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Synthesis of (−)-astrogorgiadiol

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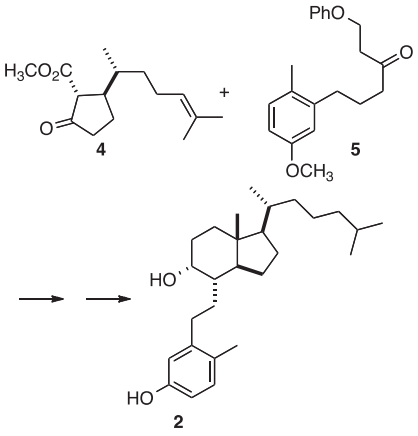
ABSTRACT

Astrogorgiadiol is a naturally occurring Vitamin D analogue that, in cell culture, downregulates the production of the cytokine osteopontin (OPN). OPN has been implicated in virulent asthma, and OPN knockout mice do not develop osteoporosis. As we have pursued whole animal studies with astrogorgiadiol, we have increased the scale of the synthesis. We report an improved preparation of the A-ring synthon and the scale-up of the diastereomerically pure D-ring/sidechain chiron.

1. Introduction

We have described[1,2] the total syntheses of astrogorgiadiol **2** (Eq. 1) and calicoferol B **3**.[3] Remarkably, while the active metabolite of Vitamin D, 1α,25-dihydroxy Vitamin D_3 (calcitriol) **1** upregulates the cytokine osteopontin (OPN) in cell culture, 30 nM **2** downregulates OPN.[3] This is the first small molecule known to downregulate this cytokine. Osteopontin has been shown to play a significant role in the development of virulent asthma,[4] and OPN knockout mice do not develop osteoporosis.[5] As we have pursued whole animal studies of astrogorgiadiol **2**, we have needed a more robust supply. We describe here a second generation preparation of the A-ring synthon **5** (Scheme 1), and a scale-up of the diastereomerically pure D-ring/sidechain chiron **4**, which are combined[1] via Robinson annulation to make **2**.



Scheme 1. Synthesis of astrogorgiadiol.

2. Results and discussion

2.1. Preparation of the β-ketoester 4

The D-ring/sidechain chiron **4** was prepared as before (Scheme 2) from commercial (*R*)-citronellal **6**. It is not necessary to purify either the citronellol from the $LiAlH_4$ reduction nor the benzenesulfonate **7** prepared from it. Exposure of the crude benzenesulfonate to an excess of the dianion[6] of methyl acetoacetate led to the β-ketoster **8**, that was purified as before by short path distillation. Passage of the diazo ketone **9** through a plug of silica gel was sufficient to prepare it for Rh-mediated cyclization.

We were pleased to observe that 10.1 g of the diazo ketone **9** prepared in this manner cyclized smoothly to the previously observed[1] 70:30 mixture of β-ketoesters **4** and **10**, using just 0.02 mol % of the Hashimoto[7] catalyst Rh_2(*S*)-$PTPA_4$. We had previously[1] cyclized chromatographically-purified **9** with the Hashimoto[7] catalyst on a 2.0 g scale using 0.48 mol % of the catalyst. The diastereomers **4** and **10** do not separate on TLC, but direct crystallization of the chromatographed mixture from the cyclization of 10.1 g of the diazo ketone delivered 2.73 g of the pure crystalline **4**.

