The Concise Synthesis of a Key Intermediate for the Total Synthesis of Fumagillin, TNP-470, and Ovalicin

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Received 27 December 2007; revised 21 January 2008

Abstract: The facile synthesis of a key intermediate for the total synthesis of the antiangiogenic compound fumagillin, its semisynthetic analogue TNP-470, and ovalicin is described. The methodology employs a Diels–Alder strategy and a zinc-mediated ring-opening reaction to realize the cyclohexane backbone.

Key words: angiogenesis inhibitors, Diels–Alder reaction, *syn* reduction, dihydroxylation, HIV

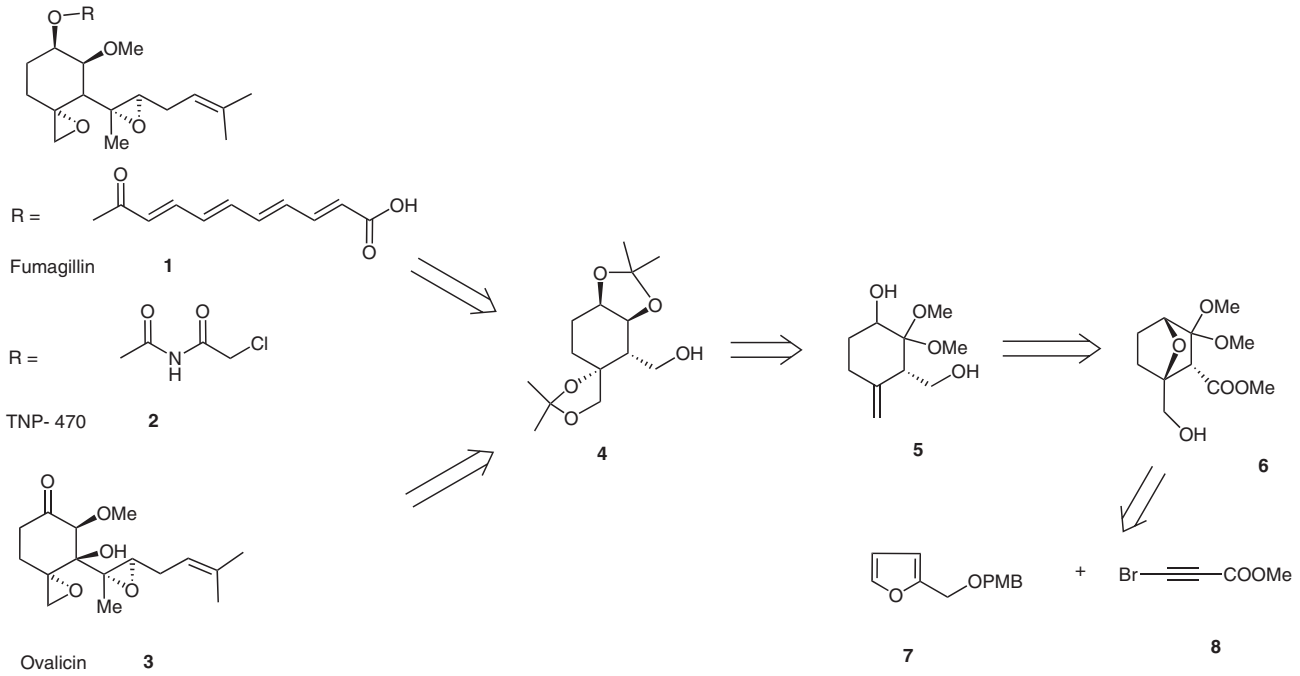
Abnormal angiogenesis has been recognized as the most prevalent feature of many proliferative diseases, including diabetic retinopathy, psoriasis, and rheumatoid arthritis.[1] Because tumor metastasis is highly dependent upon angiogenesis, the inhibition of angiogenesis has become increasingly important as an alternative promising method for cancer therapy.[2] Toward this goal, large efforts have been made to develop specific antiangiogenic drugs, which starve and thus reduce the tumor cells by eliminating their blood supplies, and these investigations have resulted in the discovery of various antiangiogenic compounds, such as fumagillin,[3] RK-805,[4] endostatin,[5] angiostatin,[6] ovalicin,[7] and the synthetic analogue TNP-470.[8] Thus, these compounds and the synthesis of their more potent and stable derivatives have become challenging targets for chemists. Initially, fumagillin was found to be an effective antibiotic and antiparasitic agent, as well as a potential drug for the treatment of malaria and leishmaniasis;[9] later, it was used for the treatment of intestinal microsporidiosis in HIV-infected patients.[10] More recently, fumagillin has been found to reverse the growth inhibitory activity of Vpr in yeast and human cells, and to inhibit the HIV-1 infection of human macrophages.[11] This significant property may make it a lead compound for the development of AIDS therapeutic drugs that target Vpr activity. The profound activity of fumagillin has attracted chemists and culminated in several synthetic approaches to give the compound and its analogues, from Corey and Snider's first elegant total synthesis[12] to various other formal and total syntheses of both the racemic and enantiomeric forms.[13]

