# Synthesis of 7-Substitutedoxymethyl-3-methyl-6,8-dioxabicylo[3.2.1]octa-2-one as a key intermediate for the Natural Product Synthesis

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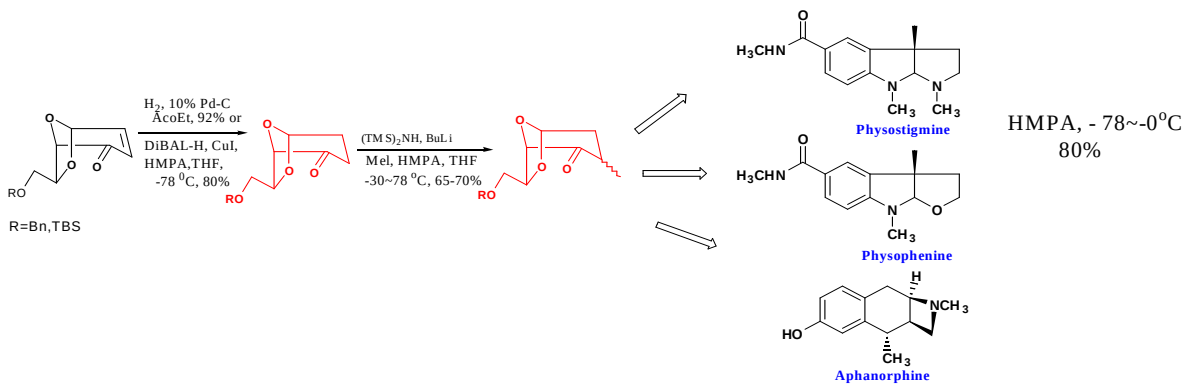
## Abstract

The difficulties involved in monoalkylating aldehyde and ketones are well known, because the alkylation usually leads to mixtures of structurally isomeric alkylated products. In this work the alkylation of 7-substitutedoxymethyl-6,8-dioxabicyclo[3.2.1]octa-2-one **3** was done succesivlly in high yield to give Synthesis of 7-Substitutedoxymethyl-3-methyl-6,8-dioxabicylo[3.2.1]octa-2-one which represent a key intermediate in the synthesis of many natural compounds,[1-3] that has variety of the biological activities.

## Introduction

7-Substitutedoxymethyl-3-methyl-6,8-dioxabicylo[3.2.1]octa-2-one **3** is very important and crucial intermediate in the synthesis of a larg number of natural products e.g. aphanorphine alkaloide and calabar bean alkaloids (physovenine and physostigmine) (Scheme 1).




***(scheme-1)***

**Results and Discussion**

The reaction 7-substituted-6,8-dioxabicyclo[3.2.1]octen-2-one[3] **1** with thiophenol and paraformaldehyde in the presence of triethylamine in ethanol under reflux condition afforded methylthiophenol (2). The conversion of the latter compound to α-methylketone undergoes the following reaction.

When reacted with L-selectride in THF at −78°C gave a mixture of the target compound **3** in 30% yield and compound **4**, when refluxed with Ranny nickel in ethanol, unfortunately, undergo debenzylaton and dethiobenzylation to afford the diol **5** in quantitative yield, so when use more mild condition to obtain the monomethylketone under catalytic hydrogenation,[1,3], we obtain the target compound 45% yield and the starting material 50% after one week. When the compound **2** undergo Birch reduction[4] unfortunately, debenzylation occur and give the alcohol **6**.

When compound **2** react with mixture of LAH and CuI[2] to give *in-situ* generated cuprous hydride (soft reducing agent) in the presence of HMPA in THF at −78°C afford mixture of enone **7** in 54% and enol **8** in 18% yield , respectively (Scheme 2).

When compound **1** undergo Baylis-Hilman[5] reaction via stirring in 36% formaldehyde solution in THF at r.t. in the presence of DMAP as catalyst afforded the corresponding alcohol after 1.5 h, if the reaction continue for more long time afforded the corresponding diol **10**, when compound **9** react with methansulfonyl chloride in dichloromethane at 0°C in the presence of TEA unfortunately, it will be decomposed. So, the protection of compound **9** with T.B.S give compound **11** which when react with L-selectride and supper hydride in THF afforded the target compound **3** in 30% yield and

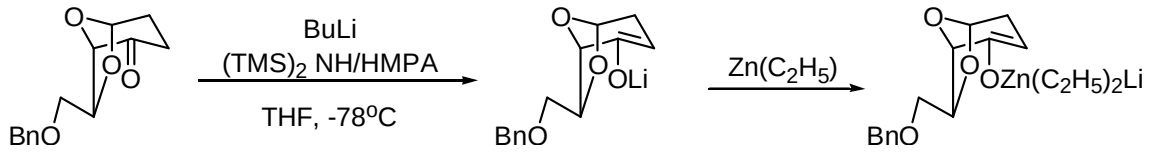
enol **12** respectively. When compound **11** undergo soft reducing agent DIBAL-H in the presence of CuI and HMPA in THF at −78°C (*in-situ* generated CuH) undergo 1,4 reduction to afford ketone **13** (Scheme 3).

The compound **1** was reacted with $H_2O_2$ in the presence of NaOH[6] in THF to afford the epoxyketone **14** followed by reductive alkylation via Gilaman's reaction but the starting material were recovered. The compound **1** when reacted with MeI in the presence of L-slectrid at −78°C in THF the dimethylketone **15** was obtained.

So the enone **1** undergo selective 1,4 addition reaction[2] when reacted with DIBAL-H in the presence of CuI in THF in the presence of HMPA at −78°C to give the ketone **16** in 80% yield, which reacted with TAMA and paraformaldehyde[7,8] in hot THF afforded α-methyleneketone **2** in low yield which can be easily converted to α-methylketone **3**.