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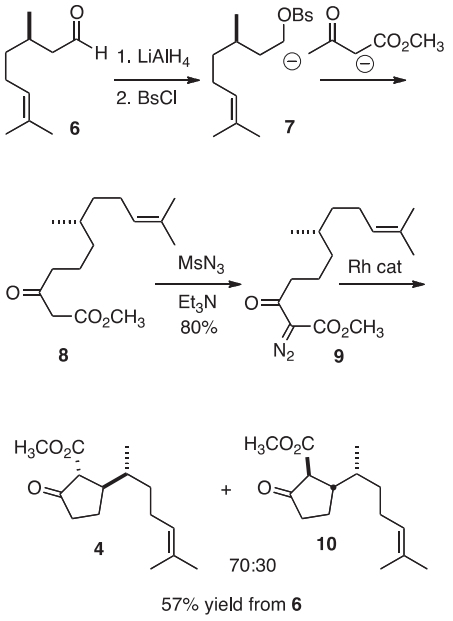
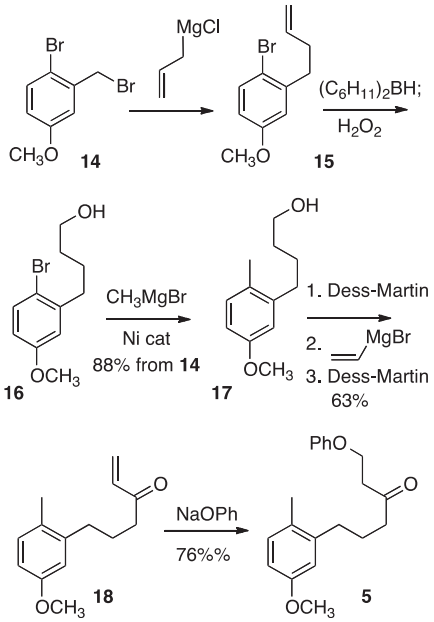


Scheme 2. Preparation of the β-ketoester **4**.



Scheme 3. Previous preparation of the ketone **5**.

The progress of the crystallization was followed by monitoring the ratio of the ^{1}H NMR doublet at δ 2.95 (**4**) to the doublet at δ 2.97 (**10**). Selective RuBINAP-mediated hydrogenation[8] of **10** in the residual mixture of **4** and **10** as we have described[1] allowed the separation of additional quantities of pure crystalline **4**.

2.2. Preparation of the ketone 5

The previous preparation[1] of **5** is outlined in Scheme 3. The Ni-catalyzed coupling was not perfectly clean, giving a product that was about 5% desmethyl. Although this could be removed by recrystallizing **5**, on scale-up **5** was found to be unstable. We were not able to find alternative conditions that gave acceptably clean methylation of **16**.

We therefore envisioned a new approach to **5**, based on the addition (Scheme 4) of the Grignard reagent derived from **25** to the epoxide **20**.[9] Gram quantities of the epoxide **20** were readily prepared by dehydrohalogenation[10] of the commercial bromide **11**, followed by epoxidation.

The preparation of the alcohol **24** by reduction of the cyclic ether **23** had been described.[11] We prepared the requisite *m*-methoxy phenethyl alcohol by reduction of the commercial acid **21**. In our hands, cyclization of the derived MOM ether gave **23** contaminated by about 5% of **22**, that had to be separated by column chromatography. Reduction of **23** with $LiAlH_4/AlCl_3$ then gave **24**, as had previously been described.[11]

Conversion[12] of the alcohol **24** to the bromide **25** proceeded smoothly, as did Grignard formation and addition to the epoxide **20** to give **26**. Using this approach, we routinely prepare several hundred milligrams of clean alcohol **26** in a run. As we had previously observed, the ketone **5** was only marginally stable. It was best to carry out the oxidation[13] and purification quickly, as needed, then directly take **5** into the Robinson annulation.

3. Conclusion

We have scaled up the cyclization to prepare the diasteromerically pure D-ring/sidechain chiron **4** (Scheme 1) and have developed a more robust synthetic route to the A-ring synthon **5**. Using the materials so prepared, we have been able to produce enough astrogorgiadiol **2** to support the ongoing whole animal studies.