In continuation of our research on the synthesis of biologically active compounds, we recently accomplished a formal total synthesis of ovalicin, an angiogenesis inhibitor.[14] Because of the vast research oriented toward the biological properties of fumagillin for its enhanced activities, we became interested in the total synthesis of fumagillin. The three compounds fumagillin (**1**), TNP-470 (**2**), and ovalicin (**3**) have a similar carbocyclic backbone (Scheme 1). Therefore, we targeted a key intermediate that could be used further for the total synthesis of these three molecules; herein, we describe the synthesis of this potential key intermediate. The retrosynthetic analysis of fumagillin (**1**), TNP-470 (**2**), and ovalicin (**3**) is shown Scheme 1. We envisaged that the target molecules could be easily synthesized from the key intermediate **4**, which in turn could be formed from the bicyclic compound **6** using a zinc-mediated ring-opening reaction and further manipulations. Compound **6** could be easily obtained via a Diels–Alder reaction of protected furfuryl alcohol **7** with methyl bromopropiolate (**8**).

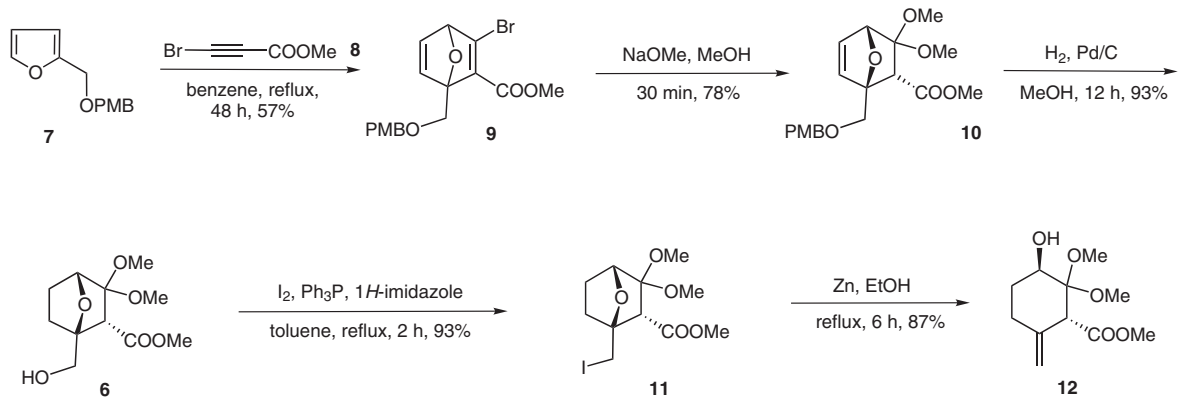
We started with readily available furfuryl alcohol, which was protected as the 4-methoxybenzyl (PMB) ether **7** using 4-methoxybenzyl bromide and sodium hydride. Commercially available methyl propiolate was brominated using the known protocol[15] to give dienophile **8**. The Diels–Alder reaction of diene **7** and dienophile **8** provided adduct **9** in 57% yield with the required regiospecificity (Scheme 2).[16] To realize the hydroxy group at C-2, bromide **9** was converted into dimethoxy ketal **10** on reaction with sodium methoxide in methanol.[17] Treatment of the unsaturated bicyclic compound **10** with hydrogen and palladium on carbon resulted in one-pot hydrogenation and also PMB deprotection to give the primary alcohol **6**.[18] Alcohol **6** was then converted into iodo compound **11** using iodine, triphenylphosphine, and 1*H*-imidazole, and product **11** was further subjected to a zinc-mediated ring-opening reaction,[19] by applying the known protocol, to give olefinic alcohol **12** (Scheme 2).

To reduce the number of steps involved, the dimethoxy ketal deprotection was attempted at this stage; the reaction resulted in the aromatization of compound **12**. To overcome this problem, olefin **12** was converted into diol **13** and then was protected as acetonide **14**. However, compound **14** was not stable under any of the reaction conditions employed for either the protection of the C-3 alcohol or the deprotection of the dimethoxy ketal,[20] and the starting material always decomposed (Scheme 3).

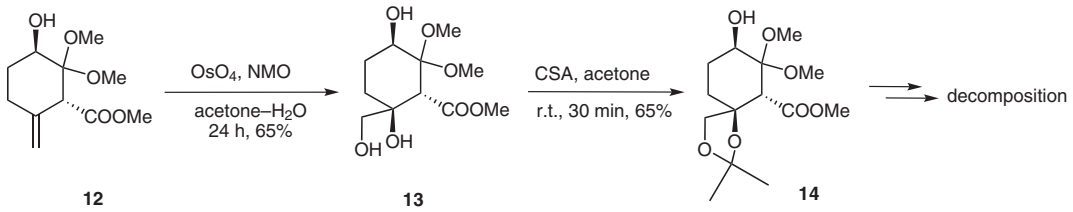
SYNTHESIS 2008, No. 9, pp 1460–1466
Advanced online publication: 16.04.2008
DOI: 10.1055/s-2008-1067030; Art ID: Z29807SS



