Synthesis of L-669,262, a Potent HMG-CoA Reductase Inhibitor†

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Synthesis of L-669,262, isosimvastatin-3-one, has been achieved in seven steps from simvastatin (MK-733) and has been shown to be one of the most potent inhibitors of HMG-CoA reductase found to date. The synthesis of the 6-methyl homolog of simvastatin is also described.

Simvastatin (**1**) is a lactone prodrug whose ring-opened dihydroxy acid is a specific and potent inhibitor of HMG-CoA reductase, the rate-limiting enzyme in the *de novo* synthesis of cholesterol. When the sodium salt of **1** in its dihydroxy acid form was added to a growing culture of *Nocardia autotrophia* subsp. *amethystina*, one of the oxygenated compounds produced in low yield (ca. 10 mg as lactone from 400 g of **1**) by microbial transformation was the salt of isosimvastatin-3-one[1] (**8**). Because of its high inhibitory activity (about 6 to 7 times as active as compound **1**), a practical synthetic route to **8** was sought. This paper describes the synthesis of **8** from **1** and the 6-methyl homolog of **1** (**14**) from **8**.

The synthesis of **8** is shown in Scheme 1. The starting material **1** was converted to the 4a (*S*) hydroxy derivative **4** in three steps according to established procedures.[2] The 1,3-oxidative rearrangement of enol **4** to enone **5**[3] was accomplished in high yield with the use of pyridinium chlorochromate absorbed on alumina. Conversion of enone **5** to silyl enol ether **6** was accomplished under normal conditions followed by a Saegusa oxidation[4] to give dienone **7** in high yield. Completion of this synthetic route was accomplished by simply treating **7** with acetic acid-buffered tetrabutylammonuim fluoride[5] in tetrahydrofuran at 50 °C to afford **8** in high yield.

However, because of a number of problems attendent with this sequence, namely the use of toxic tributyltin hydride, the need to use an inert atmosphere with anhydrous conditions, and particularly the need for a stoichiometric amount of palladium, a shorter and simpler method was sought.

Scheme 2 delineates a high-yield three step transformation of chlorohydrin **3** to dienone **8**. Initial 1,3-oxidative rearrangement to enone **9** was followed by aqueous hydrofluoric acid desilylation to enone **10**. The ultimate and key step in the sequence was a sodium iodide mediated dehydrochlorination in 2-butanone[6] to give **8** in good yield. The mechanism of this dehydrohalogenation has not been investigated in this instance but may be caused by an initial S_N2 displacement of chloride followed by a trans elimination of HI with iodide (present in excess in the reaction medium) acting as an "external" base. Alternative procedures and modifications were examined to effect this dehydrochlorination but were found to be less efficient. The use of lithium bromide–lithium carbonate in dimethylformamide[7] at 150 °C gave a complex mixture as did heating **10** in collidine at 170 °C for 4 h.[6] Replacement of 2-butanone with acetonitrile resulted in no reaction while use of dimethylformamide or 3-pentanone gave a more complex product mixture.

A methylmagnesium bromide conjugate addition to dienone **7** gave the 6,6 dimethyl adduct **11** in good yield (Scheme 3). Cerium(III) chloride mediated borohydride reduction[8] gave desired enol **12** in moderate yield as the only isolable product.[9] In the absence of the cerium(III) chloride, only a 1:1 mixture of enol **12** and starting enone **11** was formed after 2 h at −20 °C. Desilylation by aqueous hydrofluoric acid at 50 °C was accompanied by an allylic dehydration to yield diene **13**. An identical deprotection of enone **11** gave enone **14**. When diene **13** and enone **14** were evaluated as their ring-opened sodium dihydroxy carboxylate forms for their ability to inhibit solubilized partially purified rat liver HMG-CoA reductase, they were 75 and 100%, respectively, as effective as simvastatin.

The synthetic routes described herein constitute efficient procedures for the preparation of dien-3-one **8** and the 6-methyl homolog of simvastatin (**13**). This methodology can also be applied to the synthesis of other 6-alkyl adducts of **8**.

Experimental Section

Capillary melting points are uncorrected. Elemental analyses were determined with a Perkin-Elmer Model 240 elemental analyzer. ^1H NMR spectra were recorded in $CDCl_3$ at 300 MHz. TLC analyses were conducted on Fisher silica gel 60ÅMK6F with spots detected by UV or PMA solution. HPLC analyses were performed employing a μ-Bondapak C-18, 3.9 × 300 mm column with a gradient from 95% of 0.1% aqueous TFA–acetonitrile to 5% of 0.1% aqueous TFA–acetonitrile over 25 min at room temperature.