The compound **16** when reacted with methylcyanoformate[9,10] in the presence of hexamethyldisilazide at −78°C, unfortunately, afforded o-estere **17** instead of c-ester **18**, which can be easily alkylated. Also, compound **17** was obtained via reaction of **16** with methylchloroformate in the presence of k.t. butoxide in THF at °C, the later compound can be easily hydrolysed by stirring with $K_2CO_3$ in $CH_3OH$ to recover compound **19**. When the hydrolysis were done via NaH in THF in the presence of methyliodide afforded the dimethylketone **15** (Scheme 4).

The presence of dimethyl zinc in the reaction of lithium enolate and electrophiles effectively suppresses undesired α-proton exchange reaction and enhances the efficiency of enolate alkylation (Scheme 5).




**(Scheme 5)**

So when compound **16** reacted with MeI in the presence of HMDS and dimethyl zinc in the presence of HMPA in THF at −78°C ~30°C afforded the target compound **3** in 30%, compound **4** in 7% and compound **16** in 33% yield, respectively.

When compound **16** reacted with $CH_3I$ in the presence of base as proton scavenger (LDA, NaH, NaOEt and t.butoxide) afforded dimethylketone **15**.

When compound **1** undergo cycloaddition reaction via Diels-Alder condition[11] afforded the Diels-Alder isomeric Adduct **20** and **21** in 6.6:1 as epimeric mixture respectively in 97% yields. Diels-Alder adduct can be easily alkylated when react with methyl iodide in the presence of LDA and HMPA in THF at −78~0°C to afford the α-monomethylketone **22** and **23** in 94% yield. The later compound when undergo retro Diels-Alder[12] in diphenyl ether at 280°C or in o-dichlorobenzene at 170°C it will give compound **3** in 95% yield (Scheme 6).

Finally, we were obtained the target compound in total yield 87% rather than the reported method[3] in total yield 56%.

**Experimental**

$^1$H NMR were recorded on a Varian Gemini 2000 (300MHz) spectrometer. Chemical shifts are given in δ (ppm) values downfield from $Me_4Si$ as an internal standard. IR spectra were recorded on a JASCO-IR-700 spectrometer. Mass spectra were recorded on Jeol JMS-DX 303 instrument. Thin layer chromatography was performed on Merck 5 x 10 cm plates, precoated with silica gel $GF_{254}$ using short wavelength UV light for visualization ($CHCl_3$, methanol 10:1). All of the fine chemicals and reagents used were purchased from Aldrich.

**(±)-7-Benzyloxymethyl-3-phenylsulfanylmethyl-6,8-dioxabicyclo[3.2.1]oct-3-en-2-one (2).**

The mixture of **1** (2.00 mmol) and thiophenol (2.00 mmol) and aqueous formaline 36% (5 mmol) was refluxed in ethanol (20 ml) Containing triethylamine (5 drops) for 3 hours, after cooling, the mixture was evaporated under reduced pressure to give the residue which was diluted with water and extracted with AcOEt. The extract was washed successively with 10% NaOH and brine, dried over anhydrous $MgSO_4$, evaporated under reduced pressure and chromatographed ($SiO_2$, 60 gm, elution with hexan-AcOEt 10:1 v/v as pale yellow oil 85% yield).

**(±)-7-Benzyloxymethyl-3-methyl-6,8-dioxabicyclo[3.2.1]octa-2-one (3).**

**Method A**

A mixture of compound **2** (2 mmol) in THF (20 ml) was stirred at −78°C for 1 hour, L-selectride (2 mmol) was added and the reaction mixture was stirred at −78°C for 1 hrs, the mixture was diluted with $Et_2O$ (10 ml) and $H_2O$ (5 ml) and stirred at r.t. for 1 hour. The

mixture was filtered through celite and washed successively with $H_2O$ and brine, dried over anhydrous $MgSO_4$, evaporated under reduced pressure and chromatographed ($SiO_2$, 70 g elution with hexane-AcOEt, 7:1 v/v) to afford **3** as pale yellow oil 30% yield and (±)-7-Benzyloxymethyl-3-phenylsulfanylmethyl-6,8-dioxa-bicyclo[3.2.1]octan-2-ol **4** as yellow oil 34% yield.

**Method B**

A suspension of **2** (2 mmol and 10% pd-c in AcOEt (20 ml) was stirred under hydrogen atmosphere at r.t. For one week. The suspension was filtered through celite pad, the filtrate was evaporated under reduced pressure and chromatographed ($SiO_2$, 60 gm elution with hexane-AcOEt 10:1 v/v) to afford compound **3** in 45% yield as pale yellow oil.

**Method C**

A solution of $(TMS)_2$ NH (2 mmol) in THF (15 ml) and n-BuLi (1.54 M in hexane, 2 mmol) was stirred at 0°C for 30 minutes, HMPA (2 mmol) and ketone (±)-7-Benzyloxymethyl-6,8-dioxabicyclo[3.2.1]octa-2-one **16** (2.5 mmol) in THF (10 ml) were added and the mixture was stirred at −78°C for 1 hour. Dimethyl zinc (1 mmol) was added and the reaction mixture was stirred at the same temperature for 1 hour, methyliodide (1 mmol) was added and the mixture was stirred at −30°C for 1 hour.

The reaction mixture was diluted with $Et_2O$ (5 ml) and $H_2O$ (3 ml), stirred at r.t. for 1 hour, filter through celite pad, the filtrate was washed with brine, dried over anhydrous $MgSO_4$, evaporated under reduced pressure and chromatographed ($SiO_2$, elution with hexane – AcOEt 10:1 v/v) to give compound **3**, (±)-7-Benzyloxymethyl-3,3-dimethyl-6,8-

dioxabicyclo[3.2.1]octa-2-one **15** and (±)-7-Benzyloxymethyl-6,8-dioxabicyclo[3.2.1]octa-2-one **16** in 30%, 7% and 33%, respectively.

**Method D**

A solution of compounds **20** and **21** (3.5 mmol) in o-dichlorobenzene (ODB) (15 ml) was heated at 170°C for 2 hours. The reaction mixture allowed to cool and chromatographed ($SiO_2$, elution with hexane-AcOEt 7:1 v/v) to give a compound **3** as pale yellow oil in 95% yield.