Scheme 1 Retrosynthesis of fumagillin, TNP-470, and ovalicin

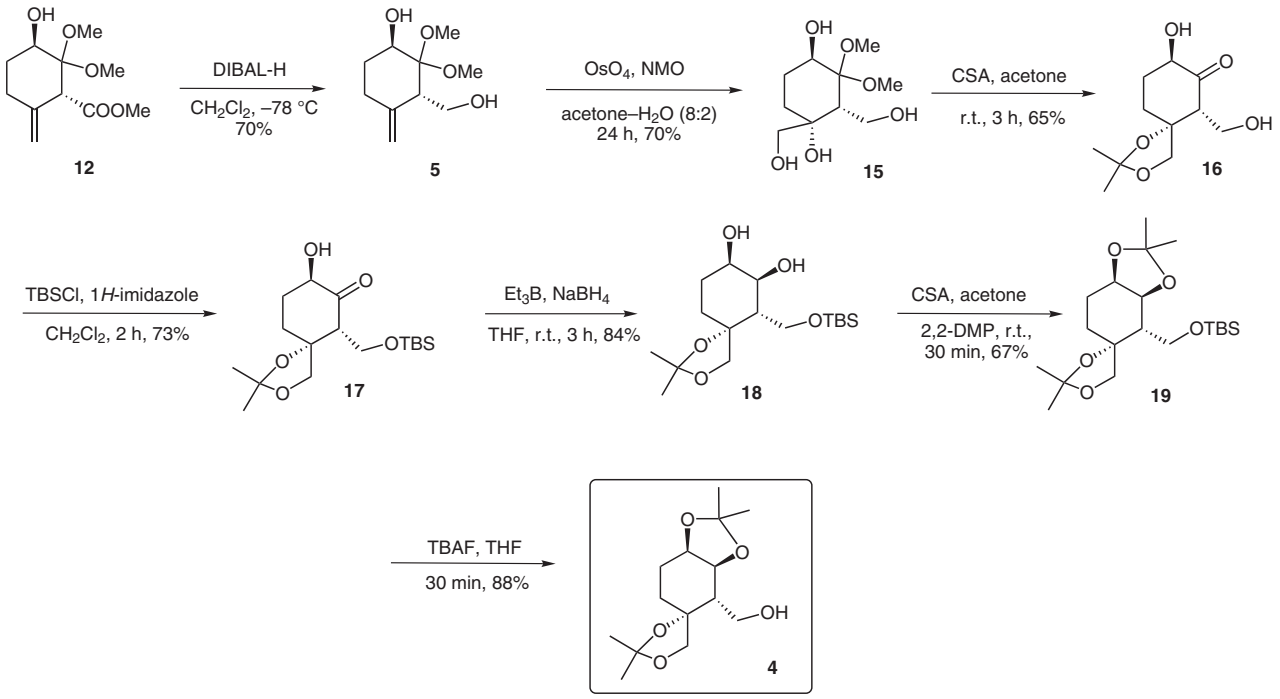


Scheme 2

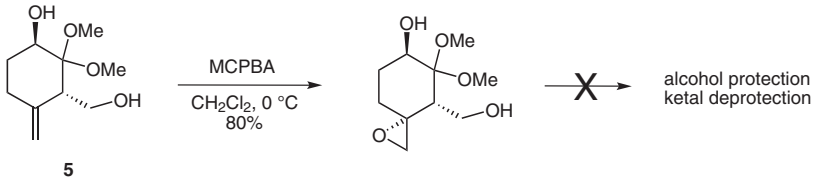


Scheme 3

Next, the ester functionality in compound **12** was reduced to alcohol **5** using DIBAL-H at low temperature (Scheme 4). Because all three target molecules, i.e. fumagillin (**1**), TNP-470 (**2**), and ovalicin (**3**), have an epoxide moiety at C-6, we decided to perform an epoxidation on the olefin moiety of **5**. Thus, olefin **5** was converted into the corresponding epoxide using 2-chloroperoxybenzoic acid at 0 °C in 80% yield.[21] Although the epoxidation was successful, further manipulations were not possible as the epoxide product was not stable to any of the reaction conditions applied for proceeding further with either the protection of the alcohol or the deprotection of the dimethoxy ketal (Scheme 5).[20] Hence, we returned to using dihydroxylation as a method for forming a product that could be converted into the desired epoxide at a later stage. Thus, dihydroxylation of compound **5** yielded tetrol **15**, which was subjected to isopropylidene protection with acetone in the presence of 10-camphorsulfonic acid (Scheme 4).



Scheme 4



Scheme 5

Interestingly, during this reaction simultaneous dimethoxy ketal deprotection occurred to give the keto compound **16**. The primary hydroxy group was then protected as the *tert*-butyldimethylsilyl (TBS) ether to give **17** using *tert*-butyldimethylsilyl chloride in the presence of 1*H*-imidazole.

