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# A Stereoselective Asymmetric Synthesis of Antibiotic (-)-Fumagillol Using Claisen Rearrangement and Intramolecular Ester Enolate Alkylation as Key Steps

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(-)-Fumagillol (**1**), a hydrolysis product of fumagillin, has been synthesized by several group from commercially available 1,2:5,6-*di*-*O*-isopropylidene-α-D-allofuranose in a highly stereoselective manner. Chiral centers on C5 and C6 came from D-allofuranose and the asymmetric center on C4 was accomplished by 1,3-chirality transfer using the Claisen rearrangement on a chiral allyl alcohol. Chirality, which is necessary on an epoxide consisting of the spiro-ring system, was diastereoselectively constructed by the well-known reaction, intramolecular ester enolate alkylation (IEEA), which showed that this reaction can be applied to the alpha-alkoxy ester system. The epoxide on the side chain was regioselectively introduced by the difference between the number of substituents on the vinyl groups. This accomplishment proved that IEEA can be a useful tool for the synthesis of complex molecules.

**Key words:** Fumagillol, Fumagillin, Total synthesis, Stereoselective, 1,3-Chirality transfer

## INTRODUCTION

Fumagillin **1**, an antibiotic isolated from certain strains of *Aspergillus fumagatus,* has been reported (Hanson, 1949) that the cultures showed antibiotic activity against *Staphylococcus aureus*. The chemical structures of (-)-fumagillin (**1**) and (-)-fumagillol (**2**), the hydrolysis product, have been disclosed by X-ray crystallography and confirmed by chemical degradation analysis (McCowen, 1951; Katznelson, 1952; Killough, 1952; Tarbell, 1960; Tarbell, 1961).

The anti-angiogenic activity of (-)-fumagillin has previously been reported (Ingber, 1990; Folkman, 1992; Ingber, 1992). Employing inhibitors of angiogenesis has been regarded as a good approach for the therapy of cancer. Several group synthesized a series of fumagillin analogues to find good therapeutic candidates (Fardis, 2003; Kim, 2003). TNP-470 (Zhang, 2002) and CKD-732 (Han, 2000) were reported as selective inhibitors of the cobalt-containing metalloprotease methionine amino-peptidase-2 (MetAP-2) (Sin, 1997; Griffith, 1997) and shown to have highly potent activity. TNP-470 is 50 times more potent and CKD-732 is 50,000 times more potent than (-)-fumagillin. TNP-470 and CKD-732 are two drug candidates currently are in Phase III and II clinical trials, respectively (Fig. 1).

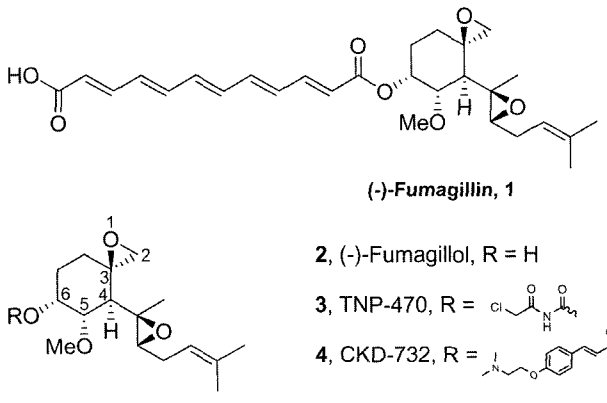


**Fig. 1** Fumagillin (**1**) and fumagillol (**2**), the hydrolysis product and derivatives.

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The fascinating biological activity of (-)-fumagillin (**1**), coupled with its novel structural features with highly sensitive functionalities, has stimulated the interest of several groups regarding its synthesis. The first total synthesis of (±)-fumagillin was published by Corey and Snider (Corey, 1972) based on an elegant Diels-Alder strategy. In 1997, our group reported the first asymmetric synthesis of (-)-fumagillol as communication (Kim, 1997). Recently, Sorensen's racemic synthesis (Vosburg, 1999; Vosburg, 2003) and Taber's enantioselective synthesis were published (Taber, 1999). These two groups introduced a long side chain by conjugate addition of vinyl cuprate. Also other stereoselective syntheses were performed; a concise synthesis (Hutchings, 2001), synthesis using ring-closure metathesis (Boiteau, 2001; Eustache, 2004), a stereoselective formal synthesis (Bedel, 2004). Herein, this article is a follow-up of a previous communication and the detailed synthetic procedure of synthesis of (-)-fumagillol (**2**) are provided.

## MATERIALS AND METHODS

### Chemicals

IR spectra were measured as neat oils or as nujol on a Perkin-Elmer 1710 Fourier Transform spectrometer. $^1$H-NMR spectra ($CDCl_3$) were obtained at 400 MHz with a JEOL JNM-GCX 400 spectrophotometer. Chemical shifts are reported in ppm units with $Me_4Si$ as the internal standard. $^{13}$C-NMR spectra ($CDCl_3$) were recorded with a Bruker AP200 or JEOL JNM-GCX 400 instrument. Low resolution MS were recorded with VG Trio-2 GC-MS and high resolution MS with VG 70-SEQ. Optical rotations were determined on a JASCO DIP 360 polarimeter in methanol or ethanol or chloroform. Melting points were taken in capillaries with a Buchi 535 melting point apparatus and are uncorrected. Elemental analysis was performed in an organic laboratory of Sõgang University. The purification of crude products was carried on a silica gel ($Kieselgel_{60}$, 70-230 mesh, Merck) column.

All solvents were purified and dried by standard techniques just before use. All reactions were routinely carried out under an inert atmosphere of dry nitrogen or argon.

Unless otherwise noted, materials were obtained from commercial supplier, Sigma-Aldrich and were used without purification. Methylene chloride, chloroform and methyl ethylketone were purified by refluxing with $P_2O_5$. THF, ether and benzene were freshly distilled from sodium and benzophenone. Acetonitrile, toluene and pyridine were purified by refluxing with $CaH_2$. Carbontetrachloride, hexane and ethyl acetate were simply distilled.

### Chemistry

#### 5,6-Dideoxy-1,2-di-*O*-isopropylidene-3-*O*-methyl-α-D-allohex-5-enofurannose (12)

To a stirred solution of diol **11** (5 g, 21.2 mmol) and dry triethylamine (9.58 mL, 68.7 mmol) in dry methylene chloride (40 mL) at -20°C ~ -30°C was added methanesulphonyl chloride (3.72 mL, 48.1 mmol) with a syringe over a 10 min period. After 30 min at -10°C ~ -20°C, the resulting mixture was poured into cold water (100 mL), extracted with ethyl acetate (300 mL), and the organic layer was successively washed with a saturated sodium bicarbonate solution (50 mL) and brine (2 × 50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to give crude dimesylate as a yellow oil (8.7 g). This material was employed in the next experiment without further purification.

A mixture of crude dimesylate (prepared in the previous experiment) and solid sodium iodide (11.5 g, 76.7 mmol) in dry methyl ethyl ketone (140 mL) was stirred at 100°C for 9 h and partitioned between ethyl acetate (300 mL) and a saturated sodium thiosulfate solution (100 mL). The organic layer was separated, successively washed with a saturated sodium thiosulfate solution (2 × 50 mL), a saturated sodium bicarbonate solution (50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The resulting oil was chromatographed (200 g of silica, 9% ethyl acetate/hexane) to afford **12** as a colorless oil (3.26 g, 77%): $[\alpha]_D$ = + 61.89 (c = 1.44, $CHCl_3$); $^1$H-NMR ($CDCl_3$, 400 MHz) δ 5.84 (m, 1H), 5.76 (d, *J* = 3.7 Hz, 1H), 5.43 (bd, *J* = 17.6 Hz, 1H), 5.25 (bd, *J* = 10.0 Hz, 1H), 4.66 (dd, *J* = 4.4, 3.7 Hz, 1H), 4.37 (dd, *J* = 8.8, 6.7 Hz, 1H), 3.47 (s, 3H), 3.36 (dd, *J* = 8.8, 4.4 Hz, 1H), 1.57 (s, 3H), 1.34 (s, 3H); $^{13}$C-NMR ($CDCl_3$, 100 MHz) δ 134.75, 118.67, 112.71, 103.47, 84.70, 78.86, 77.05. 58.45, 26.51, 26.22; IR (film) 2927, 2855, 1459, 1300, 1217, 1168, 1144, 1032, 1023, 992, 927, 870, 691, 500 cm-1; HRMS m/z (M+ - $CH_3$) calcd 185.0814, found 185.0822.

#### 5-Deoxy-1,2-di-*O*-isopropylidene-3-*O*-methyl-α-D-allofurannose (14)

To a stirred solution of olefin **47** (6.38 g, 31.86 mmol) and dry tetrahydrofuran (70 mL) at -40°C was dropwise added a 0.5 M 9-borabicyclo[3.3.1]nonane solution (in tetrahydrofuran, 76.5 mL, 38.3 mmol) with a syringe. After the addition was complete, the reaction mixture was warmed gradually to room temperature and stirred overnight. The reaction mixture was cooled to 0°C - 5°C. A 3N sodium hydroxide solution (20 mL, 60 mmol) was added, followed by the careful addition of 30% hydrogen peroxide (20 mL, 172 mmol). After the addition was complete, the reaction mixture was stirred at 60°C - 70°C for 2 h. Brine (50 mL) was added and the aqueous layer was saturated with

sodium chloride and extracted with ethyl acetate (4 × 150 mL). The combined extracts were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to give an oil that was purified by column chromatography (200 g of silica, 33% ethyl acetate/hexane to ethyl acetate only) yielding primary alcohol **14** (6.46 g, 93%): $[\alpha]_D$ = + 128.89 (c = 2.13, MeOH); $^1$H-NMR ($CDCl_3$, 400 MHz) δ 5.75 (d, *J* = 3.7 Hz), 4.66 (dd, *J* = 4.0, 3.7 Hz, 1H), 4.06 (m, 1H), 3.76 (m, 2H), 3.49 (s, 3H), 3.36 (dd, *J* = 8.8, 4.0 Hz, 1H), 1.90 (m, 2H), 1.57 (s, 3H), 1.34 (s, 3H); $^{13}$C-NMR ($CDCl_3$, 100 MHz) δ 112.85, 103.81, 84.61, 77.18, 77.16, 76.49, 60.16, 58.08, 35.09, 26.49, 26.31; IR (film) 3503, 2926, 1461, 1377,1218, 1024, 871, 723 $cm^{-1}$; HRMS m/z ($M^+$) calcd 218.1154, found 218.1147.

