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Synthesis of heteroaromatic natural products

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Synthesis of heteroaromatic natural products

by

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TABLE OF CONTENTS

GENERAL INTRODUCTION

The synthesis of biologically active natural products has been used for the discovery of new drugs. Organic synthesis is designed for a target molecule like a novel compound by selecting optimal reactions from optimal starting materials. Each reaction and each step of a synthesis should give a good yield for the product with little work.

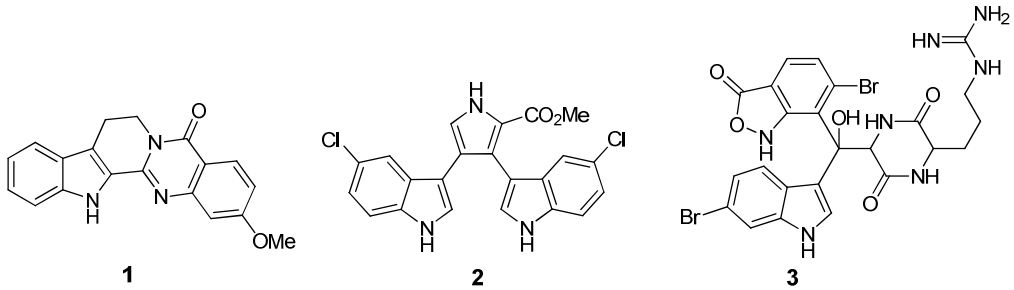
In this thesis, we explored both total synthesis and methodology of several natural products and analogs, especially heteroaromatic natural compounds. Chapter 1 describes an efficient synthesis of 2-substituted and 2,3-disubstituted indoles via a two-step approach in one pot involving a six-electron ring closure. Chapter 2 describes the direct synthesis of neocryptolepine in four steps in two pots. Chapter 3 is about synthesis studies towards the unique κ opioid receptor agonist salvinorin A. Chapter 4 describes a direct approach to the synthesis of methyllycaconitine, one of the diterpenoid alkaloids.

CHAPTER 1. A FLEXIBLE SYNTHESIS OF 2-SUBSTITUTED AND 2,3-DISUBSTITUTED INDOLES FROM AMINOBENZYL PHOSPHONIUM SALTS

Introduction

Although a number of versatile indole syntheses have been reported, the development of new methods for the synthesis of indoles remains an active area of research.[1] This is in part due to the continual emergence of novel biologically active indole-containing natural products, such as the recently discovered indoles **1**-**3** and also due to the development of useful synthetic pharmaceuticals bearing the indole subunit (Figure 1).[2] Compound **1** exhibits potent immunomodulatory and cytotoxic activity.[3] Indole **2** was active against methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium*.[4] Compound **3** shows settlement inhibition of barnacle larvae (*Balanus impro*V*isus*) with an EC_{50} value of 15 nM.[5]

Figure 1

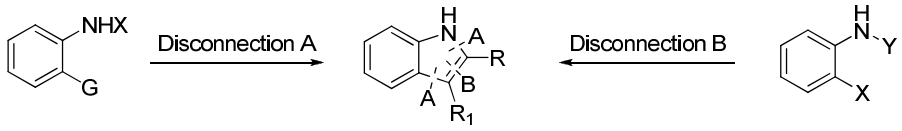


Many widely used indole syntheses have the retrosynthetic analysis represented by disconnection A (Scheme 1). These reactions include the Fischer indole synthesis,[6] the Japp-

Klingemann route,[7] the Gassman indole synthesis,[8] the Sugasawa indole synthesis, and the Bischler indole[9] synthesis. When G is a bromide or iodide, this is the starting material for several organopalladium-mediated synthetic routes to indoles.[10]

In contrast, relatively few indole syntheses are represented by disconnection B. Several groups have reported a reductive cyclization of *ortho*-ketoamides.[11, 12] The Madelung reaction involves cyclization of the dianion of an anilide at elevated temperature.[13] Various cyclizations using intramolecular Claisen condensations and Wittig reactions have been reported.[14] Two groups have employed radical-mediated conjugate additions.[15, 16]

Scheme 1



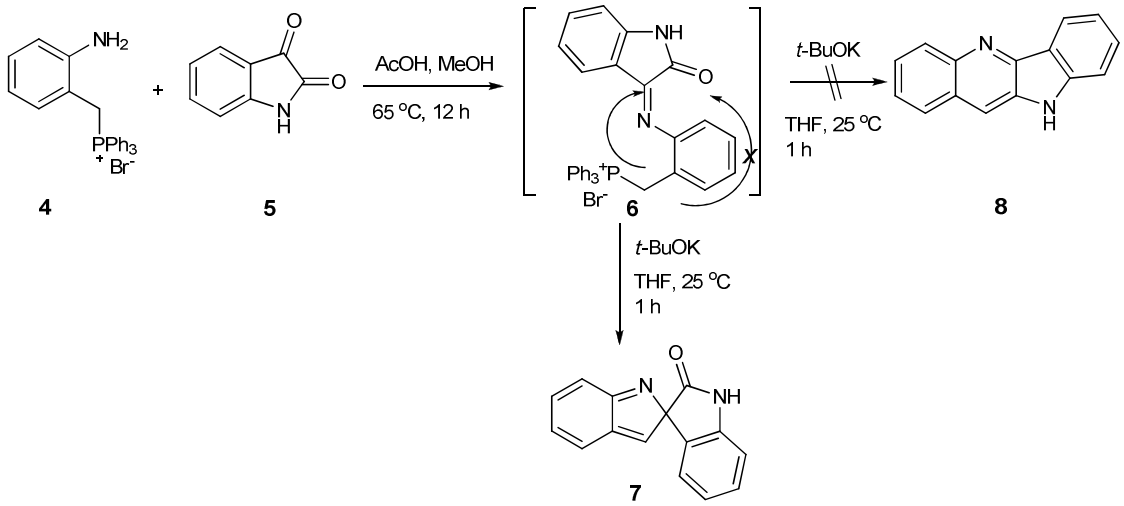
Despite the fact that these reactions are synthetically useful, they suffer from several disadvantages: (i) high temperatures and long times (above 125 °C and 12 h), (ii) expensive transition-metal catalysts, (iii) multistep and moderate yields, as well as high sensitivity to moisture. We report herein a new approach that can successfully afford 2-substituted and 2,3-disubstituted indoles in high yields in one pot under very mild conditions.

Results and Discussion

In an approach to the indoloquinoline alkaloids, we condensed commercially available phosphonium salt **4** with isatin **5** to form imine **6** under the conditions shown in

Scheme 2. Treatment of imine **6** with potassium *tert*-butoxide in either THF or toluene provided adduct **7** in around 21% yield.

Scheme 2

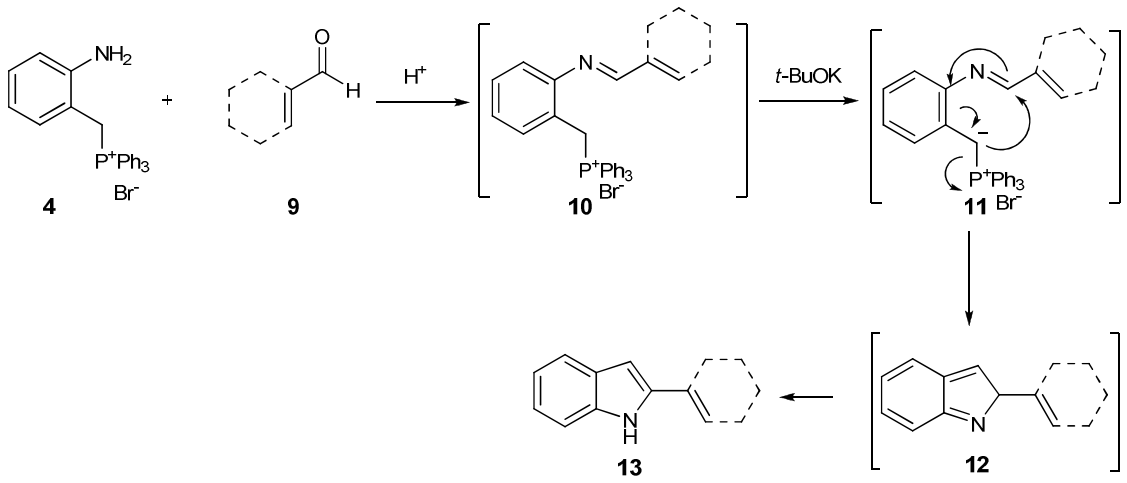


Although we had expected the product to be compound **8**, an intermediate in the synthesis of cryptolepine,[17] our proton and carbon NMR spectra did not match the published spectra.[18] After considering its mass spectrum (which showed the mass of **8** plus an oxygen atom) and the ^{13}C NMR spectrum (which showed a resonance at 99 ppm as the most downfield resonance), we tentatively assigned the product structure **7**. Compound **7** had been reported[19] and its major mass spectral fragmentation patterns were identical to those of our adduct.

We reasoned that if a spiro compound, such as **7,** had formed, such an intermediate might be employed in a general synthesis of 2-substituted indoles. Since these compounds are intermediates for the synthesis of indole natural products, a one-pot synthesis from

commercially available starting materials would be useful. The strategy for the formation of the 2-substituted indoles **13** from **4** via **10** and **11** is illustrated in Scheme 3.

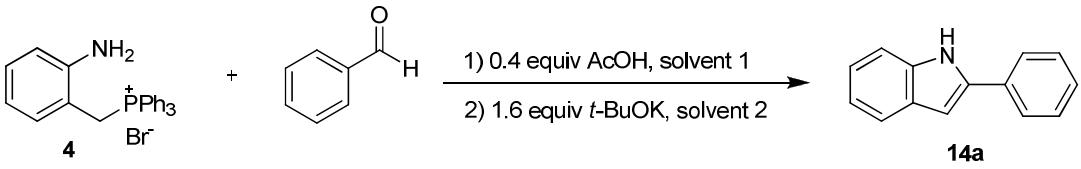
Scheme 3



Initial studies were aimed at finding the optimal reaction conditions for the acid-catalyzed imine formation from the aniline and aromatic aldehydes. Our investigation began with the reaction of phosphonium salt **4** and benzaldehyde (Table 1). The reaction was first attempted using 1 equivalent of phosphonium salt **4**, 1 equivalent of benzaldehyde and acetic acid (0.4 equivalent) as the catalyst in boiling solvents. The best conditions are shown in entry 5, which involves boiling methanol for 12 h. This provided almost a quantitative yield of the desired imine according to ^{1}H NMR spectroscopy. The imine was not isolated, but was immediately dissolved in THF and treated with 1.6 equivalents of potassium *tert*-butoxide. The second step in the process involves a six-electron electrocyclic ring closure. This step is facile even at -78 ^{o}C and efficiently generated the desired 2-phenyl indole (**14a**) in 96%

isolated yield after one hour at ambient temperature. The solvent has to be THF, because methanol reacts with the imine intermediate.

Table 1. Reaction conditions for 2-substituted indole formation



entry	solvent 1	temp. 1 (°C)	time 1 (h)	solvent 2	temp. 2 (°C)	time 2 (h)	yield (%)
1	toluene	110	12	toluene	25	5	25
2	THF	65	12	THF	25	5	23
3	methanol	65	12	methanol	25	5	complex
4	methanol	65	12	THF	-78→25	8	95
5	methanol	65	12	THF	25	1	96[a]
6	methanol	65	10 min	THF	25	1	73
7	methanol	80	10 min	THF	25	1	95[b]

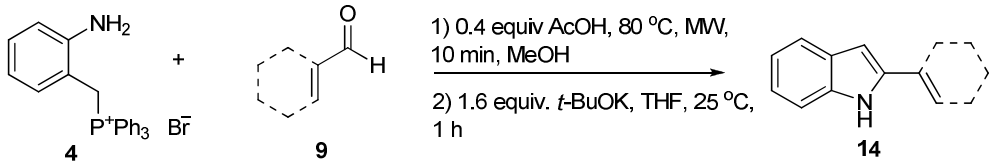
[a] Reaction conditions: 2-aminobenzyl phosphonium salt (0.5 mmol), benzaldehyde (0.5 mmol), AcOH (0.4 mmol), *t*-BuOK (1.4 mmol), solvent (3 mL). [b] Microwave assisted

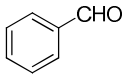
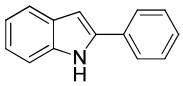
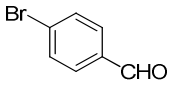
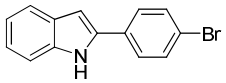
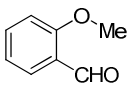
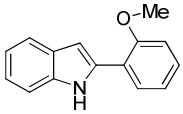
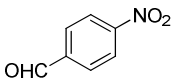
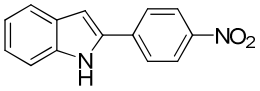
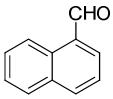
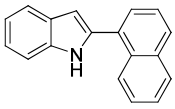
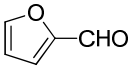
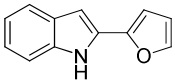
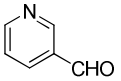
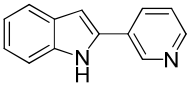
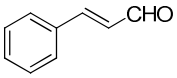
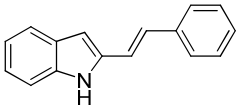
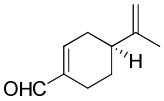
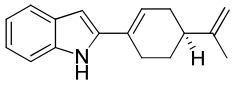
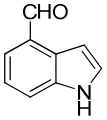
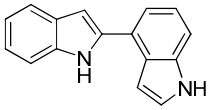
Microwave-assisted organic synthesis is an efficient method for the synthesis of heterocyclic compounds.[20,21] As opposed to conventional heating, the application of microwave energy has the major advantage of shorter reaction times, because of the rapid core heating associated with microwaves. Therefore, microwave reactions frequently exhibit cleaner product profiles and use minimal quantities of solvent. Many reviews have been published that give more detail about this new application.[22] This prompted us to synthesize imines under microwave conditions. The conditions we applied in a CEM microwave oven

were similar to the conventional procedure. The phosphonium salt **4** and benzaldehyde with a catalytic amount of acetic acid were dissolved in methanol and heated in a sealable tube to 80 ^{o}C, compared to 65 ^{o}C under the conventional conditions (entry 7, Table 1). As expected, the reaction time was reduced dramatically. The imine formation that took 12 hours by conventional heating was speeded up to 10 minutes. After the base-mediated step, we obtained the 2-phenylindole (**14a**) in 95 % yield. The mild reaction conditions, as well as the high yield of this reaction, encouraged us to extend this methodology to a range of aldehydes.

In view of this promising result, several aromatic and α, β-unsaturated aldehydes were reacted with **4**. The results of these experiments are collected in Table 2. As the results in Table 2 indicate, a wide range of functionalized aldehydes react effectively with phosphonium salt **4**, including a variety of electron-donating and electron-withdrawing substituents, such as aromatic ethers, halides, nitro and aryl groups (entries 2-5), and also heterocyclic aldehydes (entries 6 and 7). In addition, reactions with *α,β*-unsaturated aldehydes (entries 8 and 9) also proceeded very smoothly and gave high yields under these conditions.

Table 2. Reaction of **1** with aldehydes to generate 2-aryl and 2-vinylic indoles[a]



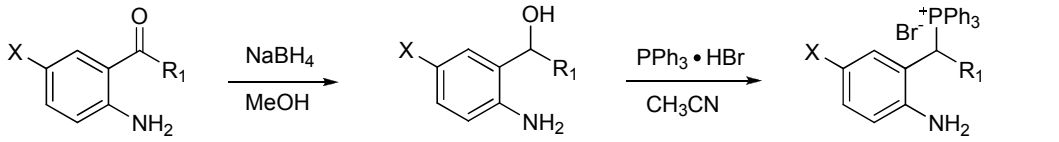
entry	aldehydes **9**	product		yield[b] (%)	melting point (°C) (Lit. mp)
1			**14a**	95	188-190 (188-189)[10l]
2			**14b**	95	211-213 (208-212)[10l]
3			**14c**	81	82.5-83 (83)[23a]
4			**14d**	86	248-250 (249-251)[23b]
5			**14e**	93	97-99 (99-102)[10l]
6			**14f**	86	120-123
7			**14g**	85	175-176 (170-175)[23c]
8			**14h**	97	202-204 (197-199)[23d]
9			**14i**	83	164-165
10			**14j**	87	202-203 (199-202)[24b]

[a] Reaction conditions: (i) phosphonium salt **4** (1 mmol), aldehyde (1 mmol), AcOH (0.4 eq.), methanol (2 mL), (ii) *t*-BuOK (1.6 eq.), THF (2 mL).[b] Isolated yield.

With all these successful results for 2-substituted indoles, we wished to expand this electrophilic cyclization strategy as a practical and convenient synthetic method for the synthesis of 2,3-disubstituted indoles.

Initially, we synthesized a set of phosphonium salts **15a-c** bearing substituents on the benzylic carbon (Scheme 4). Successful reactions of these phosphonium salts would provide a useful synthesis of 2,3-disubstituted indoles. Phosphonium salts **15a, 15b** and **15c** were readily prepared by reduction of the commercially available aromatic ketones, followed by treatment of the resulting amino alcohols with 1 equivalent of triphenylphosphine hydrobromide. The functional group R_1 will be at the indole 3-position after the ring closure. Compound **15a** will be the precursor for 2,3-disubstituted indoles with an aryl group in the 3-position and **15b** will be the precursor for alkyl substitution in the 3- position. Compound **15c** will also probe the compatibility of halogen substitution.

Scheme 4

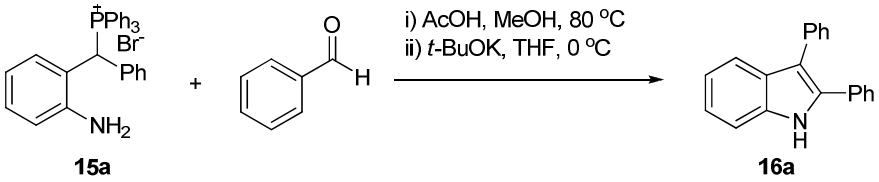


15a: R_1 = Ph, X = H (95%)
15b: R_1 = Me, X = H (92%)
15c: R_1 = Ph, X = Cl (95%)

Initial studies were aimed at finding the optimal reaction conditions for acid-catalyzed imine formation of the anilines **15** from aromatic aldehydes. Our investigation began with the reaction of phosphonium salt **15a** and benzaldehyde (Scheme 5). The conditions we applied were similar to the 2-substituted indole procedure. The phosphonium

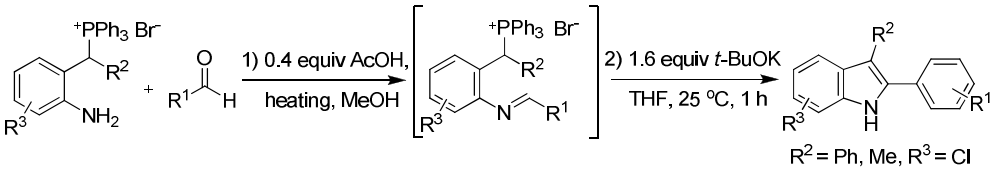
salt **15a** and benzaldehyde with a catalytic amount of acetic acid were dissolved in methanol and heated in a sealable tube to 80 °C for 10 minutes. After the base mediated step, we obtained the 2,3-diphenylindole in 92 % yield. The mild reaction conditions, as well as the high yield of this reaction, encouraged us to extend this methodology to a range of aldehydes.

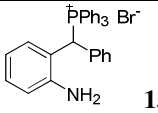
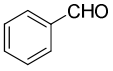
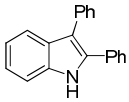
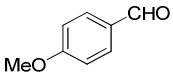
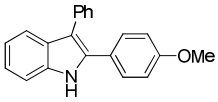
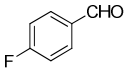
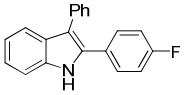
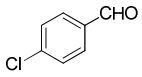
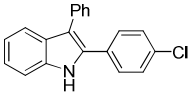
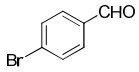
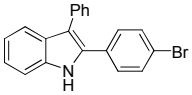
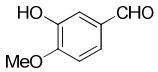
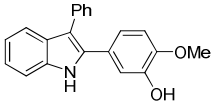
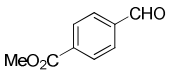
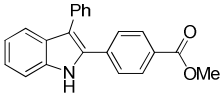
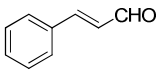
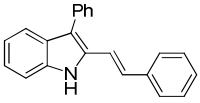
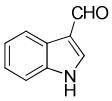
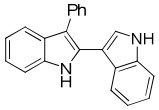
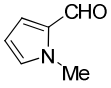
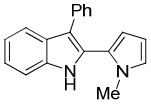
Scheme 5



Next, the scope and limitations of this reaction were examined. Table 3 summarizes the results from the reactions of phosphonium salts **15a**-**15c** with an array of aldehydes under the optimized reaction conditions. We tried a few examples using both conventional thermal and microwave conditions (entries 1, 11 and 18). These results show that the reaction proceeds very efficiently under both thermal and microwave conditions, but the latter conditions are more efficient. The cyclization proceeds smoothly when the substituents in the α-position of the phosphonium salt are aryl or alkyl. However, the indole formed by the cyclization of phosphonium salt **15a** with methyl 4-formylbenzoate (entry 7) gave a slightly lower yield (45%). The reason is that this compound is unstable during column chromatography. The only way that we could purify the compound was to use a very short column to remove most of the triphenylphosphine and then recrystalize the crude material to get pure indole **16h**.

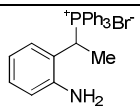
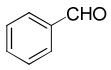
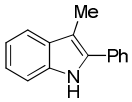
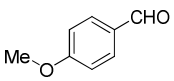
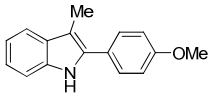
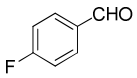
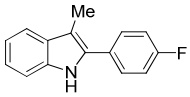
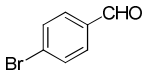
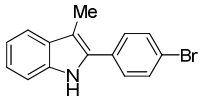
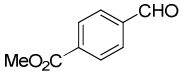
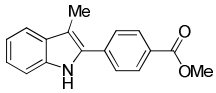
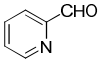
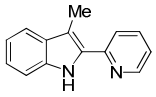
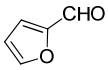
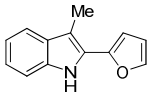
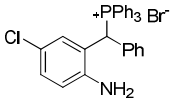
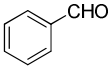
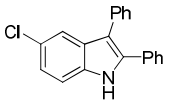
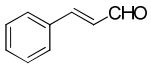
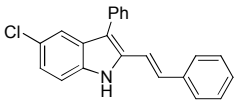
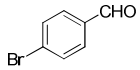
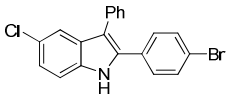
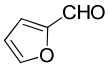
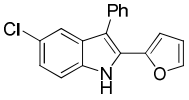
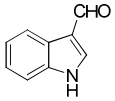
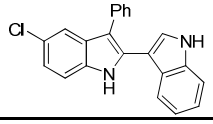
Table 3. Reaction of **5a-c** with aldehydes to generate 2,3-disubstituted indoles[a]



entry	phosphonium salt	aldehyde	product		isolated yield (%)[b]
1	 **15a**			**16a**	93 (92)[c]
2				**16b**	100
3				**16c**	84
4				**16d**	90
5				**16e**	86
6				**16f**	100
7				**16g**	45
8				**16h**	88
9				**16i**	96
10				**16j**	56

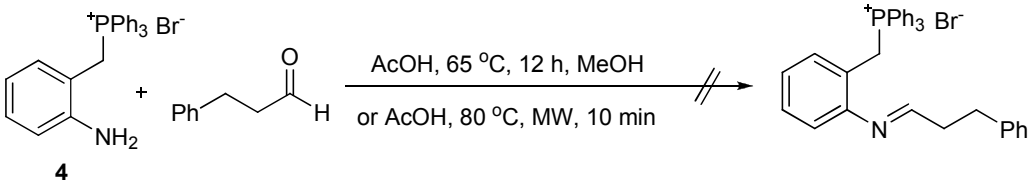
[a] Reaction conditions: (i) phosphonium salt 4 (1 mmol), aldehyde (1 mmol), AcOH (0.4 mmol), methanol (2 mL), (ii) *t*-BuOK (1.6 mmol), THF (2 mL). [b] Isolated yield.
[c] Conventional thermal yield.

Table 3. (continued)

entry	phosphonium salt	aldehyde	product		isolated yield (%)[b]
11	 **15b**			**16k**	97 (95)[c]
12				**16l**	85
13				**16m**	84
14				**16n**	79
15				**16o**	72
16				**16p**	88
17				**16q**	78
18	 **15c**			**16r**	100 (96)[c]
19				**16s**	92
20				**16t**	96
21				**16u**	100
22				**16v**	93

A wide range of aldehydes react effectively with phosphonium salts **15a-c**, including those bearing a variety of electron-donating and electron-withdrawing substituents, such as aromatic ethers, halides, an ester and hydroxy and aryl groups (entries 2-7, 12-15, and 19-20). The yields range from 72-100% for most of the cases. A series of heterocyclic aldehydes has been examined using this method and shown undergo to smooth cyclization at room temperature to afford the corresponding 2,3-disubstituted indoles in excellent yield (entries 9, 10, 16, 17, 21 and 22). In addition, we have also expanded this methodology to *α,β*-unsaturated aldehydes (entries 8, 19) which also gave high yields. Unfortunately, alkyl aldehydes, such as hydrocinnamaldehyde and heptanal, did not form the imine intermediates with phosphonium salt **4** under either conventional thermal or microwave conditions (Scheme 6). This may be because the alkyl aldehydes are not as stable as the aryl or *α,β*-unsaturated aldehydes under the acid conditions and undergo an aldol reaction. Further studies are ongoing.

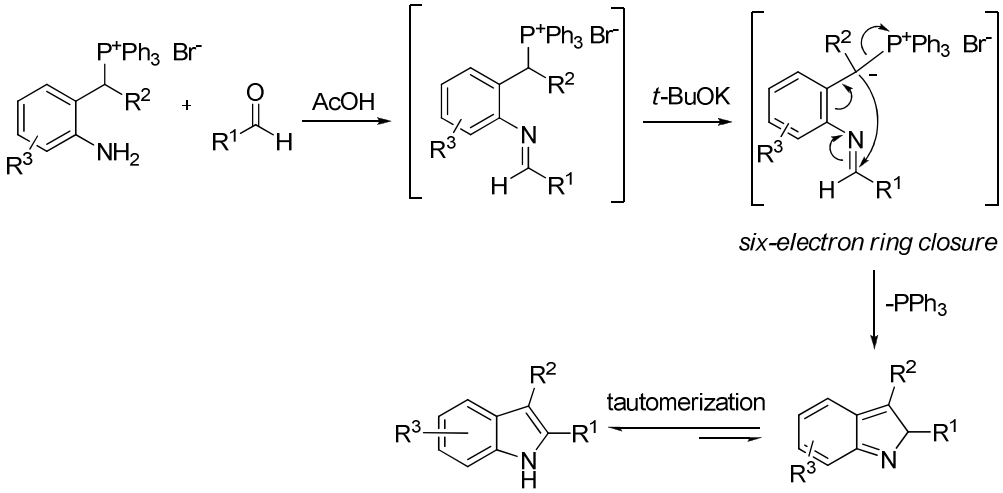
Scheme 6



We believe that these cyclizations proceed by imine formation, followed by six-electron ring closure, to form the desired 2,3-disubstituted indoles as shown in Scheme 7. The success of this reaction may be due to several factors: 1) the imine intermediates are

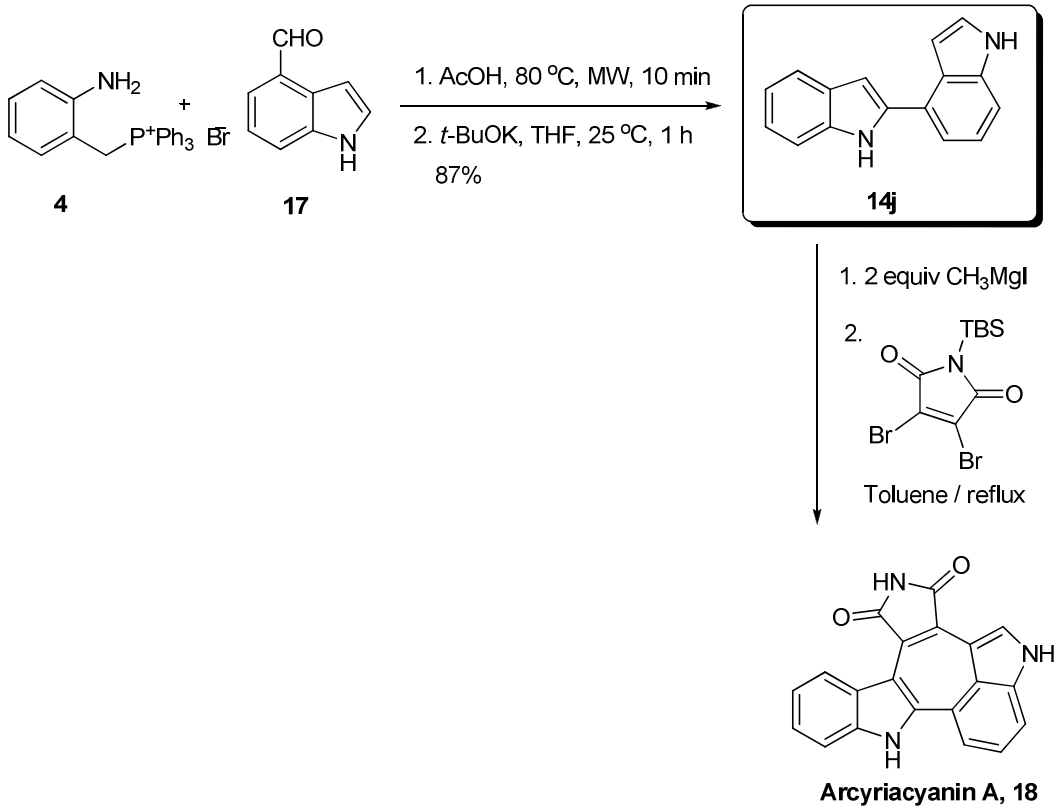
conjugated with the aromatic system which makes them very good acceptors; 2) the triphenylphosphine group is a bulky leaving group and readily eliminates.

Scheme 7



Arcyriacyanin A (**18**), a pigment of the slime mold of *Arcyria obvelata Onsberg*, is an effective inhibitor of protein kinase C and protein tyrosine kinase.[24] Since compound **14j** has been transformed into **18** using 3,4-dibromomaleimide as shown in Scheme 8,[25] the synthesis of compound **14j** constitutes a formal *two-step* total synthesis of **18** from commercially available starting materials, a Wittig salt **4** and indole-3-carboxaldehyde **17**.

