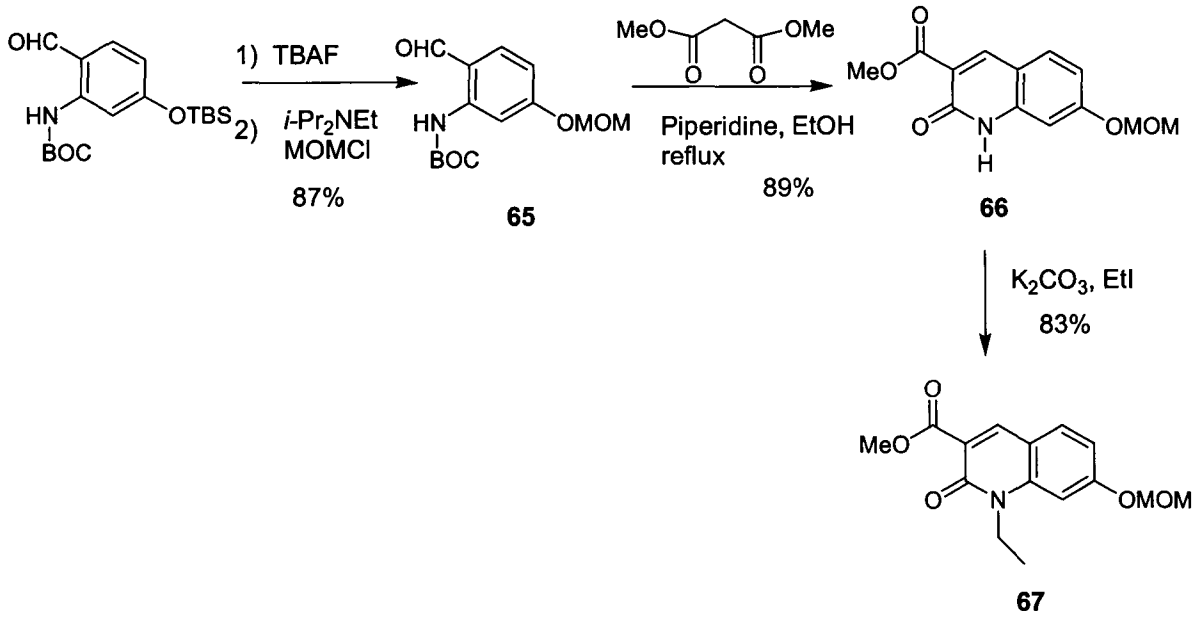
Scheme 15 provides us an opportunity to construct the F through an aldol reaction. The ABE segment could be constructed from BE segment through the *para*-C-alkylation reaction. Finally, substituted 3-aminophenol could act as the B ring.

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 *ortho*-metalation[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 *ortho*-directing group. One of the *ortho* positions is selectively blocked by bulky the TBS group, leading to selective *ortho*-metallation. The silyl ether was deprotected using TBAF to yield phenol **64**.



Scheme 16.

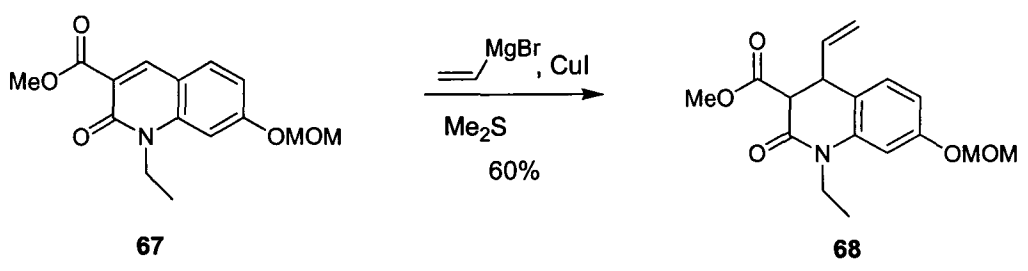
The phenol was converted to a MOM ether using methoxymethyl chloride and diisopropylethylamine to give compound **65**. heating aldehyde **65** with dimethyl malonate in presence of piperidene led to the isolation of lactam **66** in 90% yield. This reaction occurs through α-β-unsaturated diester which 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 lycoctonine alkaloid.



Scheme 17.