**(2*E*,4*S*,5*R*)-5.7-Dihydroxy-4-methoxy-2-methyl-2-heptenoic acid, methyl ester (18)**

Primary alcohol **14** (5.55 g, 25.43 mmol) was heated on water (100 mL) with Dowex $50X_2$-200 resin (5.55 g) for 50 min at 100°C. The resin was removed by filtration and sufficiently washed with distilled water. The filtrate and washings were concentrated *in vacuo* to give crude hemiacetal **15** as a viscous, pale yellow liquid. The crude hemiacetal **15** (4.85 g) was dissolved in 33% water/acetone (190 mL). Sodium metaperiodate (5.93 g, 27.7 mmol) was portionwise added, and the reaction mixture was stirred at room temperature for 2 h. Ethanol (900 mL) and solid sodium bicarbonate (373 mg, 4.44 mmol) were added and the resulting mixture was stirred at room temperature for 30 min. The precipitate was filtered off and washed with ethanol. After, the filtrate and washings were concentrated *in vacuo*. The residue was filtered through a short column (50 g of silica, 75% ethyl acetate/hexane) to give crude formylated pyranose **16** (4.48 g), which contained the unreacted starting material. The crude formyl pyranose **16** (4.48 g) was dissolved in dry acetonitrile (108 mL). (Carbomethoxyethylidene)triphenylphosphorane (11.51 g, 33.06 mmol) was added in one pot, and the reaction mixture was stirred at 100°C - 110°C (external temperature) for 20 h. After acetonitrile was removed *in vacuo*, the residue was dissolved in 20% ethyl acetate/hexane (200 mL), filtered through a short column (50 g of silica), washed with 60% ethyl acetate/hexane to remove phosphine oxide and the filtrate and washings were concentrated to give crude Wittig product **17** (5.89 g) as a colorless oil. The crude Wittig product **17** (5.89 g) was dissolved in dry methanol (120 mL). Anhydrous potassium carbonate (115 mg, 0.83 mmol) was added in one pot, and the reaction mixture was stirred at room temperature for 4 h. After methanol was removed *in vacuo*, the residue was purified by column chromatography (200 g of silica, 50% ethyl acetate/hexane to 8% methanol/ethyl acetate) to give the desired diol **18** (3.50 g, 63% four steps yield).: $[\alpha]_D$ = + 37.93 (c = 5.03, MeOH); $^1$H-NMR ($CDCl_3$, 400 MHz) δ 6.61 (d, *J* = 8.8 Hz, 1H), 3.98 (dd, *J* = 8.8, 4.0 Hz, 1H), 3.93 (m, 1H), 3.78 (m, 2H), 3.73 (s, 3H), 3.28 (s, 3H), 1.90 (s, 3H), 1.55-1.76 (m, 2H); $^{13}$C-NMR ($CDCl_3$, 100 MHz) δ 167.72, 137.98, 132.18, 80.43, 71.72, 60.08, 56.60, 51.81, 33.77, 13.05; IR (film) 3418, 2953, 1718, 1654, 1439, 1250, 1192, 1073, 960, 752 $cm^{-1}$; Anal. Calcd for C10H18O5: C, 55.03; H, 8.31. Found: C, 54.81; H, 8.46.

**(2*E*,4*S*,5*R*)-7-((1,1-Dimethylethyl)diphenylsiloxy)-5-hydroxy-4-methoxy-2-methyl-2-heptenoic acid, methyl ester (19)**

To a stirred solution of diol **18** (3.67 g, 16.8 mmol) in dry methylene chloride (84 mL) at room temperature were added dry triethylamine (3.56 mL, 25.5 mmol), 4-(dimethylamino)pyridine (21 mg, 0.17 mmol) and *tert*-butyldiphenylsilyl chloride (4.37 mL, 16.8 mmol). The reaction mixture was stirred at room temperature for 20 h, diluted with ethyl acetate (200 mL) then washed with brine (3 × 50 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The resulting residue was chromatographed (200 g of silica, 13% ethyl acetate/hexane) to afford monosilyl ether **19** (7.14 g, 93%) as a white solid.: m.p. 65.4-66.3°C; $[\alpha]_D$ = +22.46 (c = 2.49, MeOH); $^1$H-NMR ($CDCl_3$, 400 MHz) δ 7.33-7.69 (m, 10H), 6.38 (bd, *J* = 8.8 Hz, 1H), 4.00 (dd, *J* = 8.8, 4.4 Hz, 1H), 3.75-4.04 (m, 3H), 3.74 (s, 3H), 3.299 (s, 3H), 1.92 (d, *J* = 0.7 Hz, 3H), 1.64-1.78 (m, 2H), 1.04 (s, 9H); $^{13}$C-NMR ($CDCl_3$, 100 MHz) δ 167.70, 138.30, 135.43, 133.12, 133.05, 129.66, 127.63, 80.48, 71.85, 62.09, 56.77, 51.83, 34.08, 26.72, 18.97, 13.21.; IR (film) 3517, 2926, 1722, 1466, 1378, 1240, 1112, 824, 738, 703, 614, 506 $cm^{-1}$; Anal. Calcd for $C_{26}H_{36}O_5Si$: C, 68.39; H, 7.95. Found: C, 68.54; H, 8.02. Lactone **24**; $^1$H-NMR ($CDCl_3$, 400 MHz) δ 7.29 7.75 (m, 10H), 6.62 (bs, 1H), 4.58 (m, 1H), 3.77 3.99 (m, 3H), 3.43 (s, 3H), 1.92 (s, 3H), 1.81 2.14 (m, 2H), 1.07 (s, 9H).

**(2*E*,4*S*,5*R*)-5-Benzyloxy-7-((1,1-dimethylethyl)diphenylsiloxy)-4-methoxy-2-methyl-2-heptenoic acid, methyl ester (20)**

To a stirred solution of alcohol **19** (3.90 g, 8.54 mmol) and benzyl trichloroacetimidate (3.17 mL, 17.1 mmol) in 33% methylene chloride/cyclohexane (45 mL) at room temperature, was added trifluoromethane sulfonic acid (0.1 mL). The reaction mixture was stirred at 25°C - 30°C for 15 h, and then diluted with hexane (50 mL). The white precipitate was filtered off through a plug of celite and washed with 5% ethyl acetate/hexane. The filtrate and washings were concentrated *in vacuo* and the resulting residue was chromatographed (120 g of silica, 9% ethyl acetate/hexane) to give O-benzyl ether **20** (5.30 g), which

contained an unknown compound probably from benzyl trichloroacetimidate).: (an analytical sample obtained from chromatography) $[\alpha]_D$ = +16.19 (c = 2.91, $CHCl_3$); $^1$H-NMR ($CDCl_3$, 400 MHz) δ 7.20-7.70 (m, 15H), 6.72 (bd, *J* = 8.8 Hz, 1H), 4.72 (A of AB part, *J* = 11.7 Hz, 1H), 4.56 (B of AB part, *J* = 11.7 Hz, 1H), 4.13 (dd, *J* = 8.8, 3.3 Hz, 1H), 3.70-3.89 (m, 3H), 3.76 (s, 3H), 3.31 (s, 3H), 1.86 (s, 3H), 1.71-1.82 (m, 2H), 1.06 (s, 9H); $^{13}$C-NMR ($CDCl_3$, 100 MHz) δ 167.71, 139.28, 138.53, 135.46, 133.74, 133.68, 131.22, 129.51, 128.19, 127.79, 127.56, 127.43, 80.06, 77.61, 72.97, 60.18, 57.04, 51.80, 33.96, 26.79, 19.09, 13.17; IR (film) 2931, 2958, 1719, 1429, 1390, 1242, 1112, 824, 790, 740, 703, 615, 506 $cm^{-1}$; HRMS m/z ($M^+$ - *t*$BuCH_3OH$) calcd 457.1872, found 457.1836.

**(2E,4S,5R)-5-Benzyloxy-7-((1,1-dimethylethyl)diphenylsiloxy)-4-methoxy-2-methyl-2-hepten-1-ol (21)**

To a cooled (-78°C), stirred solution of ester **20** (crude 5.30 g, prepared in previous experiment) in dry toluene (50 mL) was dropwise added a 1M solution of diisobutylaluminium hydride in toluene (21.32 mL, 21.32 mmol). The reaction was held at -78°C for 1.5 h, followed by the dropwise addition of methanol (21.32 mL). The temperature was allowed to rise to room temperature, and stirring was continued for 2 h at the same temperature. The white precipitate was filtered off through a plug of celite and washed with ethyl acetate (100 mL). The filtrate and washings were concentrated *in vacuo* and purified by chromatography (100 g of silica, 25% ethyl acetate/hexane) to afford **21** (4.18 g, 89% two steps yield).: $[\alpha]_D$ = +32.8 (c = 1.92, $CHCl_3$); $^1$H-NMR ($CDCl_3$, 400 MHz) δ 7.19-7.69 (m, 15H), 5.42 (bd, *J* = 8.8 Hz, 1H), 4.73 (A of AB part, *J* = 11.2 Hz, 1H), 4.53 (B of AB part, *J* = 11.2 Hz, 1H), 3.98 (s, 2H), 3.70-4.05 (m, 4H), 3.28 (s, 3H), 1.64 (s, 3H), 1.60 1.76 (m, 2H), 1.04 (s, 9H); $^{13}$C-NMR ($CDCl_3$, 100 MHz) δ 140.19, 138.92, 135.54, 133.88, 129.53, 128.20, 127.84, 127.59, 127.38, 122.74, 79.74, 78.11, 72.97, 68.11, 60.50, 56.45, 34.06, 26.68, 19.17, 14.23; IR (film) 3420, 3070, 2932, 2958, 2362, 1589, 1472, 1428, 1390, 1190, 1111, 824, 790, 738, 703, 614, 506 $cm^{-1}$; HRMS m/z ($M^+$ - *t*$BuCH_3OH$) calcd 429.1885, found 429.1893.