**(±)-7-Hydroxymethyl-3-methyl-6,8-dioxabicyclo[3.2.1]octan-2-ol (5).**

A suspension of **2** (2 mmol) refluxed in EtOH containing Ranny nickel 10% for 2 hours. The suspension was filtered through celite pad, the filtrate was evaporated under reduced pressure and chroamtographed ($SiO_2$, 50 g, elution with hexane-AcOEt 1:1 v/v) to afford **5** as pale yellow oil in 100% yield.

**(±)-7-Hydroxymethyl-3-phenylsulfanylmethyl-6,8-dioxa-bicyclo[3.2.1]octan-2-one (6).**

To a stirred solution of Li (1 mmol) in THF (15 ml) at −78°C for 30 minutes, $NH_3$ gas was pupelled into the solution and stirred at the same temperature for 30 minutes. The ketone **2** (10 mmol) in THF (5 ml) was added at the same temperature and the mixture was stirred for 1 hour.

The reaction mixture was diluted with $Et_2O$ (5 ml) and $H_2O$ (3 ml) and stirred at r.t. for 1 hour. The mixture as filtered through celite pad, washed successively with $H_2O$ and brine, dried over anhydrous $MgSO_4$ and evaporated under reduced pressure and chromatographed ($SiO_2$, elution with hexane-AcOEt 1:1 v/v) to afford compound **6** as pale yellow oil in 73% yield.

**(±)-7-Benzyloxymethyl-3-methylene-6,8-dioxabicyclo[3.2.1]octan-2-one (7).**

**Method A**

To a stirred suspension of (CuI, 3 mmol) in THF-HMPA (4:1), (20 ml) at −78°C LAH (1 mmol) was added and the mixture was stirred at −78°C for 1 hour. The compound **2** (2.0 mmol) in THF-HMPA (4:1) (10 ml) was added at the same temperature and the mixture was stirred for 1 hour. The mixture was diluted with $Et_2O$ (5 ml) and $H_2O$ (2 ml) and stirred at r.t. for 1 hour.

The mixture was filtered through celite pad, washed successively with $H_2O$ and brine, dried over anhydrous $MgSO_4$, evaporated under reduced pressure and chromatographed ($SiO_2$, elution with hexan-AcOEt 8:1 v/v) to afford compound **7** and (±)-7-Benzyloxymethyl-3-methylene-6,8-dioxabicyclo[3.2.1]octan-2-ol **8** in 54% and 18% yield respectively as yellow oil.

**Method B**

A mixture of compound **16** (3 mmol), TAMA (5 mmol) and formalin solution 36% (10 mmol) was refluxed in THF for 3 hours. The reaction mixture was extracted with AcOEt, the extract was washed successively with brine, dried over $MgSO_4$, evaporated under reduced pressure and chromatographed ($SiO_2$ elution with hexane-AcOEt 8:1), to afford compound **7** as pale yellow oil in 30% yield.

**(±)-7-Benzyloxymethyl-3-hydroxymethyl-6,8-dioxabicyclo[3.2.1]oct-3-en-2-one (9).**
**(±)-7-Benzyloxymethyl-4-hydroxy-3-hydroxymethyl-6,8-dioxabicyclo[3.2.1]oct-3-en-2-one (10).**

To a stirred solution of compound **1** (5 mmol) in THF (15 ml), the catalytic amount of DMAP (2 ml) of 36%formaldehyde solution was added and the reaction mixture was stirred at room temperature for 1.5-2.5 hours.

The reaction mixture was diluted with water (10 ml) and extracted with AcOEt, the extract was washed successively with water and brine, dried over anhydrous $MgSO_4$, evaporated under reduced pressure and chromatographed ($SiO_2$, elution with hexane-AcOEt 4:1 and 2:1) to obtain compounds **9** and **10**, respectively as pale yellow oil.

**(±)-7-Benzyloxymethyl-3-(*tert*-butyl-dimethylsilanyloxymethyl)-6,8-dioxabicyclo [3.2.1]oct-3-en-2-one (11).**

To a stirred solution of **9** (3 mmol) in $CH_2Cl_2$ (20 ml), $Et_3N$ (0.5 mmol) and TBSCl (4 mmol) were added at 0°C and the mixture was stirred for 2 hours. The mixture was diluted with water (10 ml) and extracted with AcOEt, the extract was washed successively with water and brine, dried over anhydrous $MgSO_4$, evaporated under reduced pressure and chromatographed ($SiO_2$, elution with hexane-AcOEt 15:1 v/v) to afford compound **11** as yellow oil in 55% yield.

**(±)-7-Benzyloxymethyl-3-(*tert*-butyl-dimethyl-silanyloxymethyl)-6,8-dioxa-bicyclo[3.2.1]oct-3-en-2-ol (12).**

A suspension of compound **11** (1 mmol) in THF (15 ml) was added to a stirred solution of supper hydride (1 mmol) in TMF (15 ml) at −78°C, the mixture was stirred at the same temperature for 1 hour. The mixture was diluted with $Et_2O$ (5 ml) and $H_2O$ (5 ml) and stirred at the r.t. for 1 hour. The mixture was filtered through cellite pad, washed

successively with $H_2O$ and brine, dried over anhydrous $MgSO_4$, evaporated under reduced pressure and chromatographed ($SiO_2$, elution with hexane-AcOEt 10:1 v/v) to give compound **12** as yellow oil in 35% yield.

**(±)-7-Benzyloxymethyl-3-(*tert*-butyldimethylsilanyloxymethyl)-6,8-dioxabicyclo[3.2.1] octan-2-one (13).**

To a stirred suspension of CuI, (3 mmol) in THF-HMPA (4:1), (20 ml) at −78°C DIBAL-H (1 mmol) was added and the mixture was stirred at −78°C for 1 hour. The compound **2** (2.0 mmol) in THF-HMPA (4:1) (10 ml) was added at the same temperature and the mixture was stirred for 1 hour. The mixture was diluted with $Et_2O$ (5 ml) and $H_2O$ (2 ml) and stirred at r.t. for 1 hour.

