JOC*Note*

De Novo Synthesis of (+)-Isofregenedol

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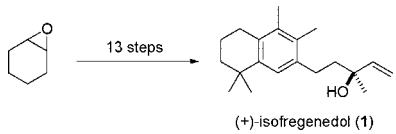
Received June 27, 2008



An efficient enantioselective synthesis of (+)-isofregenedol was achieved in 13 steps from commercially available cyclohexene oxide without the use of protecting groups. The tetrahydronaphthalenic core of isofregenedol was obtained via a gold(I)-catalyzed benzannulation recently developed in our laboratory.

In 1991, Niemeyer and co-workers isolated from the aerial parts of a Chilean flower, *Haplopappus parvifolius*, a novel diterpene, isofregenedol (**1**) (Scheme 1).[1] NMR spectroscopy revealed that isofregenedol (**1**) possesses a substituted tetrahydronaphthalene framework which is encountered in few naturally occurring products notably in fregenedane and isofregenedane diterpenoid family **1**−**3**.[2] Conversely, this scaffold is found in a number of medicinally important molecules.[3] On the basis of biogenetic hypotheses, it was first proposed that the absolute configuration at C13 was *R*. However, a synthesis of (+)-isofregenedol (**1**) from the cationic rearrangement of labdane diterpenes zamoranic acid (**4**) and sclareol (**5**) by Marcos and co-workers (Figure 1) established the absolute configuration at C13 as being *S*.[4]

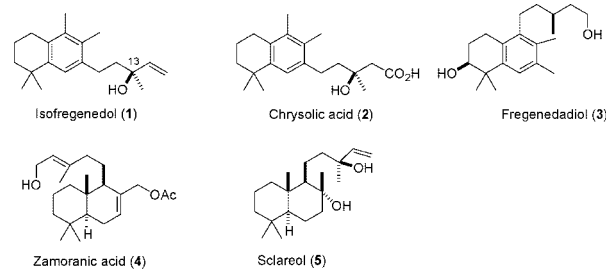
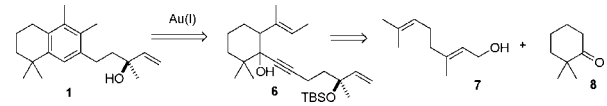
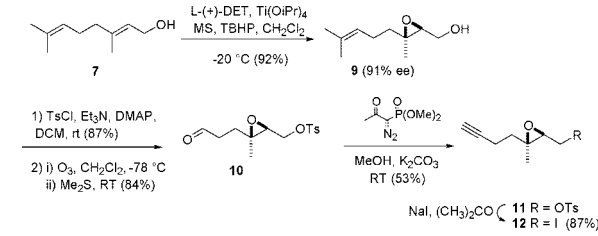


FIGURE 1. Structure of fregedane, isofregenedane, and labdane diterpenes.

SCHEME 1



SCHEME 2



Recently, we reported a novel gold(I)-catalyzed benzannulation of 3-hydroxy-1,5-enynes as an efficient method to synthesize substituted tetrahydronaphthalenes.[5] A cursory inspection of fregenedane and isofregenedane structures prompted us to utilize **1** as a testing ground for our new benzannulation method. Retrosynthetically, we envisioned that **1** could be directly synthesized from a gold(I)-catalyzed cyclization of **6** (Scheme 1). The latter could be quickly assembled from commercially available geraniol **7** and 2,2-dimethylcyclohexanone **8**. Herein, we reported a short and de novo synthesis of (+)-isofregenedol (**1**).

The synthesis began by the enantioselective Sharpless epoxidation of geraniol to give epoxide **9** in 92% yield (91% ee) (Scheme 2).[6] Tosylation of the primary alcohol followed by an ozonolysis afforded aldehyde **10** in 84% yield. The resulting aldehyde was then converted to the corresponding alkyne **11** in 53% yield by treatment with the modified Ohira reagent.[7] Refluxing tosylate **11** in acetone in the presence of sodium iodide gave **12** in 87% yield.

Treatment of **12** with zinc dust in acetic acid followed by protection of the resulting tertiary alcohol as a TBS ether

(1) Zdero, C.; Bohlmann, F.; Niemeyer, H. M. *Phytochemistry* **1991**, *30*, 3683.