The selective *syn* reduction of α-hydroxy ketone **17** was successfully achieved with sodium borohydride in the presence of triethylborane to give the required diastereomer **18** exclusively.[22] This compound was further treated with 2,2-dimethoxypropane (2,2-DMP) to yield the acetonide-protected product **19** (Scheme 5). Thus, the required geometry at C-2 was realized in a practical manner.

To confirm the exact stereochemistry at all of the stereocenters of the product, we tried to simplify its structure by removing the TBS protecting group which was also essential for further proceedings. Thus, deprotection of compound **19** with tetrabutylammonium fluoride afforded the key intermediate **4** in 88% yield (Scheme 5). At this stage, the compound was fully characterized by ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry. Further detailed spectral studies of this molecule (i.e., 1D proton decoupling experiments, gDQCOSY, TOCSY, NOESY, and gHSQC) revealed that it adopts a deformed chair conformation. The nuclear Overhauser effect (NOE) cross peaks between H-4–H-10, H-11–H-4, H-2–H-4, H-12–H-9, and H-6–H-9 confirmed this molecular conformation (Figure 1). The acetonide moiety makes the C-2–C-3 sin-

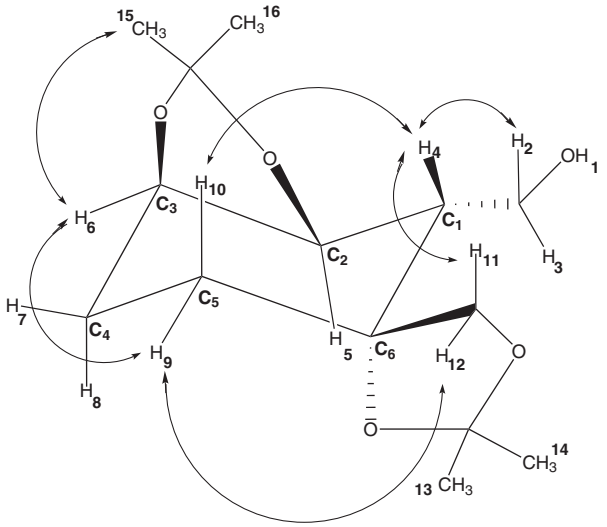


Figure 1 Structure of compound **4** showing the observed NOE interactions

gle bond rigid, resulting in the H-5 (3.98) and H-8 (2.21) protons having a distance greater than 5 angstroms, which could be the reason for not observing the NOE between H-5–H-8.

In conclusion, we have described a concise synthetic route for the synthesis of the potential key intermediate **4**, which can be used further for the synthesis of various biologically active compounds, such as fumagillin (**1**), TNP-470 (**2**), and ovalicin (**3**). Moreover, the free primary alcohol present in this intermediate allows for extensive derivations of the side chain to give more-potent molecules. Further studies toward the total synthesis of fumagillin (**1**) and its derivatives using this key intermediate are currently being investigated.

All solvents were dried and distilled prior to use. Melting points were measured on a Buchi R-535 apparatus and are uncorrected. Column chromatography was performed using silica gel 60–120 mesh. Infrared spectra were recorded on a Perkin-Elmer IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on Varian Gemini 200, Bruker Avance 300, or Varian Unity 400 MHz instruments using TMS as an internal standard. Mass spectra were recorded on a Micromass VG 7070H mass spectrometer for EI MS, a VG Autospec mass spectrometer for FAB MS, and a Micromass Quatro LC triple quadrupole mass spectrometer for ESI MS analysis. HRMS data were obtained on an AB Systems QSTAR plus mass spectrometer following ESI-QTOF high-resolution technique.

2-[(4-Methoxybenzyl)oxymethyl]furan (7)

To a mixture of NaH (57.6 mg, 2.4 mmol) in Et_2O (2 mL) under a N_2 atmosphere was added dropwise furfuryl alcohol (98.0 mg, 1.0 mmol) in dry Et_2O (3 mL) at 0 °C, and the mixture was stirred for 30 min. To this stirred solution, PMBBr (201 mg, 1.0 mmol) in dry Et_2O (3 mL) was added dropwise, and the resulting mixture was stirred for a further 6 h. After completion of the reaction, the excess NaH was quenched with ice flakes, and the resulting ethereal layer was washed with brine solution (3 × 10 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography (EtOAc–hexane, 5:95) to give product **7** as a yellow liquid. Yield: 230 mg (98%).

IR (neat): 1611, 1513, 1248, 1070, 1033, 818, 743 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.80 (s, 3 H), 4.46 (s, 2 H), 4.49 (s, 2 H), 6.30–6.39 (m, 2 H), 6.90 (d, *J* = 8.0 Hz, 2 H), 7.30 (d, *J* = 8.7 Hz, 2 H), 7.42 (d, *J* = 2.0 Hz, 1 H).

^{13}C NMR (200 MHz, $CDCl_3$): δ = 55.2, 63.5, 109.2, 110.2, 113.8, 129.5, 130.0, 142.7, 151.9, 159.3.

LCMS: *m*/*z* = 241 (M^+ + 23).