The mixture was filtered through celite pad, washed successively with $H_2O$ and brine, dried over anhydrous $MgSO_4$, evaporated under reduced pressure and chromatographed ($SiO_2$, elution with hexan-AcOEt 15:1 v/v) to afford compound **13** as yellow oil.

**(±)-7-Benzyloxymethyl-3,8,9-trioxatricyclo[4.2.1.$0^{2,4}$]nonan-5-one (14).**

A solution of compound **1** (4.0 mmol) in THF (20 ml) and (0.5 N NaOH) (3 ml) was stirred at r.t., $H_2O_2$ (30% 3 ml) were added and the reaction mixture was stirred for 50 minutes. The reaction mixture was extracted with AcOEt, the extract was washed with brine, dried over $MgSO_4$ evaporated under reduced pressure and chromtoagraphed ($SiO_2$, elution with hexane-AcOEt 5:1) to give compound **14** as pale yellow oil in 66% yield.

**(±)-7-Benzyloxymethyl-3,3-dimethyl-6,8-dioxabicyclo[3.2.1]octa-2-one (15).**

**Method A**

A mixture of compound **2** (2 mmol) in THF (20 ml) was stirred at −78°C for 1 hour, L-selectride (2 mmol) was added and the reaction mixture was stirred at −78°C for 1 hrs, the mixture was diluted with $Et_2O$ (10 ml) and $H_2O$ (5 ml) and stirred at r.t. for 1 hour. The mixture was filtered through celite and washed successively with $H_2O$ and brine, dried over anhydrous $MgSO_4$, evaporated under reduced pressure and chromatographed ($SiO_2$, 70 g elution with hexane-AcOEt, 7:1 v/v) to afford **15** as pale yellow oil.

**Method B**

A solution of **16** (1 mmol) in THF were added to a solution of LDA, HMDS, k, t-butoxide, NaOMe or NaH in TMF or EtOH (10 ml) at 0°C and the reaction mixture as stirred at the same temperature for 1 hour, $CH_3I$ was added and stirred for 1 hour at the same temperature.

The reaction mixture was diluted with $Et_2O$ (5 ml) and $H_2O$ (3 ml), stirred at r.t. for 2 hours, filter through celite pad, the filtrate was washed with brine, dried over anhydrous $MgSO_4$, evaporated under reduced pressure and chromatographed ($SiO_2$, elution with hexane-AcOEt 7:1 v/v) to give a compound **15** as pale yellow oil.

**Method C**

A solution of compound **17** (1 mmol) in THF (10 ml) was stirred with NaH (1.2 mmol) at −30°C for 1 hour, methyl iodide (1 mmol) was added and the reaction mixture was stirred at the same temperature for 1 hour.

The reaction mixture was diluted with $Et_2O$ (5 ml) and $H_2O$ (3 ml), stirred at r.t. for 2 hours, filter through celite pad, the filtrate was washed with brine, dried over anhydrous

$MgSO_4$, evaporated under reduced pressure and chromatographed ($SiO_2$, elution with hexane-AcOEt 7:1 v/v) to give a compound **15** as pale yellow oil.

**(±)-7-Benzyloxymethyl-6,8-dioxabicyclo[3.2.1]octa-2-one (16).**

To a stirred suspension of (CuI, 3 mmol) in THF-HMPA (4:1), (20 ml) at −78°C DIBAL-H (1 mmol) was added and the mixture was stirred at −78°C for 1 hour. The compound **1** (2.0 mmol) in THF-HMPA (4:1) (10 ml) was added at the same temperature and the mixture was stirred for 1 hour. The mixture was diluted with $Et_2O$ (5 ml) and $H_2O$ (2 ml) and stirred at r.t. for 1 hour.

The mixture was filtered through celite pad, washed successively with $H_2O$ and brine, dried over anhydrous $MgSO_4$, evaporated under reduced pressure and chromatographed ($SiO_2$, elution with hexan-AcOEt 10:1 v/v) to afford compound **16** as yellow oil in 80% yield[(3)].

**(±)-7-Benzyloxymethyl-6,8-dioxabicyclo[3.2.1]oct-2-en-2-yl methyl ester (17).**

**Method A**

A solution of $(TMS)_2$ NH (2 mmol) in THF (15 ml) and n-Buli (1.54, M in hexane, 2 mmol) was stirred at 0°C for 30 minutes. HMPA (2 mmol) and ketone (**16**) (2.5 mmol) in THF (10 ml) were added and the mixture was stirred at −78°C for 1 hour, methylcyanoformate (2 mmol) was added at the same temperature and stirred for 2 hours. The reaction mixture was diluted with $Et_2O$ (5 ml) and $H_2O$ (3 ml), stirred at r.t. for 1 hour, filter through celite pad, the filtrate was washed with brine, dried over $MgSO_4$, evaporated under reduced pressure and chromatographed ($SiO_2$, elution with hexane-AcOEt 4:1 v/v) to give compound **17** as pale yellow oil in 74% yield.

**Method B**

A mixture of compound **16** (2 mmol) in THF (15 ml) k. t-butoxide (2 mmol) was stirred at 0°C for 1 hour, methylchloroformate (2 mmol) were added and the reaction mixture was stirred at the same temperature for 2 hours. The reaction mixture was diluted with $H_2O$ (5 ml) stirred at r.t. for 1 hour, filter through celite pad, the filtrate was extracted with AcOEt, the extract was washed with brine, dried over $MgSO_4$, evaporated under reduced pressure and chromatographed ($SiO_2$, elution hexane-AcOEt 4:1 v/v) to give compound **17** as pale yellow oil in 77% yield.