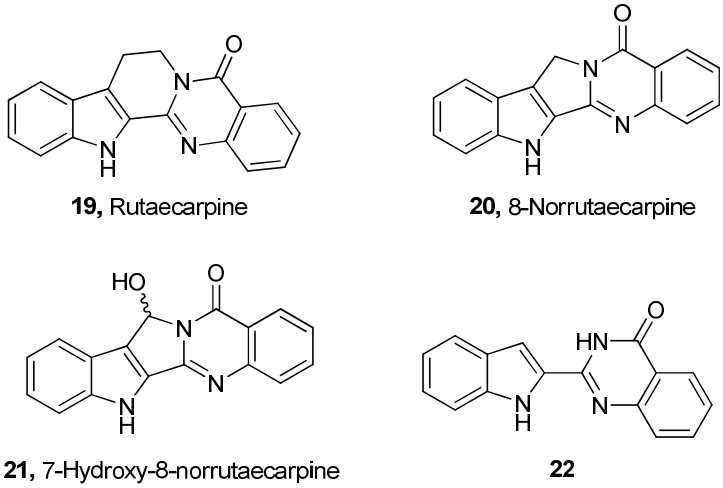
Scheme 8



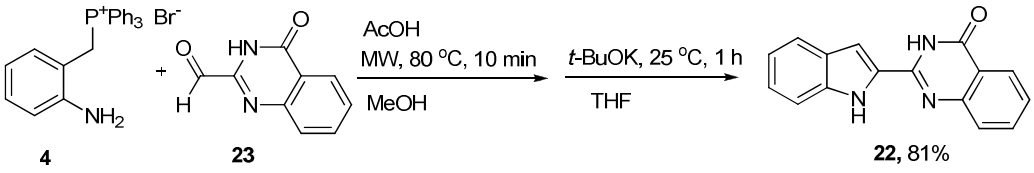
Rutaecarpine (**19**) is an indolopyridoquinazolinone alkaloid isolated from *Evodia rutaecarpa*, which has shown anti-thrombotic, anti-cancer, anti-inflammatory, analgesic, and anti-obesity activity (Figure 2). It has been synthesized by several groups.[26] Recently, biologically active "hybrid" analogs, nor-rutaecarpines **20** and **21** have been isolated and synthesized.[27] The studies show that these compounds exhibit activity against a range of ailments including rheumatism, influenza, leukemia and hepatitis.[28] The indole **22** is an advanced intermediate for these rutaecarpine analogs. Lee and co-workers have reported a synthesis of compound **22** in 4 steps in 31% overall yield.[29] Recently, Mate and co-workers reported another synthesis of intermediate **22** by a Fisher indole synthesis. It required four

steps and afforded a 48% overall yield.[27] Our route begins with known aldehyde **23**, which can be synthesized in one step from commercially available 3-methyl quinoxazoline.[30] The indole **22** can be generated from aldehyde **23** and commercially available phosphonium salt **4** in 81% yield (Scheme 9).

Figure 2



Scheme 9



Conclusions

In conclusion, we have developed a very efficient synthesis of 2-substituted and 2,3-disubstituted indoles by a two-step approach in one pot involving imine formation and six-electron ring closure, followed by a 1,5-hydrogen shift. These reactions proceed under very

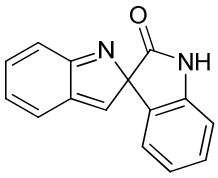
mild conditions and remarkably short reaction times. A wide range of aryl or α,β-unsaturated aldehydes undergo this process in excellent yield. The adduct from indole-4-carboxaldehyde is an advanced intermediate in the synthesis of arcyriacyanin A, which can be synthesized in two steps in 35% overall yield. The adduct from 4-oxo-3,4-dihydroquinazoline-2-carboxaldehyde is an advanced intermediate in the synthesis of several rutaecarpine analogs.

Experimental Section

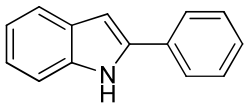
All ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz respectively. All melting points are uncorrected. Unless otherwise indicated, all reactions were carried out under argon. Microwave reactions were conducted in a capped vial using a CEM Discover System. Thin layer chromatography was performed using commercially prepared 60-mesh silica gel plates (Whatman K6F), and visualization was effected by short wavelength UV light (254 nm). High resolution mass spectra were recorded on a Kratos MS50TC double focusing magnetic sector mass spectrometer using EI at 70 eV. All reagents were used directly as obtained commercially unless otherwise noted. All yields reported represent an average of at least two independent runs.

General procedure for the synthesis of 2,3-disubstituted indoles from substituted 2-aminobenzyl phosphonium salts. In a 10 mL microwave reaction vessel (CEM Discover System) equipped with a magnetic stir bar, phosphonium salt **5a** (262 mg, 0.5 mmol), the aldehyde (0.5 mmol) and glacial acetic acid (11.4 μL, 0.2 mmol) were added to 3 mL of distilled methanol. The vial was capped properly and placed in the microwave. Microwave irradiator was carried out at 300 W, 80 ºC for 10 min. After cooling the vial to room

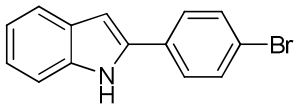
temperature, methanol was removed in vacuum. Four mL of THF were added to the mixture and 0.8 mL of a 1 M *t*-BuOK solution in THF was added dropwise. The resulting mixture was stirred at 25 ºC under the argon for 1 h. The saturated NH_4Cl solution (10 mL) was added to quench the reaction. The aqueous layer was extracted with ethyl acetate (3 x 10 mL). The organic layers were combined and washed with brine (2 x 10 mL). The organic layer was separated, dried with $MgSO_4$ and filtered. The filtrate was concentrated under vacuum and the residue was purified by silica gel column chromatography using a mixture of ethyl acetate and hexanes as the eluent.



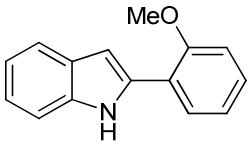
Spiro[indole-2,3'-indolin]-2'-one (7): The product was purified by chromatography on silica gel (R_f = 0.25 in 75% hexanes/25% EtOAc). The product (**7**) was obtained as a white solid (101.0 mg, 86% yield); mp ≥ 250 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) 11.37 (br s, 1H), 8.54-8.56 (m, 1H), 8.09-8.11 (dd, J = 8.0, 1.2 Hz, 1H), 7.73-7.76 (m, 1H), 7.41-7.45 (td, J = 8.4, 1.2 Hz, 1H), 7.34-7.37 (m, 3H), 7.22-7.27 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) 147.2, 134.3, 134.1, 133.4, 129.7, 129.5, 123.7, 123.5, 123.1, 120.3, 115.5, 115.4, 113.6, 98.3; HRMS electrospray (m/z) calcd for $C_{15}H_{10}N_2O$, 234.0793; found, 234.0796.



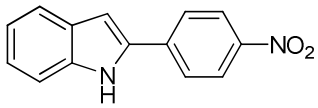
2-Phenyl-indole (14a): The product was purified by chromatography on silica gel (R_f = 0.3 in 83% hexanes/17% EtOAc). The product (**14a**) was obtained as a white solid (91.7 mg, 95% yield); mp = 188-190 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) 11.55 (s, 1H), 7.86-7.88 (d, J = 8.0 Hz, 2H), 7.53-7.55 (d, J = 8.0 Hz, 1H), 7.41-7.48 (q, J = 8.0 Hz, 3H), 7.29-7.33 (t, J = 7.2 Hz, 1H), 7.09-7.13 (t, J = 7.2 Hz, 1H), 6.99-7.03 (t, J = 7.6 Hz, 1H), 6.90 (d, J = 1.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) 137.6, 137.1, 132.2, 128.9, 128.6, 127.4, 125.0, 121.6, 120.1, 119.4, 111.3, 98.7; HRMS electrospray (m/z) calcd for $C_{14}H_{11}N$, 193.0892; found, 193.0895.



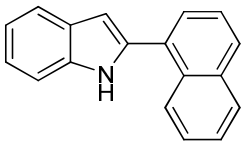
2-(4-Bromophenyl)-indole (14b): The product was purified by chromatography on silica gel (R_f = 0.45 in 80% hexanes/20% EtOAc). The product (**14b**) was obtained as a white solid (129.0 mg, 95% yield); mp = 211-213 ºC; ^{1}H NMR (400 MHz, Acetone-d_6) 10.73 (br s, 1H), 7.79-7.81 (d, J = 8.4 Hz, 2H), 7.57-7.62 (m, 3H), 7.41-7.43 (d, J = 8.4 Hz, 1H), 7.11-7.15 (t, J = 7.2 Hz, 1H), 7.02-7.06 (t, J = 7.6 Hz, 1H), 6.93 (s, 1H); ^{13}C NMR (100 MHz, Acetone-d_6) 139.0, 138.0, 133.3, 130.6, 128.2, 123.5, 121.9, 121.7, 121.1, 112.6, 101.1; HRMS electrospray (m/z) calcd for $C_{14}H_{10}BrN$, 270.9997; found, 271.0001.



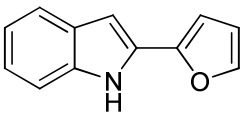
2-(2-Methoxyphenyl)-indole (14c): The product was purified by chromatography on silica gel (R_f = 0.40 in 80% hexanes/20% EtOAc). The product (**14c**) was obtained as a white solid (90.5 mg, 81% yield); mp = 83 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) 9.69 (br s, 1H), 7.86-7.88 (d, *J* = 7.6 Hz, 1H), 7.65-7.67 (d, *J* = 7.6 Hz, 1H), 7.43-7.45 (d, *J* = 8 Hz, 1H), 7.29-7.33 (t, *J* = 7.2 Hz, 1H), 7.19-7.22 (t, *J* = 7.2 Hz, 1H), 7.11-7.15 (t, *J* = 7.2 Hz, 1H), 7.04-7.09 (t, *J* = 8 Hz, 2H), 6.93 (s, 1H), 4.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 136.3, 136.2, 128.8, 128.5, 128.3, 122.0, 121.8, 120.8, 120.5, 120.0, 112.1, 111.1, 100.0; HRMS electrospray (m/z) calcd for $C_{15}H_{13}NO$, 223.0997; found, 223.1000.



2-(4-Nitrophenyl)-indole (14d): The product was purified by chromatography on silica gel (R_f = 0.35 in 83% hexanes/16% EtOAc). The product (**14d**) was obtained as a yellow solid (102.4 mg, 86% yield); mp = 248-250 ºC; ^{1}H NMR (400 MHz, Acetone-d_6) 10.97 (br s, 1H), 8.31-8.33 (d, *J* = 8.8 Hz, 2H), 8.11-8.13 (d, *J* = 8.8 Hz, 2H), 7.63-7.65 (d, *J* = 8 Hz, 1H), 7.45-7.47 (d, *J* = 8 Hz, 1H), 7.16-7.21 (m, 2H), 7.06-7.10 (t, *J* = 8 Hz, 1H); ^{13}C NMR (100 MHz, Acetone-d_6) 147.4, 139.8, 139.3, 136.4, 130.0, 126.3, 125.2, 124.2, 121.9, 121.2, 112.5, 103.6; HRMS electrospray (m/z) calcd for $C_{14}H_{10}N_2O_2$, 238.0742; found, 238.0747.

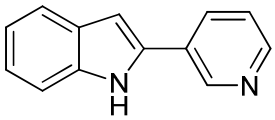


2-(Naphthalen-1-yl)-indole (14e): The product was purified by chromatography on silica gel (R_f = 0.45 in 83% hexanes/17% EtOAc). The product (**14e**) was obtained as a white solid (113.1 mg, 93% yield); mp = 97-99 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) 8.11-8.36 (m, 2H), 7.91-7.94 (m, 2H), 7.73-7.75 (d, *J* = 7.6 Hz, 1H), 7.65-7.67 (dd, *J* = 6.8, 0.8 Hz, 1H), 7.53-7.58 (m, 3H), 7.46-7.48 (d, *J* = 8.0 Hz, 1H), 7.19-7.29 (m, 2H), 6.82-6.83 (d, *J* = 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 136.9, 136.6, 134.1, 131.7, 131.3, 129.0, 128.8, 128.7, 127.4, 126.9, 126.4, 125.9, 125.6, 122.4, 120.8, 120.4, 111.1, 103.9; HRMS electrospray (m/z) calcd for $C_{18}H_{13}N$, 243.1048; found, 243.1051.

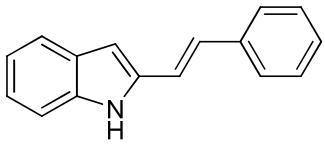


2-(Furan-2-yl)-indole (14f): The product was purified by chromatography on silica gel (R_f = 0.3 in 83% hexanes/17% EtOAc). The product (**14f**) was obtained as a white solid (79.0 mg, 86% yield); mp = 120-123 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) 8.44 (br s, 1H), 7.63-7.65 (d, *J* = 7.6 Hz, 1H), 7.48-7.49 (d, *J* = 1.6 Hz, 1H), 7.38-7.40 (d, *J* = 8.0 Hz, 1H), 7.20-7.24 (td, *J* = 8.0, 1.2 Hz, 1H), 7.13-7.17 (t, *J* = 8.0 Hz, 1H), 6.77-6.78 (d, *J* = 1.6 Hz, 1H), 6.64-6.65 (d, *J* = 3.2 Hz, 1H), 6.52-6.54 (multiple peaks, 1H); ^{13}C NMR (100 MHz, $CDCl_3$)

147.9, 141.9, 136.3, 129.4, 129.0, 122.7, 120.9, 120.6, 112.0, 111.1, 105.6, 99.0; HRMS electrospray (m/z) calcd for $C_{12}H_9NO$, 183.0684; found, 183.0686.

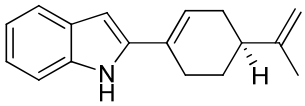


2-(Pyridin-3-yl)-indole (14g): The product was purified by chromatography on silica gel (R_f = 0.20 in 60% hexanes/40% EtOAc). The product (**14g**) was obtained as a white solid (83.0 mg, 85% yield); mp = 175-176 ºC; ^{1}H NMR (400 MHz, Acetone-d_6) 10.90 (br s, 1H), 9.12-9.13 (m, 1H), 8.51-8.53 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.18-8.21 (td, *J* = 8.0, 2.0 Hz, 1H), 7.60-7.62 (d, *J* = 8.0 Hz, 1H), 7.42-7.45 (m, 2H), 7.13-7.17 (td, *J* = 8.0, 0.8 Hz, 1H), 7.04-7.08 (td, *J* = 8.0, 0.8 Hz, 1H), 7.02-7.03 (d, *J* = 1.6 Hz, 1H); ^{13}C NMR (100 MHz, Acetone-d_6) 149.2, 147.4, 138.7, 135.8, 132.8, 130.1, 129.5, 124.7, 123.3, 121.4, 120.8, 112.2, 101.2; HRMS electrospray (m/z) calcd for $C_{13}H_{10}N_2$, 194.0844; found, 194.0846.

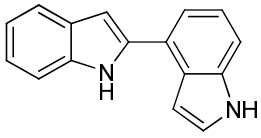


(*E*)-2-Styryl-indole (14h): The product was purified by chromatography on silica gel (R_f = 0.40 in 83% hexanes/17% EtOAc). The product (**14h**) was obtained as a white solid (106.2 mg, 97% yield); mp = 202-204 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) 8.24 (br s, 1H), 7.59-7.61 (d, *J* = 7.6 Hz, 1H), 7.51-7.53 (d, *J* = 7.6 Hz, 2H), 7.35-7.41 (t, *J* = 7.2, 5.2 Hz, 3H),

7.29-7.31 (d, *J* = 7.2 Hz, 1H), 7.19-7.23 (t, *J* = 7.2 Hz, 1H), 7.10-7.16 (m, 2H), 6.90-6.94 (d, *J* = 16.4 Hz, 1H), 6.64 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 137.1, 137.0, 136.5, 129.2, 129.0, 128.0, 127.3, 126.5, 123.1, 120.9, 120.4, 119.2, 110.8, 104.1; HRMS electrospray (m/z) calcd for $C_{16}H_{13}N$, 219.1048; found, 219.1052.

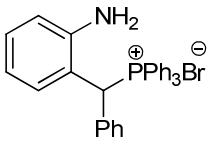


(*S*)-2-(4-(Prop-1-en-2-yl) cyclohex-1-enyl)-indole (14i): The product was purified by chromatography on silica gel (R_f = 0.45 in 90% hexanes/10% EtOAc). The product (**14i**) was obtained as a white solid (98.4 mg, 83% yield); mp = 164-165 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) 8.10 (br s, 1H), 7.57-7.59 (d, *J* = 7.6 Hz, 1H), 7.32-7.34 (d, *J* = 8.4 Hz, 1H), 7.15-7.19 (t, *J* = 8.0 Hz, 1H), 7.07-7.11 (t, *J* = 8.0 Hz, 1H), 6.47 (s, 1H), 6.14-6.15 (t, *J* = 2.4 Hz, 1H), 2.62-2.67 (m, 1H), 2.48-2.55 (m, 1H), 2.38-2.42 (m, 1H), 2.27-2.33 (m, 1H), 2.16-2.23 (m, 1H), 1.99-2.04 (m, 1H), 1.82 (s, 3H), 1.60-1.71(m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 149.7, 139.2, 136.4, 129.1, 129.0, 122.3, 122.1, 120.6, 120.0, 110.6, 109.2, 99.2, 41.1, 31.2, 27.7, 26.8, 21.1; HRMS electrospray (m/z) calcd for $C_{17}H_{19}N$, 237.1518; found, 237.1521.

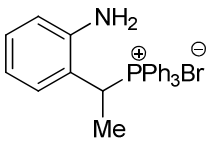


2,4'-Biindole (14j): The product was purified by chromatography on silica gel (R_f = 0.30 in 67% hexanes/33% EtOAc). The product (**14j**) was obtained as a white solid (101.1

mg, 87% yield); mp = 202-203 ºC; ^{1}H NMR (400 MHz, Acetone-d_6) 10.57 (br s, 1H), 10.47 (br s, 1H), 7.63-7.65 (d, J = 7.6 Hz, 1H), 7.46-7.52 (m, 4H), 7.21-7.25 (t, J = 7.6 Hz, 1H), 7.12-7.16 (t, J = 7.2 Hz, 1H), 7.04-7.08 (t, J = 7.2 Hz, 1H), 7.01 (s, 2H); ^{13}C NMR (100 MHz, Acetone-d_6) 139.4, 138.03, 138.02, 130.4, 126.5, 126.2, 125.9, 122.4, 122.3, 121.0, 120.3, 118.3, 112.0, 111.9, 102.3, 101.7.; HRMS electrospray (m/z) calcd for $C_{16}H_{12}N_2$, 232.1001; found, 232.1004.

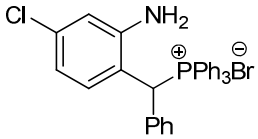


[(2-Aminophenyl) (phenyl) methyl] triphenylphosphonium bromide (15a): The product was obtained as light yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6) 7.88-7.91 (t, J = 7.2 Hz, 3H), 7.61-7.75 (m, 13H), 7.24-7.32 (m, 5H), 7.04-7.08 (t, J = 7.6 Hz, 1H), 6.78-6.80 (d, J = 8.0 Hz, 1H), 6.65-6.67 (d, J = 7.6 Hz, 1H), 6.56-6.61 (d, J = 20 Hz, 1H), 6.36-6.40 (t, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) 147.5, 135.9, 135.8, 135.3, 135.2, 134.0, 133.8, 132.54, 132.50, 131.34, 131.28, 130.9, 130.8, 130.3, 130.1, 130.0, 129.7, 129.5, 129.42, 129.37, 119.4, 118.6, 117.7, 116.8, 116.5, 57.0.

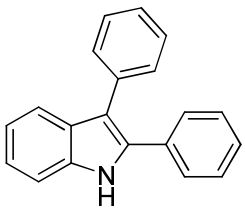


[1-(2-Aminophenyl)ethyl] triphenylphosphonium bromide (15b): The product was obtained as light yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6) 7.90-7.93 (m, 3H), 7.65-

7.76 (m, 13H), 7.01-7.04 (t, *J* = 8.0 Hz, 1H), 6.70-6.73 (d, *J* = 8.4 Hz, 1H), 6.29-6.33 (t, *J* = 7.2 Hz, 1H), 6.13-6.15 (d, *J* = 8.0 Hz, 1H), 5.32-5.37 (m, 1H), 2.08 (s, 2H), 1.67-1.73 (dd, *J* = 14.8, 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) 148.2, 148.1, 135.74, 135.71, 135.1, 135.0, 130.9, 130.8, 130.1, 129.1, 129.08, 118.9, 118.0, 117.1, 117.0, 116.7, 116.6, 29.7, 29.2, 18.3.

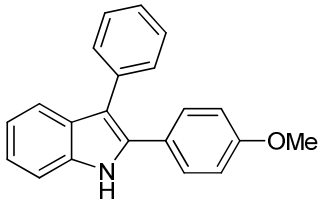


[(2-Amino-4-chlorophenyl) (phenyl)methyl] triphenylphosphonium bromide (15c): The product was obtained as a yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6) 7.92 (bs, 3H), 7.69-7.74 (m, 12H), 7.29 (s, 5H), 7.08-7.10 (d, *J* = 8.8 Hz, 1H), 6.81-6.83 (d, *J* = 8.4 Hz, 1H), 6.70-6.75 (d, *J* = 19.6 Hz, 1H), 6.42 (s, 1H), 6.04 (bs, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) 136.1, 136.0, 135.4, 135.3, 135.2, 133.9, 132.9, 132.7, 132.69, 132.2, 132.14, 132.10, 131.2, 131.1, 131.0, 130.97, 130.8, 130.1, 129.6, 129.5, 129.4, 129.37, 119.0, 118.9, 118.2.

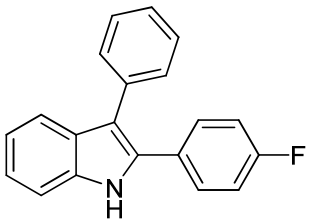


2, 3-Diphenyl-indole (16a): The product was purified by chromatography on silica gel (R_f = 0.45 in 90% hexanes/10% EtOAc). The product (**16a**) was obtained as a white solid

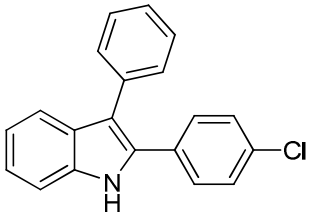
(134 mg, 100% yield); mp = 123-124 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) 8.20 (br s, 1H), 7.70-7.72 (d, *J* = 8.0 Hz, 1H), 7.38-7.48 (m, 7H), 7.24-7.35 (m, 5H), 7.16-7.20 (t, *J* = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 1326.0, 135.2, 134.2, 132.8, 130.3, 128.9, 128.8, 128.6, 128.3, 127.8, 126.3, 122.8, 120.5, 119.8, 115.1, 111.0; HRMS electrospray (m/z) calcd for $C_{20}H_{15}N$, 269.1205; found, 269.1214.



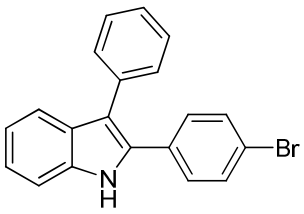
2-(4-Methoxyphenyl)-3-phenyl-indole (16b): The product was purified by chromatography on silica gel (R_f = 0.20 in 80% hexanes/20% EtOAc). The product (**16b**) was obtained as a yellow solid (142 mg, 95% yield); ^{1}H NMR (400 MHz, $CDCl_3$) 8.22 (br s, 1H), 7.77-7.79 (d, *J* = 8.0 Hz, 1H), 7.53-7.55 (m, 2H), 7.35-7.48 (m, 6H), 7.22-7.33(m, 2H), 6.89-6.92 (m, 2H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 159.3, 135.9, 135.4, 134.3, 130.3, 130.0, 129.6, 129.5, 128.9, 128.6, 128.5, 126.2, 125.3, 122.5, 120.4, 119.6, 55.4.



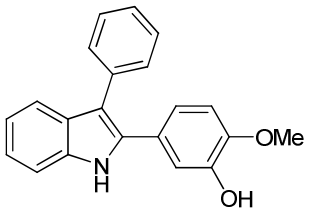
2-(4-Fluorophenyl)-3-phenyl-indole (16c): The product was purified by chromatography on silica gel (R_f = 0.40 in 90% hexanes/10% EtOAc). The product (**16c**) was obtained as a yellow solid (120.5 mg, 84% yield); mp = 165-166 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) 8.16 (br s, 1H), 7.74-7.76 (d, *J* = 8.0 Hz, 1H), 7.34-7.45 (m, 8H), 7.21-7.33 (m, 2H), 7.00-7.05(t, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 163.6, 161.1, 136.0, 135.0, 133.3, 130.2, 130.1, 130.0, 128.92, 128.89, 128.75, 128.7, 126.5, 122.9, 120.7, 119.8, 116.0, 115.8, 115.1, 111.1.



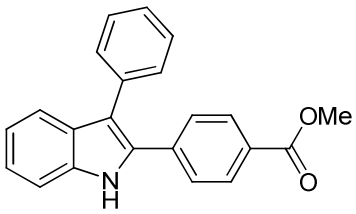
2-(4-Chlorophenyl)-3-phenyl-indole (16d): The product was purified by chromatography on silica gel (R_f = 0.40 in 90% hexanes/10% EtOAc). The product (**16d**) was obtained as a yellow solid (136 mg, 90% yield); mp = 123-124 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) 8.22 (br s, 1H), 7.74-7.76 (d, *J* = 8.0 Hz, 1H), 7.43-7.50 (m, 5H), 7.30-7.40 (m, 6H), 7.22-7.26(td, *J* = 8, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 136.1, 134.9, 133.6, 133.0, 131.2, 130.2, 129.5, 129.0, 128.8, 128.78, 126.6, 123.1, 120.7, 120.0, 115.6, 111.1.



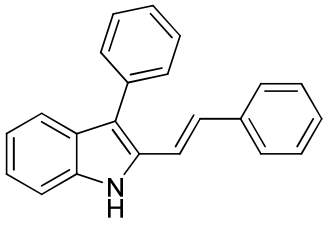
2-(4-Bromophenyl)-3-phenyl-indole (16e): The product was purified by chromatography on silica gel (R_f = 0.40 in 90% hexanes/10% EtOAc). The product (**16e**) was obtained as a yellow solid (150 mg, 86% yield); ^{1}H NMR (400 MHz, $CDCl_3$) 8.21 (br s, 1H), 7.73-7.75 (d, *J* = 8.0 Hz, 1H), 7.43-7.50 (m, 7H), 7.36-7.40 (m, 16H), 7.27-7.34 (m, 3H), 7.21-7.25 (td, *J* = 8, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 136.1, 134.9, 133.6, 132.9, 131.9, 131.7, 130.2, 129.8, 128.8, 128.79, 126.6, 123.1, 121.9, 120.7, 119.9, 115.6, 111.2.



2-(4-Methoxy-3-phenol)-3-phenyl-indole (16f): The product was purified by short chromatography on silica gel (R_f = 0.35 in 80% hexanes/20% EtOAc). The product was obtained as a yellow solid (157 mg, 100% yield); mp = 72-74 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) 8.33 (s, 1H), 7.34-7.54 (d, *J* = 8.0 Hz, 1H), 7.51-7.53 (d, *J* = 6.8 Hz, 2H), 7.19-7.45 (m, 5H), 7.08-7.09 (d, *J* = 2.0 Hz, 1H), 6.90-6.92 (m, 1H), 6.72-6.74 (d, *J* = 8.4 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 146.5, 145.7, 135.9, 135.4, 134.2, 130.3, 128.9, 128.7, 126.3, 126.1, 122.5, 120.7, 120.4, 119.6, 114.5, 114.3, 111.1, 111.0, 55.98; HRMS electrospray (m/z) calcd for $C_{21}H_{17}NO_2$, 315.1259; found, 315.1264.

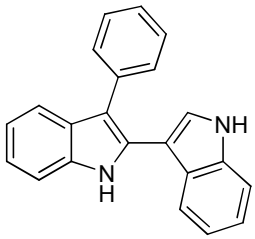


Methyl 4-(3-phenyl-indol-2-yl) benzoate (16g): The product was purified by short chromatography on silica gel (R_f = 0.30 in 90% hexanes/10% EtOAc). The product was obtained by recrystillization from the mixture of CH_2Cl_2 and hexane as a white solid (74 mg, 45% yield); mp = 192-193 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) 11.76 (s, 1H), 7.91-7.93 (d, *J* = 8.4 Hz, 2H), 7.58-7.60 (d, *J* = 8.4 Hz, 2H), 7.49-7.51 (d, *J* = 8.4 Hz, 2H), 7.29-7.43 (m, 5H), 7.19-7.23 (m, 1H), 7.05-7.08 (t, *J*=7.6 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) 166.4, 137.6, 137.0, 135.3, 133.1, 130.3, 129.8, 128.6, 128.4, 126.9, 123.2, 120.5, 119.4, 115.5, 112.2, 52.6; HRMS electrospray (m/z) calcd for $C_{22}H_{17}NO_2$, 327.1259; found, 327.1263.

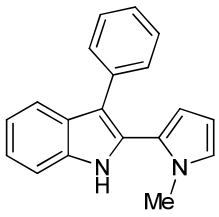


(*E*)-3-Phenyl-2-styryl-1H-indole (16h): The product was purified by chromatography on silica gel (R_f= 0.70 in 80% hexanes/20% EtOAc). The product (**16h**) was obtained as a yellow solid (130 mg, 88% yield); mp = 106-107 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) 8.29 (br s, 1H), 7.75-7.77 (d, *J* = 8.0 Hz, 1H), 7.17-7.62 (m, 14H), 6.88-6.92 (d, *J* =

16.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 137.1, 136.6, 134.7, 132.7, 130.3, 128.9, 128.8, 128.3, 127.8, 127.5, 126.7, 126.5, 123.7, 120.6, 119.8, 118.9, 110.8.

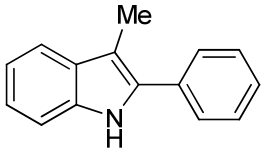


3-Phenyl-2,3'-biindole (16i): The product was purified by short chromatography on silica gel (R_f = 0.15 in 75% hexanes/25% EtOAc). The product was obtained as a yellow solid (117 mg, 76% yield); mp = 202-204 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) 11.40 (s, 1H), 11.30 (s, 1H), 7.59-7.61 (d, J = 8.0 Hz, 1H), 7.39-7.50 (m, 5H), 7.29-7.33 (t, J = 7.6 Hz, 2H), 7.05-7.20 (m, 5H), 6.83-6.87 (t, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) 136.7, 136.6, 130.8, 129.6, 128.9, 128.3, 125.9, 125.7, 125.5, 122.1, 121.6, 120.4, 120.0, 119.8, 118.4, 112.6, 112.2, 111.7, 108.2; HRMS electrospray (m/z) calcd for $C_{22}H_{16}N_2$, 308.1313; found, 308.1319.

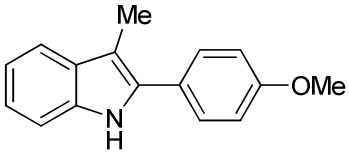


2-(1-Methyl-pyrrol-2-yl)-3-phenyl-indole (16j): The product was purified by short chromatography on silica gel (R_f = 0.25 in 80% hexanes/20% EtOAc). The product was

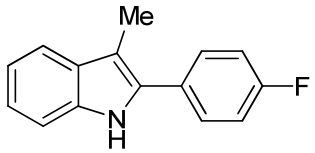
obtained as a yellow solid after recrystalation (76 mg, 56% yield); mp = 60-61 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) 8.14 (s, 1H), 7.86-7.88 (d, *J* = 7.6 Hz, 1H), 7.35-7.43 (m, 5H), 7.19-7.30 (m, 3H), 6.65-6.67 (t, *J* = 2.0 Hz, 1H), 6.41-6.42 (m, 1H), 6.26-6.28 (t, *J* = 3.2 Hz, 1H), 3.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 135.8, 135.7, 128.9, 128.7, 127.5, 127.0, 126.0, 125.6, 123.8, 122.7, 120.5, 119.6, 115.8, 111.0, 110.5, 108.3, 34.43; HRMS electrospray (m/z) calcd for $C_{19}H_{16}N_2$, 272.1313; found, 272.1318.



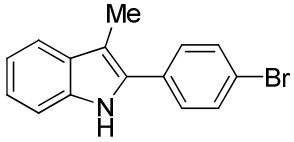
3-Methyl-2-phenyl-indole (16k): The product was purified by short chromatography on silica gel (R_f = 0.35 in 90% hexanes/10% EtOAc). The product was obtained as a yellow solid (100.4 mg, 97% yield); mp = 93-94 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) 8.00 (s, 1H), 7.68-7.70 (d, *J* = 8.0 Hz, 1H), 7.62-7.64 (m, 2H), 7.52-7.56 (t, *J* = 7.6 Hz, 2H), 7.40-7.44 (m, 4H), 7.22-7.31 (m 2H), 2.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 136.0, 134.2, 133.8, 133.5, 132.3, 132.2, 130.1, 128.9, 128.7, 128.68, 128.62, 128.6, 127.9, 127.4, 122.4, 119.6, 119.0, 110.9, 108.7, 9.82.