(2) (a) Urones, J. G.; Marcos, I. S.; Basabe, P.; Garrido, N. M.; Jorge, A.; Moro, R. F.; Lithgow, A. M. *Tetrahedron* **1993**, *49*, 6079. (b) Urones, J. G.; Jorge, A.; Marcos, A. I.; Basabe, P.; Diez, D.; Garrido, N. M.; Lithgow, A. M.; Fonseca, M. O.; Rodilla, J. M. *Tetrahedron Lett.* **1996**, *37*, 1659. (c) Urones, J. G.; Jorge, A.; Marcos, A. I.; Basabe, P.; Laderas, M.; Diez, D.; Garrido, N. M.; Lithgow, A. M.; Fonseca, M. O.; Rodilla, J. M.; Barata, I. G. *Tetrahedron* **2003**, *59*, 2333.

(3) Here are few examples: (a) methionine aminopeptidase-2 reversible inhibitor: Sheppard, G. S.; Wang, J.; Kawai, M.; Fidanze, S. D.; BaMaung, N. Y.; Erickson, S. A.; Barnes, D. M.; Tedrow, J. S.; Kolaczkowski, L.; Vasudeva, A.; Park, D. C.; Wang, G. T.; Sanders, W. J.; Mantei, R. A.; Palazzo, F.; Tucker-Garcia, L.; Lou, P.; Zhang, Q.; Park, C. H.; Kim, K. H.; Petros, A.; Olejniczak, E.; Nettesheim, D.; Hajduk, P.; Henkin, J.; Lesniewski, R.; Davidsen, S. K.; Bell, R. L. *J. Med. Chem.* **2006**, *49*, 3832. (b) Glucocorticoid receptor agonist: Barker, M.; Clakers, M.; Copley, R.; Demaine, D. A.; Humphreys, D.; Inglis, G. G. A.; Johnson, M. J.; Jones, H. T.; Haase, M. V.; House, D.; Loiseau, R.; Lesley, N.; Pacquet, F.; Skone, P. A.; Shanahan, S. E.; Tape, D.; Vinader, V. M.; Washington, M.; Uings, I.; Upton, R.; McLay, I. M.; Macdonald, S. J. F. *J. Med. Chem.* **2006**, *49*, 4216. (c) Serotonin 5-HT$_7$ receptor agonist: Holmberg, P.; Sohn, D.; Leideborg, R.; Caldirola, P.; Zlatoidsky, P.; Hanson, S.; Mohell, N.; Rosqvist, S.; Nordvall, G.; Johansson, A. M.; Johansson, R. *J. Med. Chem.* **2004**, *47*, 3927.

(4) Marcos, I. S.; Laderas, M.; Diez, D.; Basabe, P.; Moro, R. F.; Garrido, N. M.; Urones, J. G. *Tetrahedron Lett.* **2003**, *44*, 5419.

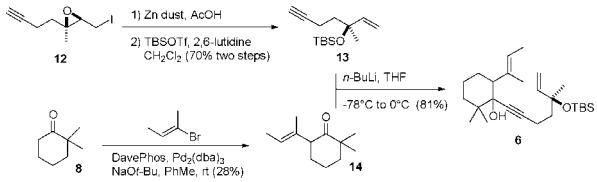
(5) (a) Grisé, C. M.; Barriault, L. *Org. Lett.* **2006**, *8*, 5905. (b) Grisé, C. M.; Rodrigue, R. M.; Barriault, L. *Tetrahedron* **2008**, *64*, 797.

(6) (a) Hanson, R. M.; Sharpless, B. K. *J. Org. Chem.* **1986**, *51*, 1922. (b) Taber, D. F.; Bui, G.; Chen, B. *J. Org. Chem.* **2001**, *66*, 3423.

(7) Roth, G. J.; Liepold, B.; Müller, S. G.; Bestmann, H. J. *Synthesis* **2004**, 59.

10.1021/jo801365z CCC: $40.75
Published on Web 08/13/2008

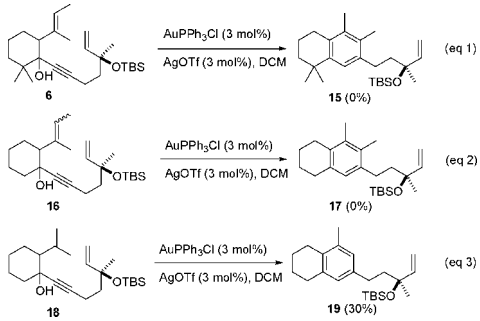
SCHEME 3



afforded alkyne **13** in 70% yield for two steps (Scheme 3). Having synthesized the alkyne fragment **13**, the next step was to couple it with ketone **14**. To this end, ketone **14** was prepared via a palladium-catalyzed vinylation of 2,2-dimethylcyclohexanone **8** using conditions developed by Buchwald and coworkers (Scheme 3).[8] Despite various attempts to optimize the reaction yield, the desired ketone **14** was isolated in 28% yield.[9] Deprotonation of **13** with *n*-BuLi in THF followed by the addition of ketone **14** produced alcohol **6** in 81%.