**(±)-7-Benzyloxymethyl-6,8-dioxabicyclo[3.2.1]octan-2-ol (19).**

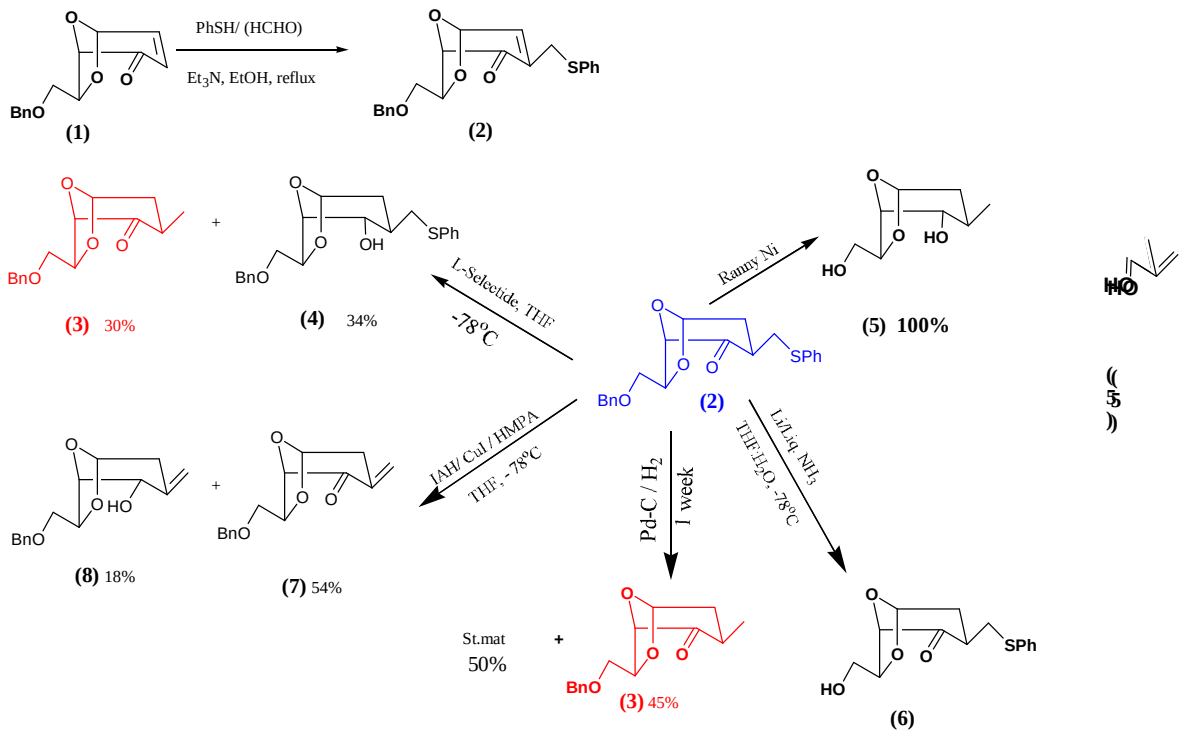
To a solution of compound **17** (1 mmol) in EtOH (15 ml), $K_2CO_3$ (5 mmol) were added and the reaction mixture was stirred at r.t. for 30 minutes. The mixture was diluted with $H_2O$ (2 ml) and extracted with AcOEt (10 ml), the extract washed was $H_2O$ and brine, dried over $MgSO_4$, evaporated under reduced pressure and chromatographed ($SiO_2$, elution hexone-AcOEt 10:1) to give alcohol **19** in 94% yield.

**Compound 20, 21**

To a stirred solution of compound **1** (5 mmol) in toluene (40 ml), $ZnCl_2$ (10 mmol) were added and the mixture was stirred at r.t. for 30 minutes. The reaction mixture was cooled to 0°C, cyclopentadiene (7 mmol) were added and stirred at the room temperature for 1 hour. The reaction mixture was washed successively with 10% $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, evaporated under reduced pressure and chromatographed ($SiO_2$ elution with hexane-AcOEt 6:1 v/v) to afford compounds **20** and **21** mixture as pale yellow oil in 97% yield.

**Compound 22, 23**

A solution of disopropylamine (3.5 mmol) in THF (20 ml) and n-Buli (1.54 M in hexane 3.5 µ.Mol) was stirred for 30 minutes at 0°C. The HMPA (3.5 mmol) and the ketone **20** and **21** (3.5 mmol) in THF (20 ml) were added and the mixture was stirred at − 78°C for 1 hour, methyliodide (3.5 mmol) was added at the same temperature and the reaction mixture was stirred at 0°C for 2 hours. The reaction mixture was diluted with $Et_2O$ (10 ml) and $H_2O$ (3 ml), stirred at r.t. for 1 hour, filter through celite pad, the filtrate was washed with brine, dried over $MgSO_4$, evaporated under reduced pressure and chromatographed ($SiO_2$, elution with hexane – AcOEt 10:1) to give compound **22** and **23** as pale yellow oil in 80% yield.