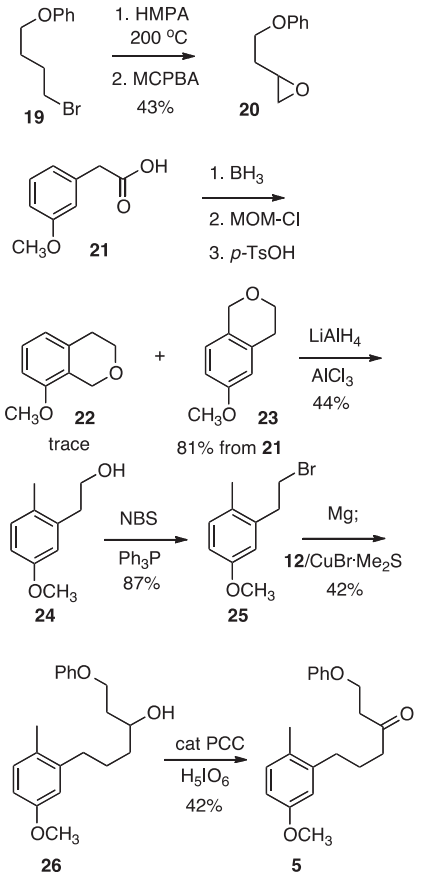
4. Experimental section

4.1. General

^{1}H NMR and ^{13}C NMR spectra were recorded, as solutions in deuteriochloroform ($CDCl_3$) unless otherwise indicated, at 400 MHz and 100 MHz, respectively. ^{13}C multiplicities were determined with the aid of a JVERT pulse sequence, differentiating the signals for methyl and methine carbons as 'd' from methylene and quaternary carbons as 'u'. The infrared (IR) spectra were determined as neat oils. R_f values indicated refer to thin layer chromatography (TLC) on 2.5×10 cm, 250 μm analytical plates coated with silica gel GF and developed in the solvent system indicated. All glassware was oven dried and rinsed with dry solvent before use. THF was distilled from sodium metal/benzophenone ketyl under dry nitrogen. Toluene, dichloromethane, and acetonitrile were distilled from calcium hydride under dry nitrogen. CH_2Cl_2 is dichloromethane, MTBE is methyl-*tert*butyl ether and PE is petroleum ether. All reactions were conducted under N_2 and stirred magnetically.

*4.1.1. Methyl (1R,5R)-2-oxo-5-((1R)-1,5-dimethyl-4-hexenyl)cyclopentanecarboxylate (**4**).*

4.1.1.1. Preparation of citronellol. Powdered $LiAlH_4$ (2.50 g, 65.8 mmol) was introduced into a 1 L round bottom flask that contained 400 mL of dry THF. The system was mechanically stirred, kept at 0 °C, and under constant N_2. Citronellal **6** (20.0 g, 130 mmol) was added neat over 10 min, and the residue was rinsed and added with a few mL of THF. The slurry was allowed to stir for approximately 1 h (followed by TLC). The system was quenched[14] by the dropwise addition of water, 15% aqueous NaOH and water, with stirring after each addition. The reaction mixture was filtered through Na_2SO_4 and the solids were rinsed with MTBE. After concentration, the crude residue was distilled to yield citronellol (18.3 g, 91%) as a clear oil, TLC R_f (10% MTBE/PE)=0.09. ^{1}H NMR ($CDCl_3$, δ): 5.10 (m, 1H), 3.66 (m, 2H), 2.1–1.8 (m, 3H), 1.68 (s, 3H), 1.7–1.5 (m, 2H), 1.60 (s, 3H), 1.4–1.3 (m, 2H), 1.17 (m, 1H), 0.90 (d,



Scheme 4. New preparation of the ketone **5**.

J=6.66 Hz, 3H). ^{13}C NMR ($CDCl_3$, δ): (u) 131.2, 61.0, 39.8, 37.1, 25.4; (d) 124.6, 29.1, 25.6, 19.4, 17.6. IR (cm^{-1}): 3331 (b), 2927, 1454, 1377, 1058. MS (m/z, %): 55 (64), 69 (100), 82 (44), 95 (33), 109 (14), 123 (18), 138 (6), 156 (6). HRMS calcd for $C_{10}H_{20}O$: 156.1514, found 156.1514. $[\alpha]_D^{17}$ +3.74 (c 1.02, EtOH).