6(*R*)-[2-[8(*S*)-((2,2-Dimethylbutyryl)oxy)-2(*S*),6(*R*)-dimethyl-1,2,6,7,8,8a(*R*)-hexahydronaphth-1(*S*)-yl]ethyl]-4(*R*)-((*tert*-butyldimethylsilyl)oxy)-3,4,5,6-tetrahydro-2*H*-pyran-2-one (2). *tert*-Butyldimethylsilyl chloride (8 g, 52 mmol) was added to a stirred solution of **1** (20 g, 48 mmol) and imidazole (6.8 g. 0.1 mol) in DMF (150 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 5 min and then warmed to room temperature and stirred for 5 h. TLC analysis of an aliquot indicated that the reaction was complete, R_f = 0.66 (hexane/ethyl acetate, 2:1 v:v). The reaction mixture was

† Dedicated to the memory of Dr. Ta-Jyh Lee.

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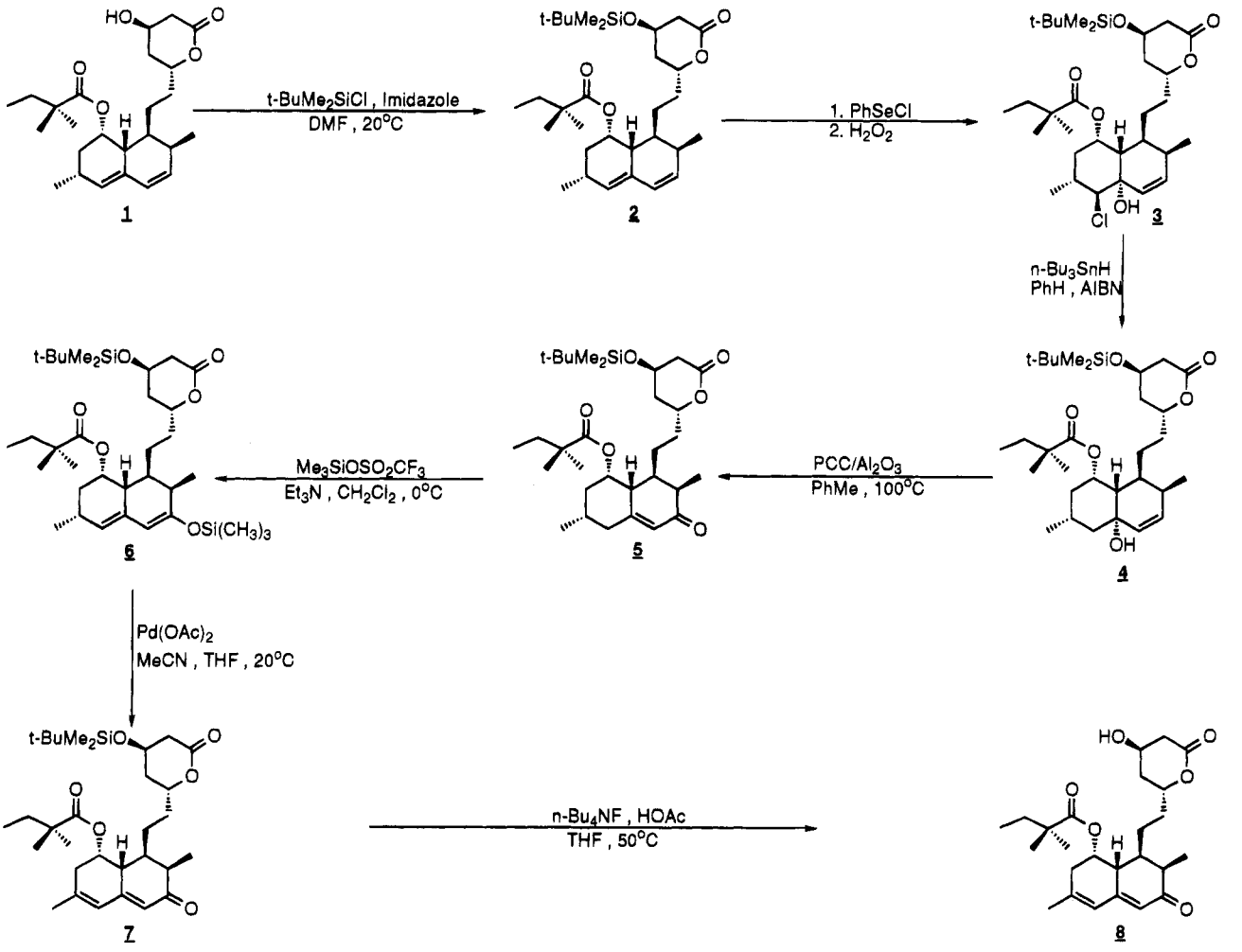
(9) The stereochemistry of the alcohol at **3** was determined earlier using these conditions on the reduction of **8**: Stokker, G. E. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1767.