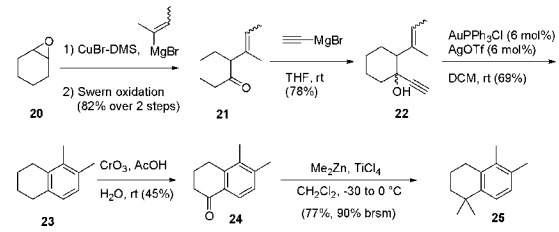
Having the desired 3-hydroxy-1,5-enyne **6** in our hands, the Au(I)-catalyzed benzannulation reaction was then attempted. To our disappointment, treatment of alcohol **6** under standard benzannulation conditions, $AuPPh_3Cl$ (5 mol %) and AgOTf (5 mol %), did not afford desired tetrahydronaphthalene **15** (eq 1). Rigorous inspection of the ^1H NMR spectrum of the crude reaction mixture showed no trace of the desired product. At first glance, one might suggest that the steric congestion which is exerted on the alkyne moiety by the neighboring *gem*-dimethyl group could probably prevent binding of the gold catalyst. In these circumstances, no benzannulation reaction would be possible and other background reactions could take place. To verify this hypothesis, 3-hydroxy-1,5-enynes **16** and **18** were exposed to benzannulation conditions. In the first case, no desired product was detected; again only degradation was observed by NMR of the crude mixture (eq 2). On the other hand, Au(I) benzannulation of **18** gave the desired product **19** in 30% yield (eq 3). One can suggest that the presence of an extra olefinic methyl group could, even in the absence of a *gem*-dimethyl substituent, prevent the benzannulation from occurring.

These results were a surprise for us since we reported Au(I)-catalyzed benzannulation of trisubstituted 3-hydroxy-1,5-enynes possessing an internal alkyne leading to the corresponding 1,2,3-substituted tetrahydronaphthalenes.[5] However, the inability to cyclize **6** and **16** combined with the poor yield to obtain ketone **14** precluded pursuing this approach.

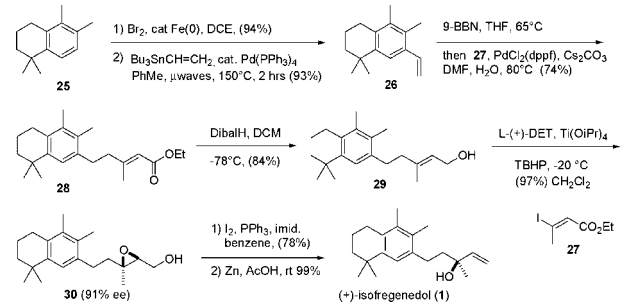


After a careful examination of various scenarios, we opted to install the *gem*-dimethyl group after the benzannulation process. The side chain containing the allylic alcohol could be grafted on the tetrahydronaphthalene framework via palladium-catalyzed cross-coupling reactions. The second approach commenced by a copper-mediated addition of 2-butenemagnesium bromide (mixture of *E* and *Z* isomers) to cyclohexene oxide **20** to give the corresponding alcohol. The latter underwent a Swern oxidation, yielding ketone **21** as a mixture of geometrical isomers in 82% yield over two steps (Scheme 4).[10] Addition of ethynyl magnesium bromide to ketone **21** provided **22** in 78% yield as a mixture of diastereomers (dr = 1:1). Gratifyingly, exposure of **22** to the standard benzannulation conditions gave the desired tetrahydronaphthalene **23** in 69% yield on a multigram scale. The *gem*-dimethyl unit was then installed via a benzylic oxidation with CrO_3 (45% yield) followed by treatment of the resulting ketone **24** with Me_2Zn in the presence of $TiCl_4$ to afford **25** in 77% yield.[11]