*4.1.1.2. Benzenesulfonate **7**.* A solution of the above crude citronellol (18.3 g, 118 mmol) in 250 mL of CH_2Cl_2 in a 500 mL round bottom flask at 0 °C was stirred. Triethylamine (36.1 mL, 260 mmol) was added in one portion, followed by 4-dimethylaminopyridine (123 mg, 1.01 mmol). Finally benzenesulfonyl chloride (25.0 g, 140 mmol) was added dropwise via pipette. The mixture was stirred at 0 °C for 2 h. The slurry was partitioned between 10%MTBE/PE and, sequentially, 5% aqueous HCl, water, and brine. The organic extract was dried (Na_2SO_4) and concentrated to leave citronellyl benzenesulfonate **7** (40.3 g) as thick yellow oil, TLC R_f (10% MTBE/PE)=0.41, (7.5%:7.5% MTBE/DCM/PE)=0.53. ^{1}H NMR ($CDCl_3$, δ): 7.92 (m, 2H), 7.66 (m, 1H), 7.56 (m, 2H), 5.03 (m, 1H), 4.09 (m, 2H), 1.91 (m, 2H), 1.68 (m, 1H), 1.67 (s, 3H), 1.57 (s, 3H), 1.52 (m, 1H), 1.44 (m, 1H), 1.24 (m, 1H), 1.11 (m, 1H), 0.81 (d, J=6.49 Hz, 3H). ^{13}C NMR ($CDCl_3$, δ): (u) 136.1, 131.4, 69.2, 36.6, 35.5, 25.1; (d) 133.6, 129.1, 127.7, 124.2, 28.7, 25.6, 18.9, 17.5. IR (cm^{-1}): 2914, 1449, 1360, 1188, 944.

*4.1.1.3. Keto ester **8**.* Sodium hydride (21.8 g, 60% in mineral oil, 545 mmol) was dispersed in 350 mL of dry THF that was stirring in a 1 L round bottom flask at 0 °C under N_2. Next methyl acetoacetate (35.0 g, 300 mmol) was added dropwise via syringe. After stirring for 10 min n-butyl lithium (136 mL, 2.0 M) was added rapidly dropwise via syringe. After 10 min the crude citronellyl benzenesulfonate **7** (40.3 g, 136 mmol) was introduced via cannula under positive N_2 pressure and the mixture was allowed to stir at rt for 1 h. The mixture was quenched cautiously by pouring into saturated aqueous NH_4Cl, then partitioned between MTBE and, sequentially, H_2O and brine. The combined organic extracts were dried (Na_2SO_4) and concentrated to yield a brownish oil. This was distilled bulb-to-bulb at 0.7 Torr. At a bath temperature of 100 °C a clear oil distilled over and was discarded. The product **8** distilled at 140–160 °C. The β-ketoester **8** (26.1 g, 75%) was isolated as clear yellow oil, TLC R_f (10% MTBE/PE)=0.39, TLC R_f (7.5%:7.5% MTBE/DCM/PE)=0.41, ^{1}H NMR ($CDCl_3$, δ): 5.08 (m, 1H), 3.74 (s, 3H), 3.45 (s, 2H), 2.52 (t, J=7.34 Hz, 2H), 1.96 (m, 2H), 1.68 (s, 3H), 1.60 (s, 3H), 1.6–1.2 (m, 6H), 1.13 (m, 1H), 0.87 (d, J=6.85 Hz, 3H). ^{13}C NMR ($CDCl_3$, δ): (u) 202.6, 167.5, 130.9, 48.8, 43.2, 36.8, 36.1, 25.3, 20.8; (d) 124.7, 52.1, 32.1, 25.6, 19.2, 17.5. IR (cm^{-1}): 2925, 1748, 1716.

Alternatively, the product could be purified by column chromatography, allowing concomitant recovery of unreacted citronellyl benzenesulfonate. A unique mobile phase was used, 1:1 MTBE/CH_2Cl_2 in PE. This ternary mobile phase allowed for increased resolution between the **7** and **8**.