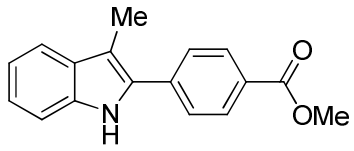
2-(4-Methoxyphenyl)-3-methyl-indole (16l): The product was purified by short chromatography on silica gel (R_f = 0.20 in 80% hexanes/20% EtOAc). The product was obtained as a yellow solid (99 mg, 83% yield); mp = 126-127 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) 7.95 (s, 1H), 7.63-7.64 (d, *J* = 7.6 Hz, 1H), 7.49-7.51 (d, *J* = 8.8 Hz, 2H), 7.33-7.35 (d, *J* = 8.0 Hz, 1H), 7.18-7.25 (m, 2H), 7.02-7.04 (d, *J* = 8.8 Hz, 2H), 3.28 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 159.0, 135.8, 134.1, 130.2, 129.1, 126.0, 122.0, 119.5, 118.9, 114.4, 110.7, 107.8, 55.5, 9.74.



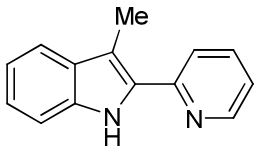
2-(4-Fluorophenyl)-3-methyl-indole (16m): The product was purified by short chromatography on silica gel (R_f = 0.60 in 80% hexanes/20% EtOAc). The product was obtained as a white solid (94.5 mg, 84% yield); mp = 148-149 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) 7.89 (s, 1H), 7.62-7.64 (d, *J* = 7.6 Hz, 1H), 7.50-7.53 (m, 2H), 7.34-7.36 (d, *J* = 8.0 Hz, 1H), 7.16-7.26 (m, 4H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 163.4, 161.0, 135.9, 133.2, 130.0, 129.6, 129.5, 129.49, 122.5, 119.7, 119.1, 116.0, 115.8, 110.8, 108.7; HRMS electrospray (m/z) calcd for $C_{15}H_{12}FN$. 225.0954; found, 225.0956.



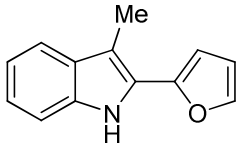
2-(4-Bromophenyl)-3-methyl-indole (16n): The product was purified by short chromatography on silica gel (R_f = 0.60 in 90% hexanes/10% EtOAc). The product was obtained as a yellow solid (110 mg, 77% yield); mp = 168 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) 7.97 (s, 1H), 7.57-7.62 (m, 3H), 7.40-7.42 (d, *J* = 8.4 Hz, 2H), 7.33-7.35 (d, *J* = 7.6 Hz, 1H), 7.22-7.25 (t, *J* = 7.2 Hz, 1H), 7.15-7.19(t, *J* = 7.2 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 136.0, 132.9, 132.3, 132.0, 130.0, 129.2, 122.7, 121.4, 119.8, 119.2, 110.9, 109.3, 9.78; HRMS electrospray (m/z) calcd for $C_{15}H_{12}BrN$. 285.0153; found, 285.0156.



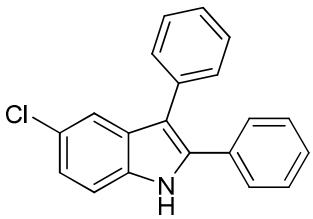
Methyl 4-(3-methyl-indol-2-yl) benzoate (16o): The product was purified by short chromatography on silica gel (R_f = 0.30 in 90% hexanes/10% EtOAc). The product was obtained as a white solid (95.4 mg, 72% yield); mp = 186-187 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) 11.35 (s, 1H), 8.07-8.09 (d, *J* = 8.4 Hz, 2H), 7.83-7.85 (d, *J* = 8.4 Hz, 2H), 7.56-7.58 (d, *J* = 7.6 Hz, 1H), 7.40-7.42 (d, *J* = 7.6 Hz, 1H), 7.14-7.18 (t, *J* = 7.2 Hz, 1H), 7.02-7.06 (t, *J* = 7.2 Hz, 1H), 3.88 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) 166.5, 138.1, 136.9, 132.9, 130.1, 129.8, 128.0, 127.7, 122.9, 119.4, 119.3, 111.7, 109.5, 52.6, 10.6; HRMS electrospray (m/z) calcd for $C_{17}H_{15}NO_2$. 265.1103; found, 265.1106.



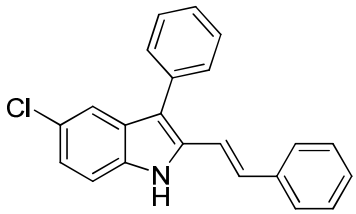
3-Methyl-2-(pyridin-2-yl)-indole (16p): The product was obtained as a yellow solid (86 mg, 83% yield); mp = 93-94 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) 9.55 (s, 1H), 8.61-8.62 (m, 1H), 7.72-7.80 (m, 2H), 7.62-7.64 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.35-7.37 (d, *J* = 8.0 Hz, 1H), 7.09-7.23 (m, 3H), 2.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 151.1, 149.4, 136.5, 135.4, 132.3, 130.2, 123.3, 121.4, 121.1, 119.34, 119.30, 111.1, 110.5, 10.78.



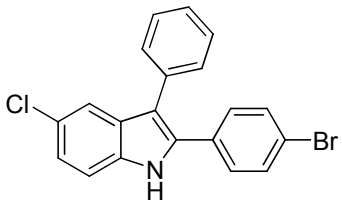
2-(Furan-2-yl)-3-methyl-indole (16q): The product was purified by short chromatography on silica gel (R_f = 0.20 in 80% hexanes/20% EtOAc). The product was obtained as a yellow solid (77 mg, 78% yield); mp: 60-61 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) 8.36 (s, 1H), 7.61-7.63 (d, *J* = 7.6 Hz, 1H), 7.508-7.511 (d, *J* = 1.2 Hz, 1H), 7.36-7.38 (d, *J* = 8.0 Hz, 1H), 7.14-7.23 (m, 2H), 6.57-6.62 (m, 2H), 2.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 147.9, 141.2, 135.6, 129.5, 125.5, 122.6, 119.6, 118.9, 111.9, 110.8, 108.4, 106.2, 9.67; HRMS electrospray (m/z) calcd for $C_{13}H_{11}NO$, 197.0861; found, 197.0863.



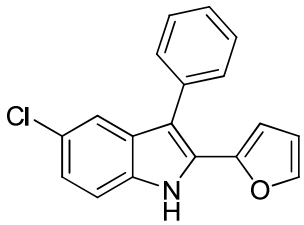
5-Chloro-2,3-diphenyl-indole (16r): The product was purified by short chromatography on silica gel (R_f = 0.30 in 80% hexanes/20% EtOAc). The product was obtained as a white solid (134 mg, 100% yield); mp = 126-127 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) 8.24 (s, 1H), 7.651-7.652 (d, *J*=0.4, 1H), 7.37-7.40 (m, 6H), 7.29-7.35 (m, 5H), 7.18-7.20 (dd, *J*=8.8, 2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 135.5, 134.5, 134.3, 132.2, 130.1, 130.0, 128.8, 128.78, 128.2, 128.1, 126.6, 126.2, 123.0, 119.2, 114.8, 112.0.



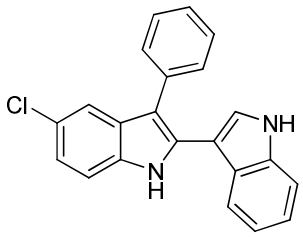
(*E*)-5-chloro-3-phenyl-2-styryl-indole (16s): The product was purified by short chromatography on silica gel (R_f = 0.30 in 80% hexanes/20% EtOAc). The product was obtained as a light yellow solid (151 mg, 92% yield); mp = 164-165 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) 8.49 (s, 1H), 7.635-7.639 (d, *J* = 1.6 Hz, 1H), 7.50-7.51 (d, *J* = 4.4 Hz, 4H), 7.38-7.42 (m, 3H), 7.31-7.35 (t, *J* = 7.2 Hz, 2H), 7.16-7.26 (m, 4H), 6.89-6.93 (d, *J* = 16.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 136.8, 134.8, 134.0, 133.9, 130.1, 129.3, 128.9, 128.2, 128.0, 126.9, 126.5, 126.1, 123.7, 119.1, 118.2, 117.6, 111.7; HRMS electrospray (m/z) calcd for $C_{22}H_{16}ClN$, 329.0971; found, 329.0971.



2-(4-Bromophenyl)-5-chloro-3-phenyl-indole (16t): The product was purified by short chromatography on silica gel (R_f = 0.45 in 80% hexanes/20% EtOAc). The product was obtained as a white solid (182 mg, 96% yield); mp = 176-178 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) 8.19 (s, 1H), 7.600-7.605 (d, *J* = 2.0 Hz, 1H), 7.28-7.43 (m, 8H), 7.17-7.24 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 134.3, 134.2, 134.1, 132.0, 131.1, 130.0, 129.9, 129.6, 128.9, 126.9, 126.4, 123.3, 122.2, 119.2, 115.3, 112.1; HRMS electrospray (m/z) calcd for $C_{20}H_{13}BrClN$, 380.9920; found, 380.9925.



5-Chloro-2-(furan-2-yl)-3-phenyl-indole (16u): The product was purified by short chromatography on silica gel (Rf = 0.40 in 90% hexanes/10% EtOAc). The product was obtained as a yellow solid (146 mg, 100% yield); mp = 90-91 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) 8.63 (s, 1H), 7.52-7.58 (m, 5H), 7.43-7.47 (m, 2H), 7.21-7.31 (m, 2H), 6.41 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 146.6, 141.7, 134.0, 133.9, 130.2, 130.0, 128.9, 127.4, 126.5, 126.2, 123.2, 119.0, 114.0, 112.1, 112.0, 107.5; HRMS electrospray (m/z) calcd for $C_{18}H_{12}ClNO$, 293.0607; found, 293.0612.



5-Chloro-3-phenyl-2,3'-biindole (16v): The product was purified by short chromatography on silica gel (R_f = 0.15 in 60% hexanes/40% EtOAc). The product was obtained as a light yellow solid (159 mg, 93% yield); mp = 220-221 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) 11.6 (s, 1H), 11.5 (s, 1H), 7.43-7.59 (m, 6H), 7.32-7.36 (d, J = 7.6 Hz, 2H), 7.10-7.24 (m, 4H), 6.88-6.92 (t, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) 136.8, 136.0, 135.1, 133.0, 129.7, 129.6, 129.0, 126.2, 126.1, 125.7, 124.6, 122.1, 121.4, 120.5, 119.8, 117.5, 113.2, 112.3, 112.2, 107.6; HRMS electrospray (m/z) calcd for $C_{22}H_{15}ClN_2$, 342.0924; found, 342.0928.

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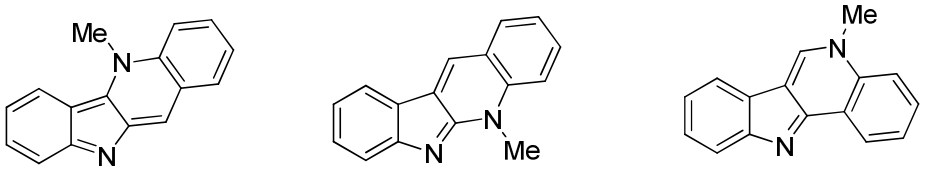
CHAPTER 2. A DIRECT SYNTHESIS OF NEOCRYPTOLEPINE

Introduction

More than 2.5 million people die annually from malaria, one of the most serious parasitic diseases in developing and industrialized nations. [1,2] The root of the west African plant *Cryptolepis sanguinlenta* have been traditionally used to treat a variety of health disorders, including malaria, rheumatism, urinary tract infections and other diseases.[3,4] The linear indolequinoline alkaloids cryptolepine (**1**), neocryptolepine (**2**) (also called cryptotackieine) and isocryptolepine (**3**) (also called cryptosanguinolentine) shown in Figure 1, were isolated from *Cryptolepis sanguinlenta* in 1996 by two groups.[5] All of these compounds can function as DNA intercalating agents, inhibiting DNA replication and transcription. These compounds also exhibit potent antiplasmodial activity. However, compound **1** has a 10-fold higher affinity for DNA than the other alkaloids and also shows stronger inhibition of human topisomerase Ⅱ.[6] Consequently, compounds **2** and **3** are more promising leads for new anti-malarial agents.



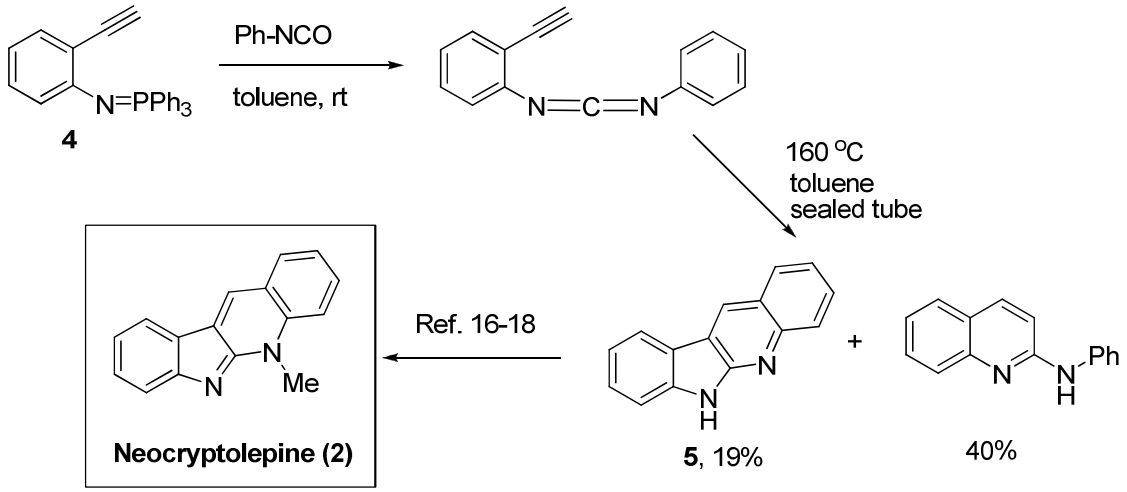
Cryptolepine (1) **Neocryptolepine (2)** **Isocryptolepine (3)**

Figure 1. The indole quinoline cryptolepine (**1**), neocryptolepine (**2**) and isocryptolepine (**3**)

In the past decade, the significant biological activity and challenging structure of this class of natural products have drawn many synthetic chemists' attention. A number of syntheses for compounds **2** [7-10] and **3** [11-16] have been reported.

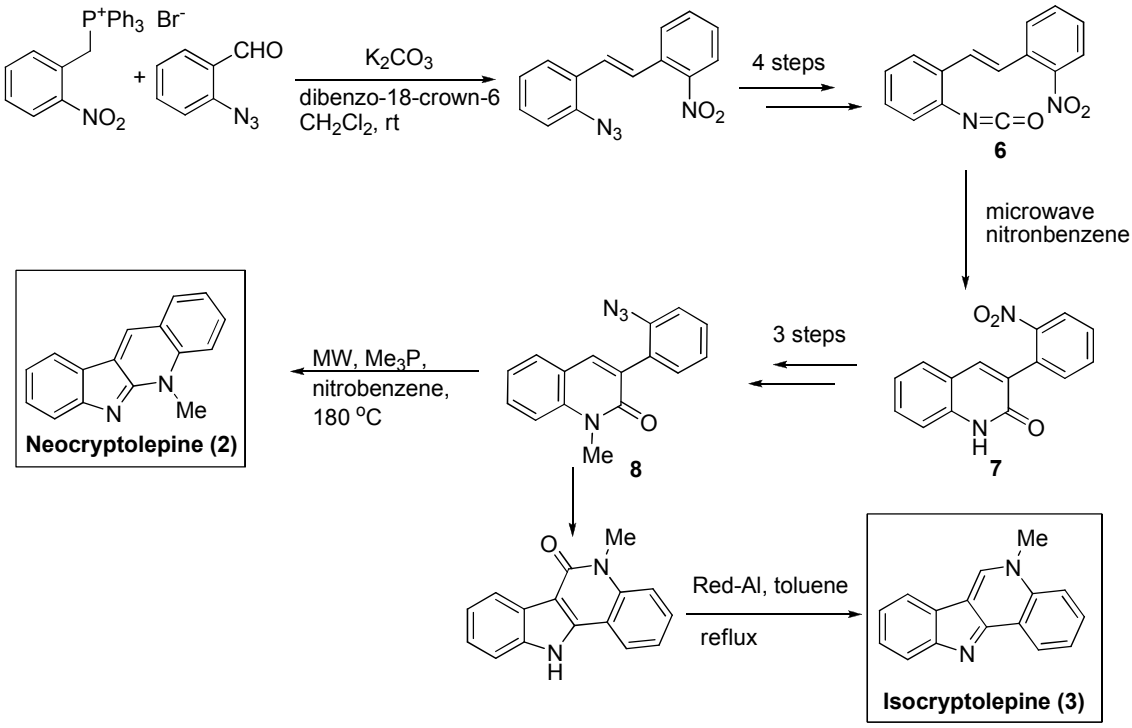
In 1997, Alajarin *et al.* reported a formal synthetic route to compound **2** using an aza-Wittig-type reaction in three steps from a known compound **4** with an overall yield of 15% as shown in Scheme 1.[7] The synthesis started from iminophosphane **4**, which was synthesized from commercially available (*o*-aminophenyl) acetylene in 47% yield,[17] followed by an aza-Wittig-type reaction with phenyl isocyanate in toluene to make the carbodiimide intermediate. After further thermal treatment, the intermediate **5** was prepared in 19% yield from **4** and 2-anilinoquinoline (40% yield) was the major by product. The target molecule neocrytolepine (**2**) could be obtained in one step from compound **5** by methylation.[18-19]

Scheme 1



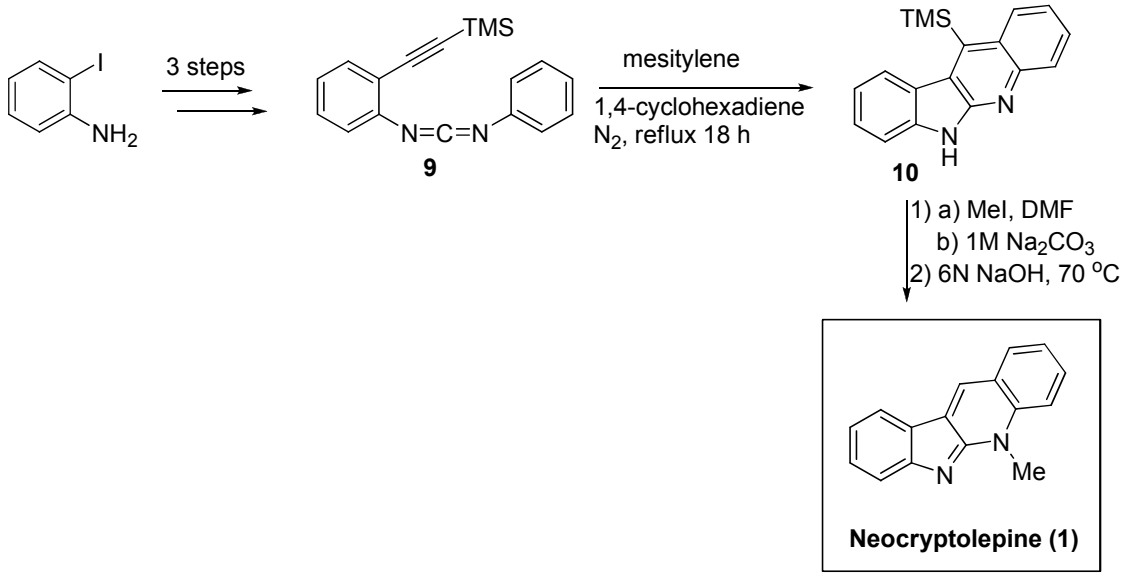
In 2001, Molina *et al.* reported a total synthesis of compound **2** in 10 steps in 9% yield and compound **3** in 11 steps in 17% yield, which shared the same key intermediate **8** as shown in Scheme 2.[8] Condensation of 2-nitrobenzyl-triphenylphosphonium bromide with 2-azidobenzaldehyde in the presence of potassium carbonate resulted in a stilbene, which could be converted in 4 steps to isocyanate **6**. The key intermediate **7** was achieved by further microwave-promoted cyclization of isocyanate **6**. Another 3 steps were needed to make the key azide **8**. With azide **8**, compound **2** can be made in one step using an intramolecular aza-Wittig reaction under the microwave assisted conditions. Compound **3** can be prepared in two steps via nitrene insertion, followed by reduction.

Scheme 2



Pieters and co-workers reported a total synthesis of compound **2** in 5 steps in 2002 using the diradical cyclization shown in Scheme 3 as the key step.[9] The reaction sequence starts with a Sonogashira coupling reaction and an aza-Wittig reaction to afford the carbodiimide **9**. After biradical cyclization in the presence of 1,4-cyclohexadiene, intermediate **10** was prepared in 60% yield. The target molecule, compound **1**, could be achieved by methylation and desilylation.

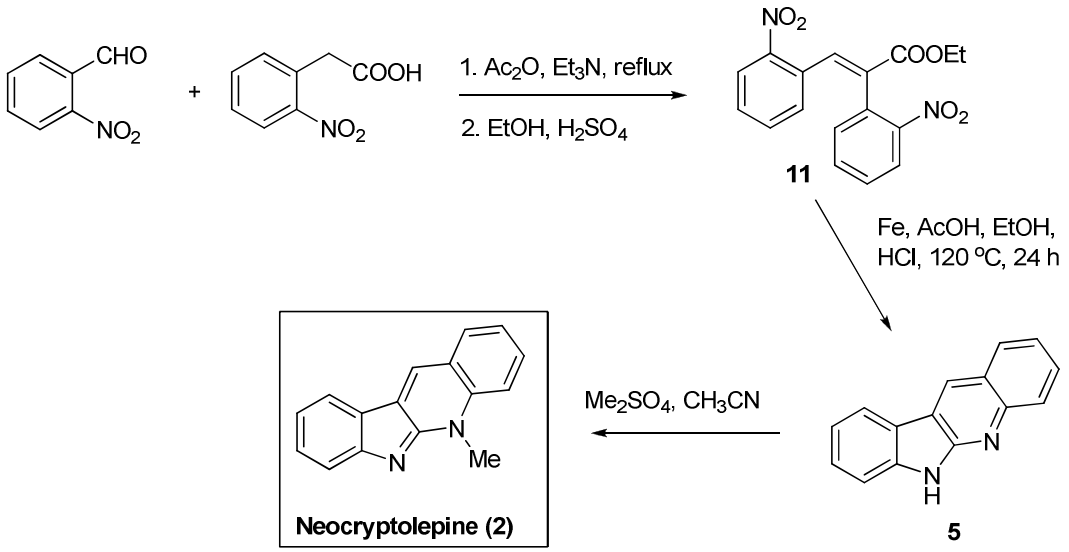
Scheme 3



More recently, Tilve and co-workers have reported a direct synthesis of compound **2** via double reductive cyclization as the key step as shown in Scheme 4.[10] The condensation of *o*-nitrobenzaldehyde and *o*-nitrophenylacetic acid, followed by esterification, afforded the stilbene **11**. Reduction of **11** with iron and acetic acid in the presence of hydrochloride acid gave intermediate **5** in 74% yield. The synthesis of compound **2** was achieved by

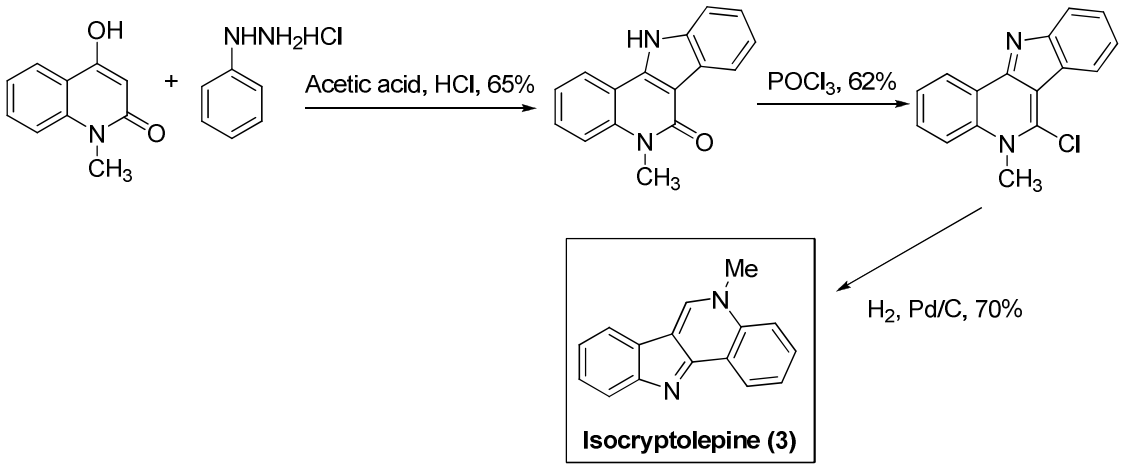
regioselective methylation in 80% yield. The overall yield for this synthesis is 42% over 4 steps, which is the highest yield reported so far.

Scheme 4



In 2006, Mohan *et al.* reported a three-step synthesis of isocryptolepine **3** in 28% overall yield involving an indole synthesis as the key step (Scheme 5).

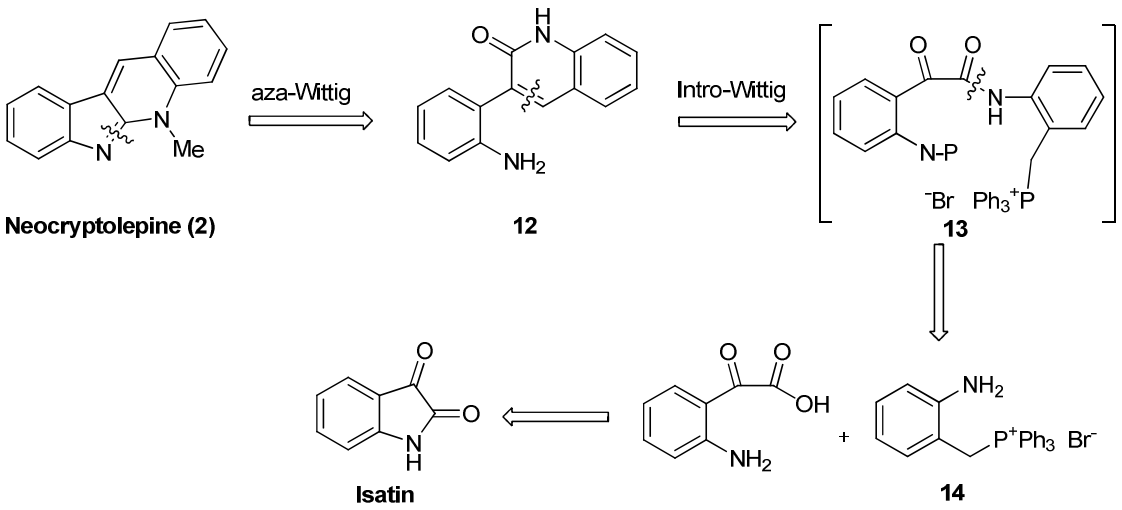
Scheme 5



Results and Discussion

The most common approach involves organometallic coupling of substituted quinolines. We report herein a direct and distinctly different strategy. Our retrosynthetic analysis of intermediate **12** showed that it could be prepared in one pot by intermediate **13** by an intramolecular Wittig reaction. Keto amide **13** could be made by a coupling reaction using commercially available Wittig salt **14** (Scheme 6). The target molecule neocryptolepine (**2**) could be prepared by an aza-Wittig reaction as shown in Scheme 2.

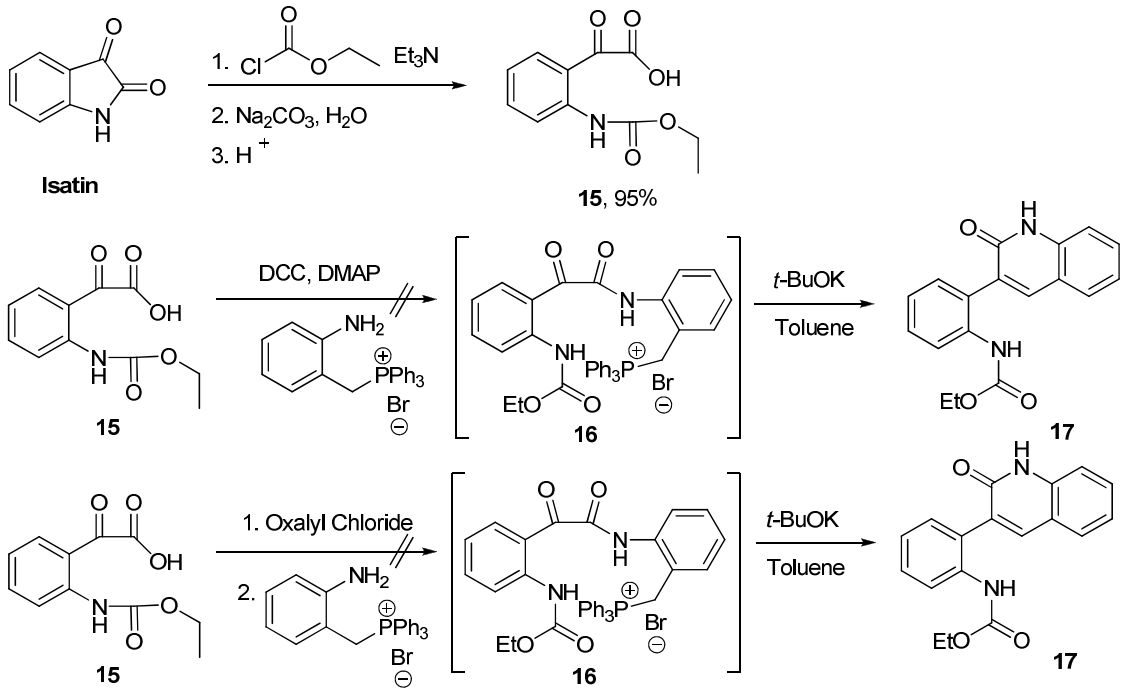
Scheme 6



In our initial approach, the reaction of isatin with ethyl chloroformate in THF with triethyl amine, followed by sodium carbonate, gave the acid **15** in 95% yield (Scheme 7). With the acid **15**, Steglich-Hasser esterification with commercially available phosphonium salt **14**, followed by an intramolecular Wittig reaction in the presence of potassium *tert*-

butoxide, gave a very complex reaction. We also tried to prepare the acid chloride in-situ first and then couple it with phosphonium salt **14**, followed the same intramolecular Wittig reaction, which also failed. After careful study, we found that the intermediate **16** did not form under these conditions.