**(2*E*,4*S*,5*R*)-5-Benzyloxy-7-((1,1-dimethylethyl)diphenylsiloxy)-4-methoxy-2-methyl-2-heptenal (22)**

A mixture of allylic alcohol **21** (4.30 g, 8.29 mmol), manganese (IV) dioxide (2.16 g, 24.8 mmol) and $CCl_4$ (30 mL) was stirred at room temperature. Additional manganese (IV) dioxide (360 mg, 4.13 mmol) was added at 30 min intervals as required. The progress of the reaction was monitored by TLC (17% ethyl acetate/hexane). The resultant mixture was filtered through a plug of celite and washed with ethyl acetate. The filtrate and washings were concentrated *in vacuo* to give α,β-unsaturated aldehyde **22** (3.85 g, 90%) as a colorless oil.: $^1$H-NMR ($CDCl_3$, 400 MHz) δ 9.44 (s, 1H), 7.20-7.72 (m, 15H), 6.40 (bd, *J* = 8.8 Hz, 1H), 4.70 (A of AB part, *J* = 11.7 Hz, 1H), 4.57 (B of AB part, *J* = 11.2 Hz, 1H), 3.32 (s, 3H), 1.74 (s, 3H), 1.64 1.82 (m, 2H), 1.04 (s, 9H); IR (film) 3854, 3749, 3649, 3070, 2930, 2858, 1696, 1648, 1590, 1472, 1428, 1362, 1200, 1109, 1009, 939, 823, 738, 702, 613, 506 $cm^{-1}$.

**(4*S*,5*E*,7*S*,8*R*)-8-Benzyloxy-10-((1,1-dimethylethyl) diphenylsiloxy)-4-hydroxy-7-methoxy-5-methyl-1,5-decadiene and (4*R*,5*E*,7*S*,8*R*)-8-Benzyloxy-10-((1,1-dimethylethyl)diphenylsiloxy)-4-hydroxy-7-methoxy-5-methyl-1,5-decadiene (23)**

To a cooled (-78°C), stirred solution of **22** (3.85 g, 7.45 mmol) in anhydrous tetrahydrofuran (80 mL) was added a 1M solution of allyl magnesium bromide in ethyl ether (8.5 mL, 8.5 mmol) with a syringe. After the addition was complete, the reaction mixture was warmed gradually to 0°C, and stirred at the same temperature for a further 1 h, quenched by a saturated ammonium chloride solution, and then brine (40 mL) was added. The mixture was extracted with ethyl acetate (2 × 250 mL), dried over anhydrous sodium sulfate, filtered and concentrated to dryness. The resulting oil was purified by column chromatography (230 g of silica, 25% ethyl acetate/hexane) to afford the desired isomer **9** (1.96 g, 47%) and epimer **23** (1.53 g, 37%).: $[\alpha]_D$ = +16.75 (c = 1.07, $CHCl_3$); $^1$H-NMR ($CDCl_3$, 400 MHz) δ 7.15-7.71 (m, 15H), 5.74 (m, 1H), 5.42 (bd, *J* = 8.8 Hz, 1H), 5.04-5.12 (m, 2H), 4.70 (A of AB part, *J* = 11.2 Hz, 1H), 4.53 (B of AB part, *J* = 11.2 Hz, 1H), 4.07 (dd, *J* = 6.8, 6.4 Hz, 1H), 4.00 (dd, *J* = 8.8, 3.0 Hz, 1H), 3.70-3.86 (m, 3H), 3.24 (s, 3H), 2.23-2.33 (m, 2H), 1.66-1.78 (m, 2H), 1.62 (s, 3H), 1.03 (s, 9H); $^{13}$C-NMR ($CDCl_3$, 100 MHz) δ 142.10, 138.98, 135.55, 134.42, 133.89, 129.54, 128.21, 127.75, 127.61, 127.37, 123.68, 117.79, 79.57, 78.15, 76.12, 72.91, 60.50, 56.40, 39.77, 34.00, 26.88, 19.19, 12.51; IR (film) 3429, 3071, 2931, 2858, 1642, 1590, 1472, 1429, 1390, 1190, 1111, 917, 824, 789, 738, 703, 614, 506 $cm^{-1}$; HRMS m/z ($M^+$ - *t*$BuCH_3OH$) calcd 469.2199, found 469.2277. **23**: $[\alpha]_D$ = +31.51 (c = 2.47, $CHCl_3$); $^1$H-NMR ($CDCl_3$, 400 MHz) δ 7.15-7.71 (m, 15H), 5.74 (m, 1H), 5.43 (bd, *J* = 8.8 Hz, 1H), 5.04-5.12 (m, 2H), 4.70 (A of AB part, *J* = 11.2 Hz, 1H), 4.52 (B of AB part, *J* = 11.2 Hz, 1H), 4.07 (dd, *J* = 6.4, 6.3 Hz, 1H), 4.00 (dd, *J* = 8.8, 3.0 Hz, 1H), 3.69-3.85 (m, 3H), 3.27 (s, 3H), 2.21-2.32 (m, 2H), 1.63-1.75 (m, 2H), 1.62 (s, 3H), 1.03 (s, 9H); $^{13}$C-NMR ($CDCl_3$, 100 MHz) δ 142.11, 138.98, 135.55, 134.42, 133.88, 129.54, 128.21, 127.77, 127.61, 127.36, 123.66, 117.87, 79.61, 78.00, 75.92, 72.89, 60.48, 56.47, 39.86, 33.95, 26.88, 19.18, 12.47; IR (film) 3420, 3071, 2931, 2858, 1641, 1590, 1472, 1429, 1390, 1190, 1110, 916, 824, 738, 702, 614, 506 $cm^{-1}$; LRMS m/z 469 ($M^+$ - *t*$BuCH_3OH$).

**(4*S*,5*E*,7*S*,8*R*)-8-Benzyloxy-4-(*O*-benzyl-glycoloyloxy)-10-((1,1-dimethylethyl)diphenylsiloxy)-7-methoxy-5-methyl-1,5-decadiene (25)**

To a stirred solution of **9** (1.77 g, 3.17 mmol), *O*-benzyl-glycolic acid (684 mg, 4.12 mmol) and 4-dimethylamino-pyridine (39 mg, 0.32 mmol) in dry methylene chloride (30 mL) at room temperature was added dicyclohexyl carboimide (719 mg, 3.48 mmol) as a solid in one pot. After stirring for 2 h at room temperature, the reaction mixture was diluted with hexane (30 mL). The white precipitate was removed by filtration through a short column (10 g of silica) with 50% ethyl acetate/hexane to elute the products. Concentration *in vacuo* provided an oil, which was chromatographed (80 g of silica, 10% ethyl acetate/hexane) to give ester **25** (2.24 g, 100%) as a colorless oil.: $[\alpha]_D$ = +3.90 (c = 1.91, $CHCl_3$); $^1$H-NMR ($CDCl_3$, 400 MHz) δ 7.20-7.70 (m, 20H), 5.68 (m, 1H), 5.47 (bd, *J* = 8.8 Hz, 1H), 5.32 (dd, *J* = 6.8, 6.4 Hz, 1H), 5.01-5.09 (m, 2H), 4.43-4.70 (m, 8H), 4.06 (A of AB part, d, *J* = 16.5 Hz, 1H), 4.01 (B of AB part, d, *J* = 16.5 Hz, 1H), 3.96 (dd, *J* = 8.8, 4.0 Hz, 1H), 3.79-3.88 (m ,3H), 3.22 (s, 3H), 2.35-2.49 (m, 2H), 1.60 1.83 (m, 2H), 1.66 (s, 3H), 1.04 (s, 9H); $^{13}$C-NMR ($CDCl_3$, 100 MHz) δ 169.46, 138.96, 137.88, 137.17, 135.53, 133.87, 133.15, 129.52, 128.42, 128.18, 127.94, 127.60, 127.30, 125.52, 127.88, 79.54 133.89, 129.54, 128.21, 127.75, 127.61, 127.37, 123.68, 117.79, 79.45, 77.97, 77.90, 73.19, 72.94, 67.16, 60.37, 56.38, 37.44, 34.04, 26.88, 19.17, 13.52; IR (film) 3069, 2931, 2958, 1656, 1496, 1455, 1428, 1391, 1195, 1112, 824, 638, 702, 614, 506 $cm^{-1}$; LMRS m/z 541 ($M^+$ - $tBuBnCH_2OH$).

**Preparation of 25 by the Mitsunobu method**

To a magnetically stirred solution of triphenylphosphine (1.25 g, 4.72 mmol) in dry tetrahydrofuran (7 mL) at 0°C in a 100 mL round-bottomed flask was dropwise added diisopropylazodicarboxylate (0.94 mL, 4.72 mmol) with a syringe. After stirring for 10 min at 0°C, the cloudy white mixture was treated dropwise with a solution of alcohol **23** (1.33 g, 2.38 mmol) and O-benzylglycolic acid in dry tetrahydrofuran (7 mL). After 30 min at 0°C, the temperature was raised to room temperature, and the reaction mixture was stirred for 1 h. The resulting mixture was diluted with hexane (20 mL), filtered through a short column (silica 15 g) and washed with 16 % ethyl acetate/hexane to elute the product. The filtrate and washings were concentrated and purified by chromatography (50 g of silica, 10% ethyl acetate/hexane) to give the desired ester **25** (1.4 g, 83%), which was identical to **25** obtained by Hasners DCC protocol in all aspects.