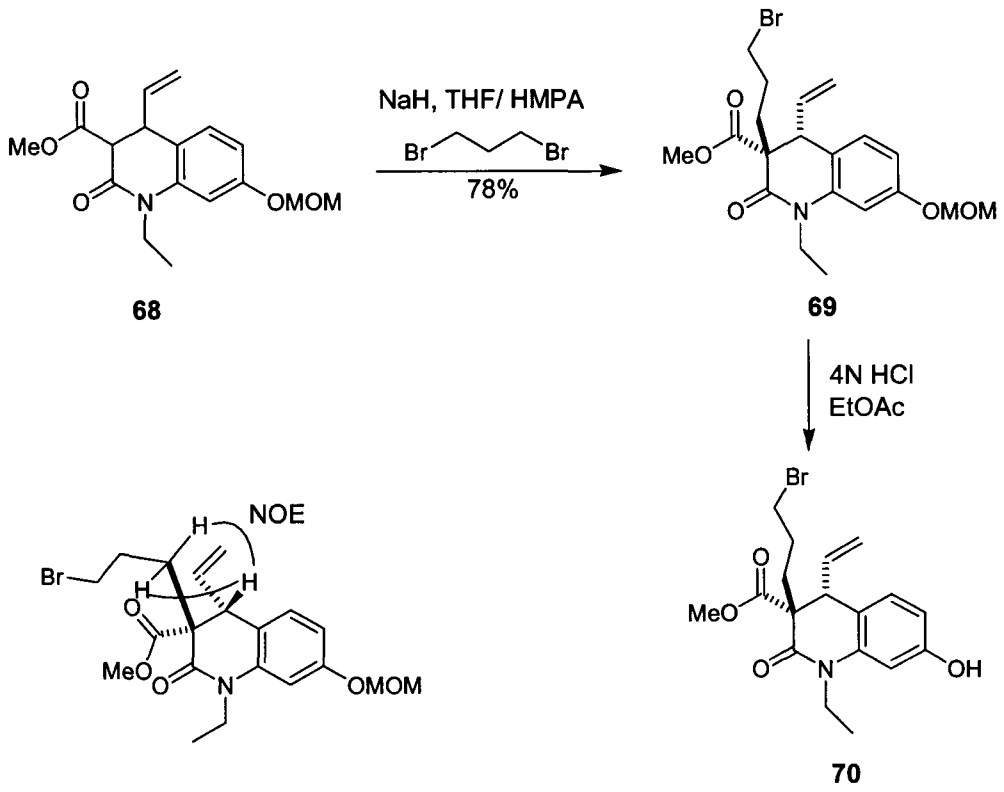
With the BE segment in hand, the next goal was to synthesize the ABE ring system of lycoctonine. However, we decided to introduce the carbon units required for the F ring at this stage. The carbon units required for the construction of the F ring were introduced by way of a vinyl unit, which could be 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



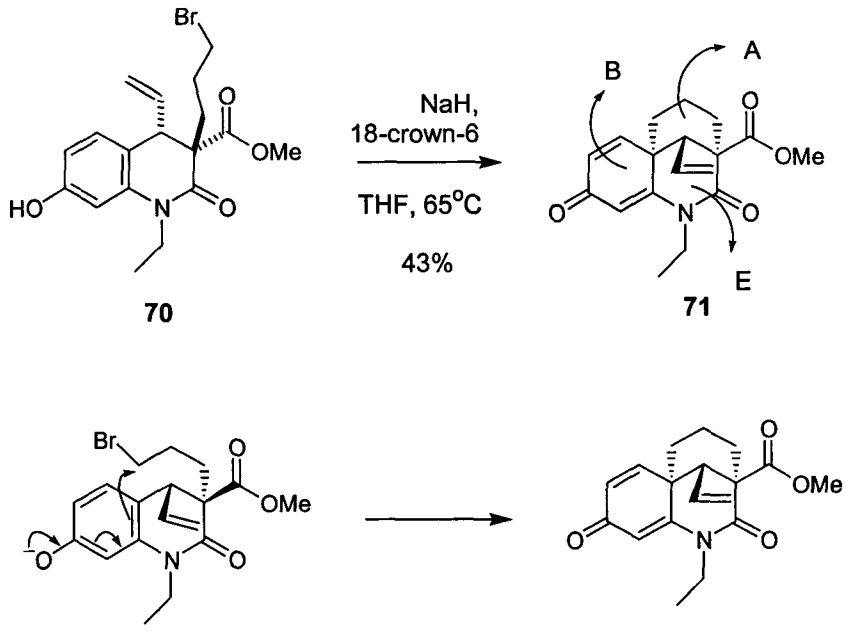
Copper Source	Additive	% yield
CuI	None	43
CuCN	None	47
CuI	TMSCl	55
CuI	Me_2S	60
None	None	17

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.



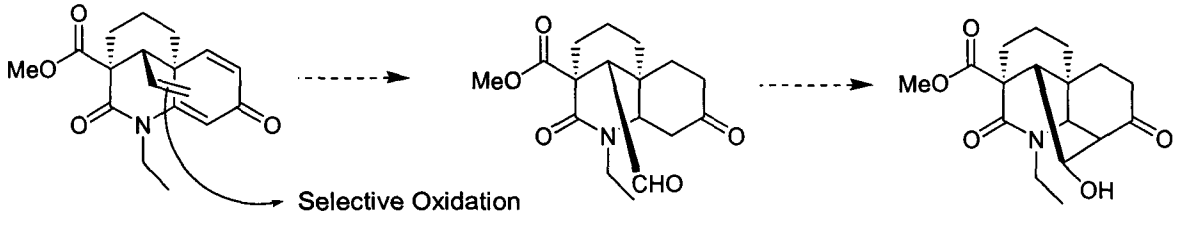
Scheme 18.

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 lycoctonine.