*4.1.1.4. Diazo ketone **9**.* Acetoacetate **8** (26.1 g, 102 mmol) was taken up in 115 mL of acetonitrile in a 250 mL round bottom flask. While stirring, triethylamine (34.8 mL, 251 mmol) and mesyl azide[15] (14.8, 122 mmol) were added neat sequentially. After overnight stirring half of the solvent was removed in vacuo, then the reaction mixture was partitioned between PE and, sequentially, 10% NaOH, and brine. The combined organic extract was dried (Na_2SO_4) and concentrated, and the residue was filtered through a plug of silica gel to yield the diazo ketone **9** (22.1 g, 78.9 mmol, 61% yield from citronellal), TLC R_f (10% MTBE/PE)=0.42, TLC R_f (7.5%:7.5% MTBE/DCM/PE)=0.50. ^{1}H NMR ($CDCl_3$, δ): 5.09 (m, 1H), 3.84 (s, 3H), 2.83 (t, J=7.85 Hz, 2H), 1.96 (m, 2H), 1.68 (s, 3H), 1.60 (s, 3H), 1.7–1.5 (m, 2H), 1.5–1.3 (m, 3H), 1.15 (m, 2H), 0.88 (d, J=6.49 Hz, 3H). ^{13}C NMR ($CDCl_3$, δ): (u) 193.0, 161.8, 131.1, 40.5, 36.9, 36.4, 25.5, 21.9; (d) 124.9, 52.1, 32.2, 25.7, 19.4, 17.6. IR (cm^{-1}): 2914, 2133, 1725, 1659, 1309. This substance was not stable to analysis by mass spectrometry.

*4.1.1.5. Cyclization of **9**.* To the ester **9** (10.1 g, 39.5 mmol) in a 1 L round bottom flask was added 550 mL of dry CH_2Cl_2 (passed through K_2CO_3).The $Rh_2(S)$-$PTPA_4$ (100 mg, 0.02 mol %) in 30 mL of dry CH_2Cl_2 was added[16] rapidly dropwise and the reaction was stirred overnight. The solvent was evaporated and the residual green oil was chromatographed to give cyclized products **4** and **10** (70:30, respectively) (8.5 g, 33.7 mmol, 85% yield). TLC R_f (10% MTBE/PE)=0.28. Moist crystals were observed upon standing. Recrystallization was performed by taking up 5.0 g of moist crystals in PE, then slowly evaporating by exposing to a steady air flow. Thin crystals are observed and the PE was removed from air flow and allowed to evaporate slowly overnight. The crystals that formed overnight were triturated with PE resulting in 1.5 g of a 16:1 ratio of diastereomers. Further crystallization yielded a total of 2.73 g (10.8 mmol, 18% yield from citronellal) of crystalline ester **4**. The spectroscopic data matched that reported.[1]

*4.1.2. 2-(2-Phenoxyethyl)-oxirane (**20**).* Bromide **19** (9.1 g, 40 mmol) and HMPA (8.96 g, 50 mmol) were combined in a 50 mL round bottom flask, then heated to 200 °C for 60 min. The solution was cooled to rt and partitioned between 15% MTBE/PE and H_2O. The combined organic extract was dried (Na_2SO_4) and concentrated.

The crude residue was dissolved in 100 mL of CH_2Cl_2 in a 250 mL round bottom flask. With stirring, 70% commercial MCPBA (15 g, 61 mmol) was added. The mixture was stirred overnight, then partitioned between CH_2Cl_2 and aqueous 5% NaOH+5% Na_2SO_3. The

organic layer was dried (Na_2SO_4) and concentrated. The crude residue was distilled bulb-to-bulb, (pot=80–100 °C, 1.0 mmHg) to give **20** (2.83 g, 43% from bromide) as a clear colorless oil. ^{1}H NMR ($CDCl_3$, δ): 7.32 (m, 2H), 6.98 (t, J=7.6 Hz, 2H), 6.94 (m, 1H), 4.14 (d, J=7.6 Hz, 2H), 3.19 (m, 1H), 2.86 (t, J=4.5 Hz, 1H), 2.62 (dd, J=2.8, 4.5 Hz, 1H), 2.13 (m, 1H), 1.98 (m, 1H). ^{13}C NMR ($CDCl_3$, δ): (u) 64.5, 47.2, 32.5; (d) 129.5, 120.9, 114.5, 49.8. IR (cm^{-1}): 3047, 2998, 2929, 2870, 1590, 1491. HRMS calcd for $C_{10}H_{16}NO_2$ (M+NH_4): 182.1181, found 182.1183.

*4.1.3. 6-Methoxyisochroman (**23**).* To 3-methoxyphenylacetic acid **21** in 50 mL THF containing 10 drops of MeOH was added $BH_3\cdot Me_2S$ in portions (foams!). After the reaction had subsided, MeOH (20 mL) was added cautiously (foams!). The solvent was removed on the rotary evaporator, then the MeOH addition and evaporation were repeated two more times. The residue was then distilled bulb-to-bulb (pot=100–120 °C, 1.0 mmHg) to give 5.47 g of crude 2-(3-methoxyphenyl)ethanol.