**(1*E*,2*S*,3*S*,4*S*,5*R*)-2,5-Dibenzyloxy-7-((1,1-dimethylethyl) diphenylsiloxy)-4-methoxy-3-(1-methyl-1,4-pentadienyl)-heptanoic acid, methyl ester (26)**

To a cooled (-78°C), stirred solution of 1M lithium bis (trimethylsilyl)amide (in dry tetrahydrofuran, 9.6 mL, 9.6 mmol) was dropwise added a solution of ester **25** (1.68 g, 2.38 mmol) and trimethylsilyl chloride/triethylamine (1/1.1, v/v, 6.21 mL) in dry tetrahydrofuran (40 mL). After stirring for 15 min at the same temperature, the reaction mixture was warmed to room temperature and stirred for 15 h, and then quenched with a 1N sodium hydroxide solution (45 mL) under ice bath cooling. The resulting mixture was stirred for 10 min at room temperature, acidified by a 3N hydrochloric acid solution, and then partitioned between ethyl acetate (70 mL) and brine (70 mL). After the organic layer was separated, the aqueous phase was extracted with ethyl acetate (2 × 50 mL) and the combined extracts were dried over anhydrous sodium sulfate, filtered then concentrated *in vacuo* to give crude acid. The crude acid was dissolved in tetrahydrofuran (30 mL) and titrated with benzyltrimethyl ammonium hydroxide (40% in methanol), which was indicated by phenolphthalein. After the violet solution was stirred at room temperature for 1 h, methyl iodide (0.6 mL, 9.64 mmol) was added with a syringe. The mixture was stirred for 2 h at room temperature, diluted with hexane (30 mL) and filtered through a short column (20 g of silica) with 50% ethyl acetate/hexane to elute the products. Concentration *in vacuo* provided an oil, which was purified by column chromatography (90 g of silica, 7% ethyl acetate/hexane) to give **26** (1.53 g, 89%) as a colorless oil.: $[\delta]_D$ = -11.91 (c = 1.46, $CHCl_3$); $^1$H-NMR ($CDCl_3$, 400 MHz) δ 7.14-7.64 (m, 20H), 5.66 (m, 1H), 5.25 (dd, *J* = 6.8, 6.4 Hz, 1H), 4.94 (bd, *J* = 17.2 Hz, 1H), 4.88 (bd, *J* = 9.9 Hz, 1H), 4.54 (A of AB part, d, *J* = 11.4 Hz, 1H), 4.49 (B of AB part, d, *J* = 11.4 Hz, 1H), 4.43 (A of AB part, d, *J* = 11.4 Hz, 1H), 4.37 (B of AB; part, d, *J* = 11.4 Hz, 1H), 4.28 (d, *J* = 10.3 Hz, 1H), 3.65-3.85 (m, 4H), 3.60 (s, 3H), 3.31 (s, 3H), 2.60-2.77 (m, 3H), 1.73-1.94 (m, 2H), 1.66 (s, 3H), 1.02 (s, 9H); $^{13}$C-NMR ($CDCl_3$, 100 MHz) δ 172.71,138.92, 137.15, 136.54, 135.55, 133.91, 129.50, 128.34, 128.26, 128.18, 127.89 12758 1275, 127.41, 127.17, 114.63. 81.43, 79.68, 77.70, 72.80, 61.71, 50.41, 54.24, 51.48, 33.59 32.25, 26.86 19.18, 15.37; IR (film) 3031, 2932, 2858, 2360, 1749, 1638, 1589, 1497, 1456, 1429, 1360, 1263, 1193, 1111, 1029, 911, 824, 737, 701, 614, 506 $cm^{-1}$; LRMS m/z 555 ($M^+$ - $tBuBnCH_2OH$).

**(1*E*,2*S*,3*S*,4*S*,5*R*)-2,5-Dibenzyloxy-7-hydroxy-4-methoxy-3-(1-methyl-1,4-pentadienyl)-heptanoic acid, methyl ester (27)**

To a stirred solution of silyl ether **26** (1.50 g, 2.08 mmol) in dry tetrahydrofuran (20 mL) at room temperature was dropwise added a 1M solution of tetra-n-butyl ammonium fluoride (3.2 mL, 3.2 mmol) in tetrahydrofuran. After stirring overnight, methyl iodide (0.5 mL, 8.03 mmol) was added and the mixture was stirred for 2 h at room

temperature and diluted with hexane (40 mL). The white precipitate was removed by filtration through a short column (10 g of silica) with 60% ethyl acetate/hexane to elute the products. The filtrate was concentrated *in vacuo* to give an oil, which was purified by column chromatography (80 g of silica, 80% ethyl acetate/hexane) to afford **27** (950 mg, 95%) as a colorless oil.: $[\alpha]_D$ = -6.94 (c = 0.90, $CHCl_3$); $^1$H-NMR ($CDCl_3$, 400 MHz) δ 7.21-7.51 (m, 10H), 5.68 (m, 1H), 5.26 (dd, *J* = 7.3, 7.0 Hz, 1H), 4.96 (bd, *J* = 17.2 Hz, 1H), 4.91 (bd, *J* = 10.3 hz, 1H), 4.56 (A of AB part, d, *J* = 11.4 Hz, 1H), 4.53 (B of AB part, d, *J* = 11.4 Hz, 1H), 4.42 (A of AB part, d, *J* = 11.4 Hz, 1H), 4.41 (B of AB part, d, *J* = 11.4 Hz, 1H), 4.23 (d, *J* = 9.5 Hz, 1H), 3.55-3.93 (m, 4H), 3.61 (s, 3H), 3.38 (s, 3H), 2.61-2.72 (m, 3H), 1.70 1.95 (m, 2H), 1.65 (s, 3H); $^{13}$C-NMR ($CDCl_3$, 100 MHz) δ 172.47, 138.14, 136.88, 136.30, 132.99, 128.29, 128.00, 127.94, 127.58, 127.51, 127.35, 114.63, 80.50, 80.22, 79.46, 72.51, 71.47, 60.48, 60.43, 54.15, 51.51, 32.10, 32.02, 15.13; IR (film) 3447, 3031, 2933, 2361, 1746, 1638, 1497, 1455, 1355, 1268, 1197, 1111, 1028, 912, 849, 738, 699, 619 $cm^{-1}$; HRMS m/z ($M^+$ - H) calcd 481.2590, found 481.2605.

**(1*R*,1*E*,2*S*,3*S*,4*R*)-1,4-Dibenzyloxy-3-methoxy-2-(1-methyl-1,4pentadienyl)-cyclohexanecarboxylic acid, methyl ester (7)**

A mixture of alcohol **27** (491 mg, 1.02 mmol), *p*-toluenesulphonyl chloride (370 mg, 2.04 mmol), dry chloroform (4.4 mL) and dry pyridine (0.6 mL, 7.42 mmol) was kept at -20°C overnight. The reaction mixture was diluted with 50% ethyl acetate/hexane (10 mL). The resulting white precipitate, pyridinium chloride, was removed by a short column (10 g of silica) and washed with 50% ethyl acetate/hexane. The filtrate was concentrated *in vacuo* to dryness. The residue was chromatographed (20 g of silica, 20% ethyl acetate/hexane) to give tosylate **8** (583 mg, 90%). This material was employed in the next experiment without further purification. To a cooled (-78°C), stirred solution of tosylate **8** (prepared in the previous experiment) in anhydrous tetrahydrofuran (120 mL) was added 1M potassium bis(trimethylsilyl)amide in tetrahydrofuran (3.67 mL, 3.67 mmol) with a syringe. After stirring for 30 min at 78°C, the reaction mixture was warmed to -40°C ~ -45°C and stirred for 10 h at the same temperature and quenched by the addition of methanol (1 mL) and a saturated ammonium chloride solution (5 mL). After stirring for 30 min at the same temperature, the resulting mixture was warmed to room temperature, stirred for 10 min then concentrated *in vacuo*. Next, the residue was partitioned between water (20 mL) and ethyl acetate (20 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated *in vacuo* and purified by column chromatography (25 g of silica, 10% ethyl acetate/hexane) to give cyclized product **7** (334 mg, 71%) as a colorless oil.; $^1$H-NMR ($CDCl_3$, 400 MHz) δ 7.24 7.44 (m, 10H), 5.76 (m, 1H), 5.19 (t, *J* = 6.6 Hz, 1H), 5.03 (dd, *J* = 17.2, 1.8 Hz, 1H), 4.99 (dd, *J* = 9.9, 1.8 Hz, 1H), 4.64 4.75 (m, 2H), 4.61 (A of AB part, d, *J* = 10.6 Hz, 1H), 4.30 (B of AB part, d, *J* = 10.6 Hz, 1H), 4.01 (bs, 1H), 3.68 (dd, *J* = 11.4, 2.9 Hz, 1H), 3.66 (s, 3H), 3.31 (s, 3H), 3.04 (d, *J* = 11.4 Hz, 1H), 2.67 2.89 (m, 2H), 2.34 (ddd, *J* = 14.3, 14.3, 3.7 Hz, 1H), 1.89 1.96 (m, 2H), 1.69 (s, 3H), 1.47 (m, 1H); $^{13}$C-NMR ($CDCl_3$, 100 MHz) δ 172.59, 139.11, 138.78, 137.17, 134.91, 128.17, 128.12, 127.54, 127.45, 127.30, 127.24, 126.61, 114.35, 86.07, 78.47, 71.22, 70.53, 66.34, 56.58, 53.28, 51.43, 32.36. 23.90, 23.67, 13.91; IR (film) 3064, 3030, 2930 1746, 1638, 1497, 1454, 1359, 1254, 1293, 1073, 911, 849, 738, 698, 555 $cm^{-1}$; HRMS m/z ($M^+$) calcd 464.2563, found 464.2541.