Scheme 19

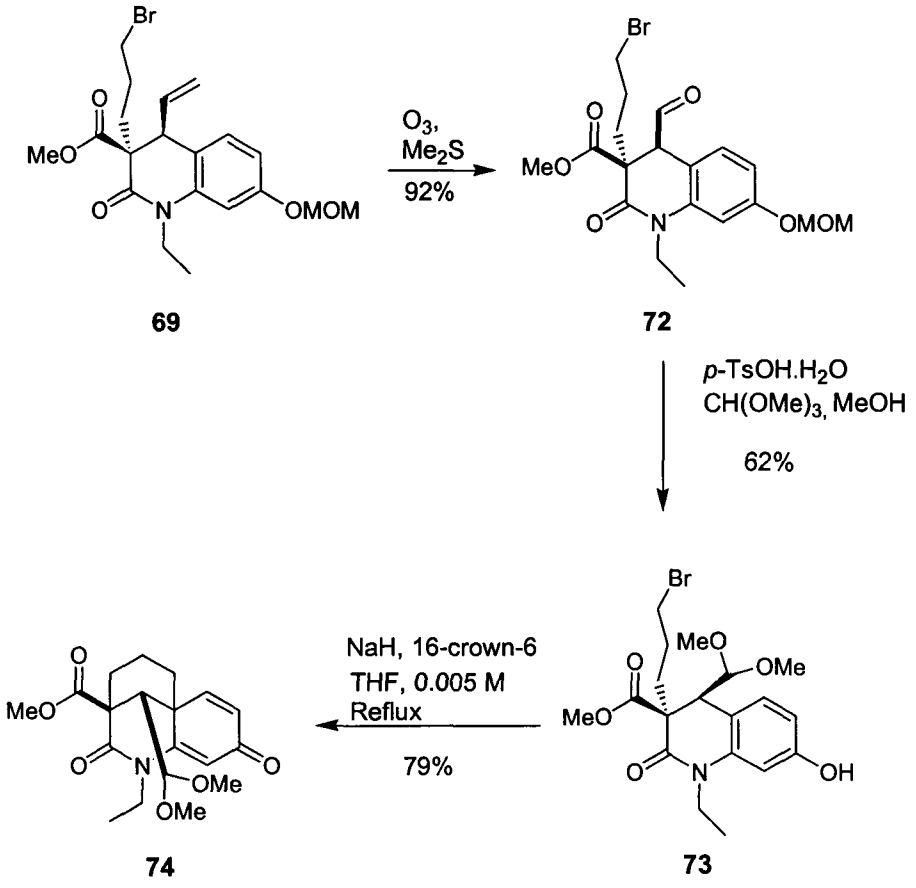
Construction of the ABEF segment required the selective oxidation of the terminal double bond in the presence of enone as shown in Scheme 20. Unfortunately, we were unable to oxidize the terminal double bond selectively. We decided on a detour as shown in Scheme 21.



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

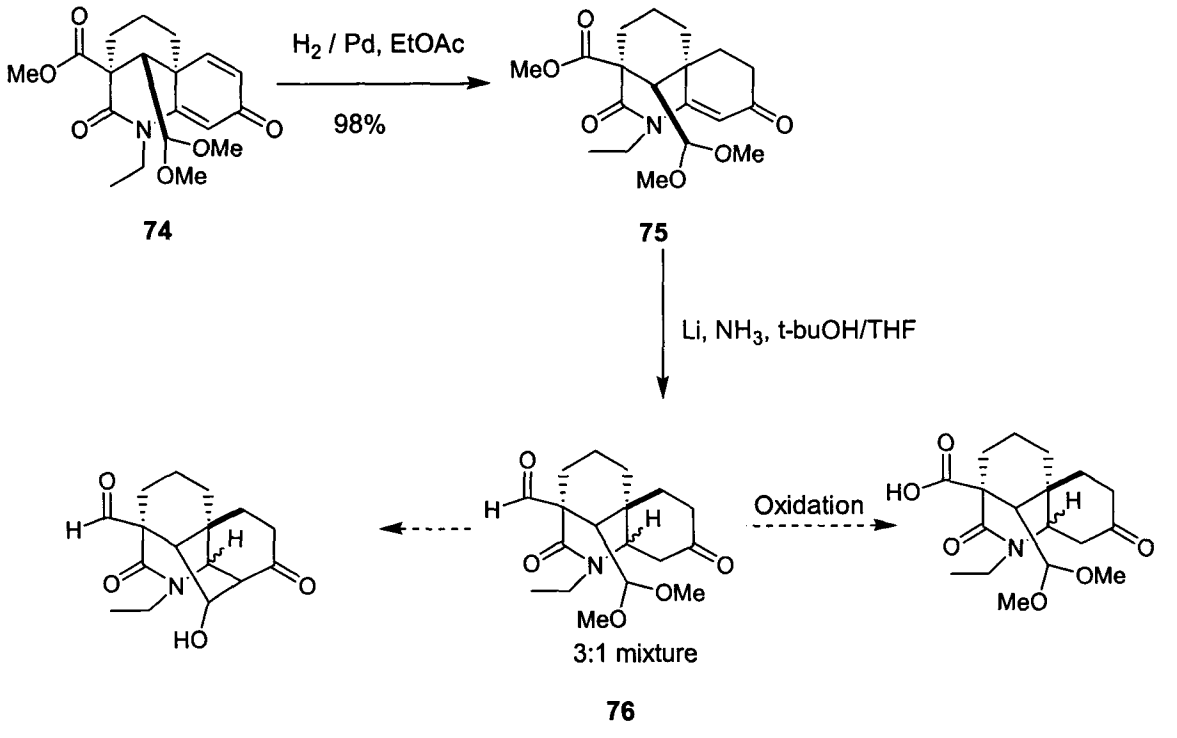
to the protection of the aldehyde as a dimethyl acetal with a subsequent removal of the MOM group to liberate phenol **73** in 62% yield. Heating phenol **73** in THF in the presence of NaH and crown-ether led to an intramolecular cyclization leading to the formation of ABE segment of lycoctonine as shown in Scheme 21.