The crude 2-(3-methoxyphenyl)ethanol (4.12 g), chloromethyl methyl ether solution[17] (16.6 M, 12 mL), and diisopropylethylamine (11.4 g, 90 mmol) were combined in 40 mL of CH_2Cl_2. After 90 min, the reaction mixture was partitioned between CH_2Cl_2 and 5% aqueous HCl. The combined organic extracts were dried (Na_2SO_4) and concentrated.

The residue was taken up in 30 mL of 1,2-dicholorethane, *p*-toluenesulfonic acid (0.8 g) was added, and the mixture was heated to reflux overnight. Water (3 mL) was added, and reflux was continued for 1 h. The cooled reaction mixture was partitioned between CH_2Cl_2 and 5% aqueous HCl. The combined organic extracts were dried (Na_2SO_4) and concentrated, and the residue was chromatographed to give **23** (2.03 g, 81% yield from **21** based on alcohol not recovered) as a colorless oil, TLC R_f (1:1:8 CH_2Cl_2/MTBE/PE)=0.45. The spectroscopic data matched that reported.[11] This was preceded by a small quantity of **22**, not isolated, TLC R_f (1:1:8 CH_2Cl_2/MTBE/PE)=0.56, and followed by recovered alcohol, 1.10 g, TLC R_f (1:1:8 CH_2Cl_2/MTBE/PE)=0.12.

*4.1.4. 2-(2-Methyl-5-methoxyphenyl)ethanol (**24**).* $AlCl_3$ (3.5 g) was added cautiously with ice/water cooling to $LiAlH_4$ (0.50 g) in diethyl ether (20 mL). The chroman **23** (2.51 g) in a little ether was added, and a reflux condenser was attached. The reaction mixture was stirred in an oil bath (T=80 °C) overnight, during which time the ether evaporated. The resulting solid mass was partitioned between ethyl acetate and saturated aqueous sodium potassium tartrate. The combined organic extract was dried (Na_2SO_4) and concentrated, and the residue was chromatographed to give **24** (1.12 g, 44% yield from **23**) as a colorless oil, 1.10 g, TLC R_f (1:4 MTBE/CH_2Cl_2)=0.55. The spectroscopic data matched that reported.[11]

*4.1.5. 6-(5-Methoxy-2-methylphenyl)-1-phenoxy-3-hexanol (**26**).*

*4.1.5.1. Bromide **25**.* 5-Methoxy-2-methyl benzeneethanol **24** (593 mg, 3.57 mmol) was dissolved in 15 mL of CH_2Cl_2 in a 50 mL round bottom flask at 0 °C Ph_3P (1.31 g, 5.0 mmol) was added, and the mixture was stirred until it dissolved. *N*-Bromosuccinimide (801 mg, 4.5 mmol) was added in portions and the progress of the reaction was followed by TLC. After completion (15 min), the reaction was partitioned between CH_2Cl_2 and 5% aqueous NaOH+5% aqueous Na_2SO_3. The combined organic extract was dried (Na_2SO_4) and concentrated, and the remaining oil was distilled bulb-to-bulb from powdered CaH_2 (bp pot=80–100 °C, 1.0 mmHg) to obtain the bromide **25** (714 mg, 87%) as a clear faintly pink oil. ^{1}H NMR ($CDCl_3$, δ): 7.11 (d, J=9.0 Hz, 1H), 6.75 (m, 2H), 3.82 (s, 3H), 3.54 (t, J=7.6 Hz, 2H), 3.17 (t, J=7.6 Hz, 2H), 2.29 (s, 3H). ^{13}C NMR ($CDCl_3$, δ): (u) 157.9, 138.2, 128.1, 37.2, 31.6; (d) 131.3, 115.2, 112.3, 55.3, 18.3. IR (cm^{-1}): 2951, 2835, 1611, 1581, 1501, 1458. HRMS calcd for $C_{10}H_{17}BrNO$(M+NH_4): 246.0489, found 246.0493.