**(1*R*,1*E*,2*S*,3*S*,4*R*)-1,4-Dibenzyloxy-3-methoxy-2-(1-methyl-1,4pentadienyl)-cyclohexanemethanol (29)**

To a cooled (-40°C), stirred solution of cyclized product **7** (492 mg, 1.06 mmol) in dry tetrahydrofuran (10 mL) was dropwise added a 1M diisobutylaluminium hydride solution in toluene (2.97 mL, 2.97 mmol) with a syringe. The reaction mixture was warmed to room temperature and stirred for 2.5 h then quenched by the addition of methanol (2.97 mL) at -20°C. After 1 h at room temperature, the resulting mixture was diluted with ethyl acetate (30 mL) and the precipitate was removed by filtration through a plug of celite and washed with ethyl acetate (30 mL). The filtrate and washings were concentrated *in vacuo* and chromatographed (20 g of silica, 20% ethyl acetate/hexane) to give an approximate 11:1 mixture of major isomer **29** (402 mg, 87%) and minor isomer **29** (37 mg, 8%).: $[\alpha]_D$ = -92.25 (c = 1.22, $CHCl_3$); $^1$H-NMR ($CDCl_3$, 400 MHz) δ 7.16-7.40 (m, 10H), 5.75 (m, 1H), 5.43 (bs, 1H), 5.00 (dd, *J* = 16.9, 1.5 Hz, 1H), 4.91 (dd, *J* = 10.3, 1.1 Hz, 1H), 4.55-4.66 (m, 2H), 4.50 (A of AB part, d, *J* = 11.0 Hz, 1H), 4.27 (B of AB part, d, *J* = 11.0 Hz, 1H), 3.92 (bs, 1H), 3.54-3.71 (m, 3H), 3.21 (s, 3H), 2.64-2.87 (m, 2H), 2.67 (d, *J* = 11.0 Hz, 1H), 1.70 (s, 3H), 1.43-1.85 (m, 4H); $^{13}$C-NMR ($CDCl_3$, 100 MHz) δ 139.48, 139.13, 137.80, 136.57, 128.20, 128.17, 137.59, 127.34, 127.24, 127.05, 114.86, 80,07, 78.91, 71.17, 70.63, 67.18, 63.70, 56.68, 54.48, 23.19, 23.15, 14.14; IR (film) 3482, 3064, 3030, 2926, 2361, 1736, 1637, 1497, 1454, 1357, 1309, 1210, 1069, 999, 911, 735, 697 $cm^{-1}$; HRMS m/z ($M^+$) calcd 405.2430, found 405.2451. **Epimer of 29**: $[\alpha]_D$ = +1.6 (c = 1.0, $CHCl_3$); $^1$H-NMR ($CDCl_3$, 400 MHz) δ 7.20-7.45 (m, 10H), 5.75 (m, 1H), 5.25 (dd, 1H, *J* = 7.3, 7.0 Hz, 1H), 5.13 (dd, *J* = 17.2, 1.8 Hz, 1H), 4.89 (dd, *J* = 9.9, 1.5 Hz, 1H), 4.69 (A of AB part, d, *J* = 12.5 Hz, 1H), 4.65 (B of AB part,

d, $J$ = 12.5 Hz, 1H), 4.61 (A of AB part, d, $J$ = 11.7 Hz, 1H), 4.53 (B of AB part, d, $J$ = 11.7 Hz, 1H), 3.96 (bs, 1H), 3.67 (A of AB part, d, $J$ = 11.4 Hz, 1H), 3.55 (B of AB part, d, $J$ = 11.4 Hz, 1H), 3.27 (s, 3H), 3.24 (dd, $J$ = 11.4, 2.6 Hz, 1H), 3.18 (d, $J$ = 11.4 Hz, 1H), 2.71-2.88 (m, 2H), 1.98 = 2.14 (m, 2H), 1.85 (m, 1H), 1.70 (s, 3H), 1.31 (m, 1H); IR (film) 3450, 2934, 1637, 1496, 1454, 1376, 1210, 1090, 1067, 999, 911, 735, 697 $cm^{-1}$; LRMS m/z 405 ($M^+$ - $CH_2OH$).

**(1R,1E,2S,3S,4R)-1,4-Dihydroxy-3-methoxy-2-(1-methyl-1,4pentadienyl)-cyclohexanemethanol (30)**

Anhydrous ammonia (approximately 10 mL) was condensed into a three-necked, round-bottomed flask containing a solution of dibenzyl ether **29** (219 mg, 0.501 mmol) in dry tetrahydrofuran (1.5 mL) at 78°C. To this mixture was added a minimum amount of lithium (ca. 30 mg) sufficient to maintain a blue color, and the resulting deep blue solution was stirred at -78°C for 2 min. Methanol was added dropwise at the same temperature until the deep blue color discharged. The colorless solution was stirred for 30 min at -78°C, and then solid ammonium chloride (3 g) was added. After stirring for 1 h at -78°C, ammonia was allowed to evaporate (5 h). Ether (20 mL) was added, and the mixture was dried over anhydrous magnesium sulfate, filtered through a plug of celite and washed with ether (100 mL). The filtrate and washings were concentrated *in vacuo* and purified by column chromatography (15 g of silica, ethyl acetate only) to afford triol **30** (78 mg, 90% recovery yield) and the starting material **29** (80 mg).: $[\alpha]_D$ = - 52.49 (c = 0.87, $CHCl_3$); $^1$H-NMR ($CDCl_3$, 400 MHz) δ 5.77 (m, 1H), 5.33 (broad t, 1H, $J$ = 7.0 Hz), 5.03 (ddd, $J$ = 16.9, 3.3, 1.7 Hz, 1H), 4.96 (ddd, $J$ = 9.9, 3.3, 1.5 Hz, 1H), 4.25 (bs, 1H), 3.51 3.64 (m, 2H, $CH_2OH$), 3.34 (s, 3H), 3.27(d, $J$ = 11.4 Hz, 1H), 1.72 (s, 3H), 1.33 1.96 (m, 4H); $^{13}$C-NMR ($CDCl_3$, 100 MHz) δ 136.34, 136.60, 125.81, 114.73, 79.17, 74.69, 69.47, 64.21, 56.8 136.34, 136.60, 125.81, 114.73, 79.17, 74.69, 69.47, 64.21, 56.84, 51.36, 32.07, 26.68, 24.62, 15.13; IR (film) 3436, 2927, 1637, 1437, 1234, 1099, 1058, 910, 862, 795, 674 $cm^{-1}$; HRMS m/z ($M^+$) calcd 238.1569, found 238.1543.

**(1*R*,1*E*,2*S*,3*S*,4*R*)-1,4-Dihydroxy-3-methoxy-2-(1-methyl-1,4pentadienyl)-cyclohexanemethanol, tosylate (31)**

A solution of triol **30** (70 mg, 0.273 mmol), dry triethylamine (0.11 mL, 0.789 mmol), 4-dimethylaminopyridine (1.4 mg, 1.124 μmol) and *p*-toluenesulphonyl chloride in dry methylene chloride (2.7 mL) was stirred at room temperature for 12 h and diluted with 50% ethyl acetate/hexane. The precipitate was removed by filtration through a short column (3 g of silica, ethyl acetate only). The filtrate was concentrated *in vacuo* and purified by column chromatography (10 g of silica, 50% ethyl acetate/hexane) to give the desired tosylate **31** (90 mg, 80%) and monoepoxide **6** (7 mg, 11%): $[\alpha]_D$ = -17.91 (c = 0.91); $^1$H-NMR ($CDCl_3$, 400 MHz) δ 7.77 (d, $J$ = 8.4 Hz, 2H), 5.19 (m, 1H), 5.00 (bd, $J$ = 17.2 Hz, 1H), 4.95 (bd, $J$ = 10.3 Hz, 1H), 4.24 (bs, 1H), 3.82-3.97 (A of AB part, m, 1H), 3.71 (B of AB part, d, $J$ = 9.5 Hz, 1H), 3.57 (m ,1H), 3.35 (s, 3H), 2.65-2.84 (m, 2H), 2.46 (s, 3H), 2.36 (d, $J$ = 11.4, 1H), 1.66 (s, 3H), 1.42 1.89 (m, 4H); $^{13}$C-NMR ($CDCl_3$, 100 MHz) δ 144.97, 136.47, 133.88, 132.47, 129.85, 127.90, 126.20, 114.56, 78.68, 76.04, 73.47, 64.10, 57.01, 50.02, 32.04, 28.48, 24.32, 21.59, 14.90; IR (film) 3524, 2928, 1634, 1637, 1599, 1455, 1359, 1250, 1177, 1097, 976, 915, 840, 708, 668, 555 $cm^{-1}$; HRMS m/z ($M^+$) calcd 410.1763, found 410.1783.