Scheme 21.

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

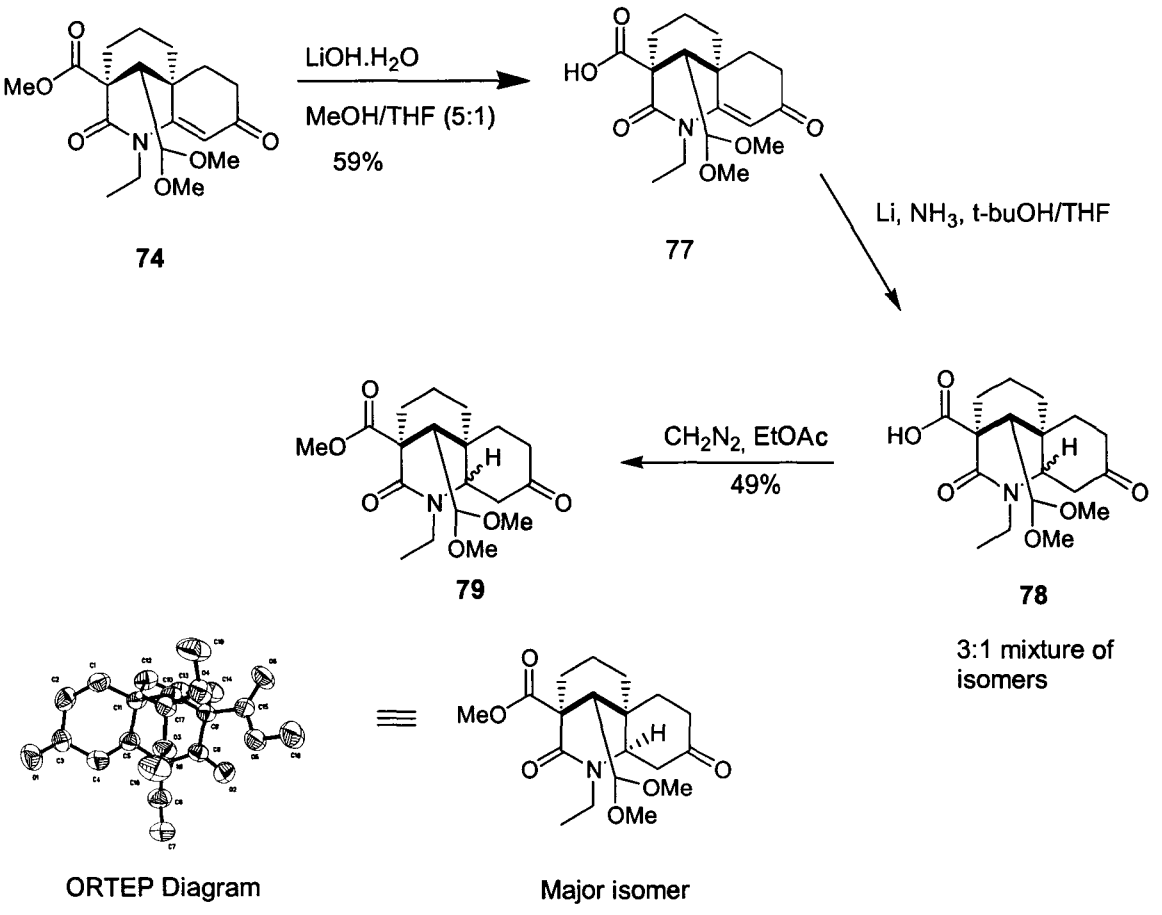
like Zn/acetic acid[20] and K-selectride[21] led to the isolation of complex mixtures. Finally, we were able to reduce the enone double bond using Li/NH_3[22] along with concomitant reduction of the ester group to an aldehyde to yield compound **76** as shown in Scheme 22.



Scheme 22.

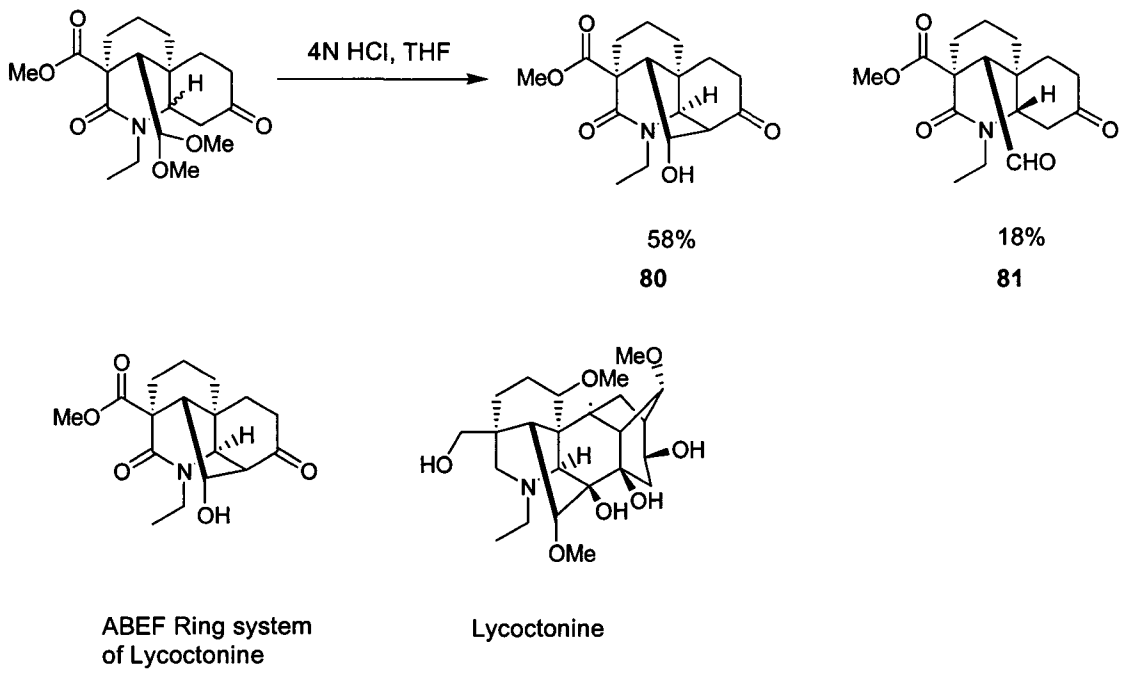
Having achieved our 1,4-reduction, we tried converting the tricyclic intermediate **76** to the ABEF ring system. Attempts to do an intramolecular aldol reaction under acidic conditions led to the decomposition of the ketoaldehyde. We attributed the failure of this reaction to the aldehyde group present 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_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.