HRMS: *m*/*z* calcd for $C_{13}H_{14}O_3Na$: 241.0840; found: 241.0835.

Methyl 3-Bromo-1-[(4-methoxybenzyl)oxymethyl]-7-oxabicyclo[2.2.1]hepta-2,5-diene-2-carboxylate (9)

Methyl bromopropiolate (**8**) (164 mg, 1.0 mmol) and PMB-protected furfuryl alcohol **7** (218 mg, 1 mmol) were added to benzene (10 mL), and the mixture was refluxed for 48 h. The solvent was removed in vacuo and the residue was subjected to column chromatography (EtOAc–hexane, 1:9) to give product **9** as a viscous liquid. Yield: 216 mg (57%).

IR (neat): 2952, 1712, 1610, 1513, 1248, 1111, 1033, 824 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.75 (s, 3 H), 3.80 (s, 3 H), 4.20 (ABq, *J* = 11.7, 20.4 Hz, 2 H), 4.52 (s, 2 H), 5.29 (s, 1 H), 6.85 (d, *J* = 8.7 Hz, 2 H), 7.01 (d, *J* = 5.1 Hz, 1 H), 7.10–7.28 (m, 3 H).

^{13}C NMR (200 MHz, $CDCl_3$): δ = 51.5, 55.1, 66.2, 73.2, 84.1, 88.4, 96.8, 113.6, 129.4, 129.7, 142.5, 143.4, 148.9, 159.1, 163.2.

LCMS: *m*/*z* = 403 (M^+ + 23).

HRMS: *m*/*z* calcd $C_{17}H_{17}O_5BrNa$: 403.0157; found: 403.0167.

Methyl 3,3-Dimethoxy-1-[(4-methoxybenzyl)oxymethyl]-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylate (10)

To Diels–Alder adduct **9** (380 mg, 1.0 mmol) in MeOH (10 mL) was added dropwise 1 M NaOMe (10 mL). During the addition, the temperature was kept below 20 °C. After completion of the reaction (30 min), the solvent was removed in vacuo and the residue was directly purified by column chromatography (EtOAc–hexane, 1:4) to give product **10** as a yellow liquid. Yield: 283 mg (78%).

IR (neat): 2925, 1735, 1611, 1512, 1245, 1174, 1069, 1029, 986 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.20 (s, 3 H), 3.21 (s, 1 H), 3.41 (s, 3 H), 3.62 (s, 3 H), 3.80 (s, 5 H), 4.51 (ABq, *J* = 6.4, 12.9 Hz, 2 H), 4.70 (s, 1 H), 6.38 (dd, *J* = 3.8, 5.1 Hz, 1 H), 6.62 (d, *J* = 5.1 Hz, 1 H), 6.80 (d, *J* = 9.0 Hz, 2 H), 7.20 (d, *J* = 9.0 Hz, 2 H).

^{13}C NMR (200 MHz, $CDCl_3$): δ = 29.6, 50.9, 51.85, 51.81, 53.8, 55.2, 67.7, 73.1, 78.3, 84.5, 90.7, 113.7, 129.3, 131.8, 135.0, 138.3.

LCMS: *m*/*z* = 387 (M^+ + 23).

HRMS: *m*/*z* calcd $C_{19}H_{24}O_7Na$: 387.1419; found: 387.1414.

Methyl 1-(Hydroxymethyl)-3,3-dimethoxy-7-oxabicyclo[2.2.1]heptane-2-carboxylate (6)

To dimethoxy compound **10** (148 mg, 0.6 mmol) in MeOH (5 mL) was added 10% Pd/C (10 mg). The mixture was kept under H_2 at 1 atm for 12 h. After completion of the reaction, the mixture was filtered through a small pad of Celite, washed with MeOH (5 mL), and the solvent was evaporated in vacuo. The residue was purified by column chromatography (EtOAc–hexane, 2:3) to give product **6** as a white solid. Yield: 239 mg (93%); mp 79–81 °C.

IR (KBr): 3448, 2952, 1734, 1440, 1314, 1203, 1147, 1073, 1039, 761 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.33–1.48 (m, 1 H), 1.63–1.81 (m, 1 H), 1.86–1.90 (m, 1 H), 2.60–2.73 (m, 1 H), 3.17 (s, 1 H), 3.18 (s, 3 H), 3.33 (s, 3 H), 3.68 (s, 3 H), 3.75 (d, *J* = 2.9 Hz, 2 H), 4.35 (d, *J* = 5.0 Hz, 1 H).

^{13}C NMR (200 MHz, $CDCl_3$): δ = 24.3, 25.6, 49.1, 50.9, 51.5, 53.3, 63.3, 83.2, 89.6, 109.2, 169.1.

LCMS: *m*/*z* = 269 (M^+ + 23).

HRMS: *m*/*z* calcd $C_{11}H_{18}O_6Na$: 269.1001; found: 269.1002.