**(1*E*,3*S*,4*S*,5*S*,6*R*)-5-Methoxy-4-(1-methyl-1,4-pentadienyl)-oxaspiro[2,5]octan-6-ol (6)**

To a stirred solution of tosylate **31** (83 mg, 0.202 mmol) in methanol (10 mL) at room temperature was added solid potassium carbonate (56 mg, 0.406 mmol). After stirring for 4 h at the same temperature, methanol was removed *in vacuo*. The residue was partitioned between brine (10 mL) and ethyl acetate (40 mL). The organic layer separated and the aqueous phase was extracted with ethyl acetate (2 × 100 mL). The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated *in vacuo* and purified by column chromatography (15 g of silica, 50% ethyl acetate/hexane) to give monoepoxide **6** (46 mg, 96%).: $[\alpha]_D$ = -88.06 (c = 1.83, CHCl3); $^1$H-NMR ($CDCl_3$, 400 MHz) δ 5.79 (m, 1H), 5.27 (m, 1H), 5.03 (broad d, $J$ = 17.2 Hz, 1H), 4.96 (broad d, $J$ = 10.3 Hz, 1H), 4.35 (pseudo q, $J$ = 2.9 Hz, 1H), 3.53 (dd, $J$ = 11.4, 2.9 Hz, 1H), 3.39 (s, 3H), 2.86 (d, $J$ = 11.4 Hz, 1H), 2.71 2.87 (m, 2H), 2.64 (A of AB part, d, $J$ = 4.8 Hz, 1H), 2.46 (B of AB part, d, $J$ = 4.8 Hz, 1H), 2.28 (m, 1H), 2.02 (m, 1H), 1.78 (m, 1H), 1.59 (s, 3H), 1.05 (m, 1H); $^{13}$C-NMR ($CDCl_3$, 100 MHz) δ 136.76, 132.68, 127.07, 114.49, 80.92, 64.43, 60.67, 56.89, 51.16, 47.99, 32.14, 27.83, 26.65, 14.64; IR (film) 3463, 2928, 2361, 1637, 1444, 1377, 1324, 1214, 1103, 997, 954, 927, 853, 701, 999, 519 $cm^{-1}$; HRMS m/z ($M^+$) calcd 238.1569, found 238.1553.

**(2*R*,3*R*,3*R*,4*S*,5*S*,6*R*)-5-Methoxy-4-[2-methyl-3-(2-propenyl)-oxiranyl]-oxaspiro[2,5]octan-6-ol (32) and (2*S*, 3*S*,3*R*,4*S*,5*S*,6*R*)-5-Methoxy-4-[2-methyl-3-(2-propenyl)-oxiranyl]-oxaspiro[2,5]octan-6-ol (the diastereomer of 32)**

A mixture of diene **6** (48 mg, 0.201 mmol), approximately 70% *meta*-chloroperbenzoic acid (55 mg, 0.22 mmol), anhydrous sodium bicarbonate (95 mg, 1.13 mmol) and dry methylene chloride (2 mL) was stirred at 0°C ~ 5°C for 4 h. Ethyl acetate (10 mL) and a 0.5N sodium hydroxide solution (10 mL) were added and the resulting mixture was stirred for 10 min at room temperature. The organic

layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated *in vacuo* and purified by column chromatography (10 g of silica, 66% ethyl acetate/hexane) to afford an approximate 11:1 mixture of major isomer **32** (43 mg, 84%) and minor isomer (3.9 mg, 7.6%), the epimer of **32**.: $[\alpha]_D$ = -52.85 (c = 0.42, CHCl3); $^1$H-NMR ($CDCl_3$, 400 MHz) δ 5.89 (m, 1H), 5.21 (broad d, *J* = 17.2 Hz, 1H), 5.15 (broad d, *J* = 10.3 Hz, 1H), 4.38 (pseudo q, *J* = 3.0 Hz, 1H), 3.63 (dd, *J* = 11.4, 3.0 Hz, 1H), 3.50 (s, 3H), 2.91 (A of AB part, d, *J* = 4.4 Hz, 1H), 2.67 (t, *J* = 6.2 Hz, 1H), 2.57 (B of AB part, d, *J* = 4.4 Hz, 1H), 2.21 2.41 (m, 2H), 2.21 (m 1H), 2.00 (m, 1H), 1.98 (d, *J* = 11.4 Hz, 1H), 1.77 (m, 1H), 1.23 (s, 3H), 0.99 (m, 1H); $^{13}$C-NMR ($CDCl_3$, 100 MHz) δ 133.26, 117.79, 80.97, 64.14, 60.55, 59.78, 58.46, 56.51, 50.91, 47.12, 32.89, 28.48, 26.54, 13.97; IR (film) 3428, 3076, 2932, 1642, 1441, 1381, 1258, 1214, 1103, 1003, 928, 867, 834, 764, 713, 690, 521, 484 $cm^{-1}$; HRMS m/z ($M^+$) calcd 223.1334, found 223.1323. The isomer of **32**: $^1$H-NMR ($CDCl_3$, 400 MHz) δ 5.83 (m, 1H), 5.19 (broad d, *J* = 17.2 Hz, 1H), 5.13 (broad d, *J* = 10.3 Hz, 1H), 4.33 (pseudo q, *J* = 1.8 Hz, 1H), 3.46 (dd, *J* = 11.4 1.8 Hz, 1H), 3.39 (s, 3H), 3.25 (A of AB part, d, *J* = 4.4 Hz, 1H), 2.71 (t, *J* = 6.3 Hz, 1H), 2.62 (B of AB part, d, *J* = 4.4 Hz, 1H), 2.15 2.41 (m, 2H), 2.16 (m, 1H), 1.99 (m, 1H), 1.92 (d, *J* = 11.4 Hz, 1H), 1.80 (m, 1H), 1.26 (s, 3H), 0.99 (m, 1H); IR (film) 3470, 2932, 1642, 1441, 1378, 1257, 1215, 1107, 991, 928, 845, 754, 714, 559 $cm^{-1}$; LRMS m/z 254 ($M^+$).

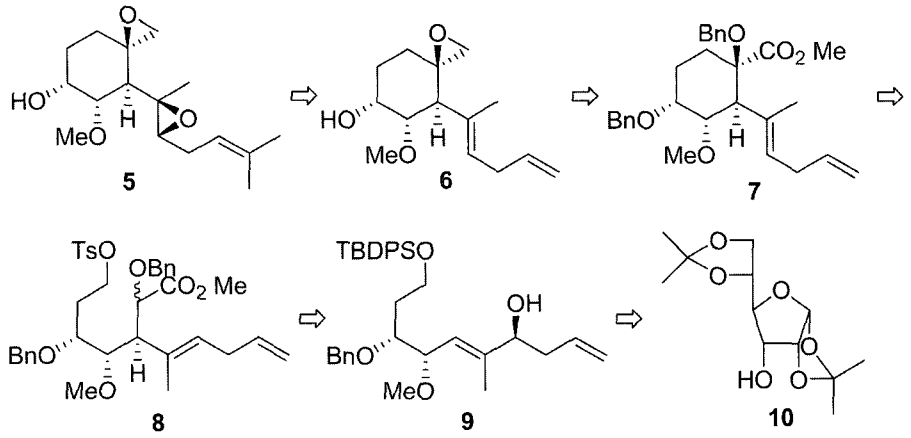
**Fumagillol (2)**

A solution of olefin **32** (28 mg, 0.109 mmol) in ethyl acetate (6 mL) was prepared in a 50 mL 3-necked round-bottom flask (equipped with a pipet inlet and drying tube outlet). After the solution was cooled to -78°C, a gaseous solution of ozone in oxygen was passed through the reaction mixture for 4 min. (The reaction was monitored by TLC). Nitrogen was then bubbled through the reaction mixture for 1 min and warmed to room temperature. The resulting mixture was concentrated and the residue was pumped to dryness (this ozonide was employed in the next experiment without further purification). To a ylide solution (isopropyltriphenylphosphonium iodide) (800 mg, 1.85 mmol), triphenylphosphine (57 mg, 0.22 mmol), a 1.6 M n-butyllithium solution (1.03 mL, 1.65 mmol) and dry tetrahydrofuran (5 mL) at -78°C, was dropwise added a solution of ozonide (prepared in the previous experiment) in dry tetrahydrofuran (3 mL). The reaction temperature was warmed to room temperature and stirred for 4 h, quenched by a saturated sodium bicarbonate solution (10 mL) and ethyl acetate (10 mL). The organic phase was separated and the aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated and chromatographed (5 g of silica, 60% ethyl acetate/hexane) to give a mixture of (-)-fumagillol (**2**) and phosphine oxide, which were difficult to separate. The above mixture was dissolved in dry methylene chloride (3 mL). To this at room temperature was added 4-dimethylaminopyridine (67 mg, 0.547 mmol) and acetic anhydride (90.042 mL, 0.44 mmol). The reaction mixture was stirred at room temperature for 4 h and partitioned between a saturated sodium bicarbonate solution (10 mL) and ethyl acetate (10 mL). The organic phase was separated and the aqueous phase was extracted with ethyl acetate (2 × 10 mL). The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated *in vacuo* and chromatographed (10 g of silica, 40% ethyl acetate/hexane) to give an acetylated fumagillol (16.6 mg). This acetylated fumagillol was dissolved in dry methanol, and anhydrous potassium carbonate (46 mg, 0.33 mmol) was added. The mixture was stirred at room temperature for 5 h. Methanol was evaporated and the residue was partitioned between a saturated sodium bicarbonate solution (10 mL) and ethyl acetate (10 mL). The organic phase was separated and the aqueous phase was extracted with ethyl acetate (2 × 10 mL). The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated *in vacuo* and chromatographed (10 g of silica, 60% ethyl acetate/hexane) to give pure (-)-fumagillol (**2**) (14 mg, 45%) as a white solid.: $[\alpha]_D$ = -67.43 (c = 0.5, EtOH); $^1$H-NMR ($CDCl_3$, 400 MHz) δ 5.20 (m, 1H), 4.37 (m, 1H), 3.63 (dd, *J* = 11.0, 2.9 Hz, 1H), 3.50 (s, 3H), 2.94 (A of AB part, d, *J* = 4.4 Hz, 1H), 2.58 (dd, *J* = 6.6 6.2 Hz, 1H), 2.54 (B of AB part, d, *J* = 4.4 Hz, 1H), 2.11 2.42 (m, 3H), 2.00 (m, 1H), 1.93 (d, *J* = 11.0 Hz, 1H), 1.70 1.83 (m, 1H), 1.74 (s, 3H), 1.66 (s, 3H), 1.22 (s, 3H), 0.98 (m 1H); $^{13}$C-NMR ($CDCl_3$, 100 MHz) δ 134.85, 118.53, 80.98, 64.10, 61.21, 59.80, 58.51, 56.49, 50.69, 47.05, 28.50, 27.36, 26.51, 25.69, 17.97, 13.95; IR (film) 3465, 2929, 1448, 1380, 1212, 1104, 1011, 931, 836, 768, 712, 689 $cm^{-1}$; HRMS m/z ($M^+$) calcd 282.1831, found 282.1826.