0022-3263/94/1959-5983$04.50/0

Scheme 1



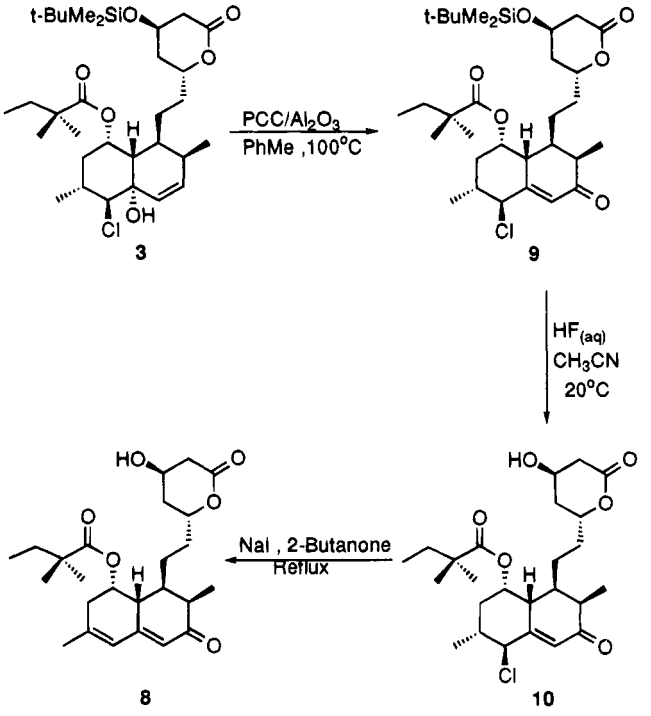
poured into cold water and extracted with ether. The ethereal extract was washed with dilute hydrochloric acid, water, and 5% sodium bicarbonate solution. After drying over $MgSO_4$, the organic extract was filtered and the filtrate was concentrated *in vacuo* to afford the desired product as a colorless, viscous oil (25.2 g, 100%, 48 mmol): NMR δ 0.84 (3 H, t, J = 7 Hz), 0.89 (3 H, d, J = 7 Hz), 0.90 (9 H, s), 1.09 (3 H, d, J = 7 Hz), 1.11 (3 H, s), 1.12 (3 H, s), 4.30 (H, m), 4.60 (H, m), 5.33 (H, m), 5.51 (H, m), 5.77 (H, dd, J = 10, 6 Hz), 5.98 (H, d, J = 10 Hz).

6(*R*)-[2-[5(*S*)-Chloro-4a(*S*)-hydroxy-8(*S*)-((2,2-dimethylbutyryl)oxy)-2(*S*),6(*R*)-dimethyl-1,2,4a,5,6,7,8,8a(*S*)-octahydronaphth-1(*S*)-yl]ethyl]-4(*R*)-((*tert*-butyldimethylsilyl)oxy)-3,4,5,6-tetrahydro-2*H*-pyran-2-one (3). A solution of phenylselenyl chloride (10 g, 52 mmol) in methylene chloride (50 mL) was added dropwise to a stirred solution of compound **2** (25.2 g, 48 mmol) in methylene chloride (350 mL) cooled in a dry ice/2-propanol bath (−78 °C). The resulting mixture was stirred at −78 °C for 20 min, poured into cold water (200 mL), and extracted with ether twice (400 mL, then 100 mL). The combined extracts were dried ($MgSO_4$), filtered, and concentrated to afford an oily residue which was dissolved in tetrahydrofuran (300 mL). This solution was chilled in an ice bath (0 °C), and 30% hydrogen peroxide (15 mL) was added. The resulting mixture was stirred at 0 °C for 5 min and then warmed to room temperature, with stirring continuing for 1 h. The reaction mixture was poured into cold water and extracted with chloroform three times (400 mL, then 2 × 100 mL). The combined extracts were dried ($MgSO_4$), filtered, and concentrated to yield a residue which was purified by flash chromatography on a silica gel column. Elution with hexane/ethyl acetate (5:1 v:v) removed the impurities.[10] Further elution with hexane/ethyl acetate (4:1 v:v) provided the chlorohydrin as a pale yellow gum which later solidified on standing (19.5 g, 33.3 mmol, 70%): mp 117−118 °C, R_f = 0.53 (hexane/ethyl acetate, 2:1 v:v); NMR δ 0.075 (3 H, s), 0.08 (3 H, s), 0.85 (3 H, t, J = 7Hz), 0.88 (9 H, s), 0.89 (3 H, d, J = 7Hz), 1.15 (3 H, s), 1.16 (3 H, s), 1.32 (3 H, d, J = 7 Hz), 1.58 (2 H, q, J = 7 Hz), 3.39 (H, s), 4.05 (H, bs), 4.30 (H, m), 4.60 (H, m), 5.32 (H, m), 5.59 (H, d, J = 11 Hz), 5.79 (H, dd, J = 11, 6 Hz). Anal. Calcd for $C_{31}H_{53}C10_6Si$: C, 63.61; H, 9.13. Found: C, 63,80; H, 9.04.