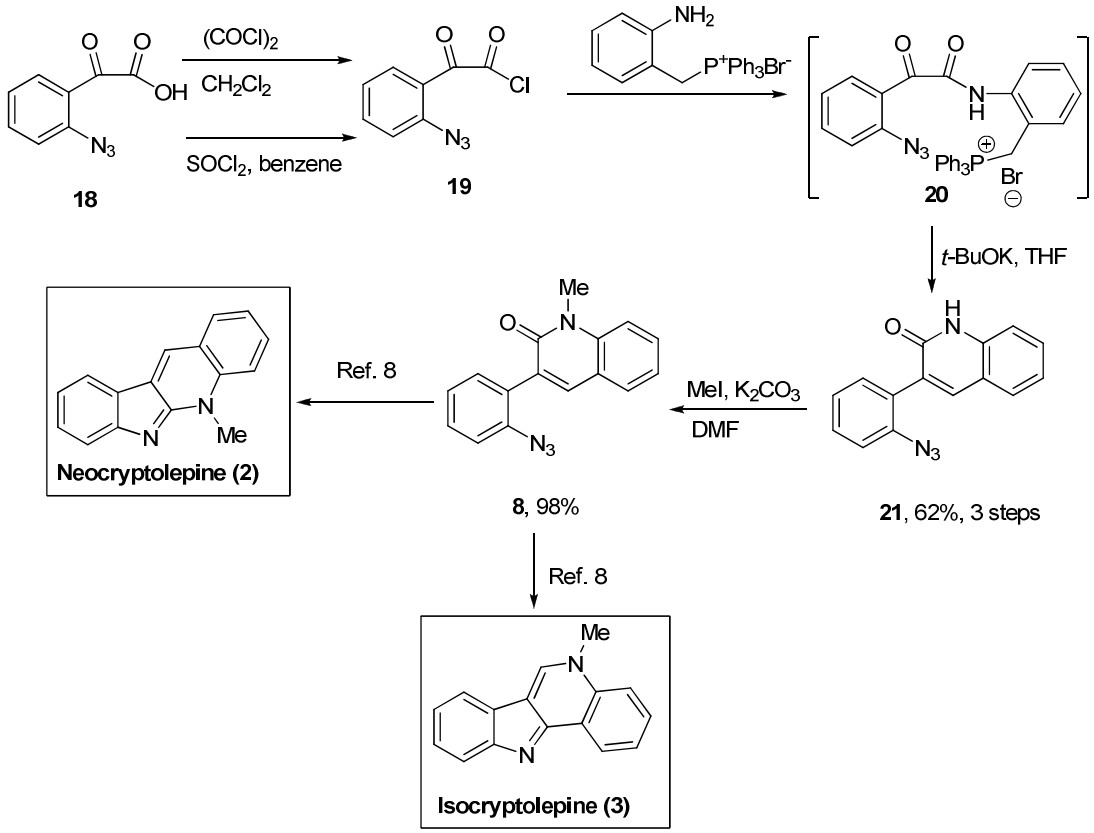
Scheme 7



Instead of using the unstable intermediate **16**, we decided to introduce an azide as the nitrogen source in the *o*-position because azides are generally stable groups under acid or base conditions. The new approach started from the known acid **18**, which can easily be made from isatin in one step in 92% yield[20] (Scheme 8). The acid chloride **19** was prepared from compound **18** by two different methods, one using oxalyl chloride in methylene chloride solution and the other using thionyl chloride. The resultant brown solid was directly

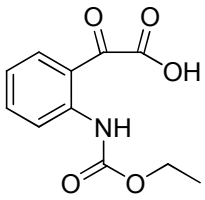
used for the next step without further purification. Condensation of (2-aminobenzyl) triphenylphosphonium bromide with compound **19** in methylene chloride, followed by intramolecular Wittig reaction with potassium *tert*-butoxide at room temperature, led to lactam **21** in 62% yield in 3 steps and one pot from compound **18**. Methylation of **18** with methyl iodide in the presence of potassium carbonate in DMF gave the known intermediate **8** in 98% yield. The overall yield of **8** was 60% over 4 steps in two pots comparing to the 22% yield over 9 steps shown in Scheme 2. Neocryptolepine (**2**) can be made in one step from **8** using an intramolecular aza-Wittig reaction under microwave assisted conditions and isocryptolepine (**3**) can be made in two steps via nitrene insertion, followed by Red-Al reduction, according to the literature.[8]

Scheme 8

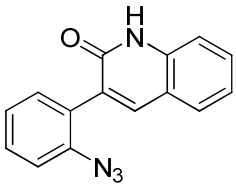


In conclution, we have established a new, efficient and straightforward formal total synthesis of neocryptolepine **2** and isocryptolepin **3**, employing the same intermediate **8**, and using an intrameolecular Wittig reaction, followed by an aza-Wittig reaction in an excellent yield.

Experimental



2-(2-(Ethoxycarbonylamino)phenyl)-2-oxoacetic acid (15): To a mixture of isatin (735 mg, 5 mmol) and Et_3N (0.7 mL, 5 mmol) in 20 mL of dry THF, ethyl chloroformate (0.5 mL, 5 mmol) was added dropwise under argon. The temperature was kept below 30 ^oC during the addition. The resultant mixture was stirred at rt for 1 h and 20 mL of H_2O was added, followed by Na_2CO_3 (1.06 g, 10 mmol). Then the reaction mixture was stirred at rt for 45 min. The product was extracted twice with ethyl acetate and the combined organic layers were washed with brine. Evaporation of the solvent, followed by column chromatography, gave compound **15** (1.12 g, 95%) as light yellow solid; mp = 144-145 ºC; ^1H NMR (400 MHz, DMSO-d_6) 10.26 (s, 1H), 8.02-8.04 (d, J = 8.0 Hz, 1H), 7.68-7.72 (m, 2H), 7.23-7.27 (m, 1H), 4.12-4.17 (q, J = 7.2 Hz, 2H), 1.22-1.25 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): 191.6, 165.6, 153.9, 141.1, 136.3, 133.0, 123.4, 120.7, 120.6, 61.7, 14.8; HRMS electrospray (m/z) calcd for $C_{11}H_{11}NO_5$, 237.0637; found, 237.0641.

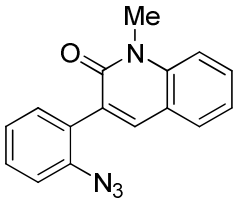


3-(2-Azidophenyl)quinolin-2-one (21): Method A: To a suspension of acid **18** (1.0 g, 5.4 mmol) in 10 mL of benzene was added thionyl chloride (3.86 g, 32.4 mmol). The mixture was boiled with stirring for 1 h and was concentrated under reduced pressure. The residue was recrystallized from benzene to give acid chloride **19** as a brown solid.

Method B: Oxalyl chloride (0.41 g, 3.24 mmol) was slowly added under an inert atmosphere to an ice cold solution of compound **18** (0.5 g, 2.7 mmol) in 5 mL of dry CH_2Cl_2. The resulting mixture was treated with a catalytic amount of DMF and allowed to react at rt for 3 h. The solvent and excess reagent were evaporated. The resultant brown solid was directly used in the next step without any purification.

The acid chloride **19** (0.1 g, 0.48 mmol) was redissolved in 5 mL of CH_2Cl_2 and phosphonium salt **14** (0.214 g, 0.48 mmol) was added. The resulting mixture was stirred at rt for 12 h. The solvent was removed under a vacuum. THF (5 mL) was added to the resultant orange solid, followed slowly by 0.57 mL of a *t*-BuOK (1 M, 0.57 mmol) solution in THF at rt. After 5 h at rt, the reaction was quenched by the addition of an aqueous NH_4Cl solution. The product was extracted twice with ethyl acetate and the combined organic layers were washed with brine. Evaporation of the solvent, followed by column chromatography, gave compound **21** (75 mg, 62% for 3 steps) as yellow powder; mp = 201-202 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) 11.94 (s, 1H), 7.91 (s, 1H), 7.68-7.70 (d, J = 7.6 Hz, 1H), 7.47-7.54 (m, 2H), 7.33-7.39 (m, 3H), 7.24-7.28 (m, 1H), 7.18-7.22 (t, J = 7.6 Hz, 1H); ^{13}C NMR (100

MHz, DMSO-d_6) 161.1, 140.0, 139.2, 138.4, 132.1, 130.9, 130.7, 130.0, 129.3, 128.6, 125.3, 122.4, 119.54, 119.49, 115.3; HRMS electrospray (m/z) calcd for $C_{15}H_{10}N_4O$, 262.0855; found, 262.0858.



3-(2-Azidophenyl)-1-methylquinolin-2(1H)-one 8: To a mixture of compound **21** (60 mg, 0.23 mmol) in 4 mL of dry DMF and anhydrous K_2CO_3 (191 mg, 1.38 mmol), methyl iodide (49 mg, 0.345 mmol) was added dropwise under argon. The resultant mixture was stirred at 60 ^oC for 8 h. The reaction was quenched by the addition of 10 mL of water. The product was extracted twice with ethyl acetate and the combined organic layers were washed with brine. Evaporation of the solvent, followed by column chromatography, gave compound **8** (62 mg, 98%) as yellow solid; mp = 168-170 ºC (Lit. mp = 169 ºC)[8]; ^1H NMR (400 MHz, $CDCl_3$) 7.67 (s, 1H), 7.54-7.58 (m, 2H), 7.34-7.42 (m, 3H), 7.16-7.25 (m, 3H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 161.1, 140.0, 138.8, 138.6, 131.6, 130.7, 130.3, 129.6, 129.0, 124.7, 122.3, 120.3, 118.6, 114.2, 30.0; HRMS electrospray (m/z) calcd for $C_{16}H_{12}N_4O$, 276.1011; found, 276.1017.

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CHAPTER 3. STUDIES TOWARDS THE TOTAL SYNTHESIS OF SALVINORIN A

Introduction

Over the past 30 years, there has been in-depth research into the biochemistry, pharmacology and biology of opioid receptors.[1-3] Some alkaloids, like morphine and codeine, which can interact with opioid receptors, are important for modern medicine.[4] Salvinorin A (**1**), a unique and selective κ opioid receptor agonist, was isolated in 1982 from the Mexican hallucinogenic plant *Salvia Divinorum*.[5-9] Recent studies indicate that compound **1** has more potent hallucinogenic effects compared to other non-nitrogenous or nitrogenous opioid agonists, such as lysergic acid diethylamide or tetrahydrocannabinol.[10-13] Since they have little structure similarity and have a different mechanism of action than other classical opoid recptor ligands, compound **1** and its analogs, including eight congeners B-I and salvinicins A and B,[14-18] are expected to be potential drug candidates and also offer opportunities to explore the role of the receptor systems in humans.

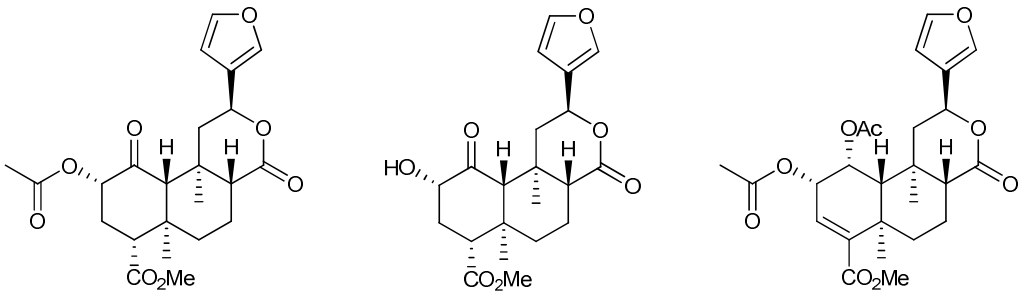


Figure 1. Typical Salvinorin A Analogs

The biosynthesis of salvinorin A (**1**) has been proposed using early labeling experiments, involving the incorporation of [1-^{13}C]glucose, [CH_3-^{13}C]methionine, and [1-^{13}C;3,4-$^{2}H_2$]-1-deoxy-D-xylulose into its structure.[19] (Figure 2). The geranyl pyrophosphate (**4**) results from the assembly of isopentenylpyrophosphate and dimethylallyl pyrophosphate.[20] Cyclization, followed by methyl shifts by enzyme catalysis of **4**, affords the labdanyl cation **5** and clerodane pyrophosphate **6**, which upon oxidation, acetylation, and methylation provide salvinorin A (**1**).

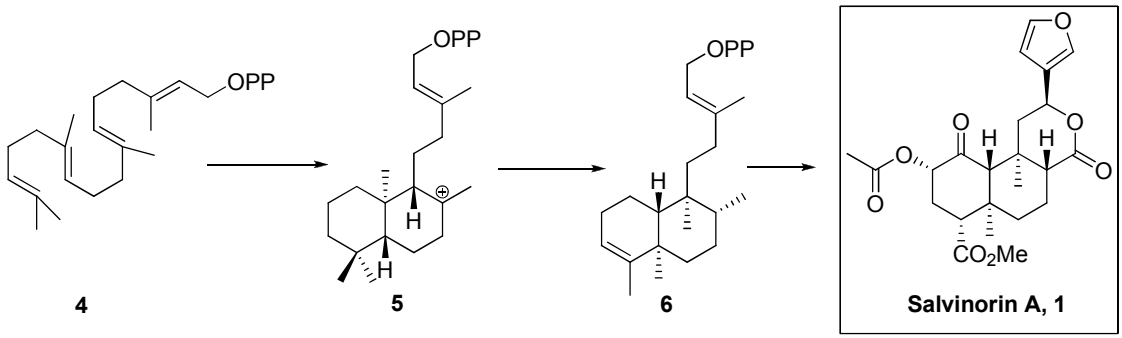


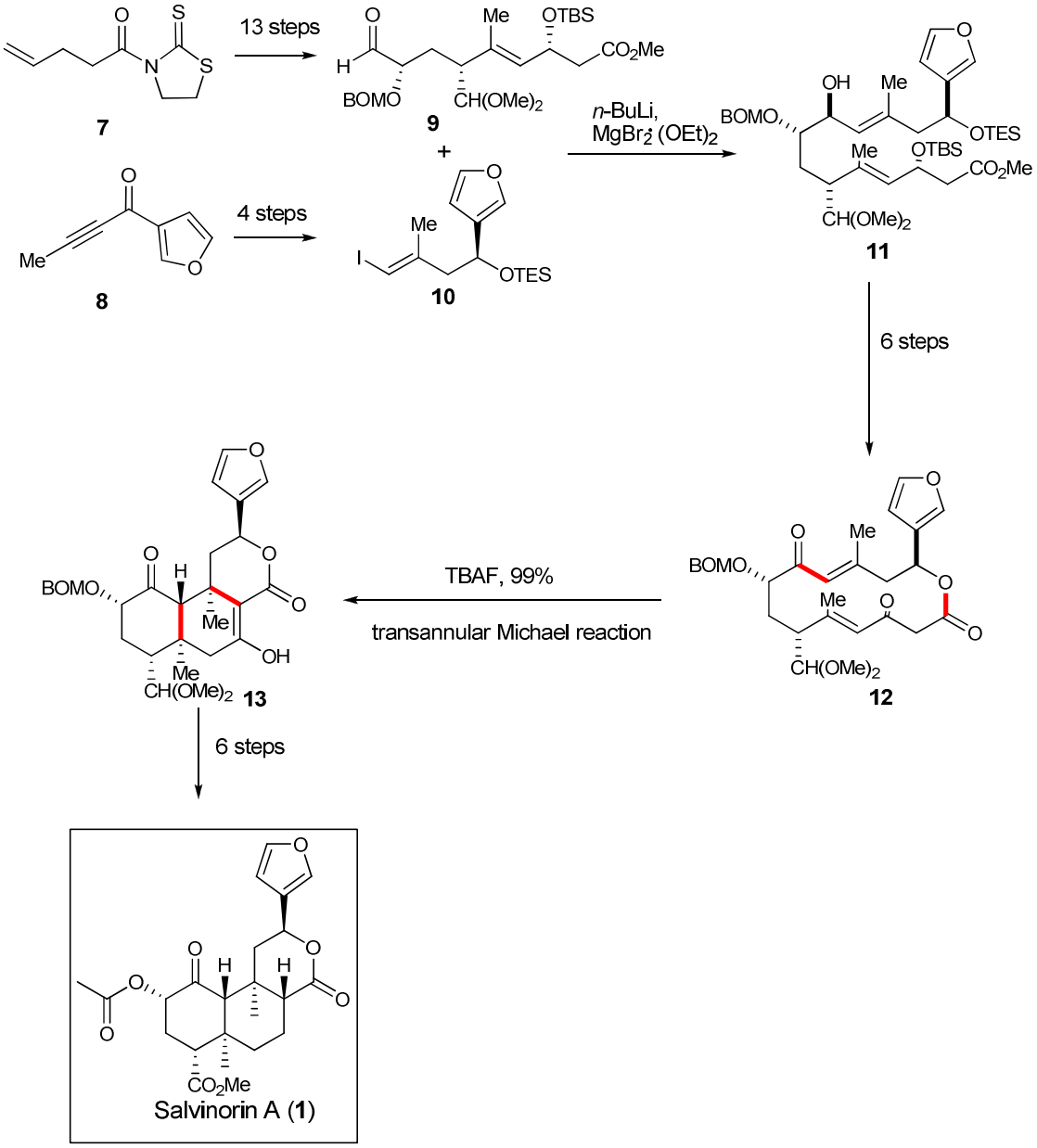
Figure 2. Proposed Biosynthesis of Salvinorin A (**1**)

In the past several years, salvinorin A (**1**) and it analogs have drawn much attention because of their significant biological activity and the challenging tricyclic core structure. The core includes seven asymmetric centers and five oxygenated functionalities. To date, only two total synthesis of **1** have been reported, while several semi-synthetic derivatives have been prepared and evaluated. [21-24]

In 2007, Evans *et al.* reported the first total synthesis of **1** in 33 steps, based on a transannular sequential Michael reaction from macrocyclic lactone **12**, as their key step, to construct the tricylic core structure (Scheme 1).[22] Initially, the aldehyde **9** was synthesized

from commercially available thiazolidinethione **7** in 13 steps. Vinylic iodide **10** was prepared by asymmetric reduction of ketone **8**, followed by alkyne isomerization, carboalumination and protection in 4 steps.

Scheme 1

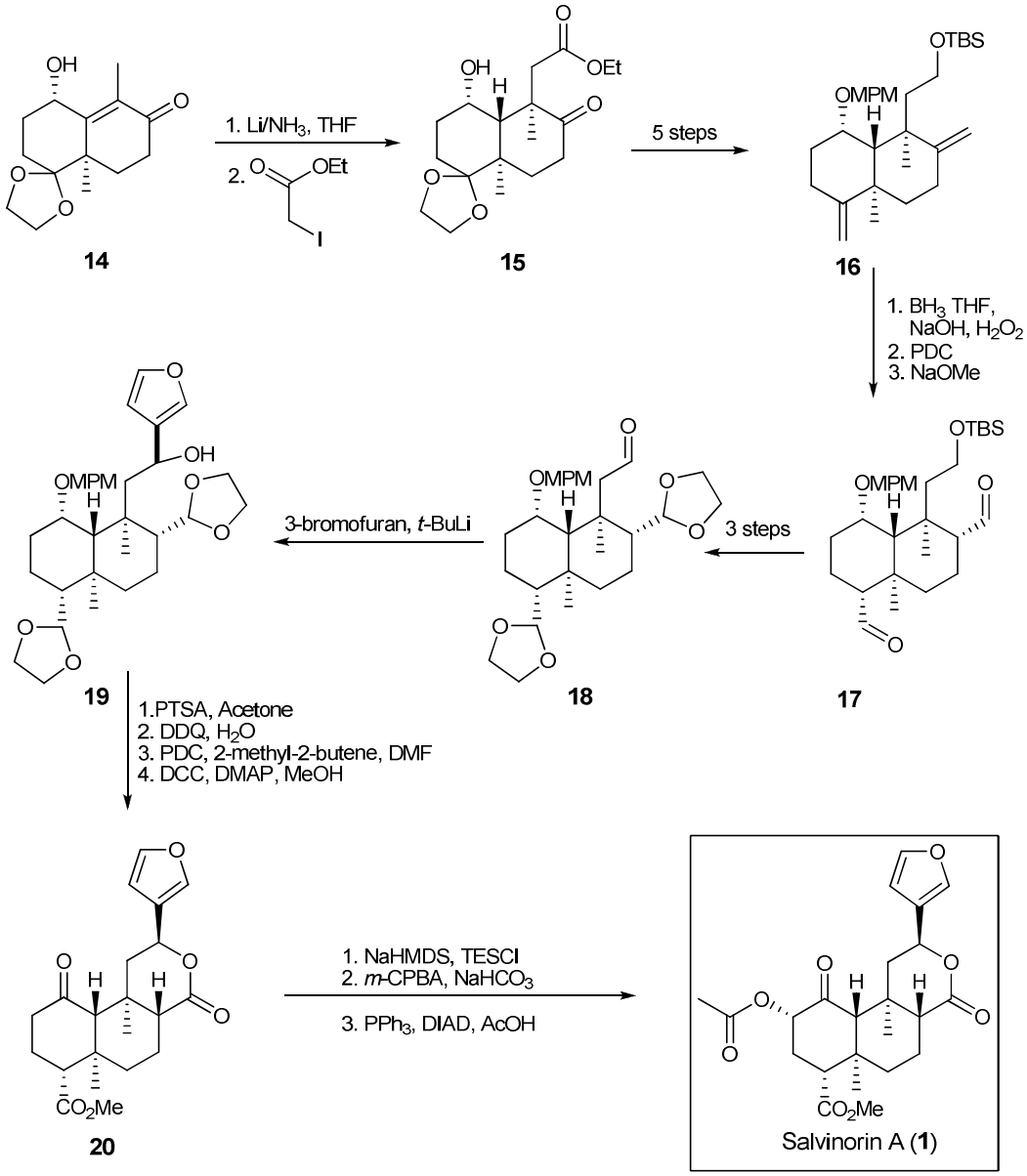


The coupling reaction of a Grignard reagent from **10** and the aldehyde **9** afforded the allylic alcohol **11**. Selective protection of secondary alcohol **11**, followed by Shiina macrolactonizaion, desilylation and oxidation, in 6 steps, produced the macrocycle **12**. The tricyclic core of **1** was accomplished by a transannular Michael reaction. Intermediate **12** was treated with TBAF at -78 ^{o}C and warmed to 5 ^{o}C to give a single diastereomer in excellent yield. Another 6 steps, involving deoxygenation and conjugate reduction, and finally epimerization completed construction of salvinorin A (**1**).

Evans' group completed the total synthesis of the target molecule by a unique synthetic strategy and this provides a new methodology to construct analogs of compound **1** with similar polycyclic core structures.

A recent report[24] from Hagiwara's group showed another total synthesis of salvinorin A (**1**) in 20 steps starting from the known Wieland-Miescher ketone **14** (Scheme 2). Reductive alkylation of **14** with lithium in liquid ammonia with ethyl iodoacetate gave intermediate **15** with three asymmetric centers. The next five steps included hydrolysis, Wittig reaction, LAH reduction and selective diol protection. This afforded the *bis*-olefin **16**. Hydroboration, followed by PDC oxidation and epimerization with sodium methoxide, gave the thermodynamically stable *bis*-aldehyde **17**. After three more steps, aldehyde **18** was achieved by protection and oxidation. Metal-halogen exchange between the bromofuran and *t*-BuLi and subsequent treatment with **18** yielded adduct **19**. Treatment of **19** with acid, followed by deprotection, oxidation and esterification, afforded compound **20**. Introduction of an α-acetoxy group in three steps completed the synthesis of salvinorin A (**1**).

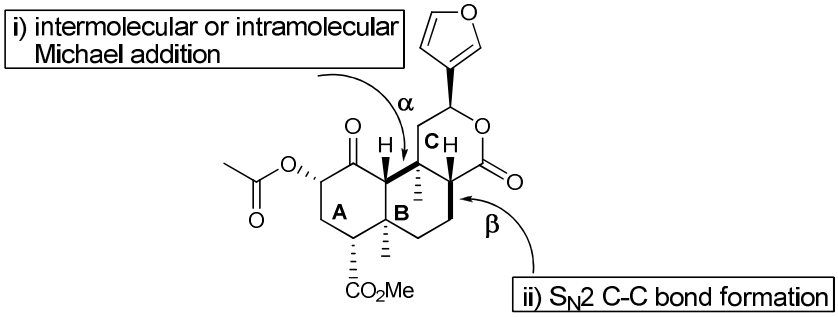
Scheme 2



Hagiwara's synthetic route is straightforward and involves some interesting strategies, but some low yielding steps limit the practical use of this synthetic method for this family of analogs.

Results and Discussion

In our initial approach, we envisioned forming the B ring from a commercially available A ring precursor (Figure 3). So our strategy focused on B ring formation involving i) an intermolecular or intramolecular Michael addition to form the bond **α** and ii) an S_N2 reaction to form the **β** bond.



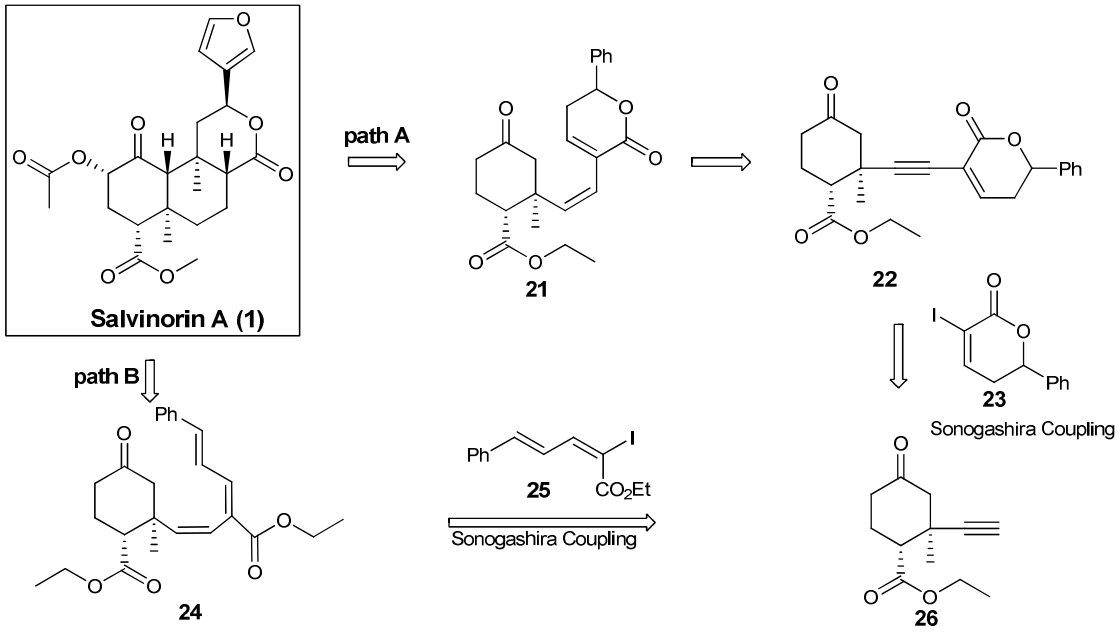
Salvinorin A (1)

Figure 3. Structure Analysis of Salvinorin A (**1**)

The following retrosythetic scheme (Scheme 3) suggests two possible pathways A and B, which could by an intramolecular Michael addition afford **α** bond and furnish the B ring. The intermediate **21** could be made via selective reduction of the internal triple bond to form the *cis*-double bond in alkyne **22** by hydrogenation. A Sonogashira coupling reaction of 5,6-dihydro-pyran-2-one (**23**) with alkyne ester **26** would afford compound **22**. The possible problem for pathway A is that the *α,β*-unsaturated pyran-2-one may not be a good Michael acceptor to furnish the B ring via an intramolecular Michael addition. To solve this problem, by an alternate pathway B, we planned to use an *α,β*-unsaturated ester as the Michael acceptor, followed by lactonization to produce compound **1**. Similarly, the Sonogashira

coupling reaction of iodo compound **25** and **26**, followed Lindlar hydrogenation, could give compound **24**.

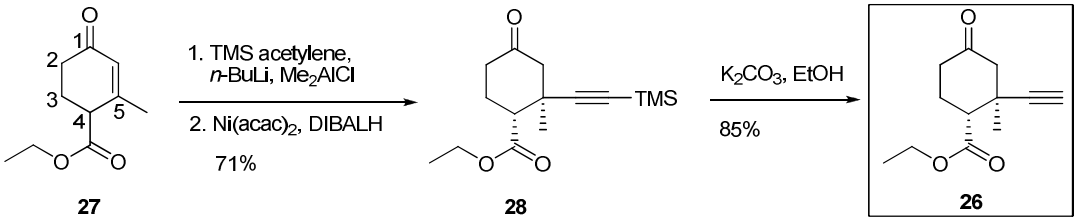
Scheme 3



The first key intermediate is alkyne **26**, which was obtained by a three-step procedure starting from commercially available **27**. Michael addition of TMS-ethynyl dimethyl aluminum to the *α,β*-unsaturated cyclohexanone **27** using $Ni(acac)_2$ and DIBALH conditions, followed by desilylation with potassium carbonate in ethanol gave a 60% isolation yield of the desired alkyne **26**. One advantage of this starting compound **27** is that it has all the necessary functional groups of the A ring for target molecule **1**, except the α-acetoxy group at C2, which can be introduced later according to Hagiwara's method. Another advantage is that the "allylic strain" between the 5-methyl and 4-ethyl ester will

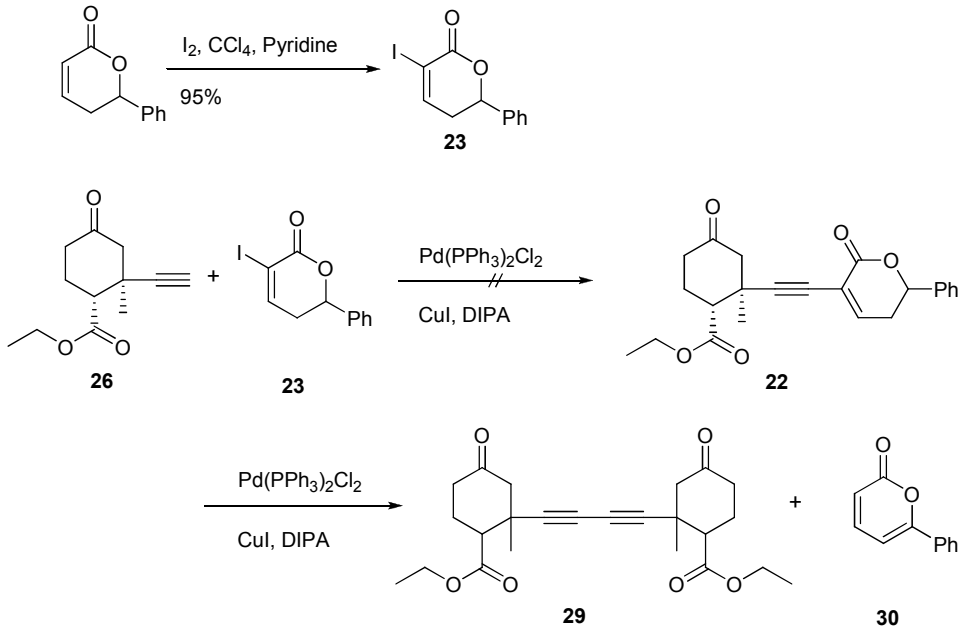
afford the Michael addition product (*cis* for the 5-methyl and 4-ester), which perfectly matches the target molecule.