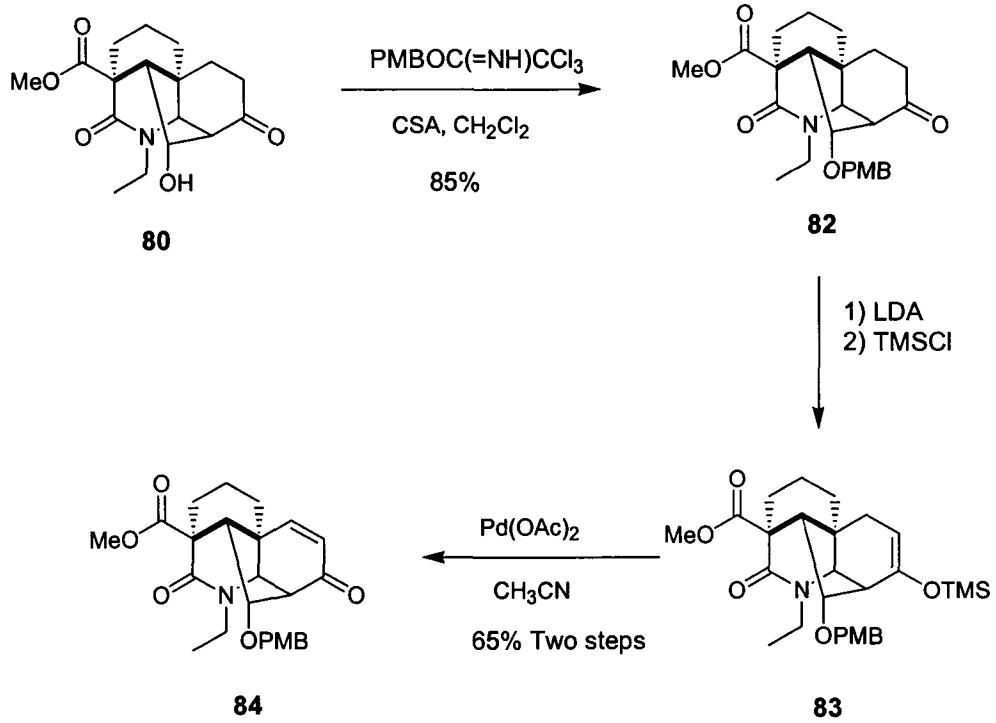
Scheme 23.

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.



Scheme 24.

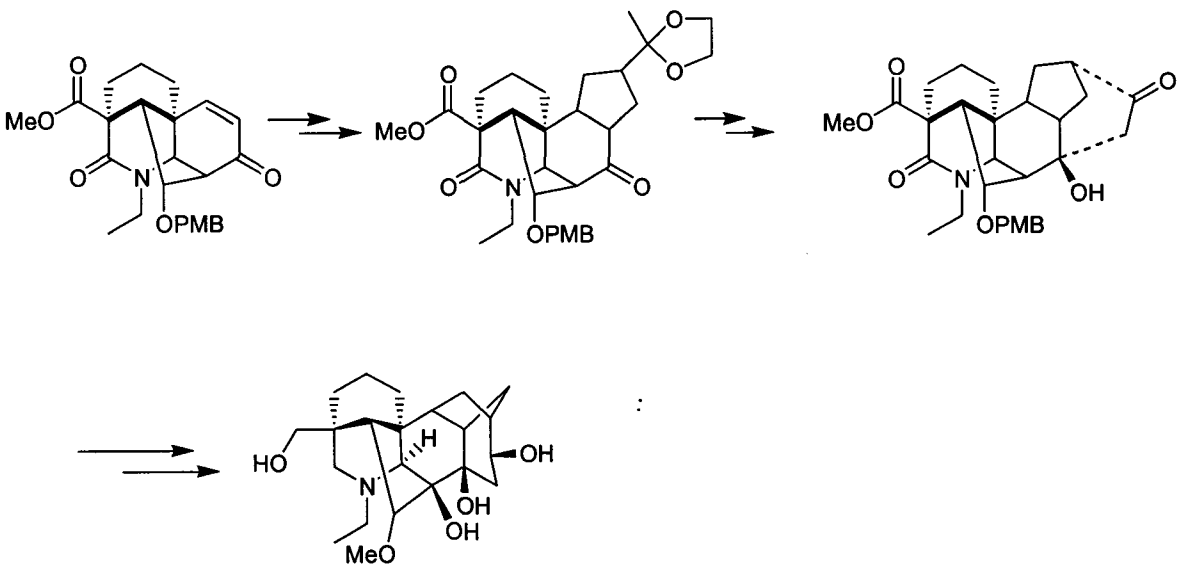
Compound **80** was elaborated to enone **84** as shown in Scheme 25. Treatment of compound **80** with CSA and *para*-methoxybenzylacetamidate[23] gave compound **82**. The silyl enol ether (generated using LDA, and TMSCl) of **82** was converted to enone **83** using $Pd(OAc)_2$.[24]