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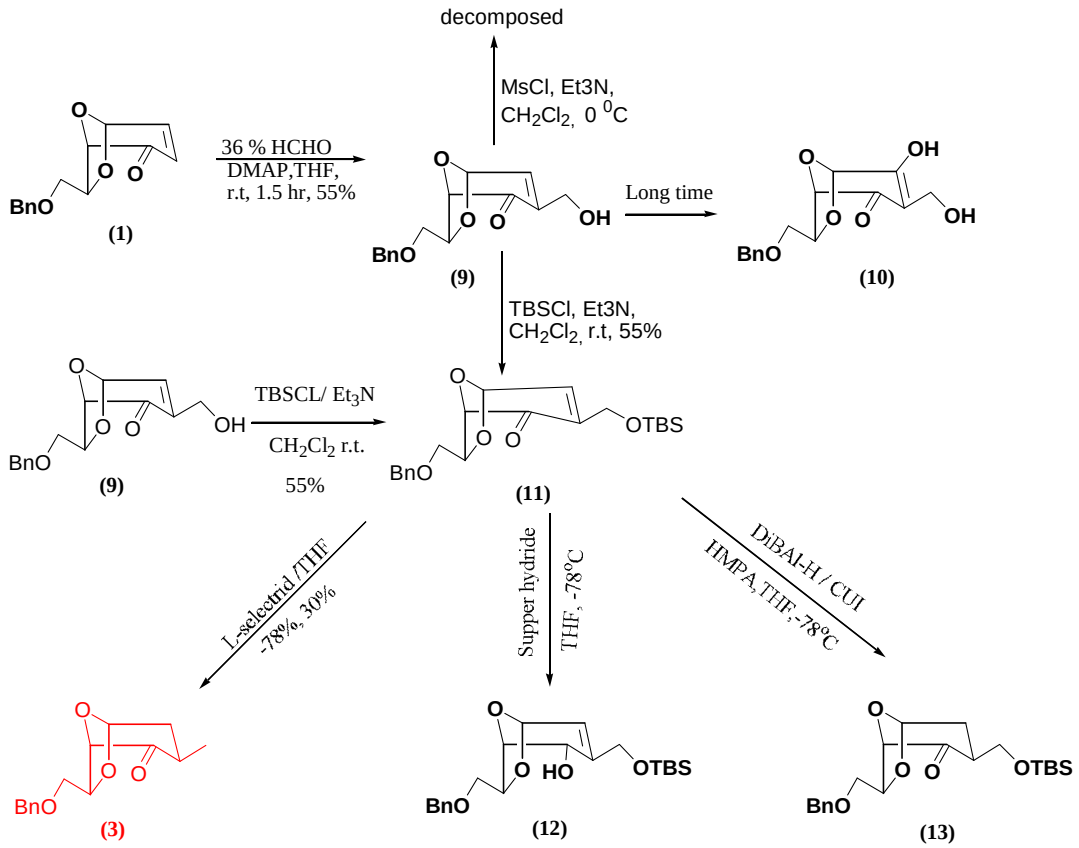
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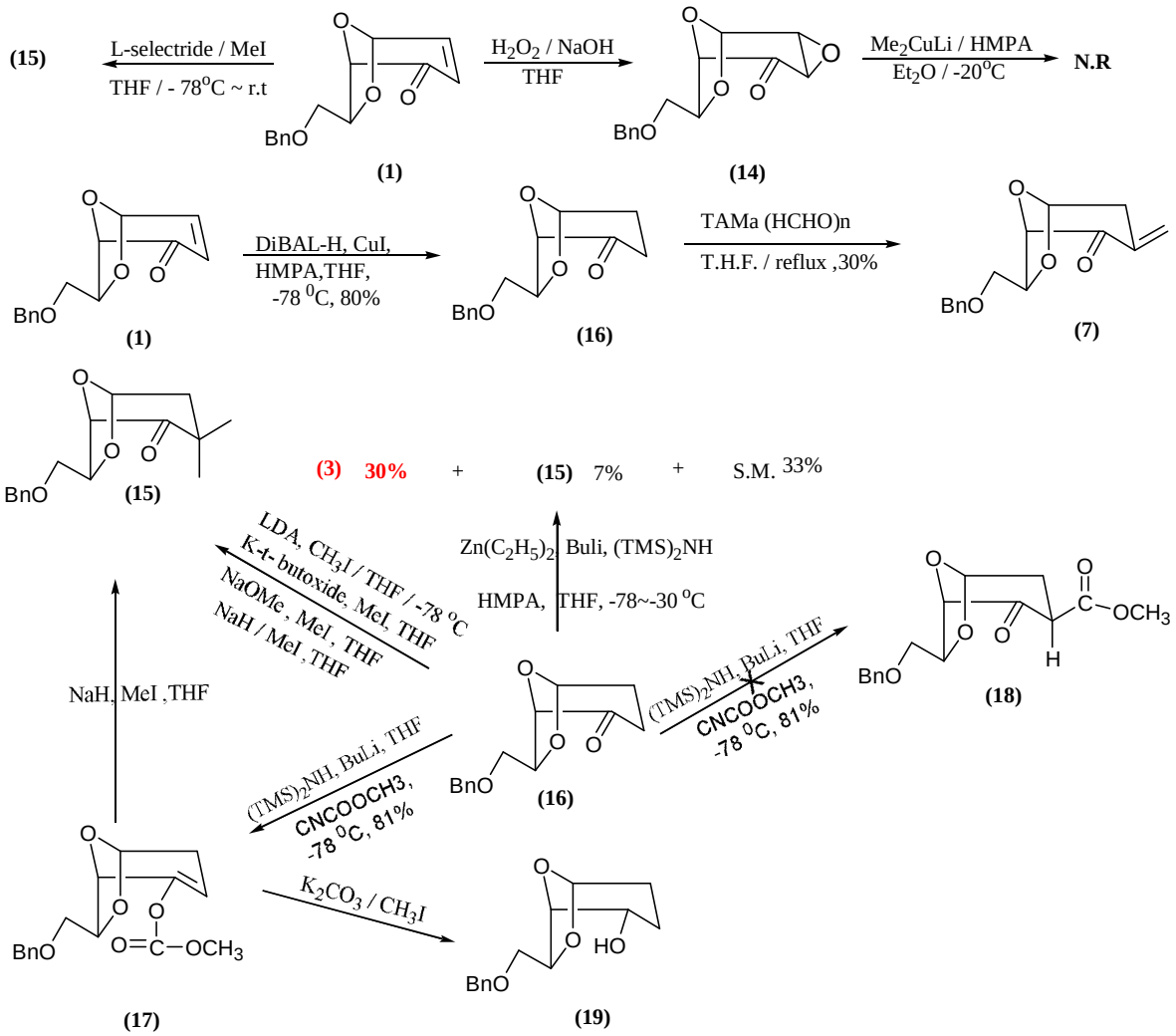