Methyl 1-(Iodomethyl)-3,3-dimethoxy-7-oxabicyclo[2.2.1]heptane-2-carboxylate (11)

To a solution of hydroxy compound **6** (246 mg, 1.0 mmol) in dry toluene (15 mL) was added Ph_3P (393 mg, 1.5 mmol), 1*H*-imidazole (238 mg, 3.5 mmol), and I_2 (379.5 mg, 1.5 mmol). The mixture was refluxed for 2 h, after which the solvent was removed in vacuo. The residue was purified by column chromatography (EtOAc–hexane, 1:4) to give product **11** as a yellow-white solid. Yield: 331 mg (93%); mp 87–89 °C.

IR (KBr): 2950, 1732, 1438, 1350, 1319, 1199, 1139, 1066, 1028, 946 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.54–1.89 (m, 2 H), 1.95–2.08 (m, 1 H), 2.79–2.92 (m, 1 H), 3.05 (s, 1 H), 3.20 (s, 2 H), 3.34 (s, 3 H), 3.50 (s, 3 H), 3.71 (s, 3 H), 4.38 (d, *J* = 5.1 Hz, 1 H).

^{13}C NMR (200 MHz, $CDCl_3$): δ = 8.2, 25.5, 28.3, 49.1, 50.8, 51.7, 57.8, 83.1, 86.0, 109.6, 168.6.

LCMS: *m*/*z* = 379 (M^+ + 23).

HRMS: *m*/*z* calcd $C_{11}H_{17}O_5INa$: 379.0018; found: 379.0022.

Methyl 3-Hydroxy-2,2-dimethoxy-6-methylenecyclohexanecarboxylate (12)

To a solution of iodo compound **11** (357 mg, 1 mmol) in EtOH (10 mL) was added Zn (2.6 g, 40 mmol), and the mixture was refluxed for 6 h. After completion of the reaction, the mixture was filtered through a small pad of Celite, washed with EtOH (35 mL), and all the solvent was evaporated. The residue was directly used for column chromatography (EtOAc–hexane, 3:7) to give product **12** as a white solid. Yield: 200 mg (87%); mp 83–85 °C.

IR (KBr): 3405, 2933, 1719, 1375, 1254, 1214, 1046, 860 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.39–1.60 (m, 1 H), 1.80–2.01 (m, 1 H), 2.12–2.27 (m, 1 H), 2.50–2.70 (m, 1 H), 3.30 (s, 3 H), 3.34 (s, 3 H), 3.64 (s, 1 H), 3.66 (s, 3 H), 4.39 (dd, *J* = 5.2, 11.7 Hz, 1 H), 4.84 (d, *J* = 10.4 Hz, 2 H).

^{13}C NMR (200 MHz, $CDCl_3$): δ = 29.3, 31.0, 49.4, 50.7, 51.8, 56.1, 71.7, 96.3, 114.0, 142.1, 170.3.

LCMS: *m*/*z* = 253 (M^+ + 23).

HRMS: *m*/*z* calcd $C_{11}H_{18}O_5Na$: 253.1051; found: 253.1059.

3-(Hydroxymethyl)-2,2-dimethoxy-4-methylenecyclohexanol (5)

A solution of 20 wt% DIBAL-H in toluene (1.5 mL, 2.2 mmol) was added dropwise at –78 °C through a syringe to ester **12** (231 mg, 1.0 mmol) dissolved in dry CH_2Cl_2 (5 mL). After completion of the reaction, the excess reagent was quenched with sat. aq sodium potassium tartrate. The resulting CH_2Cl_2 layer was washed with brine (3 × 10 mL) and dried (Na_2SO_4), and all the solvent was removed under reduced pressure. The residue was purified by column chromatography (EtOAc–hexane, 1:1) to give product **5** as a colorless liquid. Yield: 141 mg (70%).

IR (neat): 3427, 2943, 1650, 1449, 1130, 1054, 869, 753 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.50–1.64 (m, 1 H), 1.86–1.96 (m, 1 H), 2.02–2.21 (m, 2 H), 2.79–2.87 (m, 1 H), 3.32 (s, 3 H), 3.40–3.48 (m, 4 H), 3.72–3.89 (m, 2 H), 4.84 (d, *J* = 11.0 Hz, 2 H).

^{13}C NMR (200 MHz, $CDCl_3$): δ = 29.8, 31.4, 49.0, 50.3, 52.0, 61.4, 72.3, 112.4, 144.9.

LCMS: *m*/*z* = 225 (M^+ + 23).

HRMS: *m*/*z* calcd $C_{10}H_{18}O_4Na$: 225.1102; found: 225.1111.

1,2-Bis(hydroxymethyl)-3,3-dimethoxycyclohexane-1,4-diol (15)

To compound **5** (193 mg, 1.0 mmol) in acetone–H_2O (4:1, 5 mL) were added NMO (292 mg, 2.5 mmol) and OsO_4 (0.1 mL, 0.2 mmol), and the mixture was stirred for 24 h. After completion of the reaction, the mixture was concentrated under reduced pressure and the residue was passed through a small pad of silica gel to give the crude product **15** as a white oil. Yield: 149 mg (70%).