Scheme 4

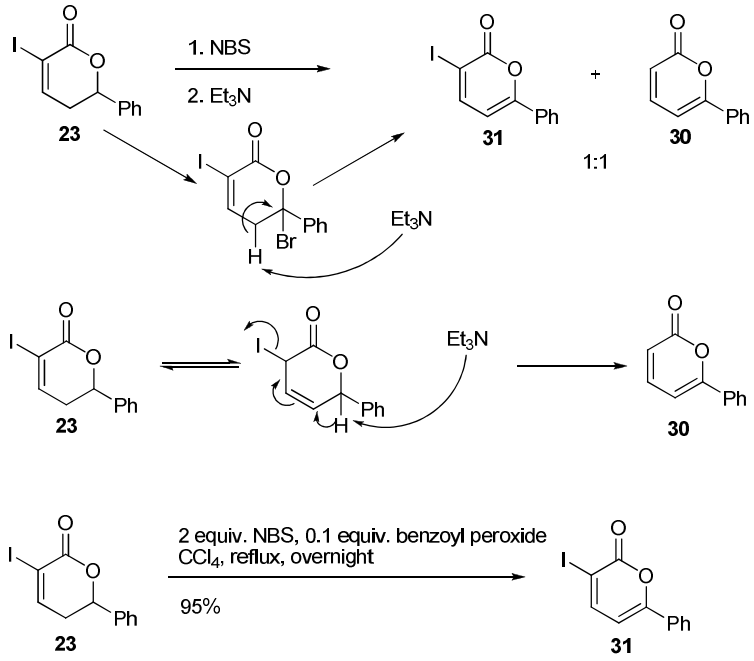


The intermediate iodopyranone **23** was obtained in one step from a known compound, 6- phenyl-5,6-dihydro-pyran-2-one**,** by iodination in carbon tetrachloride in 95% yield (Scheme 5). Unfortunately, the Sonogashira coupling reaction between compounds **26** and **23** failed under several standard conditions. Instead of the desired alkyne **22**, the self-coupling compound **29** and the oxidation product **30** were observed. The self coupling reaction from the alkyne is always a by-product of Sonogashira coupling reactions. Compound **23** may not be stable under these conditions. However, **31** might be stable under the Sonogashira reaction conditions. Two conditions have been tried to prepare the iodopyrone **31** from **23**. They are shown in Scheme 6. The first conditions only gave a 1:1 mixture of **31** and **30**. Interestingly, if using 2 equivalents of NBS and a catalytic amount of benzoyl peroxide under boiling overnight, compound **31** is produced in a 95% yield.

Scheme 5

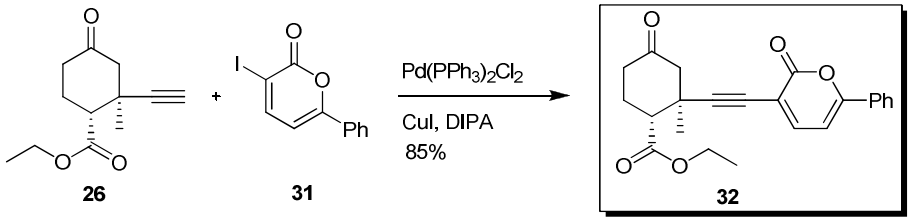


Scheme 6



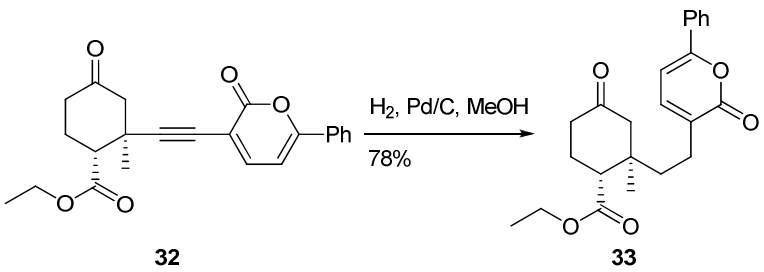
This time the Sonogashira coupling reaction between the alkyne **26** and iodo compound **31** worked very well. It gave the intermediate **32** in an excellent yield (Scheme 7).

Scheme 7

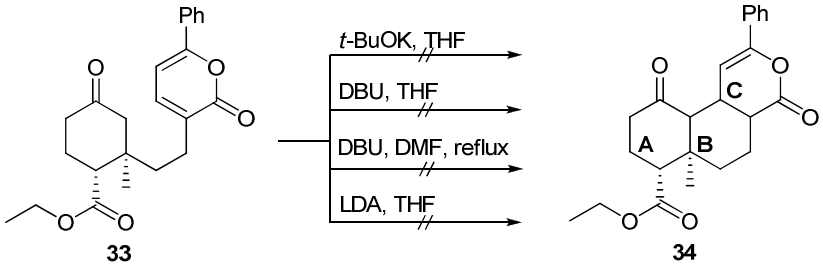


Selective hydrogenation of compound **32** in methanol produced **33** in a 78% yield (Scheme 8). With intermediate **33**, the only step left was the reaction to form the B ring via an intramolecular Michael addition according to the analysis in Scheme 3. If this reaction worked, the tricyclic core of salvinorin A (**1**) would be produced very efficiently in 5 steps. Unfortunately, all attempted intramolecular Michael additions in the presence of various bases, *t*-BuOK in THF, DBU in THF or DMF and LDA in THF, were unsuccessful (Scheme 9).

Scheme 8

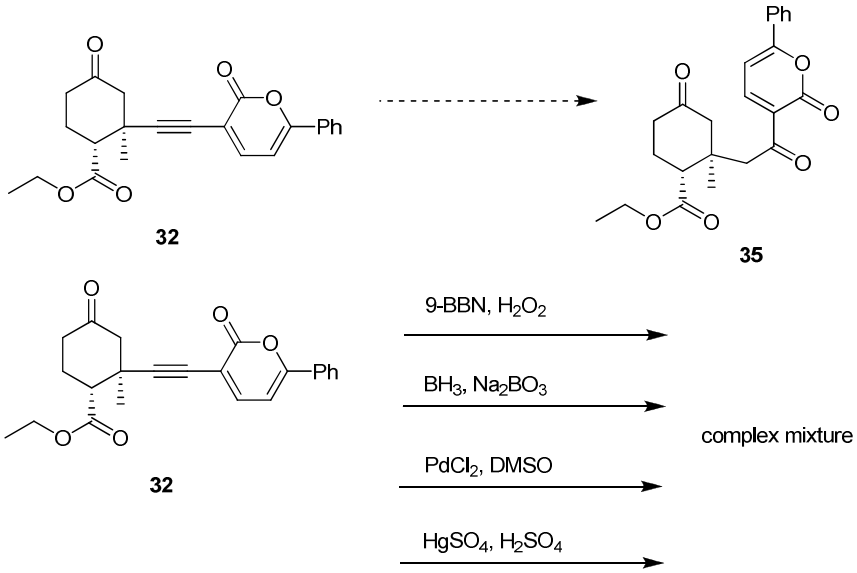


Scheme 9.



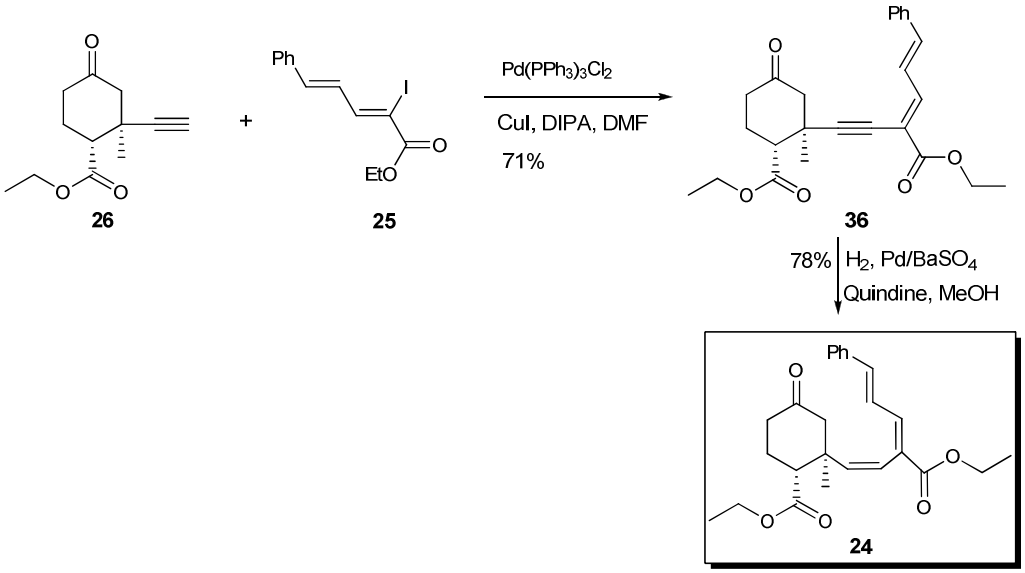
It is possible that the *α,β*-unsaturated pyran-2-one may not be a good enough Michael acceptor to furnish the B ring by an intramolecular Michael addition. To activate the double bond on the unsaturated pyranone, we tried to prepare compound **35**, in which the *α,β*-unsaturated keto ester would be a much better Michael acceptor (Scheme 10). However, all reaction conditions examined gave complex results. It appears difficult to differentiate the internal triple bond from the double bond.

Scheme 10



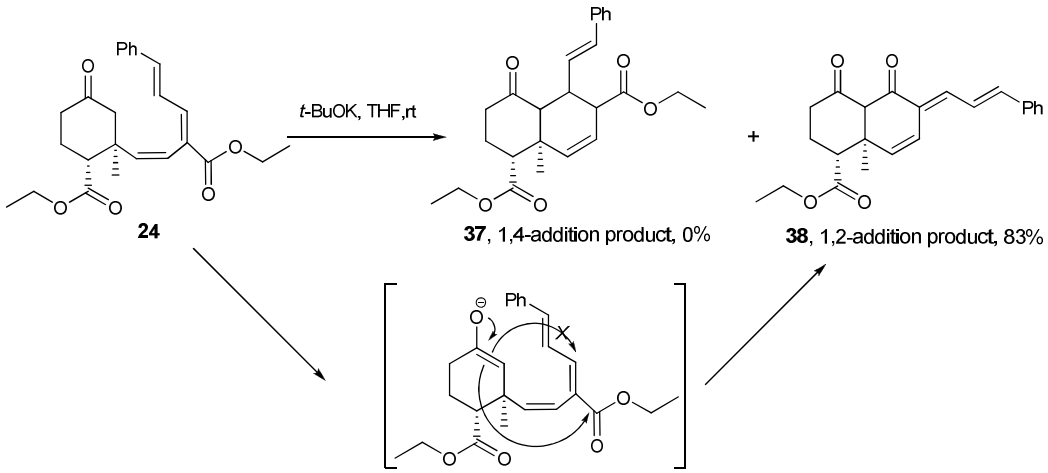
Next we tried to use the *α,β*-unsaturated ester as a Michael acceptor, to form the B ring. The intermediate was made as shown in Scheme 11. A Sonogashira coupling reaction of alkyne **26** with the known *α*-iodo ester **25** gave intermediate **36** in a 71% yield. Hydrogenation with Lindlar's catalyst successfully generated compound **24** with an internal *cis*-double bond. With intermediate **24** in hand, an intramolecular Michael addition should furnish the B ring.

Scheme 11

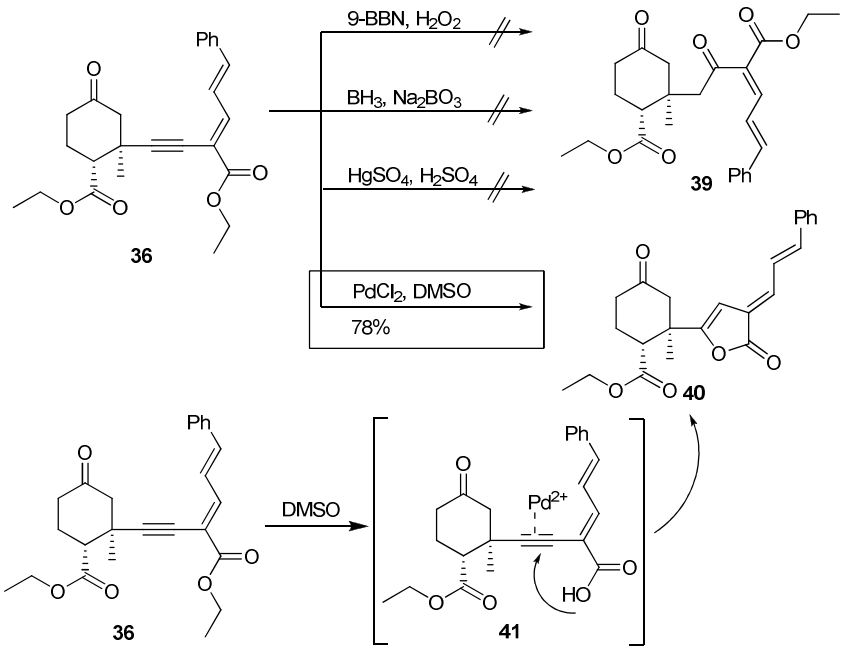


Unfortunately, the attempted carbon-carbon bond formation by an intramolecular Michael addition in the presence of *t*-BuOK in THF was not successful (Scheme 12). Instead of the desired 1,4-addition product **37**, we got the 1,2-addition product **38** in 83% yield. This shows that the *α,β*-unsaturated ester is still not a good enough Michael acceptor. All attempts to prepare compound **39** failed (Scheme 13). Interestingly, when compound **36** was treated

Scheme 12



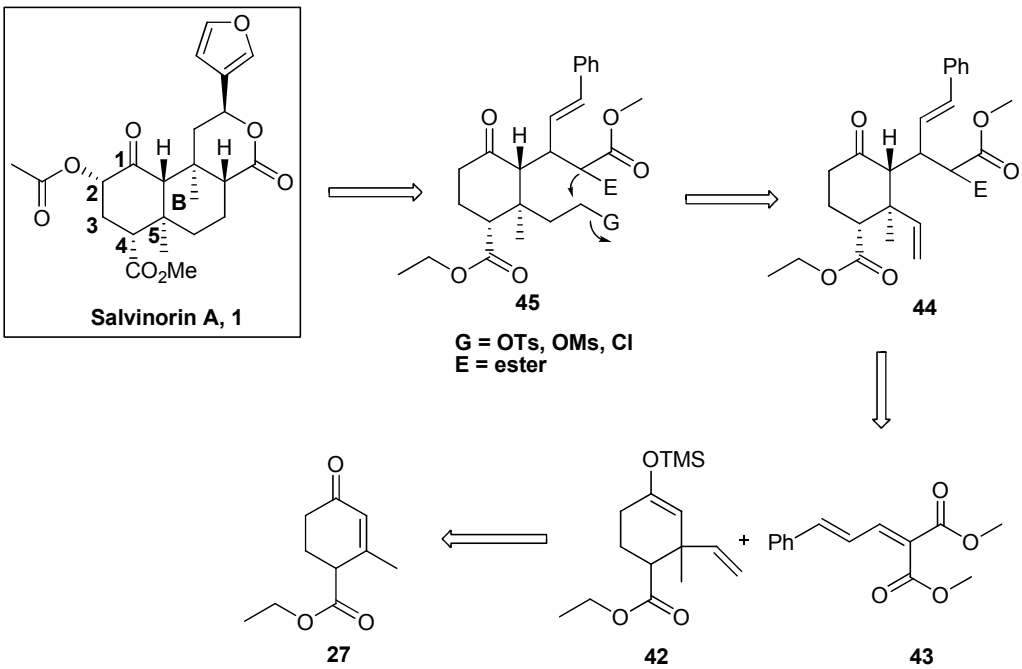
Scheme 13



with palladium chloride in DMSO and heat, furanone **40** was produced in a 72% yield. It is proposed that the ester was hydrolyzed first, followed by cyclization involving palladium assistance.

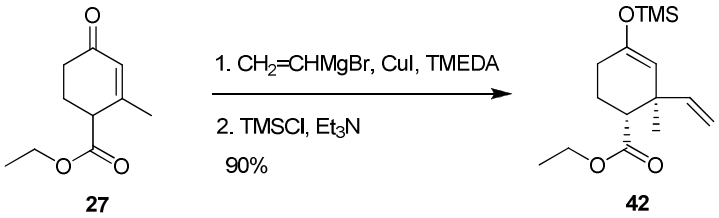
In all previous reactions, the chiral center at C5 restricts the conformations available. To solve this problem, this bond should be made at an early stage of the synthesis as shown in the retrosynthetic analysis in Scheme 14. Intermolecular Micheal addition of the TMS enol silylether **42** and the known malonate **43** could form adduct **44**. Hydroboration of the terminal double bond, selective reduction and tosylation or mesylation would give the intermediate **45**. An intramolecular S_N2 reaction should furnish the B ring and give the bicyclic core structure of salvinorin A (**1**).

Scheme 14



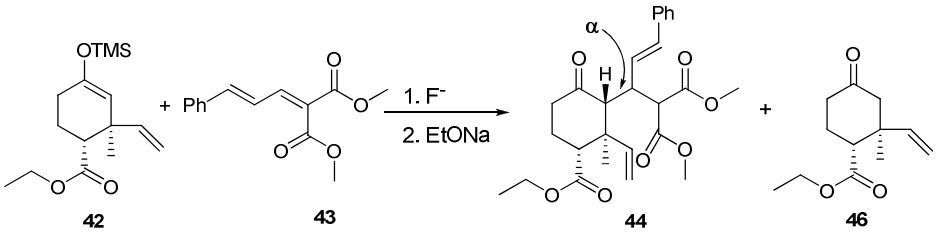
A 1,4-addition of compound **27** with vinyl Grignard and copper iodide, followed by addition of TMS choride and triethylamine, provided the enol silyl ether **42** in a 90% yield (Scheme 15).

Scheme 15



With intermediate **42** in hand, several conditions were examined for an intermolecular Michael addition with compound **43** and the results are summarized in Table 1. Under $TiCl_4$ conditions, we did not get any of the desired compound **44** and only the de-silylated by-

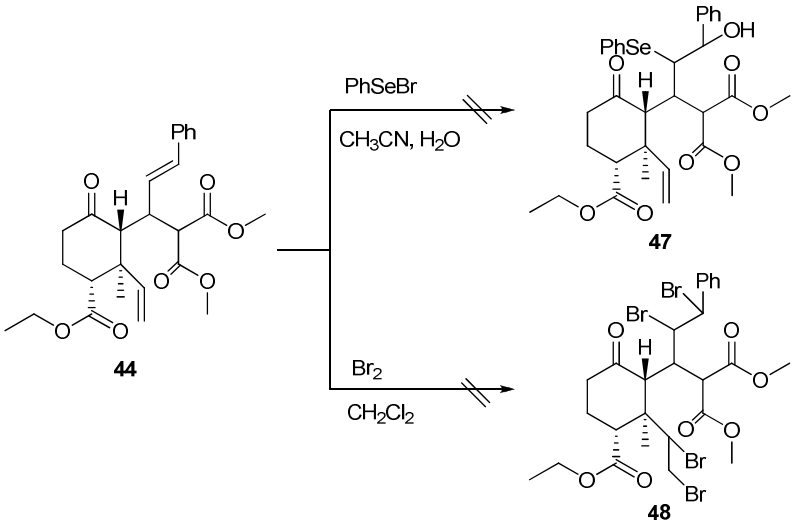
Table 1. Intermolecular Michael addition to form the α bond of B ring



entry	reagent	solvent	temperature (°C)	time (h)	yield (%)	
					44	**46**
1	$TiCl_4$	CH_2Cl_2	-78 → 0	5	0	67
2	TBAF	THF	RT	3	29	60
3	CsF	CH_3CN	RT	12	40	42
4	CsF	DMF	RT	4	52	33

product **46** was obtained in a 67% yield. Under TBAF conditions, the desired compound **44** was prepared in a 29% yield. The best yield obtained was 52% with 3 equivalents of CsF in DMF.

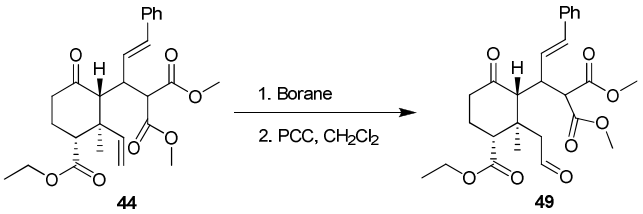
Scheme 16.



After the successful Michael addition, the next step was to explore the possibility of furnishing the B ring by an aldol reaction or S_N2 reaction. There are two double bonds in the molecule. One is a terminal double bond and the other one is an internal double bond, which is conjugated with the phenyl group. It is believed that the terminal double bond is less hindered and more electron-deficient than the internal double bond. Several conditions were tried to differentiate these two alkenes. Treating compound **44** with phenylselenium bromide in acetonitrile and water gave a very complex reaction (Scheme 16). We also tried to

brominate the two double bonds at the same time, which also gave a messy reaction. Hydroboration of the terminal double bond with borane in THF, followed by oxidization with PCC, gave the desired aldehyde **49** in a 45% yield (Table 2). After optimization (entry 3, Table 2), the best yield was 75% based on recovered starting material (72% of the starting material was recovered).

Table 2. Selective hydroboration of the terminal double bond

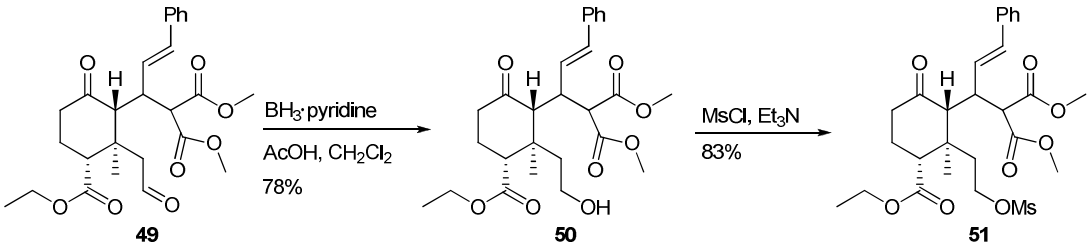


entry	Borane reagent	equivalent	temperature (^{o}C)	time (h)	SM recovered (%)	Yield[a] (%)
1	BH_3·THF	0.33	RT	3	34	45
2	BH_3·Me_2S	0.33	RT	3	44	52
3	dicyclohexyl borane	1.00	RT	12	72	75
4	dicyclohexyl borane	2.00	RT	12	55	56
5	dicyclohexyl borane	1.00	RT→reflux	3→2	50	55

[a] based on recovered starting material

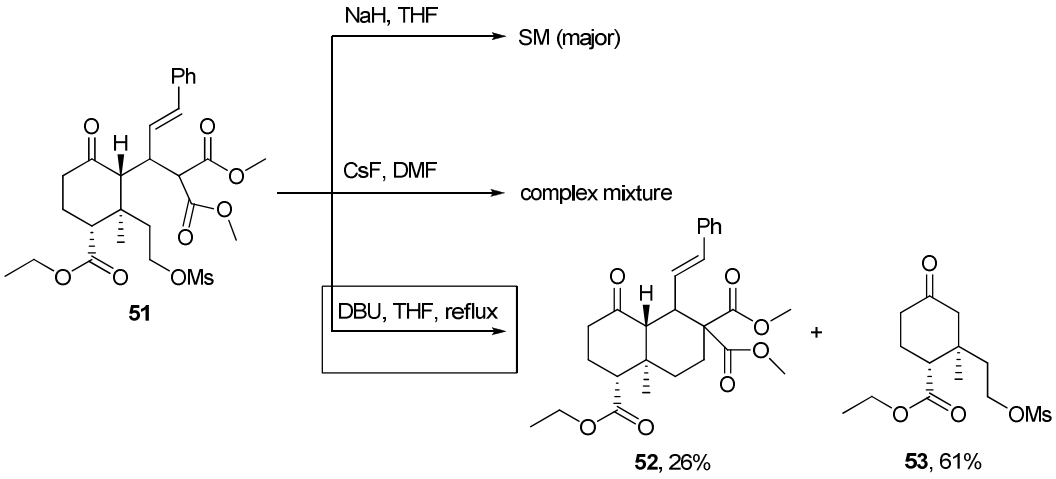
With compound **49** in hand, selective reduction of the aldehyde with a borane pyridine complex under DiMare's conditions[25] gave the desired alcohol **50** in a 78% yield (Scheme 17). Mesylation of compound **50** gave mesylate **51** in a 83% yield.

Scheme 17

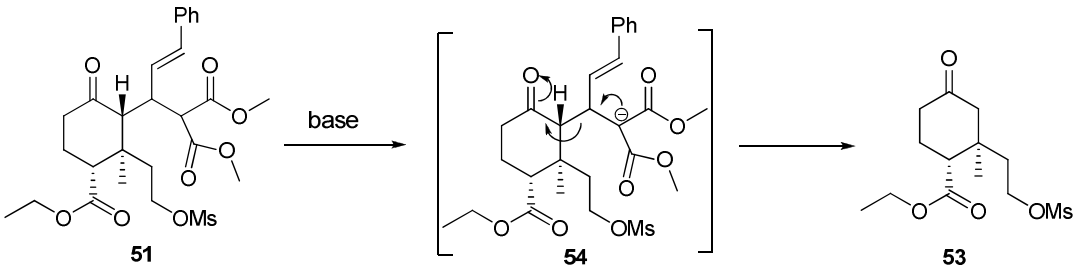


Due to the steric hinderance in mesylate **51**, the desired bicyclic compound **52** was formed in only a 26% yield and the by-product **53** was formed in a 61% yield, when treated with DBU in THF (Scheme 18). It is believed that the formation of **53** results from a retro-Michael addition via intermediate **54** (Scheme 19).

Scheme 18

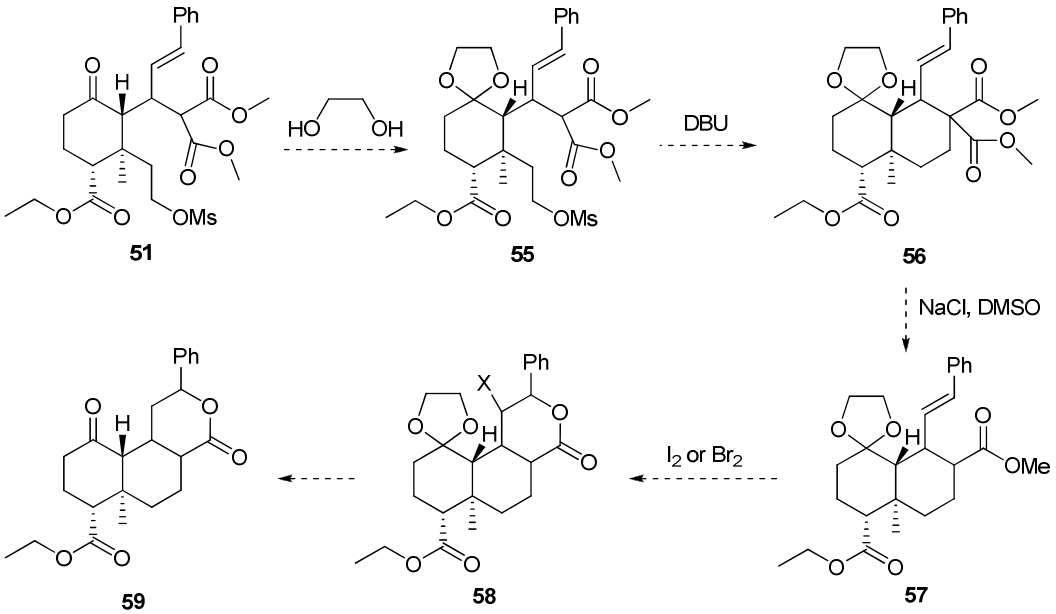


Scheme 19



Protection of the ketone as an enol would avoid the retro-Michael addition. An intramolecular S_N2 reaction should then give the bicyclic intermediate **56** (Scheme 20). The lactone ring C should be realized in several additional steps.

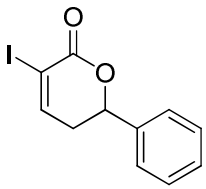
Scheme 20



In conclusion, two synthetic routes to the highly funtionalized bicyclic core skeleton of salvorin A (**1**) have been achieved. The Sonogashira coupling of an alkyne intermediate with iodo alkenes has provided some advanced intermediates with an A ring and a C ring. The second route to compound **1** using an intermolecular Michael addition and intramolecular S_N2 reaction formed the important B ring. Lactonization should give the tricyclic core structure of salvorin A (**1**).

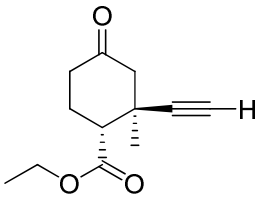
Experimetal

All ^1H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz respectively. All melting points are uncorrected. Unless as otherwise indicated, all reactions were carried out under argon. Thin layer chromatography was performed using commercially prepared 60-mesh silica gel plates (Whatman K6F), and visualization was effected with short wavelength UV light (254 nm). High resolution mass spectra were recorded on a Kratos MS50TC double focusing magnetic sector mass spectrometer using EI at 70 eV. All reagents were used directly as obtained commercially unless otherwise noted. All yields reported represent an average of at least two independent runs.



3-Iodo-6-phenyl-5,6-dihydro-pyran-2-one (23)

A mixture of compound **33** (0.09 g, 0.3 mmol), NBS (0.107 g, 0.6 mmol) and benzoyl peroxide (0.007 g, 0.03 mmol) in 8 mL of CCl_4 under the argon was boiled overnight (12 h). The reaction was concentrated, followed by column chromatography of the residue using ethyl acetate: hexanes = 1:2, to give compound **13** (89 mg, 100%) as a white solid; mp = 130-132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.60-7.62 (dd, *J* = 6.4, 2.8 Hz, 1H), 7.34-7.41 (m, 5H), 5.50-5.54 (dd, *J* = 12.0, 4.0 Hz, 1H), 2.57-2.80 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 160.2, 153.9, 137.5, 129.0, 128.9, 126.2, 89.6, 80.0, 35.6. MS electrospray (m/z): 300.



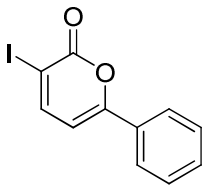
Ethyl 2-ethynyl-2-methyl-4-oxocyclohexanecarboxylate (26)

To 0.71 g (7.23 mmol) of trimethylsilyl acetylene in 20 mL of dry diethyl ether at -40 ^{o}C was added 2.9 mL (7.23 mmol) of a 2.5 M solution of *n*-BuLi in hexane slowly. The reaction mixture was allowed to stir at -40 ^{o}C for 1.5 h and then cannulated dropwise into 7.23 mL (7.23 mmol) of a 1.0 M solution of dimethylaluminum chloride in ether at rt. The reaction mixture was allowed to stir for 3.5 h at rt and then filtered to remove the LiCl precipitate.

To 0.186 g (0.723 mmol) of $Ni(acac)_2$ in 30 mL of ether at 0 ^{o}C was added 0.66 mL of a 1.0 M solution of DIBAH (0.66 mmol) in toluene. Then the solution of dimethyl TMS acetylene aluminum in ether (7.23 mmol), prepared previously, was added to this red-brown reaction mixture. The temperature of the reaction mixture was lowered to -5 ^{o}C, and 0.6 g

(3.29 mmol) of ethyl 2-methyl-4-oxo-2-cyclohexenecarboxylate in 20 mL of ether was added dropwise over 15 min to the reaction mixture. The reaction mixture was allowed to stir at -5 ^{o}C for 5 h and was hydrolyzed with saturated aqueous KH_2PO_4. Enough 10% aqueous H_2SO_4 was added to dissolve the Al salts. The organic layer was separated, extracted with ether, washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaC1, dried with Na_2SO_4, filtered, and rotary evaporated. The crude product **28** (0.66g, yield 71%) was used for next step without any further purification.

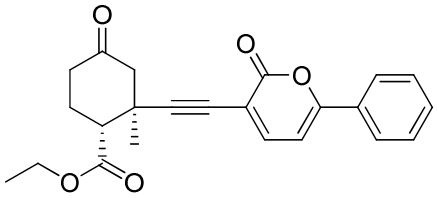
To a solution of compound **28** (202 mg, 0.72 mmol) in 15 mL of ethanol, 0.5 g of potassium carbonate (3.6 mmol) was added at rt. The mixture was stirred for 4 h, diluted with water and extracted with ether. The combined organic phases were dried, concentrated and purified by silica gel chromatography, yielding **26** (127 mg, 85% yield) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) 4.16-4.25 (m, 2H), 2.93-2.97 (dd, *J* = 14.0, 0.8 Hz, 1H), 2.86-2.88 (t, *J* = 4.8Hz, 1H), 2.58-2.63 (m, 1H), 2.30-2.45 (m, 3H), 2.29 (s, 1H), 2.09-2.16 (m, 1H), 1.37 (s, 3H), 1.28-1.32 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 208.4, 172.8, 87.4, 71.8, 60.8, 50.9, 47.7, 37.4, 37.2, 25.5, 25.4, 14.3; MS electrospray (m/z): 208.