SCHEME 4



SCHEME 5



A regioselective bromination of tetrahydronaphthalene **25** using bromine and a catalytic amount of Fe(0) in dichloroethane gave the desired brominated compound in 94% yield (Scheme 5). The latter underwent a microwave-accelerated Stille cross-coupling reaction to afford styrene **26** in 93% yield.[12] The side chain was then elongated by the use of a Suzuki reaction. Treatment of **26** with 9-BBN followed by the addition of vinyl iodide **27** in the presence of $PdCl_2$(dppf) (5 mol %) and cesium carbonate in wet DMF gave **28** in 74% yield. Reduction of the ester group with Dibal-H led to the corresponding allylic alcohol **29**, which upon exposure to Sharpless epoxidation conditions provided epoxide **30** in 97% yield and 91% ee.[4] To complete the synthesis, alcohol **30** was converted to an iodide (I_2, PPh_3, imidazole, THF), and the latter was treated with Zn in acetic acid to yield synthetic (+)-isofregenedol (**1**) whose spectral data were identical to those reported in the literature.[1,4]

In summary, we achieved a de novo enantioselective synthesis of (+)-isofregenedol (**1**) in 13 steps. The synthesis took advantage of a Au(I)-catalyzed benzannulation to construct the tetrahydronaphthalene framework. The application of this

(8) Chieffi, A.; Kamikawa, K.; Åhman, J.; Fox, J. M.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 1897.
(9) We noted, with this particular substrate, that the reaction was particularly unreliable and often produced **14** along with inseparable by products.
(10) Sauer, E. L. O.; Barriault, L. *J. Am. Chem. Soc.* **2004**, *126*, 8569.
(11) Reetz, M. T.; Westermann, J.; Kyung, S.-H. *Chem. Ber.* **1985**, *118*, 1050.
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method to the synthesis of other rearranged labdanes is underway and will be reported in due course.

Experimental Section

5,6-Dimethyl-1,2,3,4-tetrahydronaphthalene (23). AgOTf (388 mg, 1.51 mmol) and Au(PPh$_3$)Cl (747 mg, 1.51 mmol) were transferred to a flame-dried flask containing CH_2Cl_2 (230 mL). Then, a solution of **22** (4.48 g, 25.15 mmol) in CH_2Cl_2 (20 mL) was added via cannula. After stirring at room temperature for 21 h, the reaction mixture was filtered through Celite. The fritted glass funnel was rinsed with Et_2O (50 mL), and the filtrate was concentrated. The residue was purified by silica gel column chromatography (hexanes) to afford 2.76 g of **23** as a colorless oil (69% yield): IR (neat) ν_{max} 2945, 2918, 2861 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (d, J = 7.7 Hz, 1 H), 6.85 (d, J = 7.7 Hz, 1 H), 2.75 (t, J = 6.2 Hz, 2 H), 2.66 (t, J = 6.4 Hz, 2 H), 2.26 (s, 3 H), 2.13 (s, 3 H), 1.86−1.78 (m, 2 H), 1.77−1.71 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.3 (C), 134.9 (C), 134.8 (C), 133.5 (C), 127.0 (CH), 126.5 (CH), 30.1 (CH_2), 27.3 (CH_2), 23.7 (CH_2), 22.8 (CH_2), 20.4 (CH_3), 14.8 (CH_3); HRMS m/z calcd for $C_{12}H_{16}$ 160.1252 (M$^+$), found 160.1267.

5,6-Dimethyl-3,4-dihydro-2*H*-naphthalenone (24). A 10% aqueous CrO_3 acetic solution (23.42 mmol, 22.2 mL in AcOH/H_2O) was added to a solution of **23** (750 mg, 4.68 mmol) in glacial AcOH (120 mL). The resulting dark brown reaction mixture was stirred at room temperature for 2.5 h. H_2O (200 mL) was added, and the aqueous layer was extracted with Et_2O (4 × 100 mL). Combined organic phases were washed with H_2O and $NaHCO_3$ (saturated), dried, and concentrated. The residue was purified by silica gel column chromatography (5% EtOAc/hexanes) to afford 370 mg of **24** as a pale yellow solid (45% yield): mp 67−68.5 °C; IR (neat) ν_{max} 2933, 2860, 1682, 1594 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, J = 8.0 Hz, 1 H), 7.08 (d, J = 8.0 Hz, 1 H), 2.87 (t, J = 6.2 Hz, 2 H), 2.60−2.57 (m, 2 H), 2.32 (s, 3 H), 2.20 (s, 3 H), 2.15−2.09 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.7 (C), 142.5 (C), 142.4 (C), 134.4 (C), 130.9 (C), 128.0 (CH), 124.5 (CH), 38.3 (CH_2), 26.9 (CH_2), 22.6 (CH_2), 21.1 (CH_3), 14.9 (CH_3); HRMS m/z calcd for $C_{12}H_{14}O$ 174.1045 (M$^+$), found 174.1044.