## RESULTS AND DISCUSSION

Our allylic strain controlled intramolecular ester alkylation (IEEA) is a very useful tool for synthesis of diastereoselective construction of cyclic compounds. Application of IEEA on total synthesis of several natural products was so successful. IEEA would produce in a stereoselective manner the desired key cyclohexanecarboxyate (**7**, Scheme 1), from which two epoxide functionalities could be installed by internal Williamson ether synthesis and m-CPBA epoxidation or vice versa.

It is worthwhile mentioning that the mono-substituted double bond in intermediate **6** is less susceptible to the

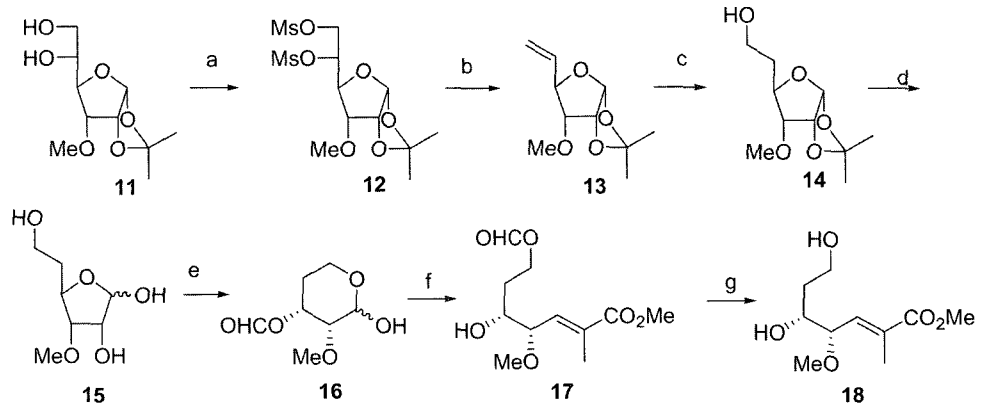


**Scheme 1.** *Retrosynthetic analysis of (-)-fumagillol*

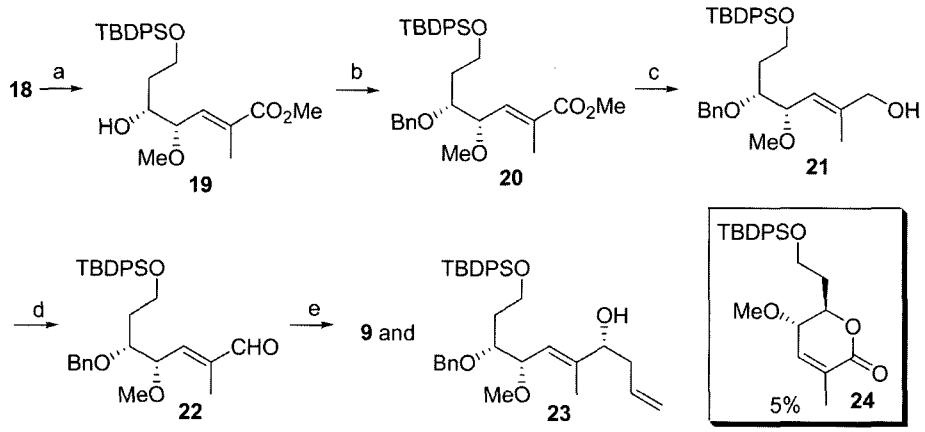
more nucleophilic trisubstituted double bond to *m*-CPBA epoxidation. And the terminal alkene can serve as a latent aldehyde functionality for a future Witting olefination. The retrosynthetic conversion of **7** to **8** relies on the basis that the base-promoted cyclization of **8** proceeds *via* chair-like transition state geometry where the enolate moiety assumes an H-eclipsed conformation. We expected that subjection of carbohydrate derived from chiron **9** to chelation-controlled Burke-Kallmerten-Fujisawa glycolate Claisen rearrangement would produce necessary key internal cyclization substrate **8** with correct configuration at C-4 position ((-)-fumagillol **2** numbering in Fig. 1) *via* a 1,3-chrality transfer process.

As shown in Scheme 2, the known diol **11** (Haga, 1972), which is readily accessible in two simple steps from commercially available 1,2;5,6-di-*O*-isopropylidene-β-D-allofuranose (**10**), was converted to primary alcohol **14** in three steps by well-established carbohydrate chemistry (Gurjar, 1987).

The dimesylation of diol **11** with MsCl and TEA in methylene chloride at -20°C to -30°C for 30 min, followed by treatment with excess NaI in methyl ethyl ketone at 100°C for 9 h, produced the corresponding olefin **13**, which was hydroborated with 9-BBN in THF at room temperature and oxidized by 30% $H_2O_2$ to yield C-5 deoxygenated primary alcohol **14** in 70% three steps yield. Acidic hydrolysis of acetonide **14** (acidic resin in $H_2O$ at 100°C for 1 h) afforded crude vicinal diol **15**, which was directly treated with $NaIO_4$ in acetone/ $H_2O$ (2/1) at room temperature. The resulting formylated δ-lactol **16** was subjected to the Wittig reaction in acetonitrile at 100~110°C for 16 h and gave crude α,β-unsaturated ester **17** (a 64% overall yield for the four steps). The migration of the formyl group in **17** to a primary hydroxyl group was confirmed by $^1$H-NMR analysis. The removal of the formyl group of **17** by treatment of a catalytic amount of $K_2CO_3$ in methanol at room temperature for 4 h and the subsequent purification by chromatography gave dihydroxy enolate **18**



**Scheme 2.** Synthesis of functionalized pyran from a known allofuranose. Reagent and conditions. (a) MsCl, TEA, $CH_2Cl_2$, -20°C to -10°C, 30 min. (b) NaI, methyl ethyl ketone, 100°C, 9 h, 77% for 2 steps. (c) 9-BBN, THF, -40°C to rt, overnight, 93%. (d) Dowex 50x2-200 resin, $H_2O$, 100°C, 50 min. (e) $NaIO_4$, acetone/$H_2O$ (2/1), rt, 2 h. (f) $Ph_3PC(CH_3)CO_2Me$, acetonitrile, 100°C to 110°C, 20 h. (g) $K_2CO_3$ (0.03 eq), $CH_3OH$, rt, 4 h, 63% for 4 steps.




**Scheme 3**. Synthesis of allyl alcohol, a precursor for a Claisen Rearrangement. Reagent and conditions. (a) TBDPSCl, DMAP (0.01 eq), TEA, $CH_2Cl_2$, rt, 20 h 93%. (b) $CCl_3(C{=}NH)OBn$, $CF_3SO_3H$ (cat), cyclohexane/$CH_2Cl_2$ (2/1), rt, 15 h. (c) DIBALH, toluene, -78°C, 1.5 h, 89% for 2 steps. (d) $MnO_2$, $CCl_4$, rt, overnight, 90%. (e) $CH_2{=}CHCH_2MgBr$, THF, -78 to 0°C, 1 h, and separation. 84% for a mixture of isomers.

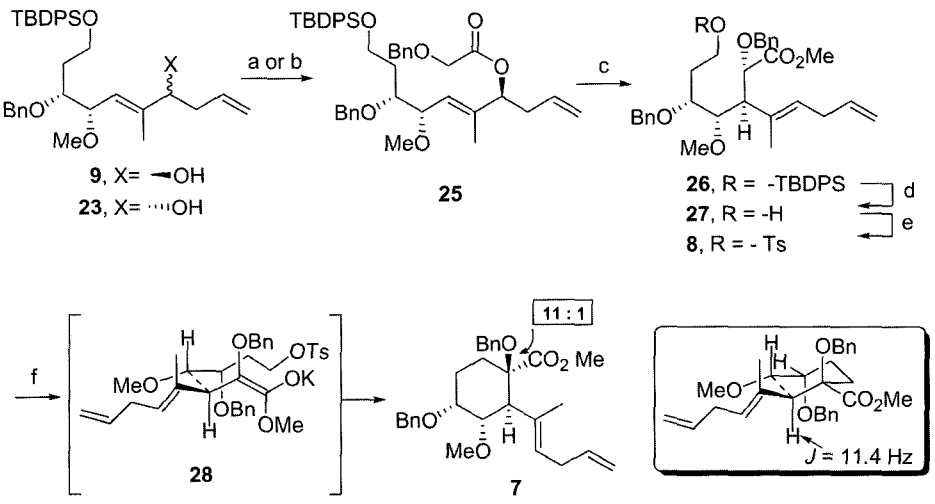
in a 63% yield for the four steps as a colorless oil.

In Scheme 3, the selective protection of the primary hydroxyl group of **18** by treatment with TBDPSCl and a catalytic amount of DMAP and TEA in $CH_2Cl_2$ at room temperature overnight produced hydroxy silyl ether **19** in a 93% yield. At this stage, **24** (5%) derived from *cis*-olefin was separated and confirmed by $^1$H-NMR (the methyl ester peak is not shown). Due to the existence of an epimerizable position in **19**, we searched for a milder benzylation. Treatment of **19** with benzyl trichloroacetimidate (Iversen, 1981) and a catalytic amount of $CF_3SO_3H$ in cyclohexane/methylene chloride (2/1) at 25°C furnished the desired *O*-benzyl ether **20**, which was converted to allylic alcohol **21** by DIBALH reduction in toluene at -78°C for 1.5 h (89% for two steps). The oxidation of **21** with $MnO_2$ in $CCl_4$ at room temperature gave enal **22** in a 90% yield. The addition of allylmagnesium bromide to aldehyde **22** in dry ethyl ether at -78°C to 0°C produced an approximate 5:4 mixture of two isomers **9** and **23** in an 84% total yield as expected, which were readily separable by chromatography.