IR (neat): 3413, 2950, 1734, 1440, 1136, 1066, 1030, 762 cm^{-1}.

LCMS: *m*/*z* = 259 (M^+ + 23).

HRMS calculated for $C_{10}H_{20}O_6Na$: calcd 259.1157; found 259.1147.

8-Hydroxy-6-(hydroxymethyl)-2,2-dimethyl-1,3-dioxaspiro[4.5]decan-7-one (16)

The crude tetrol **15** (236 mg, 1 mmol) obtained from the above reaction was taken up in acetone (3 mL), and CSA (cat.) was added at 0 °C. The mixture was stirred for 3 h at r.t., then solid $NaHCO_3$ (84 mg, 1 mmol) was added, and all the solvent was removed in vacuo. The mixture was diluted with CH_2Cl_2 (5 mL), washed with H_2O (3 × 10 mL) and brine (3 × 10 mL), and dried (Na_2SO_4). Evaporation of the solvent followed by purification by column chromatography (EtOAc–hexane, 1:1) yielded product **16** as a colorless liquid. Yield: 149 mg (65%).

IR (neat): 3519, 2946, 1714, 1119, 1048, 927, 754 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.34 (s, 3 H), 1.38 (s, 3 H), 1.86–2.08 (m, 4 H), 2.18–2.25 (m, 1 H), 2.80–2.92 (m, 1 H), 3.49 (br s, 1 H), 3.80 (d, *J* = 6.7 Hz, 2 H), 3.90 (d, *J* = 9.0 Hz, 1 H), 4.06 (d, *J* = 6.7 Hz, 1 H), 4.17–4.25 (m, 1 H).

^{13}C NMR (200 MHz, $CDCl_3$): δ = 26.4, 27.5, 29.9, 30.2, 60.9, 61.6, 71.3, 73.1, 84.5, 109.8, 210.7.

LCMS: *m*/*z* = 253 (M^+ + 23).

HRMS: *m*/*z* calcd $C_{11}H_{18}O_5Na$: 253.1051; found: 253.1060.

6-[(*tert*-Butyldimethylsiloxy)methyl]-8-hydroxy-2,2-dimethyl-1,3-dioxaspiro[4.5]decan-7-one (17)

To a solution of compound **16** (230 mg, 1.0 mmol) in CH_2Cl_2 (3 mL) was added 1*H*-imidazole (102 mg, 1.5 mmol) at 0 °C, and the mixture was stirred for 10 min. Then, TBSCl (180 mg, 1.1 mmol) was added and the mixture was stirred for a further 2 h. The mixture was then diluted with CH_2Cl_2 (5 mL), washed with H_2O (3 × 10 mL), and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue by column chromatography (EtOAc–hexane, 1:9) gave product **17** as a light-yellow liquid. Yield: 251 mg (73%).

IR (neat): 3429, 2929, 1720, 1254, 1215, 1103, 839, 762 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.06 (s, 6 H), 0.88 (s, 9 H), 1.32 (s, 3 H), 1.37 (s, 1 H), 1.83–2.08 (m, 3 H), 2.17–2.27 (m, 1 H), 2.78 (dt, *J* = 2.3, 6.0 Hz, 1 H), 3.51 (d, *J* = 3.0 Hz, 1 H), 3.75 (dd, *J* = 1.5, 6.0 Hz, 2 H), 3.77 (d, *J* = 9.0 Hz, 2 H), 3.87 (d, *J* = 9.0 Hz, 1 H), 4.08–4.19 (m, 1 H).

^{13}C NMR (200 MHz, $CDCl_3$): δ = –5.23, –5.16, 18.5, 26.2, 26.9, 28.1, 30.1, 30.8, 61.5, 62.00, 71.8, 74.0, 84.9, 96.5, 109.8, 209.6.

LCMS: *m*/*z* = 367 (M^+ + 23).

HRMS: *m*/*z* calcd $C_{17}H_{32}O_5SiNa$: 367.1916; found: 367.1934.

6-[(*tert*-Butyldimethylsiloxy)methyl]-2,2-dimethyl-1,3-dioxaspiro[4.5]decane-7,8-diol (18)

Into a solution of 1 M Et_3B in THF (5 mL, 1.1 mmol) and compound **17** (344 mg, 1.0 mmol) was bubbled a small amount of air (3 mL), and the solution was stirred for 3 h at r.t. under an Ar atmosphere. Then, the solution was cooled to –100 °C and solid $NaBH_4$ (37 mg, 1.1 mmol) was added in one portion. The mixture was stirred for 6 h at r.t. and then quenched with a mixture of 30% H_2O_2 (5 mL), pH 7 buffer (10 mL), and MeOH (15 mL). The organic solvents were evaporated under reduced pressure and the residual aqueous solution was extracted with CH_2Cl_2 (2 × 25 mL). The organic extract was dried (Na_2SO_4) and evaporated in vacuo to afford the crude product, which was purified by column chromatography (EtOAc–hexane, 2:8) to give product **18** as a colorless liquid. Yield: 290 mg (84%).