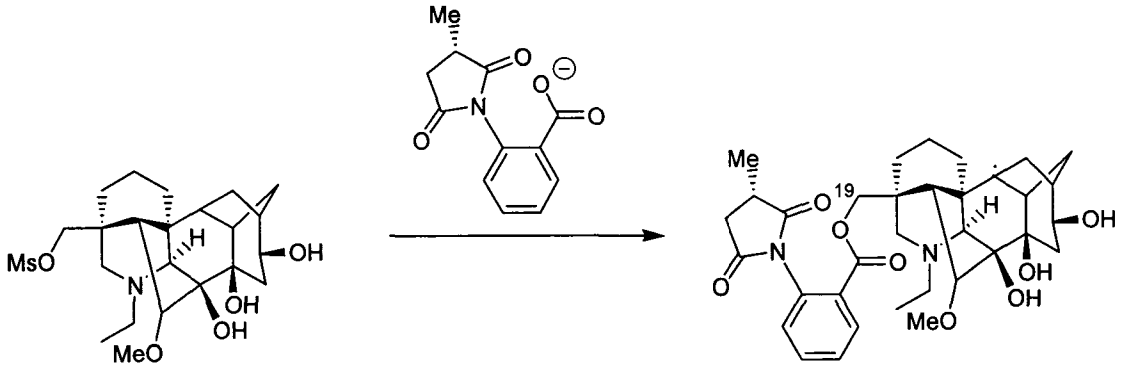
80 **82** **84** **83**

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 C_{19} neopentyl alcohol would be introduced to yield the core structure of MLA.



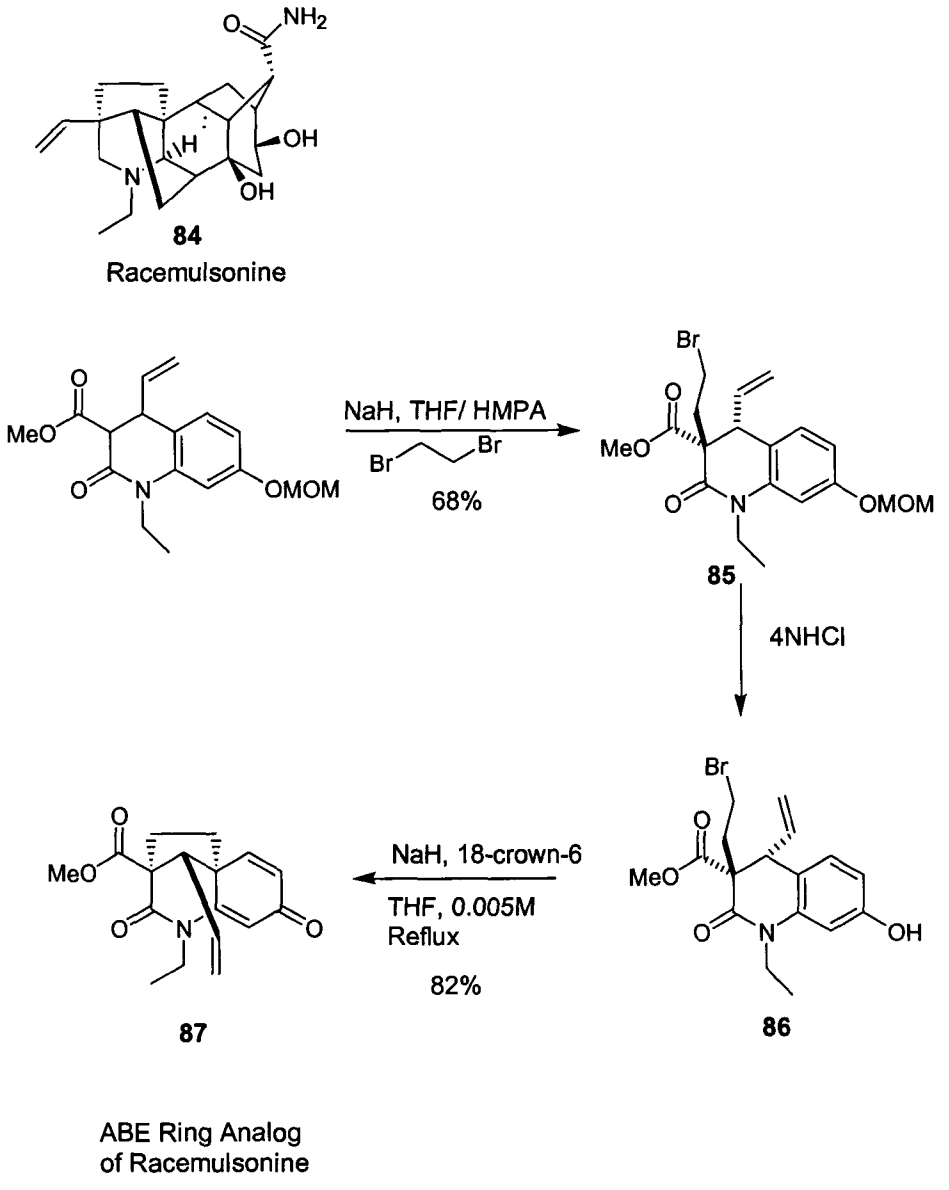
Hexacyclic Core Structure of Lycoctonine