In order to confirm the configuration of the desired alcohol **9** and to improve the diastereoselectivity of the allyation step, we attempted Roush's asymmetric allyation using (*R,R*)-diisopropyl tartrate-derived allylboronate (Roush, 1985; Roush, 1988). Two allylic alcohol isomers were easily separated by silica gel column chromatography. Also, the configuration of the incorrect stereocenter in **23** was inverted into a substrate with a correct stereochemistry for the Claisen rearrangement by the Mitsunobu reaction.

The present experiment along with the spectroscopic analysis of cyclized product **7**, and the final conversion of **7** to (-)-fumagillol **2** itself strongly suggest that the configuration of ally alcohol **9** is correct (*vide infra*).

As shown in Scheme 4, both allylic alcohol **9** and isomer **23** were converted to the desired allylic glycolate ester **25** in a single step in high yields by Steglich's DCC coupling protocol (Steglich, 1978) ($BnOCH_2CO_2H$, DMAP, DCC, $CH_2Cl_2$, rt, 1 h, 100%) and by a Mitsunobu procedure using DIAD ($BnOCH_2CO_2H$, $Ph_3P$, DIAD, THF, rt, 1.5 h, 83%), respectively (Scheme 4). Spectral data of **25** obtained by Steglichs DCC coupling were identical to those by a Mitsunobu method. We next turned our attention to the conversion of allylic glycolate **25** to γ,δ-unsaturated glycolate **26** with correct stereochemistry at C-4 (see fumagillol numbering in Fig. 1) by a 1,3-chirality transfer process of Burke-Fujisawa-Kallmerten modification (Burke, 1983; Sato, 1983; Kallmerten, 1983) of the Ireland Claisen rearrangement. By sequential treatment of **25** with LDA and TMSCl, followed by the internal quenching method and methylation (Triton B, MeI, THF, rt, 2.5 h), glycolate **26** as a single diastereomer in good yield was furnished. The stereochemistry of glycolate **26** was anticipated by invoking the 1,3- and 1,4- chirality transfer processes through chelation-controlled chair-like transition state geometry. Although the diastereoselectivity at the glycolate moiety due to the 1,4-chrality transfer is not significant in our purpose, it was helpful for us to spectroscopically characterize our synthetic intermediate **26**. The removal of the TBDPS group of **26** by treatment with tetra (*n*-butyl)ammonium fluoride in THF at room temperature gave alcohol **27** in a 95% yield as a colorless oil. The tosylation of alcohol **27** in chloroform/pyridine at -20°C overnight afforded intramolecular alkylation substrate **8** in a 90% yield. The intramolecular ester enolate alkylation of tosylate **8** with excess KHMDS in THF at -40°C ~ -45°C for 10 h provided the desired cyclohexane carboxylate **7** and its stereoisomer at the quaternary carbon center as an inseparable 11:1 mixture in a 63% overall yield for two

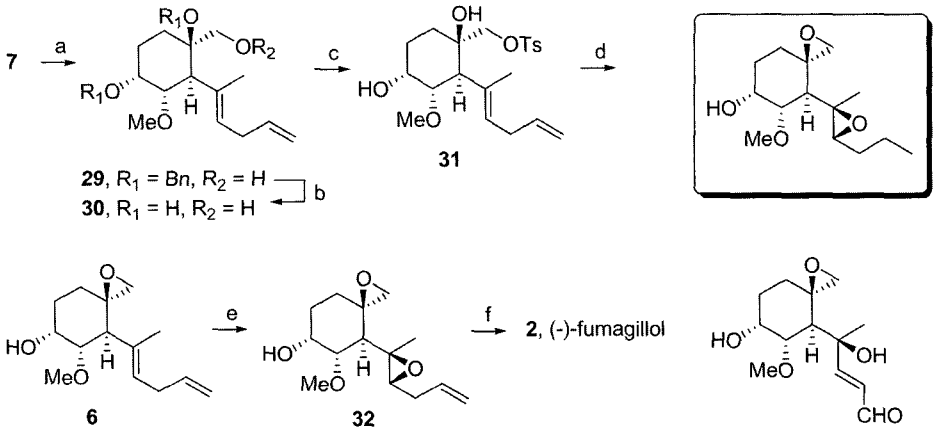


**Scheme 4.** Claisen rearrangement and IEEA. Reagent and conditions. (a) $BnOCH_2CO_2H$, DMAP, DCC, $CH_2Cl_2$, rt, 2 h, 100%. (b) $BnOCH_2CO_2H$, $Ph_3P$, DIAD, THF, rt, 1 h, 83%. (c) LHMDS, TMSCl/TEA/TEA (1/1.1), THF, -78°C to rt, 15 h, and then Triton B, MeI, THF, rt, 2 h, 89% overall yield. (d) TBAF, THF, rt, overnight, 95%. (e) TsCl, pyridine, $CHCl_3$, -20°C, overnight, 90%. (f) KHMDS, THF, -40°C - -45°C, 10 h, 71%.

steps, probably through the preferred H-eclipsed transition state geometry **28**. However, the cyclization of tosylate **8** above -40°C produced the cyclized product **7** contaminated with a varying amount of conjugated diene produced by the abstraction of a methylene proton of the 1,4-pentadienyl system. The stereoselectivity was determined by separation and weighting of the two isomers after the next step, DIBAL reduction, as described in Scheme 5. The large coupling constant ($J$ = 11.4 Hz probably by axial-axial coupling) of the allylic proton indicated by an arrow in the most stable conformation in the box, taken together with the mechanistic rationale for the [3,3]-sigmatropic rearrangement, strongly suggest that our sterochemical assignment of allylic alcohol **9** is correct.

With the key cyclization product **7** in hand, our attention was directed toward installing two epoxide functionalities to attain the final product, (-)-fumagillol (**2**). The DIBALH reduction of ester **7** in THF at room temperature for 2.5 h produced an 11:1 mixture of primary alcohol **29** and its epimer at the quaternary carbon in a 95% total yield, at which stage the minor stereoisomer was readily removed by silica gel chromatography (Scheme 5).

After some experimentation it was found that treatment of dibenzyl ether **29** with excess lithium in liquid ammonia at -78°C in a very short time period (approximately 2 mins), followed by rapidly quenching with methanol, afforded the desired triol **30** in a 91% yield based on the recovered starting material with minimum formation (~2%) of a partially reduced diene. The selective mono-tosylation of triol **30** was achieved by treatment with TsCl and DMAP



**Scheme 5.** Synthesis of (-)-fumagillol from a cyclized product. Reagent and conditions. (a) DIBALH, THF, rt, 2.5 h, 96%. (b) Li, $NH_3$, -78°C, 2 min, 90% based on the starting material. (c) TsCl, $CH_2Cl_2$, DMAP (0.04 eq), rt, 12 h, 80% with 10% epoxide. (d) $K_2CO_3$, MeOH, rt, 4 h, 96%. (e) MCPBA, $NaHCO_3$, $CH_2Cl_2$, 0°C, 4 h, 92%. (f) i) $O_3$, EtOAc, -78°C, 1 min. ii) $Ph_3PC(CH_3)_2$, THF, -78°C to rt, 4 h. iii) $Ac_2O$, DMAP, $CH_2Cl_2$, rt, 4 h. iv) $K_2CO_3$, MeOH, rt, 5 h, 45% for 4 steps.

in methylene chloride at room temperature to afford monotosylate **31** (80%) along with monoepoxide **6** (10%). The exposure of the resulting monotosylate **31** to a mild basic condition ($K_2CO_3$ in MeOH at room temperature for 4 h) produced the desired monoepoxide **6** in an 87% yield for the two steps.

The regio- and stereo-selective epoxidation of the trisubstituted double bond of monoepoxide **6** by treatment with *m*-CPBA in methylene chloride at 0°C for 4 h in the presence of $NaHCO_3$ as an acid acceptor produced an 11:1 mixture of major isomer **32** and its diastereomer in a 95% total yield. The existence of a small doublet at δ 2.84 ($J$ = 4.0 Hz) in a 400 MHz $^1$H-NMR spectrum of **32** is probably due to oxiranyl H in the oxaspirooctane skeleton.

At this stage of synthesis, what remained to be done was the conversion of the terminal methylene of bis-epoxide **32** to isopropylidene moiety by successive ozonolysis and the Wittig reaction, which turned out to be very problematic. The ozonolysis of the terminal double bond in olefin **32**, followed by treatment with triphenylphosphine, yielded a compound that strongly absorbed UV light. $^1$H-NMR spectral data of the compound were consistent with γ-hydroxy-α,β-unsaturated aldehyde, probably formed by an epoxide ring opening. To our delight, direct treatment of the crude ozonide of bis-epoxide **32** with isopropylidene phosphorane in the presence of triphenylphosphine furnished the desired (-)-fumagillol (**2**). In order to separate (-)-fumagillol (**2**) from phosphine oxide, we acetylated a mixture of (-)-fumagillol (**2**) and triphenylphosphine oxide by treatment with acetic anhydride and DMAP in methylene chloride at room temperature for 4 h, which produced 6-*O*-acetylated (-)-fumagillol. The acetylated (-)-fumagillol was separated by silica gel column chromatography, followed by saponification under a basic condition ($K_2CO_3$, MeOH at room temperature for 5 h), to produce the desired (-)-fumagillol (**2**) in a 45% overall yield for the four steps.

The conversion of (-)-fumagillol (**2**) to (-)-fumagillin (**1**) has already been reported by Corey and Snider. Spectral data ($^1$H-NMR, $^{13}$C-NMR, IF, mass, optical rotation) of synthetic (-)-fumagillol (**2**) were identical to those of an authentic sample in all aspects.

## ACKNOWLEDGEMENT

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