IR (neat): 3448, 2924, 1462, 772 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.10 (s, 6 H), 0.90 (s, 9 H), 1.37 (s, 3 H), 1.38 (s, 3 H), 1.48–1.62 (m, 1 H), 1.81–2.07 (m, 3 H), 2.14–2.26 (dt, *J* = 4.6, 8.2 Hz, 1 H), 2.56 (br s, 1 H), 3.61–3.82 (m, 4 H), 3.87 (d, *J* = 8.9 Hz, 1 H), 3.93–4.06 (m, 1 H), 4.48 (br s, 1 H).

^{13}C NMR (200 MHz, $CDCl_3$): δ = –5.35, 18.3, 22.9, 26.0, 26.3, 27.3, 29.5, 29.9, 31.2, 31.6, 67.7, 70.2, 73.5, 82.4, 108.8.

LCMS: *m*/*z* = 369 (M^+ + 23).

HRMS: *m*/*z* calcd $C_{17}H_{34}O_5SiNa$: 369.2073; found: 369.2076.

4-[(*tert*-Butyldimethylsiloxy)methyl]-2,2-dimethylhexahydrobenzo-1,3-dioxole-5-spiro-4′-(2,2-dimethyl-1,3-dioxolane) (19)

To a solution of compound **18** (346 mg, 1 mmol) in acetone (1 mL) was added 2,2-DMP and CSA at 0 °C, and the mixture was stirred at r.t. for 30 min. After completion of the reaction, solid $NaHCO_3$ (84 mg, 1 mmol) was added and the mixture was stirred for a further 10 min. After all the acetone was removed, the mixture was diluted with CH_2Cl_2 (7 mL), washed with H_2O (3 × 10 mL) and brine (3 × 10 mL), and dried (Na_2SO_4). The crude product **19** was obtained as a yellow liquid and was used as such for further reaction. Yield: 258 mg (67%).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.06 (s, 6 H), 0.90 (s, 9 H), 1.31 (s, 3 H), 1.36 (s, 3 H), 1.39 (s, 3 H), 1.42 (s, 3 H), 1.52–1.79 (m, 4 H), 2.08–2.20 (m, 1 H), 3.59 (d, *J* = 8.0 Hz, 1 H), 3.76 (dd, *J* = 3.6, 10.2 Hz, 1 H), 4.03–4.17 (m, 3 H), 4.30 (d, *J* = 8.8 Hz, 1 H).

^{13}C NMR (200 MHz, $CDCl_3$): δ = –5.46, –5.39, 18.4, 24.0, 26.1, 26.2, 26.7, 27.8, 28.7, 29.9, 32.5, 47.7, 57.8, 67.5, 72.5, 74.1, 82.8, 107.9, 108.3.

LCMS: *m*/*z* = 409 (M^+ + 23).

4-(Hydroxymethyl)-2,2-dimethylhexahydrobenzo-1,3-dioxole-5-spiro-4′-(2,2-dimethyl-1,3-dioxolane) (4)

To a solution of compound **19** (386 mg, 1.0 mmol) in THF (1 mL) was added 1 M TBAF in THF (1.2 mL, 1.2 mmol), and the mixture was stirred for 30 min. After completion of the reaction, all the THF was removed, and the mixture was diluted with CH_2Cl_2 (7 mL), washed with H_2O (3 × 10 mL) and brine (3 × 10 mL), and dried (Na_2SO_4). The crude product was purified by column chromatography (EtOAc–hexane, 3:7) to give product **4** as a colorless liquid. Yield: 239 mg (88%).

IR (neat): 3446, 2925, 1214, 760 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.32 (s, 3 H), 1.39 (s, 3 H), 1.45 (s, 3 H), 1.49 (s, 3 H), 1.59–1.66 (m, 2 H), 1.86 (td, *J* = 4.6, 10.5 Hz, 1 H), 1.93–2.00 (m, 1 H), 2.17–2.23 (m, 1 H), 3.55 (br s, 1 H), 3.66 (d, *J* = 8.9 Hz, 1 H), 3.86 (dd, *J* = 4.6, 11.7 Hz, 1 H), 3.93 (dd, *J* = 4.6, 11.7 Hz, 1 H), 3.97 (dd, *J* = 4.6, 10.5 Hz, 1 H), 3.99 (d, *J* = 8.9 Hz, 1 H), 4.15 (dt, *J* = 4.6, 1.1 Hz, 1 H).

^{13}C NMR (200 MHz, $CDCl_3$): δ = 26.4, 26.6, 26.8, 28.7, 29.6, 54.1, 60.3, 67.7, 69.6, 72.3, 76.5, 82.9, 108.8, 108.9.

LCMS: *m*/*z* = 295 (M^+ + 23).

HRMS: *m*/*z* calcd $C_{14}H_{24}O_5Na$: 295.1521; found: 295.1525.

Acknowledgment

P.S. and G.D.S. thank the Council of Scientific and Industrial Research (CSIR), New Delhi, for financial assistance.

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