Core Structure of MLA

Scheme 26.

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.



84
Racemulsonine

85

86

87
ABE Ring Analog
of Racemulsonine

Scheme 27.

Alkylating 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 $CDCl_3$ (7.26 ppm for ^1H and 77.06 ppm for ^{13}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 A°, 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 $MgSO_4$, 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 ($CDCl_3$) 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 $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by chromatography (H:EA = 1:1) to afford **30** (80mg, 71%). 300 MHz ^{1}H NMR ($CDCl_3$) 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 =6.9Hz).

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 $MgSO_4$, filtered, and evaporated in *vacuo*. The residue was purified by chromatography (H:EA = 3:1) to afford **31** (97 mg, 65%).300 MHz ^{1}H NMR ($CDCl_3$) 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), 1.50-165 (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 warmred to rt and quenched with saturated NH_4Cl. 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= 4:1) to afford **37** as mixture of isomers (255 mg, 85 % yield). 300 MHz ^{1}H NMR ($CDCl_3$) 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** (163mg, 0.32 mmol) in 0.5 mL of pyridine at 0 °C was added 116 mg (0.978 mmol) of $SOCl_2$. 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 $MgSO_4$, filtered, and evaporated in *vacuo*. The residue was purified by chromatography (H:EA = 4:1) to afford **38** (92mg, 60%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 6.99 (2H, d, J = 8.4 Hz), 6.71 (2H, d, J = 8.4 Hz), 5.94 (1H, t, J = 4.8Hz), 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 NH_4Cl. 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 **39** (46 mg, quantitative yield). 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.11 (2H, d, J = 8.7 Hz), 6.79 (2H, d, J = 8.7 Hz), 6.01 (1H, t, J = 4.8Hz), 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_4Cl. 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 ($CDCl_3$) δ 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 ($CDCl_3$) δ 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 ($CDCl_3$) δ 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_2CO_3 (970 mg, 7.02 mmol) and H_2O (2 mL). The reaction was boiled for 12 h at 85 °C. After cooling the reaction mixture, it was partioned with ethyl acetate and sat. Na_2CO_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 ($CDCl_3$) δ 7.32 (2H, d, J = 7.2 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 μL, 2.13 mmol) in THF (10 mL) was added *n*-BuLi (2.5 M solution in hexanes, 850 μL, 2.12 mmol) at –78 °C. After 15 min at 0 °C, the solution was taken back to -78 °C and hexamethylphosphoric triamide (435 μL, 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 μL, 4.79 mmol) was added to reaction mixture. After being gradually warmed up to rt, the mixture was quenched with H_2O. 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 ($CDCl_3$) δ 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_4Cl. 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 ($CDCl_3$) δ 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_4Cl. 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 ($CDCl_3$) δ 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 ($CDCl_3$) δ 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 ($CDCl_3$) δ 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_2O (1 mL/0.5 mL/0.3 mL) was added 7 mg (0.052 mmol) of NMO and 0.26 mL of OsO_4 (0.005mmol) solution (5mg/mL). The mixture was stirred at room temperature for 3 h and quenched with saturated NH_4Cl. 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 ($CDCl_3$) δ 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 CH_2Cl_2 was added 12.3 μL BF_3:Et_2O 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 NH_4Cl, 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 = 3:1) to afford **52** (19 mg, 45%) as a mixture of isomers. 300 MHz ^{1}H NMR ($CDCl_3$) 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 NH_4Cl. 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 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 $MgSO_4$, filtered, and evaporated in *vacuo*. The residue was purified by chromatography (H:EA = 4:1) to afford **58** (1.19g, 89 % yield). 300 MHz ^{1}H NMR ($CDCl_3$) 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 $MgSO_4$, filtered, and evaporated in *vacuo*. The residue was purified by chromatography (H:EA = 4:1) to afford **59** (580 mg, 81%). 300 MHz ^{1}H NMR ($CDCl_3$) 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 NH_4Cl and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, filtered, and evaporated in *vacuo*. The residue was purified by chromatography (H:EA = 3:1) to afford

60 (144 mg, 85 %). 400 MHz ^{1}H NMR ($CDCl_3$) δ 7.12 (2H, d, J = 8.4 Hz), 7.03 (2H, d, J = 8.4 Hz), 3.99 (2H, s), 3.77 (3H, s), 3.12-3.23 (2H, m), 2.11 (3H, s), 1.32 (9H, s), 1.30 (9H, s), 1.06 (3H, t, J = 7.2 Hz).