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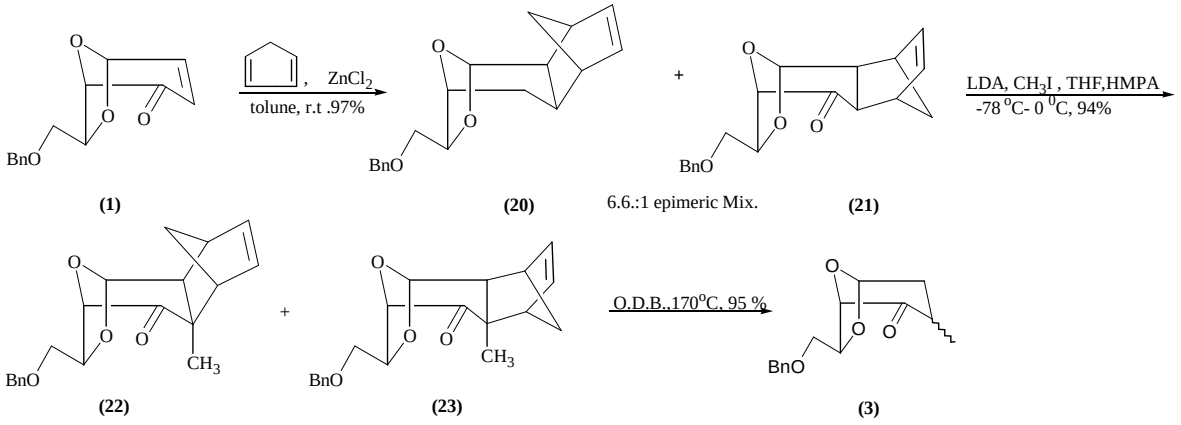


***Schem-6***

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**Table (1):** IR ($cm^{-1}$), $^1$HNMR (ppm) and mass (M/Z) spectral data of the synthesized compounds.

| Comp. | Spectral data |
|---|---|
| **1** | IR υ = 1721, 1690. $^1$H NMR ($CDCl_3$ 500 MHz) δ: 7.30-7.19 (m, 5H), 7.05 (dd, 1H), 6.01 (d, 1H), 5.75 (d, 1H), 4.52 (s, 2H), 3.96~3.93 (m, 1H), 3.56 (dd, 1H), 3.46 (2H, dd). FABMS m/z = 246 ($M^+-1$). HRMS for $C_{14}H_{14}H_{14}O_4$ Calcd: 246.2879, found 246.2863 (as reported). |
| **2** | IR υ = 1700. $^1$H NMR ($CDCl_3$) δ = 3.47~3.49 (2H, m), 3.50~3.58 (2H, m), 3.90 (1H, t), 4.8 (2H, s), 4.73 (1H, s), 5.74 (1H, d), 6.76 (1H, d), 7.22~7.36 (10H, m). MS m/z = 368. HRMS for $C_{21}H_{20}O_4S$ Calcd: 368.1081, found 368.1089. |
| **3** | IR υ = 1729 $cm^{-1}$. $^1$H NMR ($CDCl_3$) δ: 1.12 (3H, dd), 1.74~1.78 (1H, m), 2.68~2.34 (2H, m), 3.51~3.35 (2H, m), 4.20 (1H, t), 4.4 (1H, s), 4.55 (2H, s), 5.70 (1H, s), 7.27~7.34 (5H, m). MS m/z = 262 [$M^+$]. HRMS: Calcd. for $C_{15}H_{18}O_4$ = 262.1204, found 262.1212 (as reported). |
| **4** | I.R. υ = 3452 $cm^{-1}$, $^1$H NMR ($CDCl_3$) δ: 1.98~2.08 (2H, m), 2.86~2.73 (1H, m), 3.62 (2H, m), 3.68 (2H, dd), 3.78 (1H, t), 4.81 (2H, m), 4.90 (1H, d), 5.69 (1H, t), 7.27~7.36 (10H, m). MS M/z 371, HRMS: Calcd for $C_{21}H_{24}O_4S$ = 372.4872, found 372.4763. |
| **5** | I.R. υ = 3443, 3420 $cm^{-1}$. $^1$H NMR ($CDCl_3$) δ: 7.23 (1H, m), 5.7 (1H, brs), 4.81-4.74 (1H, m), 4.68 (1H, br s), 4.29-4.21 (1H, m), 3.72 (2H, d), 3.42 (1H, m), 2.60-2.30 (1H, m), 1.78-1.68 (2H, m), 1.09 (3H, dd). MS m/z = 174. HRMS: Calcd. for $C_8H_{14}O_4$ = 174.1888, found 174.1873.. |
| **6** | I.R. υ = 3450, 1700 $cm^{-1}$. $^1$H NMR ($CDCl_3$) δ = 3.65 (2H, dd), 3.78 (2H, d, d), 3.79 (1H, t), 4.6 (1H, d), 5.78 (1H, d), 6.77 (1H, d), 7.27~7.33 (5H, m). MS m/z = 278, HRMS: Calcd. for $C_{14}H_{14}O_4S$ = 278.3287, found 278.3771. |
| **7** | I.R. υ = 1714, 1617 $cm^{-1}$. $^1$H NMR ($CDCl_3$) δ: 7.34-7.21 (5H, m), 6.93-6.81 (1H, m), 6.69-6.62 (1H, m), 5.71 (1H, s), 4.71 (2H, s), 4.41 (1H, s), 4.30 (1H, t), 3.56-3.48 (2H, m), 2.58-2.32 (2H, m). MS m/z HRMS: Calcd. For $C_{15}H_{16}O_4$ = 260.2896, found = 260.2891. |
| **8** | I.R. υ = 1640, 3440 $cm^{-1}$. $^1$H NMR ($CDCl_3$) δ: 7.30-7.19 (5H, m), 5.85-5.60 (2H, m), 5.52-5.45 (1H, m), 5.01 (1H, brs), 4.56 (2H, m), 4.39 (1H, s), 4.27 (1H, t), 4.23 (1H, m), 3.51-3.42 (2H, m), 2.65-2.42 (2H, m). MS m/z = 261. HRMS: Calcd. for $C_{15}H_{18}O_4$ = 262.2975, found 262.2967. |
| **9** | I.R. υ = 3433 $cm^{-1}$, 1705 $cm^{-1}$, $^1$H NMR 2.32 ((brs, 1H), 3.48~3.65 (2H, m), 3.97 (1H, t), 4.23~4.38 (2H, m), 5.58 (2H, m), 4.59 (1H, d), 5.87 (1H, d), 7.03 (1H, d), 7.28~7.38 (5H, m). MS m/z = 276, HRMS: Calcd for $C_{15}H_{16}O_5$ = 276.2896, found = 276.2884. |
| **10** | I.R. υ = 3402, 1721. MS m/z = 294.1 HRMS: Calcd. for $C_{15}H_{16}O_6$ 292.2884, found 292.2871. |