3-Iodo-6-phenyl-pyran-2-one (31)

A mixture of compound **23** (0.09 g, 0.3 mmol), NBS (0.107 g, 0.6 mmol) and benzoyl peroxide (0.007 g, 0.03 mmol) in 8 mL of CCl_4 under the argon was boiled overnight. The reaction was concentrated, followed by column chromatography of the residue using 1:2

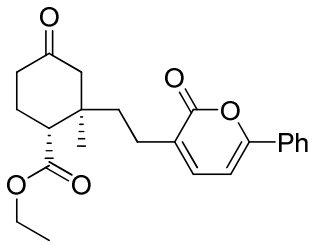
ethyl acetate: hexanes, to give compound **31** (89 mg, 100%) as white solid; mp = 130-132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.77-7.82 (m, 3H), 7.43-7.49 (m, 3H), 6.57-6.59 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 160.6, 158.4, 145.1, 131.3, 130.6, 129.1, 125.6, 109.8, 101.6; MS electrospray (m/z): 298.



Ethyl 2-methyl-4-oxo-2-[(2-oxo-6-phenyl-pyran-3-yl)ethynyl]- cyclohexanecarboxylate (32)

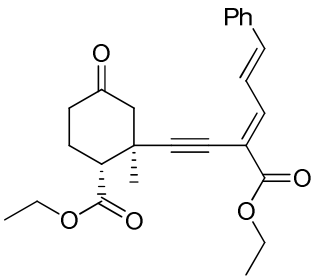
To the mixture of the lactone **31** (0.052 g, 0.174 mmol), $Pd(PPh_3)_2Cl_2$ (0.004 g, 0.0052 mmol), and CuI (0.001 g, 0.0052 mmol) in 1.7 mL of DMF, diisopropylamine (0.098 mL, 0.70 mmol) was added at rt under an argon atmosphere. Then the mixture was warmed to 70 °C over 10 min. After 5 min at 70 °C, the compound **26** (0.036 g, 0.174 mmol) in 1.7 mL of DMF was added to the reaction mixture over 10 min and stirring was continued for 4 h. The reaction was quenched by the addition of water at rt. The product was extracted twice with ethyl acetate and the combined organic layers were washed with brine. Evaporation of the solvent, followed by column chromatography of the residue using ethyl acetate: hexanes = 1:3, gave compound **32** (57 mg, 87%) as pale yellow solid; mp = 114-116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.74-7.76 (m, 2H), 7.39-7.46 (m, 4H), 6.62-6.64 (d, *J* = 7.2 Hz, 1H), 4.14-4.20 (m, 2H), 2.97-3.01(m, 2H), 2.30-2.64 (m, 4H), 2.10-2.14 (m, 1H), 1.40 (s, 3H), 1.24-1.28 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 208.4, 172.8, 160.5, 145.9, 131.2,

130.8, 129.4, 125.7, 110.0, 101.2, 99.5, 78.2, 77.5, 77.2, 76.9, 60.8, 50.7, 47.6, 38.2, 37.5, 25.5, 2.3, 14.3; MS electrospray (m/z): 378.



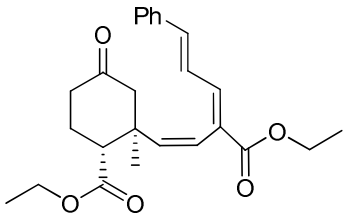
Ethyl 2-methyl-4-oxo-2-[2-(2-oxo-6-phenyl-pyran-3-yl)ethyl]- cyclohexanecarboxylate (33)

A dried round bottom flask with a stirring bar was charged with 10% Pd/C (0.03 g, 0.03 mmol), compound **32** (0.060 g, 0.16 mmol) and 1.6 mL of methanol, flushed with hydrogen and a hydrogen balloon added though a septum. After 10 min at room temperature, the reaction was quenched by filtration through a pad of Celite. Evaporation of the solvent, followed by column chromatography of the residue using ethyl acetate: hexanes = 1:2, gave compound **33** (43 mg, 72%) as colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) 7.79-7.81 (m, 2H), 7.43-7.45 (m, 3H), 7.20-7.22 (d, *J* = 6.8 Hz, 1H), 6.60-6.62 (d, *J* = 6.8 Hz, 1H), 4.16-4.22 (m, 2H), 2.79-2.82 (t, *J* = 6.0 Hz, 1H), 2.27-2.63 (m, 6H), 2.12-2.17 (m, 2H), 1.61-1.63 (m, 2H), 1.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 210.5, 173.7, 162.8, 15.8, 139.2, 131.4, 130.5, 129.0, 127.3, 125.3, 101.2, 60.6, 51.5, 47.5, 40.4, 39.2, 38.9, 24.8, 24.6, 22.0, 14.4; MS electrospray (m/z): 382.



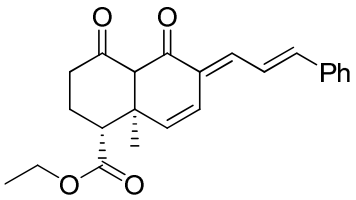
Ethyl 2-((3*E*,5*E*)-3-(ethoxycarbonyl)-6-phenylhexa-3,5-dien-1-ynyl)-2-methyl-4-oxocyclohexanecarboxylate (36)

To the mixture of the cinnamyl ester **25** (0.125 g, 0.38 mmol), $Pd(PPh_3)_2Cl_2$ (0.008 g, 0.0114 mmol), and CuI (0.002 g, 0.0114 mmol) in 3.0 mL of DMF, diisopropylamine (0.213 mL, 1.52 mmol) was added at room temperature under an argon atmosphere. Then the mixture was warmed up to 70 °C over 10 min. After stirring for 5 min at 70 °C, the compound **26** (0.079 g, 0.38 mmol) in 3.0 mL of DMF was added to the reaction mixture over 10 min and stirring was continued for 4 h. The reaction was quenched by the addition of water at room temperature. The product was extracted twice with ethyl acetate and the combined organic layers were washed with brine, and dried over Na_2SO_4. Evaporation of the solvent, followed by column chromatography of the residue using ethyl acetate: hexanes = 1:7, gave compound **36** (103 mg, 67%) as a yellow oil.



Ethyl 2-((1*Z*,3*E*,5*E*)-3-(ethoxycarbonyl)-6-phenyl-hexa-1,3,5-trienyl)-2-methyl-4-oxocyclohexanecarboxylate (24)

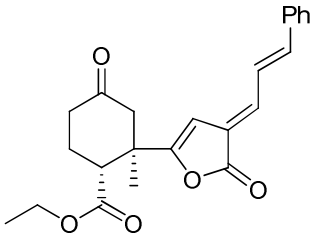
A dried round bottom flask with a stirring bar was charged with 0.013 g (0.006 mmol) of $Pd/BaSO_4$ and a drop of quinoline in 5 mL of diethyl ether. After flushing with H_2, compound **36** in 1 mL of diethyl ether was introduced. After stirring overnight with a H_2 balloon on top of the flask, the solvent was evaporated and then 10 mL of ethyl acetate was added. The organic layer was washed with 10 mL of 1 N hydrochloric acid solution, followed by 20 mL of saturated aqueous $NaHCO_3$, and then 20 mL of saturated aqueous NaC1, and dried over Na_2SO_4. The reaction mixture was concentrated, followed by column chromatography of the residue using ethyl acetate: hexanes = 1:7, gave compound **24** (40 mg, 80%) as yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) 7.49-7.50 (d, *J*=7.2 Hz, 2H), 7.29-7.38 (m, 4H), 6.90-7.05 (m, 2H), 6.01-6.04 (d, *J*=12.8 Hz, 1H), 5.70-5.73 (d, *J* = 12.8 Hz, 1H), 4.23-4.28 (q, *J* = 7.2 Hz, 2H), 4.11-4.17 (q, *J* = 7.2 Hz, 2H), 2.84-2.87 (m, 1H), 2.44-2.54 (m, 3H), 2.07-2.27 (m, 3H), 1.14-1.36 (m, 6H), 1.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 209.5, 173.2, 166.8, 140.5, 140.2, 136.3, 129.1, 128.9, 128.8, 127.4, 124.8, 122.7, 61.0, 60.5, 51.4, 49.3, 43.6, 38.7, 24.7, 21.9, 14.4, 14.3; MS electrospray (m/z): 410.



(*E*)-Ethyl-8a-methyl-4,5-dioxo-6-((*E*)-3-phenylallylidene) octahydronaphthalene-1-carboxylate (38)

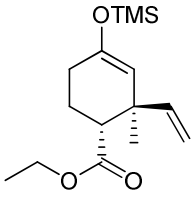
To the solution of compound **24** (0.035 g, 0.085 mmol) in 1 mL of THF, 0.043 mL of *t*-BuOK in THF (1 M, 0.043 mmol) was added at rt. The color of the mixture changed from colorless to bright yellow. After 1 h at rt, the reaction mixture was concentrated. Redesolved

in 10 mL of EtOAc and washed with 10 mL of saturated NH_4Cl and brine and dried over $MgSO_4$. Evaporation of the solvent, followed by column chromatography of the residue using ethyl acetate: hexanes = 1:2, gave compound **38** (43 mg, 72%) as yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) 7.50-7.52 (d, *J* = 8.0 Hz, 2H), 7.35-7.39 (m, 2H), 7.22-7.32 (m, 3H), 6.93-6.96 (d, *J* = 13.2 Hz, 1H), 6.71-6.74 (d, *J* = 10.4 Hz, 1H), 6.08-6.10 (d, *J* = 10.4 Hz, 1H), 4.21-4.26 (m, 2H), 2.56-2.77 (m, 4H), 2.25-2.37 (m, 1H), 2.04-2.06 (m, 1H), 1.27-1.33 (m, 3H), 1.22 (s, 3H); MS electrospray (m/z): 364.



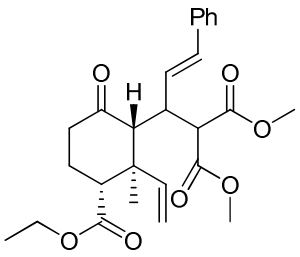
Ethyl 2-methyl-4-oxo-2-((*E*)-5-oxo-4-[(*Z*)-3-phenylallylidene)-4,5-dihydrofuran-2-yl]-cyclohexanecarboxylate (40)

To a solution of compound **36** (0.062 g, 0.155 mmol) in 3 mL of DMSO, palladium chloride (0.004g, 0.0155 mmol) was added at rt. The reaction mixture was warmed to 80 ^{o}C. After 6 h at 80 ^{o}C, the resulting mixture was filtered to remove the insoluble catalyst. EtOAc was added and the mixture was washed by brine and dried over $MgSO_4$. Evaporation of the solvent, followed by column chromatography of the residue using ethyl acetate: hexanes = 1:3, gave compound 40 (43 mg, 72%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) 7.53-7.55 (m, 2H), 7.36-7.43 (m, 2H), 7.15-7.18 (m, 1H), 7.05-7.07 (m, 2H), 6.14 (s, 1H), 4.10-4.21 (m, 2H), 3.27-3.30 (m, 1H), 2.61-2.77 (m, 3H), 2.35-2.42 (m, 1H), 2.05-2.15 (m, 1H), 1.35 (s, 3H), 1.22-1.25 (t, *J* = 7.2 Hz, 3H); MS electrospray (m/z): 380.



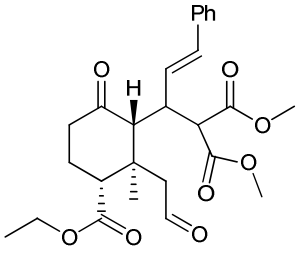
Ethyl 2-methyl-4-(trimethylsilyloxy)-2-vinylcyclohex-3-enecarboxylate (42)

At a room temperature slurry of CuI (210 mg, 1.098 mmol) in 20 ml of THF was added 2.5 mL of TMEDA (16.4 mmol) and stirred until homogeneous. The solution was cooled to -78 ^{o}C, 11 mL of vinylmagnesium bromide in THF (1.0 M, 11 mmol) was added dropwise, and the mixture was then stirred for an additional 10 min. A solution of enone **27** (1.00 g, 5.49 mmol) in 40 mL of THF was added dropwise by a cannula, and the solution was allowed to stir for 10 min further. A mixture of freshly distilled TMSCl and Et_3N (1:1 v/v, 5.5 mL) was centrifuged; the supernatant was transferred to the reaction mixture. After 5 min at -78 ^{o}C, the dry ice bath was replaced with an ice-water bath. The mixture was stirred until TLC analysis showed complete reaction (usually after 1-3 h). The reaction was quenched by adding 50 mL of EtOAc and 50 mL of aqueous NH_4OH. The combined organic solutions were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Chromatography afforded **42** (1.33 g, 86% yield) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) 5.81-5.88 (q, J = 6.8 Hz, 1H), 4.93-4.98 (m, 2H), 4.54 (s, 1H), 4.02-4.13 (m, 2H), 2.33-2.37 (m, 1H), 1.78-2.03 (m, 4H), 1.18-1.21 (t, J = 7.2 Hz, 3H), 1.04 (s, 3H), 0.16 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 173.8, 149.7, 147.5, 111.8, 59.9, 48.8, 40.5, 28.6, 22.5, 22.0, 14.3, 0.3; MS electrospray (m/z): 282.



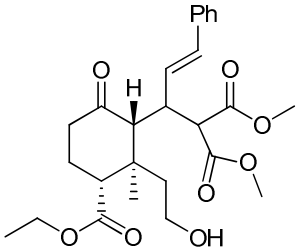
Dimethyl 2-[(*E*)-1-(3-(ethoxycarbonyl)-2-methyl-6-oxo-2-vinylcyclohexyl)-3-phenylallyl]malonate (44)

To the mixture of compound **42** (0.282 g, 1.00 mmol) and malonate **43** (0.295 g, 1.20 mmol) in 10 mL of DMF at room temperature, CsF (0.453 g, 3 mmol) was added in 3 portions over 2 h. After 4 h at rt, the reaction mixture was poured into 50 mL of ice water. The combined aqueous phases were extracted three times with EtOAc. The combined organic solutions were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Chromatography afforded **44** (0.237 g, 52% yield) as a pale oil; ^{1}H NMR (400 MHz, $CDCl_3$) 7.22-7.32 (m, 5H), 6.44-6.48 (d, *J* = 16.0 Hz, 1H), 6.08-6.15 (m, 1H), 5.56-5.64 (q, *J* = 6.8 Hz, 1H), 4.99-5.03 (m, 2H), 4.18-4.21 (m, 2H), 3.88-3.90 (d, *J* = 7.6 Hz, 1H), 3.69 (s, 3H), 3.53-3.56 (m, 1H), 3.10-3.13 (m, 1H), 2.87-2.91 (d, *J* = 14.4 Hz, 1H), 2.63 (s, 1H), 2.46-2.49 (d, *J* = 14.4 Hz, 1H), 2.08-2.09 (m, 1H), 1.82-1.85 (m, 1H), 1.25-1.32 (m, 3H), 1.09 (s, 3H). MS electrospray (m/z): 456.



Dimethyl 2-[(*E*)-1-(3-(ethoxycarbonyl)-2-methyl-6-oxo-2-(2-oxoethyl)cyclohexyl)-3-phenylallyl]malonate (49)

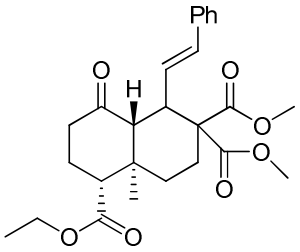
To a solution of borane dimethyl sulfide complex (0.03 g, 0.40 mmol) in 5 mL of THF, cyclohexene (0.08 mL, 0.80 mmol) was added at 0 ^{o}C. After 1 h at 0 ^{o}C, compound **44** (0.182 g, 0.40 mmol) in 2 mL of THF was added to the reaction mixture and slowly warmed to room temperature. After 12 h, the solvent was removed and 5 mL of methylene chloride was added, followed by PCC (0.258g, 1.20 mmol). The reaction mixture was boiled for 4 h. After cooling the solution down to rt, 10 mL of water was added to quench the reaction. The aqueous phases were extracted three times with CH_2Cl_2. The combined organic solutions were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Chromatography afforded **44** (0.041 g, 82% yield based on starting material recovered) as a pale oil and recovered 0.134 g of compound **44**.



Dimethyl 2-[(*E*)-1-(3-(ethoxycarbonyl)-2-(2-hydroxyethyl)-2-methyl-6-oxocyclohexyl) -3-phenylallyl) malonate (50)

To a solution of aldehyde **49** (0.472 g, 1.00 mmol) in 5 mL of methylene chloride under an inert atmosphere, glacial acetic acid (0.06 mL, 1.00 mmol) and pyridine-borane complex (0.05 mL, 0.50 mmol) were added at rt and the reaction was stirred for 3 h. Concentration of the reaction mixture and chromatography afforded alcohol **50** (0.37 g, 78%)

as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) 7.21-7.35 (m, 5H), 6.48-6.52 (d, *J* = 16.0 Hz, 1H), 6.15-6.22 (m, 1H), 4.14-4.21 (m, 2H), 3.87-3.89 (d, *J* = 6.0 Hz, 1H), 3.71-3.75(m, 1H), 3.69 (s, 3H), 3.70 (s, 3H), 3.40-3.46 (m, 1H), 3.17-3.22 (m, 1H), 2.79-2.83 (d, *J* = 13.6 Hz, 1H), 2.72-2.75 (t, *J* = 4.4 Hz, 1H), 2.27-2.30 (d, *J* = 13.6 Hz, 1H), 2.11-2.17 (m, 1H), 1.86-1.92 (m,1H), 1.62 (s, 1H), 1.52-1.58 (m, 2H), 1.26-1.32 (m, 3H), 1.05 (s, 3H); MS electrospray (m/z): 474.



Ethyl 6,6-dimethyl-8-methyl-4-oxo-5-styryloctahydronaphthalene-tricarboxylate (52)

To the solution of mesylate **51** (0.552 g, 1.00 mmol) in 10 mL of THF, 1,8-diazabicyclo[5.4.0]undec-7-ene (0.178 mL, 1.20 mmol) was added under an inert atmosphere. After boiling for 12 h, 20 mL of saturated aqueous ammonium chloride solution was added at rt to quench the reaction. The aqueous phases were extracted twice with ethyl acetate. The combined organic solutions were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Chromatography afforded **52** (0.12 g, 26%) as a clear oil; ^{1}H NMR (400 MHz, $CDCl_3$) 7.20-7.35 (m, 5H), 6.47-6.51 (d, *J* = 15.6 Hz, 1H), 6.23-6.30 (m, 1H), 4.11-4.19 (m, 2H), 3.88-3.90 (d, *J* = 6.0 Hz, 1H), 3.73 (s, 3H), 3.63 (s, 3H), 3.36-3.40 (m, 1H), 2.81-2.86 (m, 1H), 2.57-2.62 (m, 1H), 2.14-2.18 (m, 1H), 1.89-2.04 (m, 3H), 1.75-1.80 (m, 1H), 1.41-1.57 (m, 2H), 1.25-1.32 (m, 3H), 0.99 (s, 3H); MS electrospray (m/z): 456.

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CHAPTER 4. SYNTHETIC APPROACH TOWARDS METHYLLYCACONITINE

Introduction

Diterpenoid alkaloids derived from *Delphinium* species have a long history of being used as medicines, poisons and insecticides.[1] Methyllycaconitine (**1**) (Figure 1) is the principle toxic alkaloid in *Delphinium brownii*,[2] a cattle-stock poison in the western United States and it has been also reported in at least thirty different *Delphinium* species as well as in *Consolida ambigua* and *Inaularoyaleana*.[3,4] When employed in pharmacological studies, methyllycaconitine was found to be a very potent inhibitor of the nicotinic acetylcholine receptor (nAChR) binding in the mammalian and insect neural membranes. It also displayed remarkable selectivity toward neuronal [125I]-α-bunarotoxin binding sites in the mammalian brain.[5] Its high activity and selectivity as an nAChR antagonist have led to extensive use of methyllycaconitine (MLA) (**1**) as a radiolabel for distinguishing nicotinic acetylcholine receptor subtypes.[6] This selectivity of MLA has become even more important, since it has been suggested that these receptors might be implicated in Alzheimer's disease.[7]

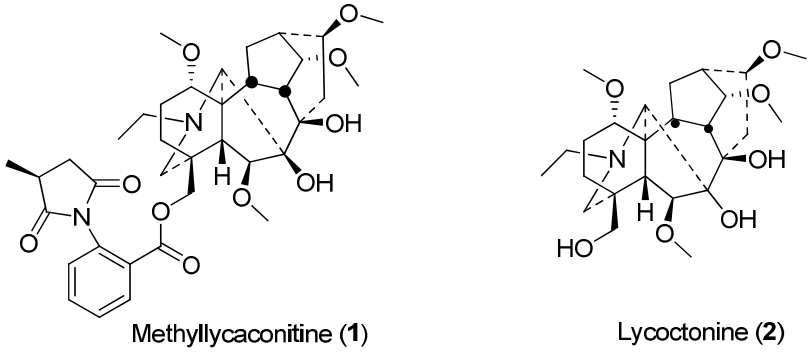


Figure 1. Representative alkaloids of the *Delphinium* species

Structure–activity analysis has indicated that the succinyl anthranilate ester moiety at C18 (Figure 2) affects alkaloid binding with neuronal nicotinic acetylcholine receptors. The substituent at C14 determines the potency and the mechanism of the nAChR blockade at neuromuscular synapses.[8] MLA (**1**) displays about 10^3 times more inhibition of α-bungarotoxin binding than its unsubstituted alkaloid lycoctonine (**2**).[9]

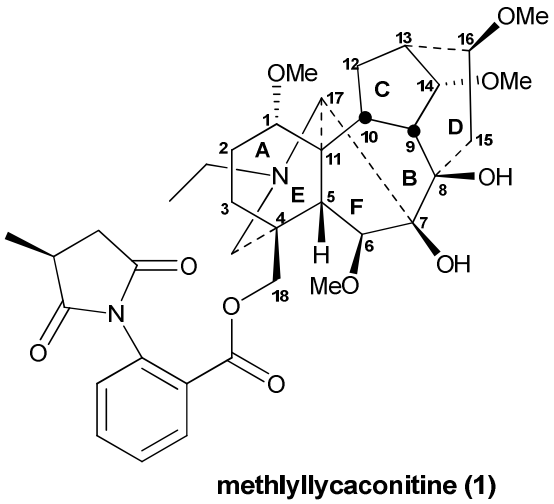
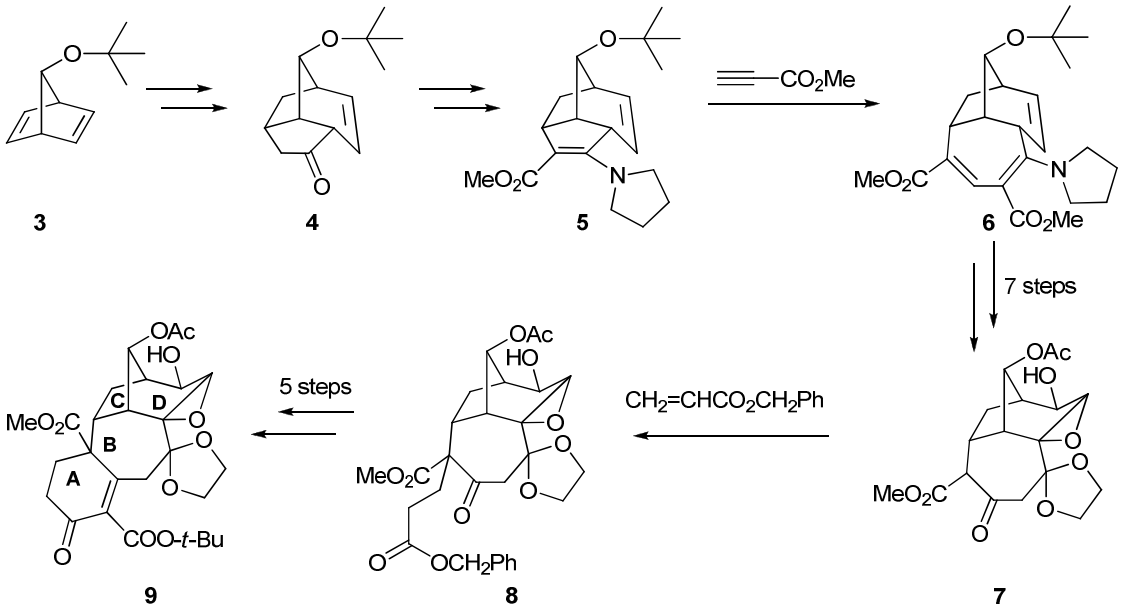


Figure 2. Structure of methyllycaconitine **1**

A number of synthetic approaches to structurally less complex analogs of MLA have been reported, including the synthesis of the E,[10] ABE,[11] AEF,[12] ABCD,[13] ABDE[14] and ABEF[15] ring systems, some of which display significant biological activities.[16,17] One of the syntheses of the norditerpenoid alkaloids by Van der Bann and co-workers led to an efficient construction of the ABCD ring system (Scheme 1).[13]

Scheme 1

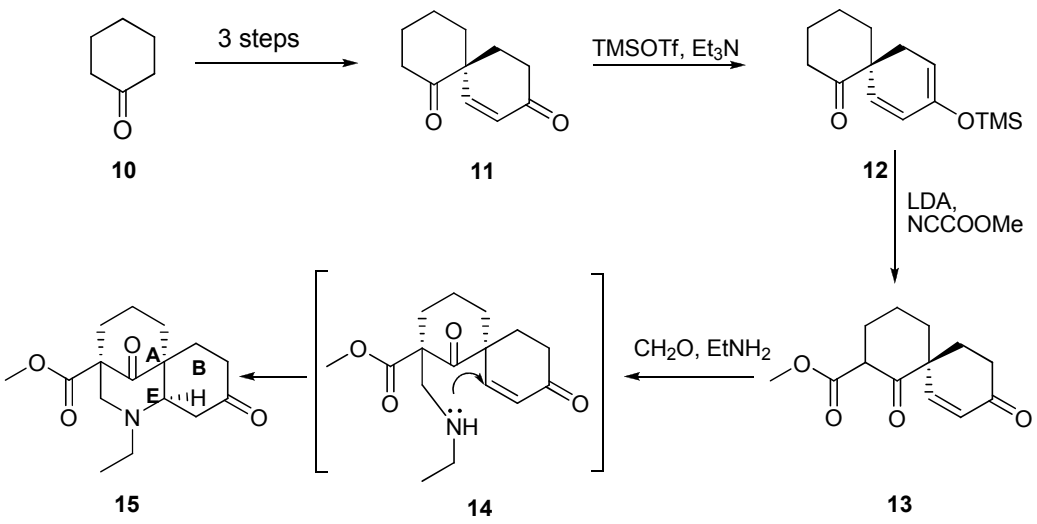


The synthesis of the substituted bicycle [3.2.1] octane derivative started from 7-*tert*-butoxynorbornadiene (**3**), which led to an efficient synthesis of the enamino ester **4**. This compound was then converted to **6**, which contained the necessary BCD ring system by a ring expansion. After the synthesis of the *β*-keto ester **7** in an additional 7 steps, Michael addition with benzyl acrylate provided compound **8**. After five more steps, compound **9** was produced in a high yield. This synthesis used a unique synthetic strategy to make the ABCD ring system. However, the inability to make the biologically significant E and F rings limits the practical application of this approach.

In 1998, Kraus and Dneprovskaia reported a direct approach for the synthesis of the ABE tricyclic segment by a novel tandem Michael addition-Mannich reaction sequence (Scheme 2).[11] The known diketone **11**[18] was obtained by a three-step procedure starting from

cyclohexanone. Selective protection of enone **11** by trimethylsilyl triflate, followed by carboxylation of the A-ring with LDA and methyl cyanoformate, provided the β-keto ester enone **13**. Treatment of enone **13** with ethylamine and formaldehyde in methanol furnished the tricyclic ABE segment by a tandem Michael addition-Mannich reaction. Unfortunately, the unusual inertness of the carbonyl group on the one carbon bridge to a variety of nucleophiles prevented continuation to the ABEF ring system.

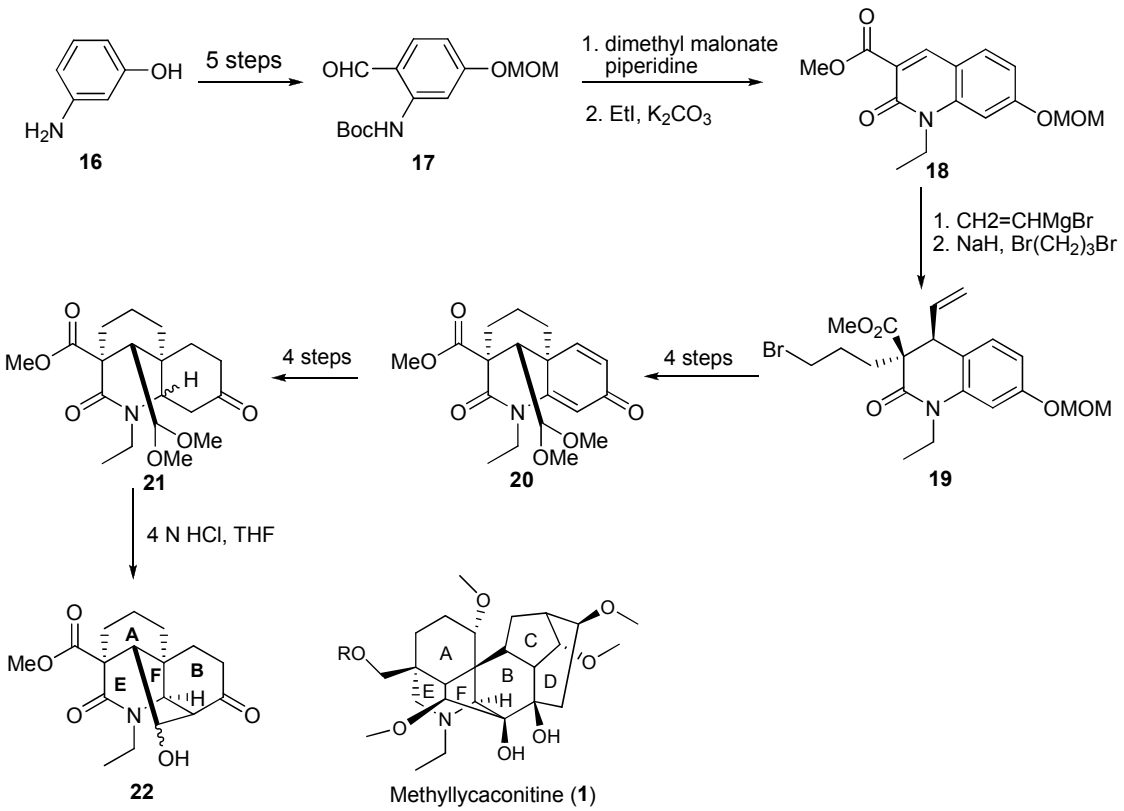
Scheme 2



A recent report from Kraus's group described a direct synthetic route to the ABEF segment of methyllycaconitine (**1**) using an intramolecular anionic spiro cyclization (Scheme 3).[15] The synthesis began with 3-aminophenol, which can be converted to aldehyde **17** in 5 steps. Condensation of aldehyde **17** with dimethyl malonate provided lactam **18** by a diester intermediate, which cyclized to form the lactam before Boc deprotection. Conjugate addition

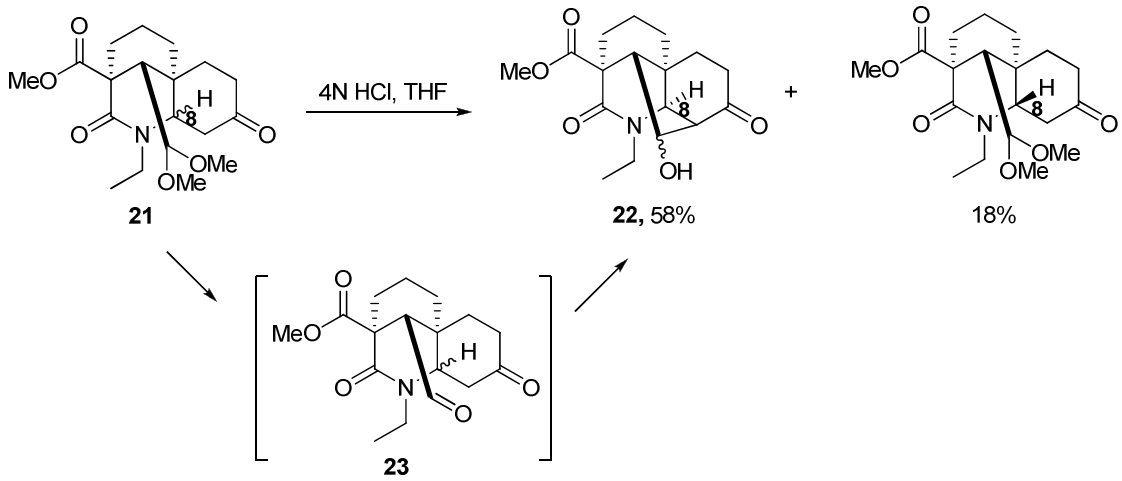
of a vinylcuprate, followed by alkylation with 1,3-dibromopropane provided the vinyl lactam **19** with the desired stereochemistry. The ABE intermediate **20** was achieved in another 4 steps through ozonolysis, deprotection, followed by cyclization using 18-crown-6 ether and sodium hydride. After the two double bonds were reduced separately via hydrogenation and Li/NH_3 reduction, the final ABEF ring system **22** was generated by treating intermediate **21** with 4N HCl in THF.