1,1,5,6-Tetramethyl-1,2,3,4-tetrahydronaphthalene (25). To a solution of freshly distilled $TiCl_4$ (625 L, 5.70 mmol) in CH_2Cl_2 (5 mL) at −30 °C was added Me_2Zn (5.7 mL of a 1.0 M solution in toluene, 5.70 mmol). The resulting orange mixture was stirred at that temperature for 10 min. A solution of **24** (450 mg, 2.58 mmol) in CH_2Cl_2 (2.2 mL) was then added dropwise via cannula. The dark red reaction mixture was slowly allowed to warm up to 0 °C over a period of about 2 h and was then poured onto ice water. The aqueous layer was separated from the organic layer and extracted with Et_2O (3 × 20 mL). Combined organic phases were washed with $NaHCO_3$ (saturated), dried, and concentrated. The residue was purified by silica gel column chromatography (hexanes then 10% EtOAc/hexanes) to afford 63 mg of **24** and 376 mg of **25** as a colorless oil (77% yield; 90% yield brsm): IR (neat) ν_{max} 2930, 2869, 1485, 1455 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, J = 8.0 Hz, 1 H), 6.99 (d, J = 8.0 Hz, 1 H), 2.65 (t, J = 6.5 Hz, 2 H), 2.26 (s, 3 H), 2.14 (s, 3 H), 1.87−1.81 (m, 2 H), 1.64−1.61 (m, 2 H), 1.29 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6 (C), 134.6 (C), 134.5 (C), 133.3 (C), 127.4 (CH), 123.9 (CH), 38.6 (CH_2), 33.9 (C), 32.1 (2 × CH_3), 28.4 (CH_2), 20.5 (CH_3), 19.7 (CH_2), 15.2 (CH_3); HRMS m/z calcd for $C_{14}H_{20}$ 188.1565 (M$^+$), found 188.1563.

1,1,5,6-Tetramethyl-7-vinyl-1,2,3,4-tetrahydronaphthalene (26). Step 1: To a mixture of **25** (479 mg, 2.54 mmol) and iron powder (28 mg, 0.50 mmol) in 1,2-dichloroethane (20 mL) at 0 °C was added Br_2 (5.60 mL of a 0.50 M solution in CH_2Cl_2, 2.80 mmol) dropwise. After stirring for 15 h at rt, cold water was added (10 mL). The aqueous mixture was extracted with Et_2O (3 × 20 mL). Combined organic phases were dried over anhydrous $MgSO_4$. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (hexanes) to afford 637 mg of the aryl bromide as a colorless oil (94% yield): IR (neat) ν_{max} 2968, 2930, 2869, 1554 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (s, 1 H), 2.57 (t, J = 6.5 Hz, 2 H), 2.36 (s, 3 H), 2.18 (s, 3 H), 1.83−1.78 (m, 2 H), 1.59−1.53 (m, 2 H), 1.25 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.3 (C), 136.6 (C), 133.9 (C), 132.6 (C), 128.2 (CH), 123.1 (C), 38.4 (CH_2), 33.9 (C), 31.9 (2xCH_3), 28.5 (CH_2), 19.935 (CH_3), 19.5 (CH_2), 16.6 (CH_3); HRMS m/z calcd for $C_{14}H_{19}Br$ 266.0670 (M$^+$), found 266.0680. Step 2: A stirred solution of the bromide (283 mg, 1.064 mmol), tributylvinyltin (560 μL, 1.916 mmol), Pd(PPh$_3$)$_4$ (98 mg, 0.085 mmol), and toluene (7 mL) in a microwave cell was deoxygenated by bubbling argon through it for 15 min. The reaction mixture was heated at 150 °C in the microwave oven for 2 h. After cooling to room temperature, the mixture was diluted with hexanes (25 mL) and washed with H_2O (20 mL), 10% aqueous NH_4OH (20 mL), and saturated aqueous NaCl (20 mL). The organic layer was dried and concentrated. The residue was purified by silica gel column chromatography (hexanes) to afford 211 mg of **26** as a pale yellow oil (93% yield): IR (neat) ν_{max} 3085, 2960, 2926, 2865, 1622 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (s, 1 H), 7.01 (dd, J = 17.3, 10.9 Hz, 1 H), 5.51 (dd, J = 17.3, 1.7 Hz, 1 H), 5.24 (dd, J = 10.9, 1.7 Hz, 1 H), 2.65 (t, J = 6.5 Hz, 2 H), 2.24 (s, 3 H), 2.15 (s, 3 H), 1.86−1.80 (m, 2 H), 1.64−1.61 (m, 2 H), 1.31 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3 (C), 136.8 (CH), 135.2 (C), 134.7 (C), 134.5 (C), 130.9 (C), 122.1 (CH), 114.9 (CH_2), 38.7 (CH_2), 33.9 (C), 32.0 (2xCH_3), 28.7 (CH_2), 16.7 (CH_2), 15.8 (CH_3), 15.6 (CH_3); HRMS m/z calcd for $C_{16}H_{22}$ 214.1721 (M$^+$), found 214.1730.