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 CH_2Cl_2. 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 $MgSO_4$, filtered, and evaporated in *vacuo*. The residue was purified by chromatography (H:EA = 2:1) to afford **62** (32.6 g, 92%). 400 MHz ^{1}H NMR ($CDCl_3$) δ 7.12 (1H, t, J = 8 Hz), 6.88 (1H, d, J = 8Hz), 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 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 temperature was gradually brought up to -40 °C. After stirring at this temperature for 2 h, the mixture was taken back to -78 °C. 10 mL DMF was added and the reaction mixture was gradually warmed to 0 °C. The mixture was quenched with saturated NH_4Cl 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 ($CDCl_3$) δ 10.45 (1H, s), 9.66 (1H,s), 7.93 (1H, s), 7.39 (1H, d, J = 8.4Hz), 6.70 (1H, d, J = 8.4Hz), 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_4Cl .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 ($CDCl_3$) δ 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 ($CDCl_3$) δ 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_2Cl_2 was added 11.3 mL of di-isopropylethylamine (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_2Cl_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 ($CDCl_3$) δ10.52 (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 ($CDCl_3$) δ 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 dimethylmalomate (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 ($CDCl_3$) δ 8.41 (1H, s), 7.75 (1H, d, J = 8.4Hz), 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_2CO_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_2Cl_2 = 1:1) to afford **67** (3.21 g, 85%). 300 MHz ^{1}H NMR ($CDCl_3$) δ 8.41 (1H, s), 7.71 (1H, d, J = 8.4Hz), 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 NH_4Cl and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, 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 ($CDCl_3$) 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, s), 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 ^{13}C NMR ($CDCl_3$) 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 NH_4Cl. 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 ($CDCl_3$) δ 6.99 (1H, d, J = 8.4 Hz), 6.66-6.72 (2H, m), 6.13 (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 (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 ($CDCl_3$) δ 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 = 8Hz), 5.41 (1H, d, J = 8 Hz), 5.25 (1H, d, J = 12Hz), 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 ($CDCl_3$) δ 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 NH_4Cl. 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 **71** as white solid (130 mg, 42% yield). 300 MHz ^1H NMR ($CDCl_3$) 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 ^{13}C NMR ($CDCl_3$) 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 $C_{17}H_{19}NO_5$ calcd 315.1471, found 315.1478.

Compound 72

To a solution of compound **69** (440 mg, 1.01 mmol) in 25 mL CH_2Cl_2/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 Me_2S 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 CH_2Cl_2 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 **72** (400 mg, 92% yield). 400 MHz ^1H NMR ($CDCl_3$) 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% $NaHCO_3$ 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 ^{1}H NMR ($CDCl_3$) 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 NH_4Cl. 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_2Cl_2 = 1:2) to afford **74** (265 mg, 72% yield). 400 MHz ^{1}H NMR ($CDCl_3$) 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 ($CDCl_3$) δ 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** (265mg, 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 ^1H NMR ($CDCl_3$) δ 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 ($CDCl_3$) δ 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_4Cl 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_2Cl_2 = 1:1) to yield **76** (18 mg, 45%) as 3:1 mixture of isomers.

Major isomer: 400 MHz ^1H NMR ($CDCl_3$) δ 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 ($CDCl_3$) δ 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 ^{1}H NMR ($CDCl_3$) δ 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 ($CDCl_3$) δ 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** (111mg, 59%). 400 MHz ^{1}H NMR ($CDCl_3$) δ 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 NH_4Cl 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 $MgSO_4$ and evaporated under *vacuo* to yield **78** as 3:1 mixture of isomers.

Major isomer: 400 MHz ^{1}H NMR ($CDCl_3$) δ4.69 (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 ^{1}H NMR ($CDCl_3$) 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 CH_2N_2 (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 $MgSO_4$, filtered, and evaporated in *vacuo*. The residue was purified by chromatography (EA:CH_2Cl_2 = 1:2) to afford **79** (58 mg, 49% for two steps) as 3:1 mixture of isomers.

Major isomer: 400 MHz ^{1}H NMR ($CDCl_3$) δ4.35 (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 ($CDCl_3$) δ4.29 (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_2Cl_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 ($CDCl_3$) δ 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 = 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); 75 MHz ^{13}C NMR ($CDCl_3$) δ 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 $C_{17}H_{22}O_4N$ calcd 321.15762, found 321.15810.

Compound 81

400 MHz ^{1}H NMR ($CDCl_3$) δ9.59 (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_2Cl_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 to yield **82** (15 mg, 85%). 400 MHz ^{1}H NMR ($CDCl_3$) δ 7.11 (2H, d, J = 8.4Hz), 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_2O. 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_3CN 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_2Cl_2 = 1:2) to afford to yield **84** (10 mg, 65 %). 400

MHz ^{1}H NMR ($CDCl_3$) δ 7.11 (2H, d, J = 8.4Hz), 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 NH_4Cl. 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 **85** (310 mg, 79%). 300 MHz ^{1}H NMR ($CDCl_3$) 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% $NaHCO_3$ solution and brine. The organic layer

was dried over $MgSO_4$, filtered, and evaporated in *vacuo*. The residue was purified by chromatography (H:EA = 1:1) to afford **70** (270 mg, quantitative yield). 300 MHz ^{1}H NMR ($CDCl_3$) δ 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, 0.68mmol) 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_4Cl. 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 **87** as white solid (180 mg, 79% yield). 300 MHz ^{1}H NMR ($CDCl_3$) δ 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).

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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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