Scheme 3



As shown in Scheme 4, the strategy for formation of the E ring used an intramolecular aldol condensation via aldehyde **23** to form the key carbon-carbon bond and to generate the correct stereochemistry at C8.

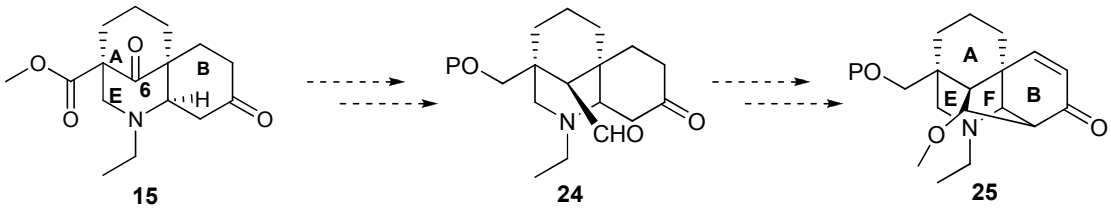
Scheme 4



Results and Discussion

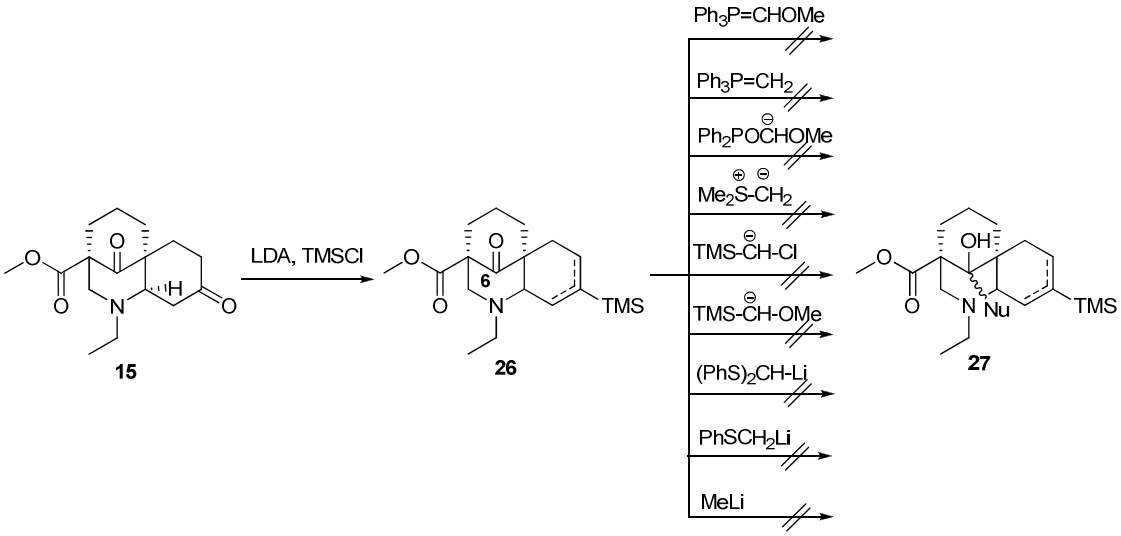
In our approach, the idea was to combine both Dneprovskaia's and Sarathy's work. In Dneprovskaia's synthesis (Scheme 2), the ABE tricyclic ring segment **15** could be efficiently achieved in 3 steps from a known diketone in high yield. If one carbon extension is realized at C6 to form aldehyde **24** (Scheme 5), the F ring could be incorporated by an intramolecular aldol reaction similar to the idea shown in Scheme 4.

Scheme 5



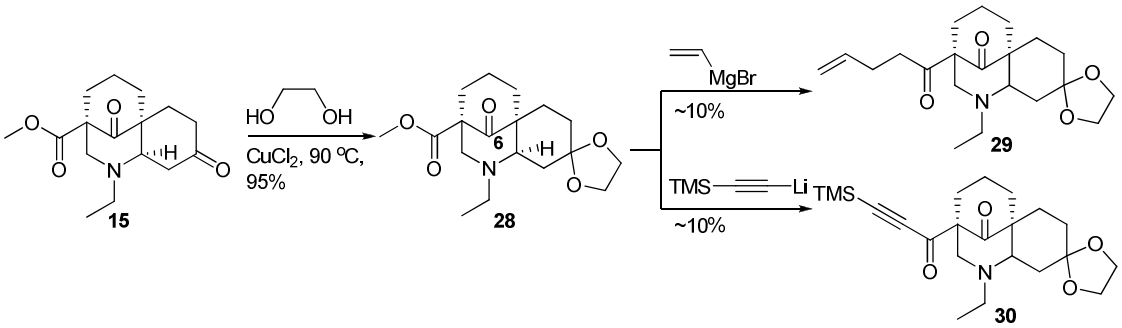
Although this looked straightforward, the unusual inertness of the carbonyl group at C6 to a variety of nucleophiles prevented elaboration to the ABEF ring system. This carbonyl group proved to be unreactive with several phosphorous and sulfur yilids, even with some that are useful with sterically hindered ketones (Scheme 6).

Scheme 6.



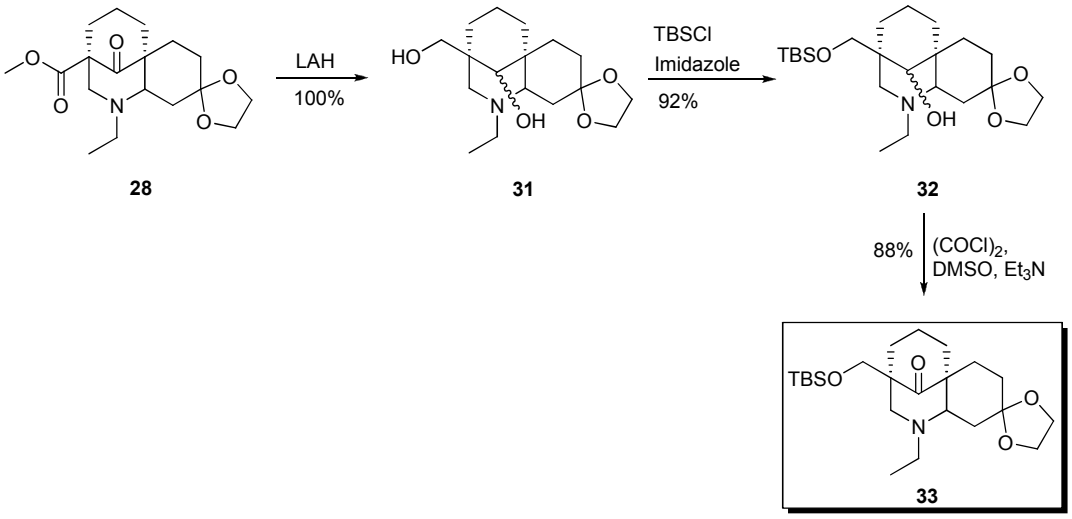
Because of the steric hindrance of the bridged carbonyl group, the less hindered ketone was selectively protected as a ketal in 95% yield (Scheme 7). Interestingly, when ketal **28** was treated with a vinyl Grignard, around 10% of compound **29** was separated. Similarly, around 10% of compound **30** was formed with the lithium anion of trimethylsilyl acetylene. It is believed that the ester group interferes with the nucleophilic addition process and affects the reactivity of the ketone at C6.

Scheme 7



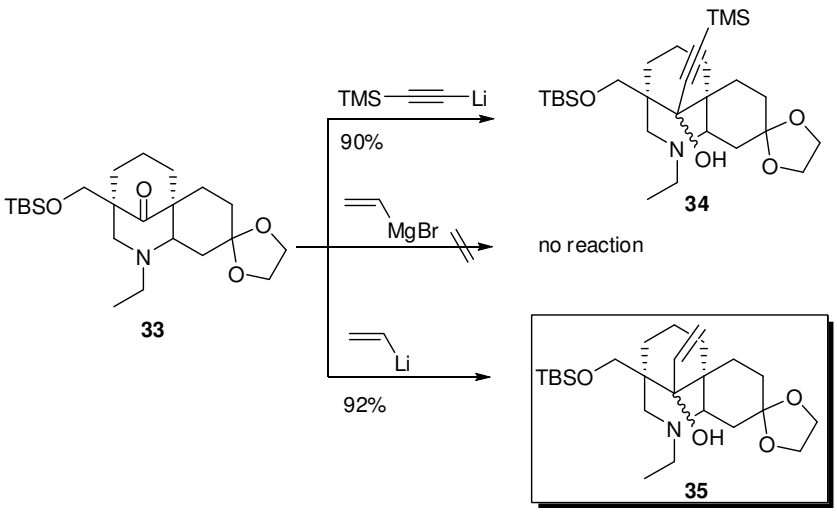
Based on these experiments, our strategy was to reduce the ester group to a primary alcohol in order to encourage reaction with the ketone at C6. The synthesis of ketone **33** commenced with the LAH reduction of ester **28**, which afforded the diol **31** in a quantitative yield (Scheme 8). Selective protection of the primary alcohol with *tert*-butyl dimethylsilyl chloride and imidazole, followed by a Swern oxidation gave ketone **33** in an excellent yield.

Scheme 8.



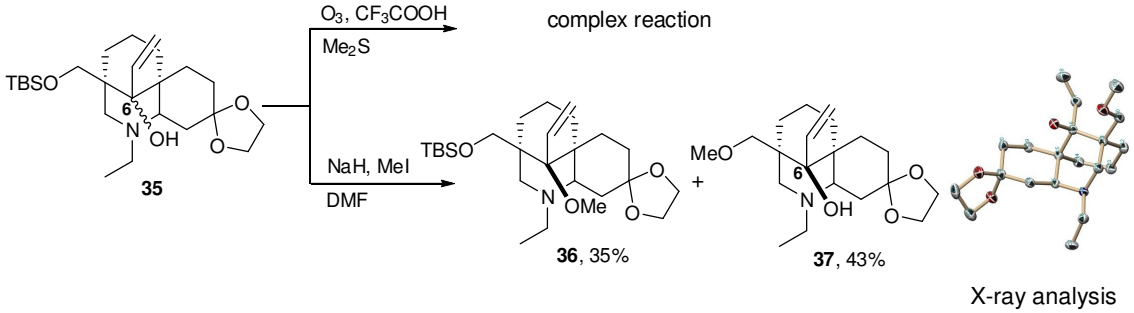
With ketone **33** in hand, several nucleophiles such as the lithium anion of trimethylsilyl acetylene, vinyl Grignard and vinyl lithium were then examined. The ketone at C6 reacted well with all of these nucleophiles except the vinyl Grignard. With vinyl lithium, which was prepared insitu from tetravinyltin and *n*-butyl lithium, the adduct **35** was produced in a 92% yield. It is believed that the aldehyde **24** in Scheme 5 could be achieved via ozonolysis of the terminal double bond. Then the F ring could be generated by an intramolecular aldol condensation.

Scheme 9.



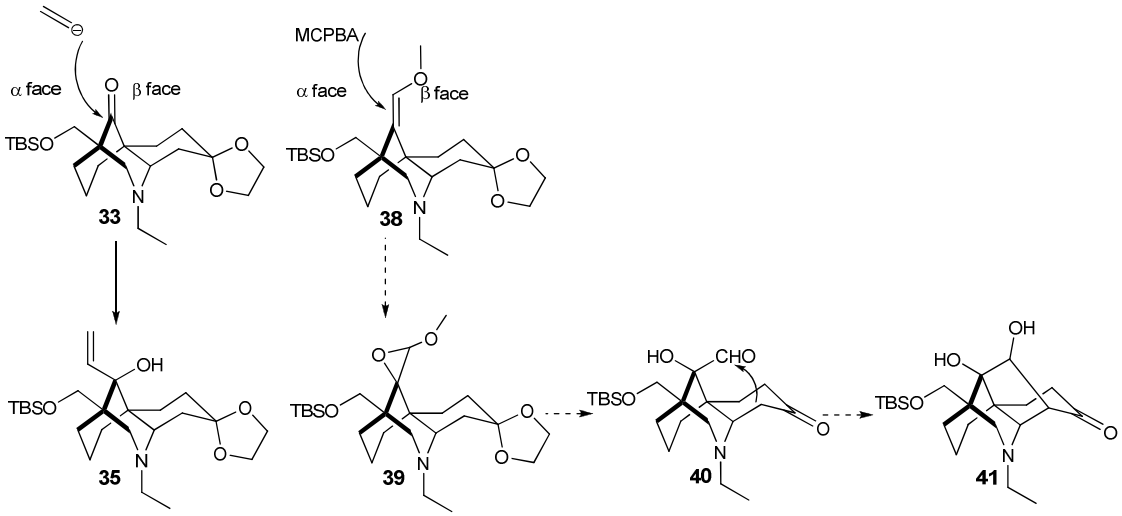
Direct ozonolysis of **35** with trifluoroacetic acid, followed by dimethyl sulfide gave a complex reaction (Scheme 10). The allylic alcohol was protected before the ozonolysis. Methylation of the tertiary alcohol gave some interesting results. Besides the desired compound **36**, alcohol **37** was also generated in a 43% yield as a clear crystalline solid. An X-ray analysis of **37** showed that the stereochemistry at C6 of adduct **35** is the opposite of what was desired.

Scheme 10.



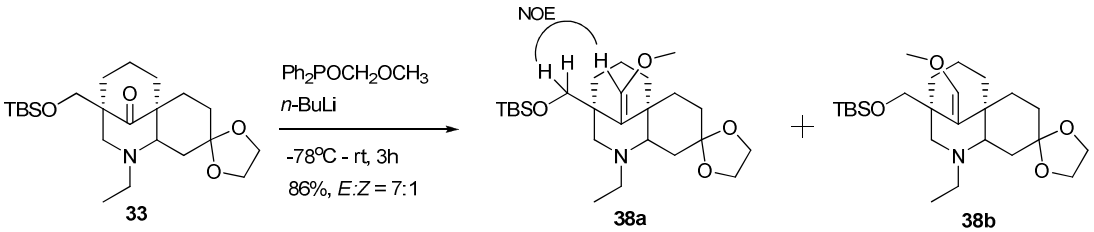
A detailed stereochemical analysis of the nucleophlic addition is shown in Scheme 11. In the tricyclic compound **33**, it is believed that the α-face is less hindered than the β-face. So only adduct **35** is formed. This is the opposite of what was desired. The β-face adduct is needed to furnish the F ring. However, if the enol ether **38** could be made, theoretically, oxidation with MCPBA would attack from the less hindered α-face to form aldehyde **40** with the desired stereochemistry. Then the ABEF compound **41** could be made by an intramolecular aldol reaction.

Scheme 11



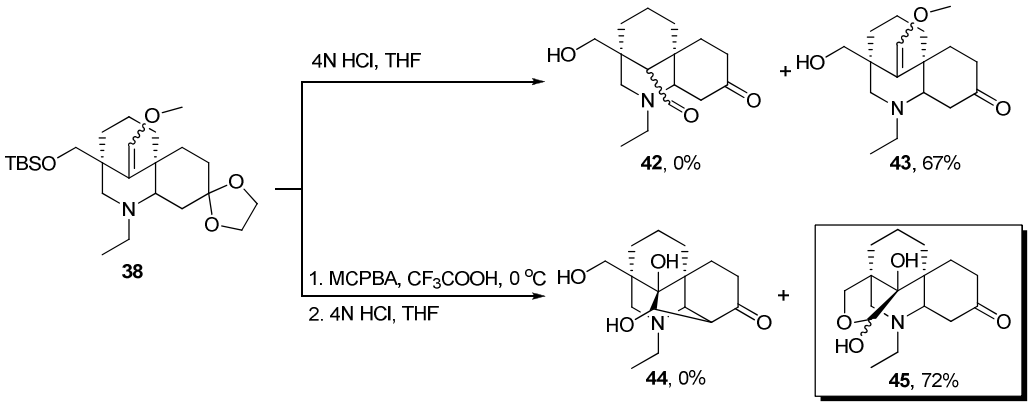
The Wittig reaction of compound **33** with methoxymethylene triphenylphosphorane afforded the desired enol ether **38** as two isomers in excellent yield (Scheme 12). Based on NOE studies, the *E* isomer **38a** is the major component, possibly because of steric hinderance from the bulky *tert*-butyldimethylsilyl group.

Scheme 12



With enol ether **38** in hand, the next task was conversion of **38** to the corresponding aldehyde with the desired stereochemistry. Hydrolysis of the enol ether **38** with 4N hydrochloride acid in THF gave only compound **43**, instead of the desired aldehyde **42** (Scheme 13). MCPBA oxidation, followed by hydrolysis with 4N HCl also

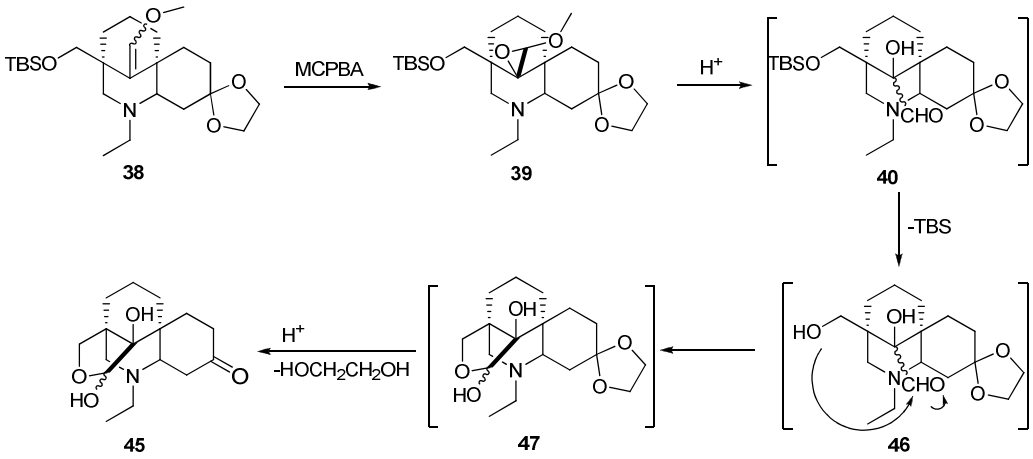
Scheme 13



did not provide the desired triol **44**, but gave an undesired lactol **45** in a 72% yield. A detailed mechanistic analysis of how compound **45** might be formed is shown in Scheme 14. According to this analysis, after the epoxide **39** is formed by MCPBA oxidation, the

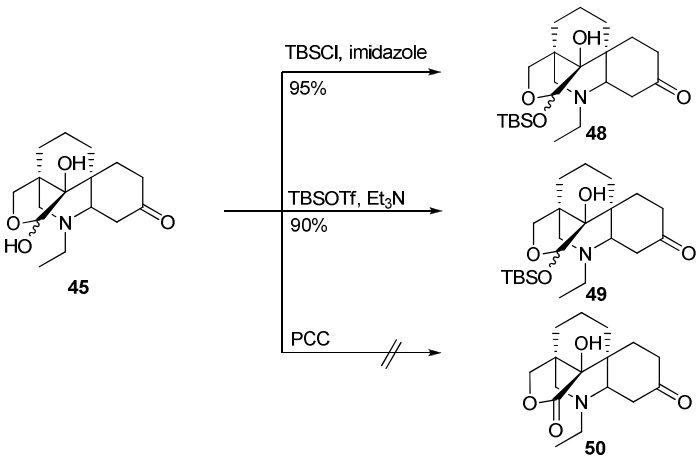
aldehyde **40** is produced by hydrolysis under the acidic conditions. However, the TBS group is also cleaved by the strong acid and the lactol **47** is formed instead.

Scheme 14



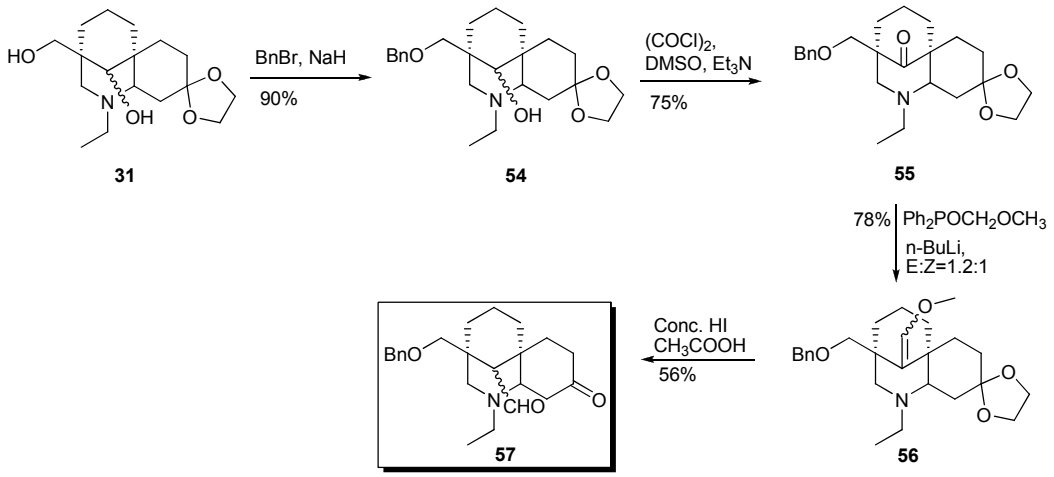
All efforts to open the lactol ring under a variety of different conditions failed (Scheme 15). Oxidation with PCC to lactone **50** also gave a complex reaction.

Scheme 15



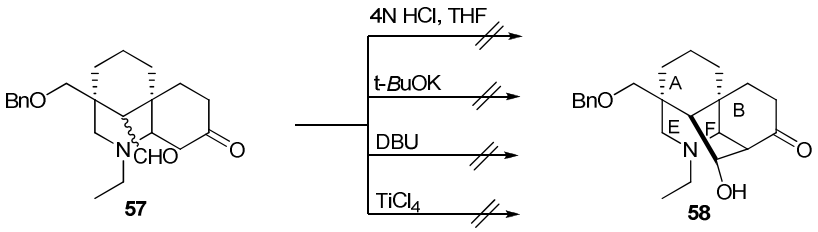
With these disappointing results, it was decided to change the acid sensitive TBS group to a benzyl group (Scheme 16). Alcohol **54**, obtained from diol **31** in a 90% yield by selective protection of the primary alcohol with benzyl bromide, was converted into ketone **55** using a Swern oxidation in a 75% yield.

Scheme 16



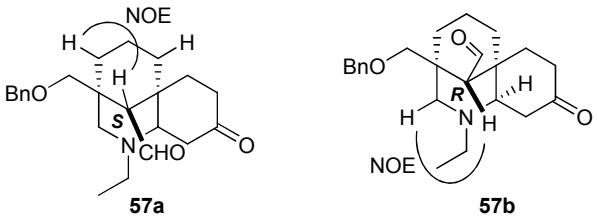
A Wittig reaction of compound **55** afforded the desired enol ether **56** as two isomers in excellent yield. Hydrolysis of the enol ether with concentrated hydriodic acid in acetic acid gave aldehyde **57** in a 56% yield. However, the reaction failed to furnish the F ring to give alcohol **58** either under acidic, basic or Lewis acid conditions (Scheme 17).

Scheme 17



Based on the NOE studies, it is believed that compound **57b** with the "*R*" configuration at C6 is the major component. The "*S*" configuration (**57a**) is needed to furnish the F ring (Scheme 18).

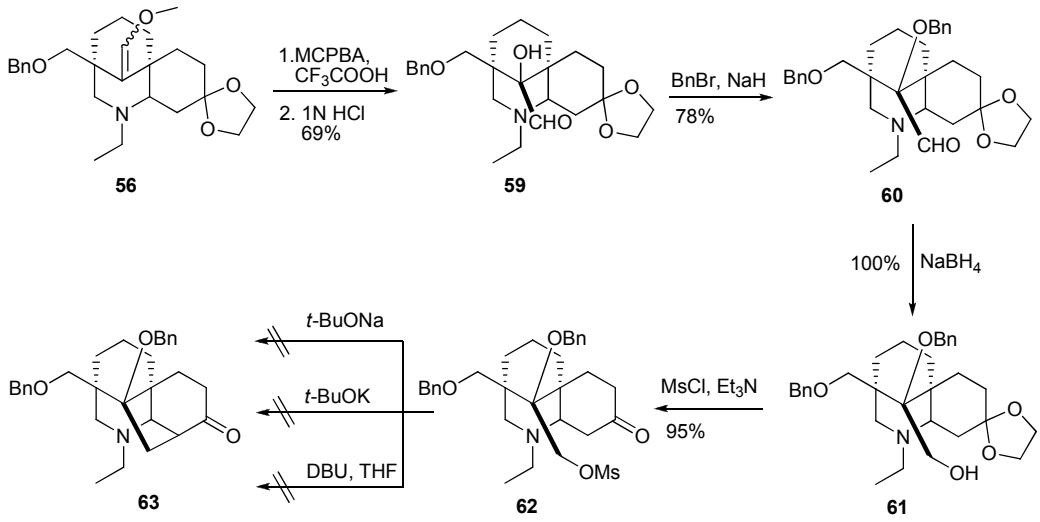
Scheme 18



At this stage, it is believed that oxidation of the less hindered face will give the right stereochemistry at C6. Instead of an intramolecular aldol reaction, an S_N2 reaction could be applied to form the key carbon-carbon bond and avoid the retro-aldol reaction (Scheme 19). The synthesis started from previously prepared enol ether **56**. Oxidation of **56** with MCPBA, followed by acid hydrolysis, afforded aldehyde **59** in a 69% yield. The alcohol **61** was achieved by benzylation, followed $NaBH_4$ reduction, from aldehyde **60** in an excellent yield

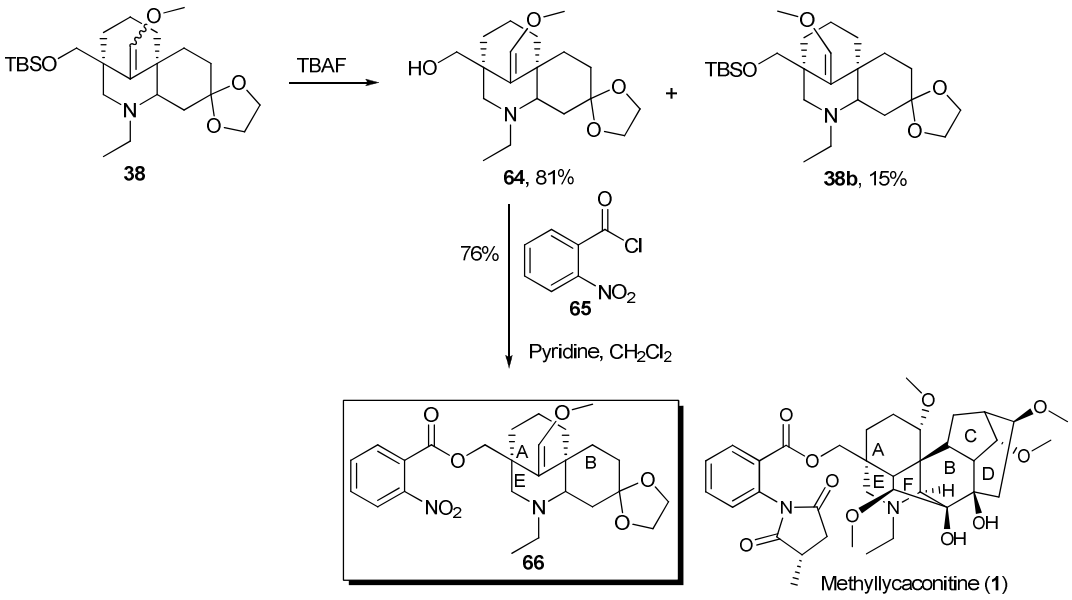
over two steps. Mesylation of **61** with mesyl chloride and triethyl amine gave the desired compound **62** in a 95% yield. Unfortunately, all attempts to prepare compound **63** using a variety of different bases, like *t*-BuONa, *t*-BuOK and DBU in THF, were unsuccessful.

Scheme 19



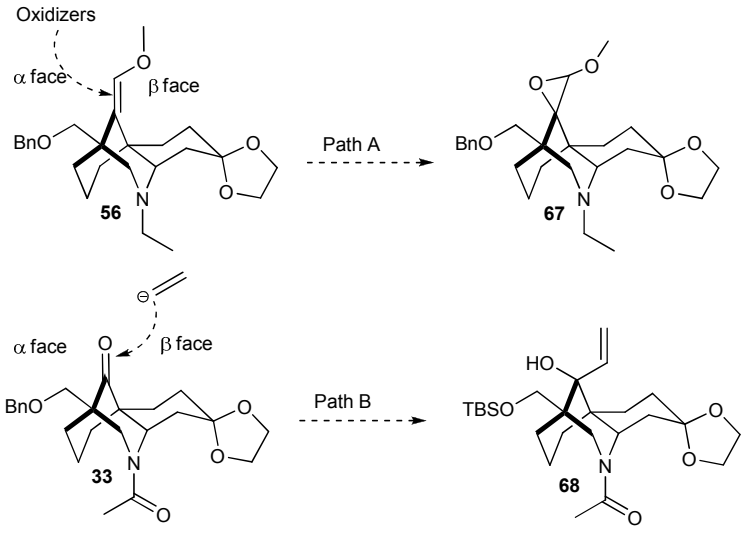
Scheme 20 shows our efforts to connect the succinyl anthranilate ester moiety to the ABE tricyclic ring system. Treatment of enol ether **38** with tetrabutylammonium fluoride at room temperature for 12 h, gave only *E*-isomer alcohol **64**. The *Z*-isomer **38b** did not react under these conditions. Coupling with commercially available 2-nitrobenzoyl chloride (**65**) afforded compound **66** in a 76% yield. The succinyl anthranilate ester moiety could easily be achieved from the nitro group based on several known procedures.[19, 20]

Scheme 20



Based on all of the experiments, two pathways could be tried in the future (Scheme 21). According to pathway A, non-acidic oxidizing reagents such as osmium tetroxide and dimethyldioxirane, should give α-face products **67**. MCPBA is an acid and may have some interaction with the amine group to give β-face oxidation products. By pathway B, an amide group could be introduced, instead of an amine group. The amide may make the β-face less hindered, which would provide β-face addition products **68** with nucleophiles like vinyl lithium, or give the aldehyde with an '*S*' configuration by direct hydrolysis of the enol ether **56**.