Ethyl (*E*)-3-methyl-5-(3,4,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)-pent-2-enoate (28). To 9-BBN (2.12 mL of a 0.5 M solution in THF, 1.06 mmol) was added a solution of **26** (75.6 mg, 0.35 mmol) in THF (750 μL) over 2 min. The mixture was heated under reflux for 1 h. In a separate flask, a solution of **27** (85 mg, 0.35 mmol) in DMF (500 μL) was added to a stirred mixture of Cs_2CO_3 (230 mg, 0.71 mmol), $PdCl_2$(dppf)·CH_2Cl_2 (29 mg, 10 mol %), Ph_3As (11 mg, 10 mol %), DMF (1 mL), and H_2O (230 μL, 36 molar equiv) The resulting mixture was stirred for 5 min. After addition of the above THF solution, the reaction mixture was heated at 80 °C for 2 h. After cooling down to room temperature, water was added (3 mL) and the mixture was extracted with Et_2O (3 × 5 mL). Combined organic layers were washed with NaCl (saturated), dried, and concentrated. The residue was purified by silica gel column chromatography (10 → 50% benzene/hexanes) to afford 86 mg of **28** as a white solid (74% yield): mp 73−76 °C; IR (neat) ν_{max} 2929, 2867, 1716, 1650 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (s, 1 H), 5.72 (d, J = 1.0 Hz, 1 H), 4.14 (q, J = 7.1 Hz, 2 H), 2.73−2.77 (m, 2 H), 2.61 (t, J = 6.5 Hz, 2 H), 2.31−2.35 (m, 2 H), 2.22 (d, J = 1.0 Hz, 3 H), 2.19 (s, 3 H), 2.13 (s, 3 H), 1.77−1.83 (m, 2 H), 1.53−1.60 (m, 2 H), 1.24−1.30 (m, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9 (C), 159.6 (C), 143.3 (C), 136.5 (C), 135.1 (C), 132.8 (C), 131.3 (C), 125.0 (CH), 115.7 (CH), 59.5 (CH_2), 42.3 (CH_2), 38.7 (CH_2), 33.8 (C), 32.8 (CH_2), 32.0 (2 × CH_3), 28.5 (CH_2), 19.7 (CH_2), 19.1 (CH_3), 15.7 (CH_3), 15.5 (CH_3), 14.4 (CH_3); HRMS m/z calcd for $C_{22}H_{32}O_2$ 328.2402 (M$^+$), found 328.2407.

(*E*)-3-Methyl-5-(3,4,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)-pent-2-enol (29). A solution of **28** (320 mg, 0.98 mmol) in CH_2Cl_2 (9.8 mL) was cooled to −78 °C, and DIBAH (3.0 mL of a 1.0 M solution in CH_2Cl_2, 3.00 mmol) was added dropwise over 5 min. After stirring at −78 °C for 1 h, a 5 M solution (4 mL) of AcOH in CH_2Cl_2 was added at −78 °C. The resulting mixture was then stirred at room temperature, and 25% aqueous sodium tartrate (5 mL) and H_2O (4 mL) were added. The mixture was extracted with CH_2Cl_2 (3 × 10 mL). Combined organic phases were washed with $NaHCO_3$ (saturated) and NaCl (saturated). The organic layer was dried and concentrated. The residue was purified by silica gel column chromatography (20% EtOAc/hexanes) to afford 236 mg of **29** as a pale yellow oil (84% yield): IR (neat) ν_{max} 3335 (br), 2927, 2866, 1668 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.00