*4.1.5.2. Alcohol **26**.* Magnesium (120 mg, 5.0 mmol) was added to a dried 25 mL round bottom flask equipped with a stir bar and an N_2 adapter. The apparatus was rinsed three times with 5 mL of THF.THF (8 mL) was added followed by bromide **25** (590 mg, 2.6 mmol). An I_2 flake was added, turning the solution a deep yellow brown. The solution was heated to reflux and a color discharge was observed. After reflux subsided the solution was heated again in the same manner and allowed to subside and stir for 30 min. The solution was warmed to reflux one more time and then the solution was chilled to −30 °C. $CuBr\cdot Me_2S$ was added (dissolved in 1 mL of THF) and stirring was continued for 5 min. Epoxide **20** (580 mg, 3.50 mmol) was diluted in a few mL of THF and added to the Grignard solution. The cooling bath was removed and the solution was allowed to warm to rt. The solution was then diluted with 5% aqueous HCl and extracted with ethyl acetate. The organic extract was dried (Na_2SO_4) and concentrated. The organic extract was then removed in vacuo and the remaining oil was chromatographed to yield the phenoxy alcohol **26** (340 mg, 42% from bromide) as a clear pale yellow oil, TLC R_f (30% MTBE/PE)=0.30. ^{1}H NMR (CDCl3, δ): 7.31 (t, J=7.3 Hz, 2H), 7.08 (d, J=8.5 Hz, 1H), 6.99 (t, J=7.3 Hz, 1H), 6.93 (d, J=7.3 Hz, 2H), 6.75 (d, J=2.5 Hz, 1H), 6.69 (dd, J=2.5, 8.5 Hz, 1H), 4.17 (m, 2H), 3.96 (m, 1H), 3.81 (s, 3H), 2.63 (m, 2H), 2.26 (s, 3H), 1.96 (m, 2H), 1.81 (m, 1H), 1.64 (m, 2H). ^{13}C NMR ($CDCl_3$, δ): (u) 158.6, 157.8, 142.7, 128.1, 65.9, 37.4, 36.4, 33.5, 26.2; (d) 131.0, 129.5, 121.0, 114.5, 114.5, 111.1, 70.0, 55.3, 18.4. IR (cm^{-1}): 3410, 2927, 2870, 1598, 1498, 1467, 1297, 1246. HRMS calcd for $C_{20}H_{30}NO_3$ (M+NH_4): 332.2226, found 332.2231.

*4.1.6. 6-(5-Methoxy-2-methylphenyl)-1-hexen-3-one (**5**).* The phenoxy alcohol **26** (124 mg, 0.39 mmol) was dissolved in 5 mL of CH_3CN in a 25 mL round bottom flask. Periodic acid (136 mg, 0.6 mmol) was added followed by pyridinium chlorochromate (10 mg, 0.046 mmol). The mixture was stirred for 15 min. Flash silica (2 g) was added, and the solvent was evaporated. The crude product was chromatographed directly yielding 6-(5-methoxy-2-methylphenyl)-1-phenoxy-3 hexanone **5** (51 mg, 42%) as a colorless oil, TLC R_f (20% MTBE/PE)=0.41. ^{1}H NMR ($CDCl_3$, δ): 7.3 (m, 2H), 7.04 (d, J=8.19 Hz, 1H), 6.94 (t, J=7.17 Hz, 1H), 6.88 (d, J=8.53 Hz, 2H), 6.69 (d, J=2.73 Hz, 1H), 6.66 (dd, J=8.19, 2.73 Hz, 1H), 4.22 (t, J=6.14 Hz, 2H), 3.76 (s, 3H), 2.86 (t, J=6.14 Hz, 2H), 2.6 (m, 4H), 2.23 (s, 3H), 1.9 (m, 2H). ^{13}C NMR ($CDCl_3$, δ): (u) 208.3, 158.5, 157.7, 140.9, 128.0, 62.8, 42.8, 42.1, 32.6, 23.6, 18.3; (d) 130.9, 129.4, 120.9, 114.7, 114.4, 110.9, 55.2, 18.3. The spectroscopic data matched that reported.[1]

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Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.tet.2011.10.027.

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