Scheme 21

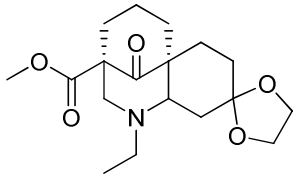


In conclusion, an advanced tricyclic intermediate fragment of methyllycaconitine (**1**) was synthesized efficiently. The carbon extension at the inert bridge carbonyl group was realized by reducing the neighboring ester group. All experiments have demonstrated that the right stereochemistry at the bridge carbon is the key point for F ring formation.

Experimental

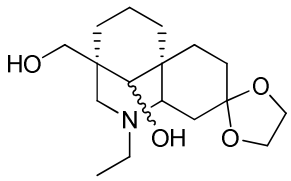
Unless otherwise noted, materials were obtained from commercial suppliers and used without purification. Tetrahydrofuran and diethyl ether were distilled from sodium and benzophenone. Dichloromethane, benzene and diisopropylamine were distilled over calcium hydride. All experiments were performed under an argon atmosphere, unless otherwise noted. Organic extracts were dried over anhydrous magnesium sulfate. Infrared spectra were obtained on a Perkin-Elmer model 1320 spectrophotometer. Nuclear magnetic resonance

experiments were performed with either a Varian 300 MHz or Bruker 400 MHz instrument. All chemical shifts are reported relative to $CDCl_3$ (7.27 ppm for ^1H and 77.23 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. Standard grade silica gel (60 Å, 32-63 μm) was used for flash column chromatography.



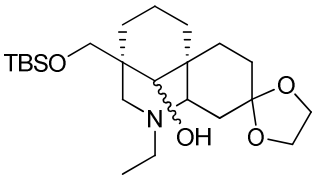
Compound 28

To a suspension of the compound **15** (0.719 g, 2.45 mmol) in 22 mL of ethylene glycol, copper chloride dihydrate (0.042 g, 0.245 mmol) was added at room temperature. The resulting mixture was warmed to 90 ^oC and stirred for 1 h. The color turned from greenish to light yellow. The reaction was quenched by the addition of brine solution. The product was extracted twice with diethyl ether and the combined organic layers were washed with brine. Evaporation of the solvent, followed by column chromatography of the residue using 1:3 ethyl acetate: hexanes, gave compound **28** (726 mg, 88%) as a clear oil; ^1H NMR (400 MHz, $CDCl_3$) 3.91-3.94 (m, 4H), 3.75 (s, 3H), 3.36-3.42 (m, 2H), 2.94-3.05(m, 2H), 2.46-2.60 (m, 3H), 2.07-2.27 (m, 2H), 1.69-2.02 (m, 4H), 1.43-1.56 (m, 3H), 1.11-1.17(m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) 213.2, 171.8, 109.5, 65.8, 64.4, 64.2, 59.2, 55.4, 52.2, 50.5, 46.7, 43.8, 38.8, 31.2, 30.4, 28.7, 21.1, 13.4; MS electrospray (m/z): 337.



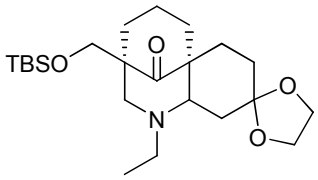
Compound 31

To a solution of lithium aluminum hydride (0.094 g, 2.48 mmol) in 8 mL of THF was added ester **28** (0.42 g, 1.24 mmol) in 8 mL of THF dropwise by canulation, The resulting mixture was allowed to stir at room temperature for 10 min. Then 0.094 mL of water, 0.094 mL of 15% NaOH solution and 0.283 mL of water were added in sequence to quench the reaction. After 30 min at rt, the precipitate was filtered by Celite and washed by 30 mL of EtOAc. The organic layer was concentrated, and the product was purified by flash column chromatography to afford diol **31** (0.4 g, 95%) as a clear oil; ^{1}H NMR (400 MHz, $CDCl_3$) 3.91-3.94 (m, 4H), 3.79 (s, 1H), 3.42-3.52 (m, 3H), 2.97-3.00(d, *J*=11.6 Hz, 1H), 2.83-2.89 (dd, *J* = 12.8, 4.4 Hz, 1H), 2.59 (s, 1H), 2.39-2.53 (m, 3H), 2.26-2.29 (d, *J* = 11.62 Hz, 1H), 2.02-2.17 (m, 2H), 1.84-1.90 (m, 1H), 1.57-1.71 (m, 3H), 1.31-1.38 (m, 3H), 1.09-1.25 (m, 2H), 1.00-1.04 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 110.6, 83.0, 71.4, 64.2, 63.9, 59.5, 49.9, 46.8, 39.8, 39.7, 37.6, 34.7, 34.2, 32.6, 30.4, 19.9, 12.2; MS electrospray (m/z): 311.



Compound 32

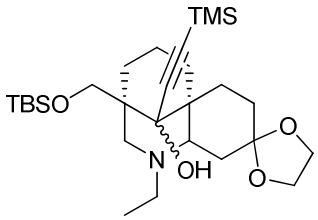
To a solution of diol **31** (0.311 g, 1.00 mmol) in 10 mL of DMF was added *tert*-butyldimethylsilyl chloride (0.15g, 1.00 mmol) and imidazole (0.10 g, 1.50 mmol). The resulting mixture was allowed to stir at room temperature for 12 h. Ten mL of water was added to quench the reaction. The product was extracted twice by ethyl acetate and the combined organic layers were washed with brine. The organic layer was concentrated, and the product was purified by flash column chromatography to afford compound **32** (0.39 g, 92%) as a clear oil; ^{1}H NMR (400 MHz, $CDCl_3$) 3.91-3.94 (m, 4H), 3.79 (s, 1H), 3.42-3.52 (m, 3H), 2.97-3.00(d, J = 11.6 Hz, 1H), 2.83-2.89 (dd, J = 12.8, 4.4 Hz, 1H), 2.59 (s, 1H), 2.39-2.53 (m, 3H), 2.26-2.29 (d, J = 11.62 Hz, 1H), 2.02-2.17 (m, 2H), 1.84-1.90 (m, 1H), 1.57-1.71 (m, 3H), 1.31-1.38 (m, 3H), 1.09-1.25 (m, 2H), 1.00-1.04 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 110.6, 83.0, 71.4, 64.2, 63.9, 59.5, 49.9, 46.8, 39.8, 39.7, 37.6, 34.7, 34.2, 32.6, 30.4, 19.9, 12.2; MS electrospray (m/z): 311.



Compound 33

To a dry round bottom flask, oxalyl chloride (0.07 mL, 0.80 mmol) was added to 10 mL of CH_2Cl_2. To this solution, 0.113 mL of DMSO (1.6 mmol) was slowly added at -78 ^{o}C. After 5 min at -78 ^{o}C, the alcohol **32** in 10 mL of CH_2Cl_2 was added, followed by 0.56 mL of Et_3N (4.0 mmol). After 30 min at -78 ^{o}C, the reaction mixture was poured into a 10 mL mixture of saturated $NaHCO_3$ and saturated NaCl solution. The product was extracted twice

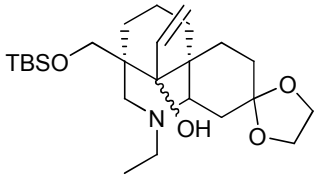
by CH_2Cl_2 and the combined organic layers were washed with brine. Evaporation of the solvent, followed by column chromatography of the residue, gave compound **33** as clear oil; ^{1}H NMR (400 MHz, $CDCl_3$) 3.88-3.95 (m, 4H), 3.51-3.66 (dd, *J* = 47.6, 10.0 Hz, 2H), 3.34-3.38 (dd, *J* = 12.8, 3.6 Hz, 1H), 3.10-3.13 (d, *J* = 11.6 Hz, 1H), 2.97-3.07 (m, 1H), 2.66-2.70 (dd, *J* = 11.6, 2.4 Hz, 1H), 2.43-2.58 (m, 2H), 2.45-2.48 (m, 1H), 2.05-2.06 (m, 1H), 1.93-1.97 (m, 1H), 1.83-1.90 (m, 1H), 1.60-1.71 (m, 3H), 1.41-1.55 (m, 2H), 1.28-1.34 (t, *J* = 12.8 Hz, 1H), 1.10-1.17 (m, 4H), 0.88-0.90 (m, 9H), 0.03-0.04 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) 218.8, 109.8, 66.4, 65.7, 64.3, 64.1, 56.1, 51.2, 50.7, 46.8, 44.7, 40.0, 31.3, 30.3, 28.5, 25.9, 21.3, 18.3, 13.5, -5.5. MS electrospray (m/z): 423.



Compound 34

First, 0.093 mL of *n*-BuLi in THF (2.5 M, 0.233 mmol) was added dropwise under argon to 0.033 mL of trimethylsilyl acetylene in 1 mL of THF (0.233 mmol) at 0 ^{o}C. After 1 h at 0 ^{o}C, compound **33** (0.033 g, 0.078 mmol) in 1 mL of THF was added by canula. After another 30 min at 0 ^{o}C, the reaction was quenched by the addition of 10 mL of saturated aqueous NH_4Cl solution. The product was extracted twice with ethyl acetate and the combined organic layers were washed with brine. Evaporation of the solvent, followed by column chromatography of the residue, gave compound **34** (39 mg, 96%) as a clear oil; ^{1}H

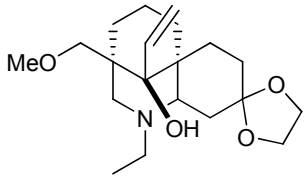
NMR (400 MHz, $CDCl_3$) 5.18 (s, 1H), 4.00-4.02 (d, *J* = 10.0 Hz, 1H), 3.91 (s, 4H), 3.22-3.26 (m, 2H), 3.04-3.09 (dd, *J* = 12.8, 4.4 Hz, 1H), 2.68-2.74 (m, 1H), 2.16-2.57 (m, 6H), 1.77-1.85 (m, 1H), 1.44-1.58 (m, 3H), 1.20-1.36 (m, 4H), 1.01-1.05 (t, *J* = 7.2 Hz, 3H), 0.88 (s, 9H), 0.16 (s, 9H), 0.05-0.08 (d, *J* = 11.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) 111.2, 107.6, 90.9, 80.9, 71.7, 64.1, 64.0, 61.3, 49.9, 47.0, 41.3, 39.8, 39.2, 33.8, 32.6, 32.4, 29.0, 25.9, 20.9, 18.2, 13.2, 0.1, -5.7, -5.8; MS electrospray (m/z): 521.



Compound 35

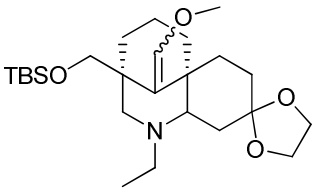
To the solution of tetravinyltin (0.077 mL, 0.425 mmol) in 1 mL of THF, 0.256 mL of *n*-BuLi (2.5 M, 0.639 mmol) in THF was added dropwise under argon at -78 ^oC. After 30 min at -78 ^oC, compound **46** (0.06 g, 0.142 mmol) in 1 mL of THF was added to this mixture and stirred for another 30 min at -78 ^oC. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution at -78 ^oC. The product was extracted twice with ethyl acetate and the combined organic layers were washed with brine. Evaporation of the solvent, followed by column chromatography of the residue, gave compound **35** (58 mg, 91%) as a clear oil; ^1H NMR (400 MHz, $CDCl_3$) 6.23-6.30 (dd, *J* = 16.8, 10.4 Hz, 1H), 5.55-5.60 (dd, *J* = 16.8, 2.8 Hz, 1H), 5.26-5.30 (dd, *J* = 10.4, 2.8 Hz, 1H), 4.43 (bs, 1H), 3.85-3.92 (dd, *J* = 16.8, 13.6 Hz, 4H), 3.52-3.55 (d, *J* = 10 Hz, 1H), 3.33-3.36 (m, 1H), 2.95-3.07 (m, 2H), 2.54-2.94 (m, 3H), 2.21-2.40 (m, 2H), 2.13-2.15 (d, *J* = 11.2 Hz, 1H), 1.40-1.70 (m, 4H), 1.20-

1.34 (m, 4H), 0.99-1.09 (m, 4H), 0.84 (s, 9H), -0.03-0.01(d, J = 4.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) 139.1, 116.8, 111.5, 81.6, 71.1, 64.0, 63.9, 63.2, 52.1, 47.1, 41.3, 39.2, 38.8, 32.7, 32.1, 31.5, 29.7, 25.8, 20.9, 18.1, 13.3, -5.79, -5.84; MS electrospray (m/z): 451.



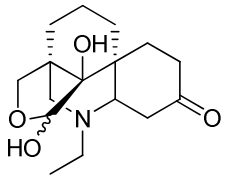
Compound 37

To a solution of compound **35** (0.451 g, 1.0 mmol) in 10 mL of DMF was added NaH (0.048g, 1.2 mmol) and methyl iodide (0.14 g, 1.0 mmol) at room temperature. The resulting mixture was allowed to stir at room temperature for 12 h. Ten mL of water was added to quench the reaction. The product was extracted twice by ethyl acetate and the combined organic layers were washed with brine. The organic layer was concentrated, and the product was purified by flash column chromatography to afford compound **37** (0.14 g, 42%) as a clear crystalline solid; ^{1}H NMR (400 MHz, $CDCl_3$) 6.29-6.36 (q, J = 6.4 Hz, 1H), 5.57-5.62 (dd, J = 19.2, 2.4 Hz, 1H), 5.30-5.34 (dd, J = 10.4, 2.4 Hz, 1H), 4.26 (bs, 1H), 3.88-3.96 (dd, J = 16.4, 13.2 Hz, 4H), 3.30-3.36 (m, 2H), 3.22 (s, 3H), 2.95-3.02 (m, 2H), 2.74-2.83 (m, 1H), 2.54-2.64 (m, 2H), 2.37-2.45 (m, 1H), 2.22-2.30 (m, 2H), 1.60-1.73 (m, 2H), 1.25-1.57 (m, 7H), 1.04-1.10 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 139.3, 116.7, 111.3, 81.4, 80.7, 64.1, 63.9, 63.1, 59.2, 52.2, 47.0, 41.9, 39.2, 38.7, 32.6, 32.2, 31.8, 29.7, 20.9, 13.2; MS electrospray (m/z): 351.



Compound 38

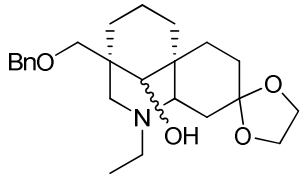
To a solution of diphenyl(methoxymethyl)phosphine oxide (1.17g, 4.75 mmol) in 35 mL of THF, 1.95 mL of *n*-BuLi (2.35 M, 4.75 mmol) in THF was added dropwise under argon at -78 °C. After 20 min at -78 °C, a solution of ketone **33** (0.67 g, 1.58 mmol) in 10 mL of THF was added. The dry ice/acetone bath was removed and the reaction mixture was allowed to stir at rt for 3 h. The reaction was quenched by the addition of 10 mL of saturated aqueous NH_4Cl solution. The product was extracted twice with ethyl acetate and the combined organic layers were washed with brine. Evaporation of the solvent, followed by column chromatography of the residue, gave compound **38** as two isomers (613 mg, 86%, E/Z=7:1); ^{1}H NMR (400 MHz, $CDCl_3$) 5.69 (s, 1H), 3.85 (s, 4H), 3.41 (s, 3H), 3.31-3.36 (m, 2H), 2.72-2.75 (m, 2H), 2.45-2.48 (d, *J* = 10.8 Hz, 1H), 2.20-2.40 (m, 4H), 1.64-1.85 (m, 2H), 1.16-1.58 (m, 8H), 0.93-0.98 (m, 3H), 0.90 (s, 9H), 0.06 (s, 6H).



Compound 45

To a solution of compound **38** (0.451g, 1.00 mmol) in 15 mL of CH_2Cl_2, 0.115 mL of trifluoroacetic acid (1.50 mmol) and MCPBA (268 mg, 1.20 mmol, 77%) were added to the mixture at 0 °C. After 1 h at rt, 20 mL of saturated aqueous sodium thiosulfate was added to

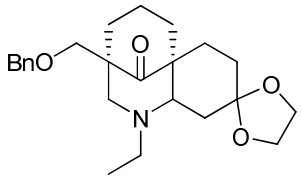
quench the reaction. The product was extracted twice with CH_2Cl_2 and the combined organic layers were washed with brine. After evaporation of the solvent, the residue was redissolved in 10 mL of THF and 2.5 mL of 4 N HCl was added to the reaction mixture. After 2 h at rt, 20 mL of water was added to quench the reaction. The product was extracted twice with ethyl acetate and the combined organic layers were washed with saturated $NaHCO_3$ solution and brine. Evaporation of the solvent, followed by column chromatography of the residue, gave compound **45** as a clear oil (212 mg, 72%); ^{1}H NMR (400 MHz, $CDCl_3$) 5.55 (s, 1H), 4.77 (s, 1H), 3.82-3.85 (d, *J* = 9.2 Hz, 1H), 3.26-3.28 (d, *J* = 9.2 Hz, 1H), 3.00-3.03 (m, 1H), 2.70-2.82 (m, 2H), 2.27-2.46 (m, 4H), 1.86-1.91 (m, 1H), 1.35-1.70 (m, 10H), 0.98-1.06 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 97.2, 96.8, 84.8, 74.0, 61.5, 51.4, 46.9, 45.9, 34.1, 33.5, 33.4, 32.3, 32.2, 29.6, 20.9, 13.3; MS electrospray (m/z): 295.



Compound 54

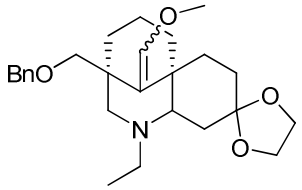
To a solution of diol **31** (0.311 g, 1.00 mmol) in 10 mL of DMF was added NaH (0.044g, 1.10 mmol) and benzyl bromide (0.18 g, 1.05 mmol) at 0 ^{o}C. The resulting mixture was allowed to stir at 0 ^{o}C for 3 h. Ten mL of water was added to quench the reaction. The product was extracted twice by ethyl acetate and the combined organic layers were washed with brine. The product was purified by flash column chromatography to afford compound **54** as a clear oil in 86% yield: ^{1}H NMR (400 MHz, $CDCl_3$); 7.29-7.38 (m, 5H), 4.44-4.53 (dd,

J = 26.8, 12.0 Hz, 2H), 3.93 (s, 4H), 3.70 (s, 1H), 3.54 (s, 1H), 3.30-3.35 (m, 2H), 2.94-3.03 (m, 2H), 2.69-2.72 (m, 1H), 2.52-2.57 (m, 1H), 2.23-2.43 (m, 4H), 1.43-1.69 (m, 6H), 1.23-1.34 (m, 3H), 1.03-1.06 (t, *J* = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 137.8, 128.7, 128.6, 128.0, 127.8, 126.9, 111.4, 82.7, 78.9, 74.0, 64.4, 64.1, 60.4, 57.0, 49.3, 47.4, 41.6, 40.1, 37.2, 36.7, 34.9, 33.0, 28.6, 21.5, 13.4; MS electrospray (m/z): 401.



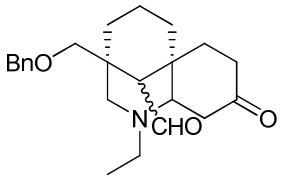
Compound 55

The product **55** was obtained as clear oil in 75% yield by a procedure similar to that used to prepare compound **33**; ^{1}H NMR (400 MHz, $CDCl_3$) 7.27-7.34 (m, 5H), 4.48-4.55 (dd, *J* = 16.0, 12.4 Hz, 2H), 3.88-3.95 (m, 4H), 3.34-3.50 (m, 3H), 3.15-3.18 (d, *J* = 11.6 Hz, 1H), 2.98-3.08 (m, 1H), 2.74-2.77 (dd, *J* = 12.0, 2.4 Hz, 1H), 2.35-2.59 (m, 3H), 2.05-2.10 (m, 1H), 1.83-1.98 (m, 2H), 1.64-1.73 (m, 3H), 1.42-1.54(m, 2H), 1.29-1.35 (t, *J* = 12.8 Hz, 1H), 1.09-1.17 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) 218.1, 138.7, 128.3, 127.5, 109.8, 73.6, 73.5, 65.6, 64.3, 64.1, 56.4, 50.64, 50.61, 46.8, 44.5, 40.2, 31.3, 30.4, 28.5, 21.3, 13.5; MS electrospray (m/z): 399.



Compound 56

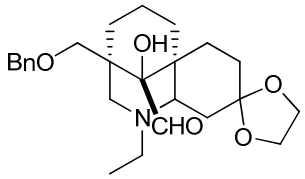
The product **56** was obtained as clear oil in 78% yield by a procedure similar to that used to prepare compound **38**; ^{1}H NMR (400 MHz, $CDCl_3$, E/Z=1.2:1) 7.26-7.39 (m, 10 H), 5.85 (s, 1H), 5.84 (s, 1H), 4.49-4.57 (m, 4H), 3.68-3.83 (dd, *J* = 12.8, 9.2 Hz, 2H), 3.52 (s, 3H), 3.51 (s, 3H), 3.27-3.38 (dd, *J* = 33.6, 9.2 Hz, 2H), 3.02-3.06 (m, 1H), 2.74-2.93 (m, 6h), 2.66-2.69 (d, *J* = 12.0 Hz, 2H), 2.51-2.63 (m, 6H), 2.13-2.42 (m, 10H), 1.94-2.08 (m, 2H), 1.83-1.89 (m, 1H), 1.32-1.74 (m, 12H), 1.02-1.07 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) 214.5, 212.8, 141.1, 139.8, 139.4, 138.5, 128.4, 128.38, 128.30, 127.63, 127.60, 127.5, 127.24, 127.20, 118.1, 117.6, 76.8, 73.4, 73.2, 66.6, 67.3, 59.9, 60.0, 54.5, 54.7, 47.29, 47.31, 44.5, 42.3, 42.4, 41.9, 40.3, 40.2, 40.0, 39.6, 38.1, 38.0, 36.6, 35.4, 35.2, 34.6, 21.69, 21.67, 13.2, 13.1; MS electrospray (m/z): 427.



Compound 57

To a solution of compound **56** (0.427 g, 1.00 mmol) in 6 mL of acetic acid was added hydriodic acid (1.12 mL, 5.00 mmol, 57%) at 0 ^{o}C. The resulting mixture was allowed to stir at 0 ^{o}C for 30 min. Ten mL of water was added to quench the reaction. The product was extracted twice by ethyl acetate and the combined organic layers were washed with saturated aqueous $NaHCO_3$ solution. The product was purified by flash column chromatography to

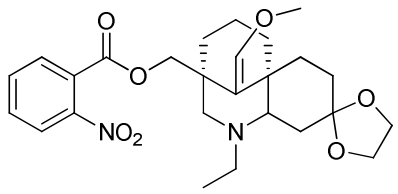
afford compound **57** as a clear oil in 56% yield; ^{1}H NMR (400 MHz, $CDCl_3$) 10.10-10.11 (m, 1H), 7.28-7.38 (m, 5H), 4.40-4.50 (dd, *J* = 28.0, 12.0 Hz, 2H), 3.15-3.26 (dd, *J* = 36.0, 9.2 Hz, 2H), 3.07-3.11 (dd, *J* = 12.0, 4.8 Hz, 1H), 2.87-3.10 (m, 1H), 2.75-2.76 (d, *J* = 5.2 Hz, 1H), 2.54-2.64 (m, 3H), 2.38-2.44 (m, 2H), 2.12-2.34 (m, 4H), 1.37-1.87 (m, 6H), 1.02-1.08 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 211.4, 205.7, 138.0, 128.4, 127.7, 127.6, 73.5, 66.6, 62.2, 54.9, 51.9, 47.1, 39.2, 37.3, 36.7, 35.7, 35.4, 33.7, 29.8, 21.1, 13.0; MS electrospray (m/z): 369.



Compound 59

To a solution of compound **56** (0.427g, 1.0 mmol) in 15 mL of CH_2Cl_2, 0.115 mL of trifluoroacetic acid (1.5 mmol) and MCPBA (268 mg, 1.2 mmol, 77%) were added to the mixture at 0 ^{o}C. After 1 h at rt, 20 mL of saturated sodium thiosulfate was added to quench the reaction. The product was extracted twice with CH_2Cl_2 and the combined organic layers were washed with brine. After evaporation of the solvent, the residue was redissolved in 10 mL of THF and 2.5 mL of 4 N HCl was added to the reaction mixture. After 2 h at rt, 20 mL of water was added to quench the reaction. The product was extracted twice with ethyl acetate and the combined organic layers were washed with saturated aqueous $NaHCO_3$ solution and brine. Evaporation of the solvent, followed by column chromatography of the

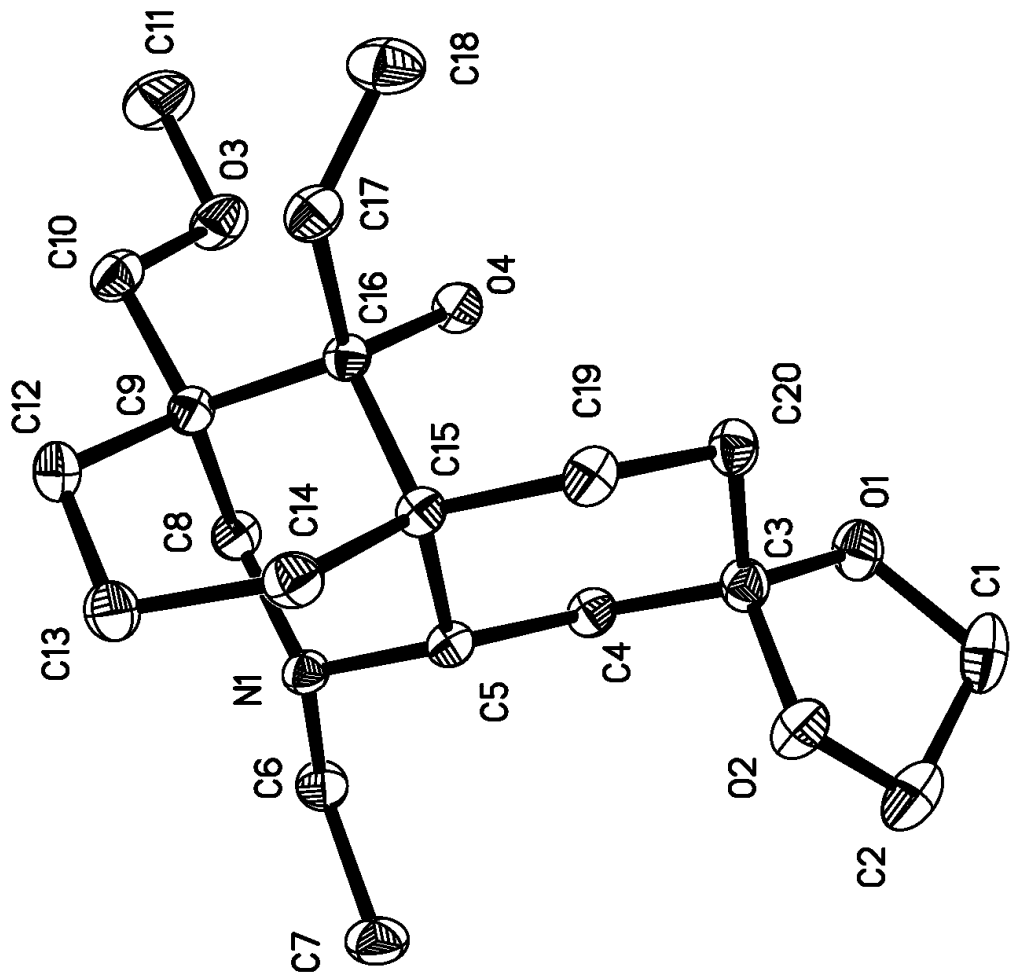
residue, gave compound **59** as a clear oil (300 mg, 69%); ^{1}H NMR (400 MHz, $CDCl_3$) 10.22 (s, 1H), 7.22-7.35 (m, 5H), 4.23-4.36 (dd, *J* = 38.8, 12.0 Hz, 2H), 3.90-3.94 (m, 4H), 3.37-3.39 (d, *J* = 8.8 Hz, 1H), 3.00-3.03 (m, 2H), 2.84-2.86 (d, *J* = 8.8 Hz, 1H), 2.71-2.74 (m, 1H), 2.34-2.60 (m, 4H), 2.20-2.23 (d, *J* = 11.2 Hz, 1H), 2.02-2.11 (m, 1H), 1.77-1.85 (m, 1H), 1.52-1.71 (m, 5H), 1.25-1.48 (m, 4H), 1.04-1.08 (t, *J* = 7.6 Hz, 1H); MS electrospray (m/z): 429.



Compound 66

To a solution of compound **64** (0.337g, 1.00 mmol) in 15 mL of methylene chloride, 1 mL of pyridine and 2-nitrobenzoyl chloride (**65**) (0.16 mL, 1.2 mmol) were added to the mixture at 0 ^{o}C. After 1 h at 0 ^{o}C, 20 mL of saturated aqueous NH_4Cl solution was added to quench the reaction. The product was extracted twice with methylene chloride and the combined organic layers were washed with brine. Evaporation of the solvent, followed by column chromatography of the residue, gave compound **59** as a clear oil (369 mg, 76%); ^{1}H NMR (400 MHz, $CDCl_3$) 7.63-7.89 (m, 4H), 5.71 (s, 1H), 4.12-4.22 (m, 2H), 3.91 (s, 4H), 3.51 (s, 3H), 2.80-3.01 (m, 2H), 2.26-2.57 (m, 4H), 1.77-1.84 (m, 2H), 1.22-1.66 (m, 9H), 1.00-1.04 (t, *J* = 7.2 Hz, 3H); MS electrospray (m/z): 486.

PPENDIX. X-RAY STRUCTURE OF COMPOUND **37**



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GENERAL CONCLUSIONS

In this dissertation, syntheses of some heteroaromatic compounds have been studied. During this process, novel synthetic methodologies have been developed.

Chapter 1 describes an efficient synthesis of 2-substituted and 2,3-disubstituted indoles by a two-step approach in one pot involving imine formation and six-electron ring closure, followed by a 1,5-hydrogen shift. These reactions proceed under very mild conditions and remarkably short reaction times. A wide range of aryl or α,β-unsaturated aldehydes undergo this process in excellent yield. The adduct prepared from indole-4-carboxaldehyde is an advanced intermediate in the synthesis of arcyriacyanin A. The adduct prepared from 4-oxo-3,4-dihydroquinazoline-2-carboxaldehyde is an advanced intermediate in the synthesis of several rutaecarpine analogs.

Chapter 2 describes a new, efficient and straightforward formal total synthesis of neocryptolepine (**2**) and isocryptolepin (**3**), employing the same intermediate **8**, and an intramolecular Wittig reaction, followed by an aza-Wittig reaction in excellent yield.

Chapter 3 describes two synthetic routes to the highly functionalized bicyclic core skeleton of salvorin A. A Sonogashira coupling of an alkyne intermediate with an iodoalkene afforded some advanced intermediates with an A ring and a C ring. The second route using an intermolecular Michael addition and an intramolecular S_N2 reaction form the important B ring. Lactonization could give the tricyclic core structure of salvorin A (**1**).

Chapter 4 describes a direct synthesis of a highly functionalized tricyclic intermediate fragment of methyllycaconitine (**1**). The carbon extension at the inert bridge carbonyl group

was realized by reducing the neighboring ester group. All of the experiments demonstrate that the right stereochemistry at the bridge carbon is the key isomer for F ring formation.

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