(s, 1 H), 5.47 (td, $J = 6.9$, 1.2 Hz, 1 H), 4.16 (d, $J = 5.8$ Hz, 2 H), 2.73−2.70 (m, 2 H), 2.62 (t, $J = 6.5$ Hz, 2 H), 2.24−2.21 (m, 2 H), 2.19 (s, 3 H), 2.13 (s, 3 H), 1.83−1.78 (m, 2 H), 1.75 (s, 3 H), 1.60−1.58 (m, 2 H), 1.26 (s, 6 H), 1.14 (br, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.0 (C), 139.7 (C), 137.1 (C), 134.8 (C), 132.4 (C), 131.2 (C), 124.8 (CH), 123.3 (CH), 59.3 (CH_2), 40.7 (CH_2), 38.5 (CH_2), 33.6 (C), 33.0 (CH_2), 31.9 (2xCH_3), 28.3 (CH_2), 19.6 (CH_2), 16.4 (CH_3), 15.6 (CH_3), 15.3 (CH_3); HRMS *m*/*z* calcd for $C_{20}H_{30}O$ 286.2297 (M^+), found 286.2284.

(−)-{3-Methyl-3-[2-(3,4,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)ethyl]oxiranyl}methanol (30). To a suspension of activated 4 Å molecular sieves (50 mg) in cold (−10 °C) CH_2Cl_2 (3 mL) was added L-(+)-DET (23 mg, 0.11 mmol, in 1 mL of CH_2Cl_2), $Ti(O\textit{i}\text{-}Pr)_4$ (21 mg, 0.07 mmol, in 1 mL of CH_2Cl_2), and TBHP (250 μL, 1.38 mmol, 5.5 M in decane). After stirring for 10 min, the mixture was cooled to −20 °C, and a solution of **29** (265 mg, 0.93 mmol) in CH_2Cl_2 (4.5 mL) was added. After stirring for 3 h, the mixture was warmed to 0 °C and 2 mL of H_2O and 1 mL of 30% aqueous NaOH saturated with solid NaCl were added. After stirring for 10 min, the mixture was extracted with CH_2Cl_2 (3 × 10 mL). Combined organic phases were dried and concentrated. The residue was purified by silica gel column chromatography (25% EtOAc/hexanes) to afford 271 mg of **30** as a pale yellow oil (97% yield): $[\alpha]_D = -5$ (*c* 0.035, $CHCl_3$); IR (neat) ν_{max} 3438 (br), 2925, 1472, 1384 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.99 (s, 1 H), 3.81−3.77 (m, 1 H), 3.70−3.65 (m, 1 H), 2.95 (dd, $J = 6.6$, 4.4 Hz, 1 H), 2.76−2.64 (m, 2 H), 2.61 (t, $J = 6.5$ Hz, 2 H), 2.17 (s, 3 H), 2.12 (s, 3 H), 1.88−1.84 (m, 1 H), 1.83−1.78 (m, 2 H), 1.75−1.69 (m, 1 H), 1.60−1.58 (m, 3 H), 1.38 (s, 3 H), 1.26 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.1 (C), 136.3 (C), 135.0 (C), 132.6 (C), 131.2 (C), 124.8 (CH), 62.6 (CH), 61.2 (CH_2), 61.0 (C), 39.4 (CH_2), 38.5 (CH_2), 33.6 (C), 31.9 (2 × CH_3), 29.6 (CH_2), 28.3 (CH_2), 19.5 (CH_2), 16.8 (CH_3), 15.6 (CH_3), 15.3 (CH_3); HRMS *m*/*z* calcd for $C_{20}H_{30}O_2$ 302.2246 (M^+), found 302.2238; retention time = 6.82 min (minor enantiomer, 4.7%), 20.20 min (major enantiomer, 95.3%).