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| **11** | I.R. υ = 1736, 1688. $^1$H NMR ($CDCl_3$) δ = 0.07 (6H, s), 0.88 (9H, s), 3.48~3.54 (2H, m), 3.95 (1H, t), 4.34~4.48 (2H, m) 4.57~4.58 (2H, s), 4.67 (1H, s), 5.88 (1H, d), 7.23~7.25 (1H, m), 7.30~7.35 (5H, m), MS m/z = 391, HRMS = $C_{21}H_{30}O_5S$: Calcd. for 390.5476, found 390.5448. |
| **12** | I.R. υ = 3452. $^1$HNMR ($CDCl_3$) δ: 0.05 (6H, s), 0.8 (9H, s), 3.14~3.49 (2H, m), 4.22 (1H, t), 4.49 (2H, dd), 4.51 (1H, d), 4.47 (2H, s), 4.75 (1H, br s), 5.46 (1H, d), 5.7 (1H, d), 7.16~7.27 (6H, m). FABM m/z = 392, HRMS: Calcd. for $C_{21}H_{32}O_5Si$ = 392.5560, found 392.5573. |
| **13** | I.R. υ = 1722 $cm^{-1}$, $^1$HNMR ($CDCl_3$) δ: 0.06 (6H, s), 0.86 (9H, s), 1.76~1.67 (2H, m), 2.60~2.56 (1H, m), 3.43~3.52 (2H, m), 355. (2H, d), 3.91 (1H, t), 4.32~4.53 (2H, s), 4.55 (1H, m), 5.84 (1H, m), 7.31~3.35 (5H, m). MS m/z = 392 HRMS: Calcd for $C_{21}H_{32}O_5Si$ = 392.5660, found 392.5536. |
| **14** | I.R. υ = 1723. $^1$H NMR ($CDCl_3$) δ: 3.3~3.54 (4H, m), 4.10 (1H, t), 4.48 (1H, s), 4.55 (2H, s), 5.87 (1H, d), 7.29~7.37 (5H, m). MS = 262; HRMS for $C_{14}H_{14}O_5$. Calcd. 262.2641, found 262.2631. |
| **15** | I.R. υ = 1727. $^1$H NMR δ: 1.24 (6H, d), 1.79 (1H, d), 2.05 (1H, d, d), 3.36~3.59 (2H, m), 4.18 (1H, t), 4.44 (1H, s), 4.55 (2H, s), 5.73 (1H, m). 7.28~7.37 (5H, m). MS = 362. HRMS: Calcd. for $C_{16}H_{20}O_4$ = 276.3324, found: 276.3318. |
| **16** | I.R. υ = 1729 $cm^{-1}$. $^1$H NMR, ($CDCl_3$) δ: 2.18~1.93 (2H, m), 2.44-2.32 (2H, m), 3.32 (1H, dd), 3.42 (1H, dd), 4.17 (1H, t), 4.29 (1H, s), 4.47 (2H, d), 5.67 (1H, d), 7.31-7.19 (5H, m). Mass m/z = 248. HRMS: Calcd. for $C_{14}H_{16}O_4$ = 248.1047, found: 248.1036 (as reported). |
| **17** | I.R. υ = 1758, 1700; NMR ($CDCl_3$) δ = 7.26~7.34 (5H, m), 5.67 (1H, d), 5.37 (1H, t), 4.64 (1H, t), 4.55 (1H, d), 4.50 (2H, s), 3.83 (3H, s), 3.38 (2H, m), 2.51~2.53 (1H, t, t), 2.15~2.16 (1H, dd). MS = 306; HRMS for $C_{16}H_{18}O_6$, Calcd. 306.1102, found 306.1099. |
| **19** | I.R. υ = 3420 $cm^{-1}$. $^1$H NMR ($CDCl_3$) δ: 7.38-7.26 (5H, m), 5.91 (1H, dd), 5.71 (1H, m), 5.53 (1H, m), 4.77 (1H, m) 4.60 (2H, s). 4.50~4.46 (2H, m), 4.28 (1H, t), 3.59 (2H, m), 3.52 (2H, m). MS m/z = 250. HRMS Calcd. for $C_{14}H_{18}O_4$ [$M^+$] = 250.1050, found 250.1043. |
| **20 & 21** | I.R. υ = 1728, 1636 cm-1. 1H NMR (CDCl3) δ: 1.5 (1H, t), 1.53 (1H, t), 2.56 (1H, dd), 2.92 (1H, dd), 2.96~3.0 (1H, m), 3.35 (1H, dd), 3.38~3.51 (2H, m), 4.06~4.10 (2H, m), 4.53 (1H, d), 4.61 (1H, t), 5.55 (1H, d), 6.03~6.05 (1H, m), 6.10~6.13 (1H, m), 7.22~7.39 (5H, m). MS m/z = 312. HRMS Calcd. For C19H20O4 = 312.3654, found 312.3662. |
| **22 & 23** | I.R. υ = 1725, 1HNMR δ: 7.25~7.33 (5H, m), 6.05~6.11 (2H, dd), 5.57 (1H, d), 4.52~4.57 (2H, s), 4.12~4.16 (1H, t), 4.05 (1H, s), 3.28~3.43 (2H, m), 2.84~2.89 (2H, d), 2.19~2.2 (1H, d), 1.43~1.59 (2H, dd), 1.25~1.26 (3H, dd).<br>MS = 326; HRMS for $C_{20}H_{22}O_4$; Calcd. 326.3916, found 326.3941. |