(+)-Isofregenedol (1). Step 1: To a solution of epoxyalcohol **30** (16.5 mg, 0.055 mmol) in benzene (1 mL) were added imidazole (20 mg, 0.294 mmol), PPh_3 (73 mg, 0.278 mmol), and I_2 (70 mg, 0.276 mmol). After stirring at 25 °C for 3 h, the reaction was diluted with Et_2O (10 mL) and saturated aqueous $NaHCO_3$ (5 mL). To this mixture was added saturated Na_2SO_3 (5 mL), and the mixture was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried and concentrated. The residue was purified by silica gel column chromatography (5% EtOAc/hexanes) to afford 16 mg of the corresponding iodide as a pale yellow oil (78% yield): $[\alpha]_D = +3$ (*c* 0.023, $CHCl_3$); IR (neat) ν_{max} 2927, 2865, 1457, 1384, 1174, 1143 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.00 (s, 1 H), 3.36 (dd, $J = 9.9$, 6.0 Hz, 1 H), 3.15 (dd, $J = 8.0$, 6.1 Hz, 1 H), 3.02 (dd, $J = 10.0$, 8.4 Hz, 1 H), 2.70 (t, $J = 8.6$ Hz, 2 H), 2.61 (t, $J = 6.4$ Hz, 2 H), 2.18 (s, 3 H), 2.13 (s, 3 H), 1.88−1.78 (m, 3 H), 1.73−1.66 (m, 1 H), 1.60−1.55 (m, 2 H), 1.37 (s, 3 H), 1.26 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.2 (C), 136.4 (C), 134.9 (C), 132.6 (C), 131.1 (C), 124.63 (CH), 64.1 (C), 62.4 (CH), 39.4 (CH_2), 38.5 (CH_2), 33.6 (C), 31.9 (2 × CH_3), 29.9 (CH_2), 28.3 (CH_2), 19.5 (CH_2), 15.8 (CH_3), 15.6 (CH_3), 15.3 (CH_3), 2.3 (CH_2); HRMS *m*/*z* calcd for $C_{20}H_{29}OI$ 412.1263 (M^+), found 412.1237. Step 2: To a solution of the iodide (94 mg, 0.23 mmol) in glacial AcOH (2.3 mL) was added zinc dust (196 mg, 3.00 mmol). After stirring for 1 h, wet Et_2O (10 mL) was added and the resulting mixture was filtered through a fritted glass funnel. The filtrate was washed successively with H_2O, Na_2SO_3 (saturated), $NaHCO_3$ (saturated), and NaCl (saturated), dried, and concentrated. The residue was purified by silica gel column chromatography (10% EtOAc/hexanes) to afford 64.5 mg of (+)-isofregenedol (**1**) as a white solid (99% yield): mp 75−77 °C; $[\alpha]_D = +21$ (*c* 0.015, $CHCl_3$), $[\alpha]_D = +20$ (*c* 0.83, $CHCl_3$) lit; IR (neat) ν_{max} 3408 (br), 2927, 2866, 1458, 1360, 1105 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.01 (s, 1 H), 5.99 (dd, $J = 17.3$, 10.8 Hz, 1 H), 5.27 (dd, $J = 17.3$, 1.1 Hz, 1 H), 5.12 (dd, $J = 10.8$, 1.1 Hz, 1 H), 2.68−2.58 (m, 4 H), 2.17 (s, 3 H), 2.12 (s, 3 H), 1.82−1.68 (m, 4 H), 1.60−1.57 (m, 2 H), 1.54 (s, 1 H), 1.34 (s, 3 H), 1.26 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.7 (CH), 143.1 (C), 137.4 (C), 134.9 (C), 132.3 (C), 131.3 (C), 124.9 (CH), 111.9 (CH_2), 73.3 (C), 43.3 (CH_2), 38.5 (CH_2), 33.6 (C), 31.9 (2 × CH_3), 28.9 (CH_2), 28.3 (CH_2), 27.9 (CH_3), 19.6 (CH_2), 15.5 (CH_3), 15.3 (CH_3); HRMS *m*/*z* calcd for $C_{20}H_{30}O$ 286.2297 (M^+), found 286.2296.

Acknowledgment. We thank the University of Ottawa, NSERC, Merck Frosst Canada, Merck and Co., Boehringer Ingelheim, and PREA for generous funding. M.R. thanks Le Fonds Québecois de la Recherche sur la Nature et les Technologies (FQRNT) for a postgraduate scholarship (B2).

Supporting Information Available: Detailed experimental procedures for **6**, **9**−**14**, and **19**−**22** and copies of ^{1}H and ^{13}C NMR for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

JO801365Z