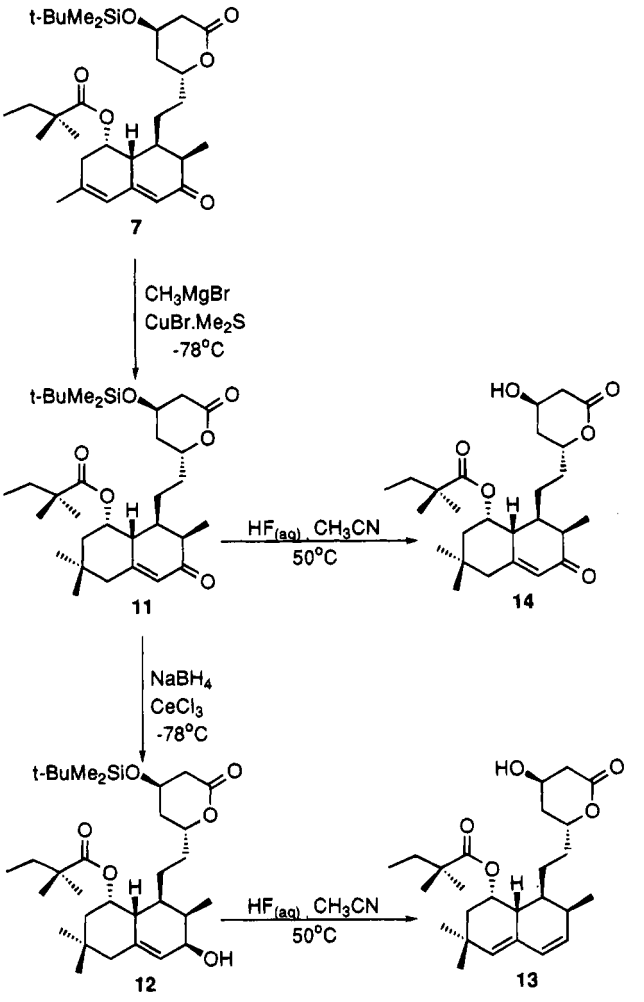
6(*R*)-[2-[4a(*S*)-Hydroxy-8(*S*)-((2,2-didimethylbutyryl)-oxy)-2(*S*),6(*R*)-dimethyl-1,2,4a,5,6,7,8,8a(*S*)-octahydronaphth-1(*S*)-yl]ethyl]-4(*R*)-((*tert*-butyldimethylsilyl)-oxy)-3,4,5,6-tetrahydro-2*H*-pyran-2-one (4). Tributyltin hydride (7.06 mL, 26.25 mmol) and AIBN (0.82 g, 5.0 mmol) were added to a magnetically stirred solution of chlorohydrin 3 (8.78 g, 15 mmol) in benzene (100 mL). The resulting solution was refluxed for 2 h, cooled, and concentrated *in vacuo* to a viscous yellow oil which was stirred with petroleum ether (200 mL) at −15 °C (ice/acetone bath) to provide 4 as a fluffy, colorless solid (6.9 g, mp 97−99 °C). The filtrate was extracted with acetonitrile (4 × 50 mL) to remove all of the product contained in the petroleum ether. The acetonitrile extracts were combined and concentrated to a colorless oil which was purified by flash chromatography on a silica gel column. Elution with ethyl acetate/hexane (1:3 v:v) gave a colorless solid (1.0 g) which was stirred in petroleum ether (25 mL) at 0 °C to remove some tin residues. The mixture was filtered to provide the enol 4 (0.71 g; total yield = 7.6 g, 13.8 mmol, 92%) as a colorless solid, mp 103−104 °C: NMR δ 0.07 (3 H,

(10) The major component of the impurities was identified as the 3,4-β-epoxide ($CDCl_3$) δ 0.09 (6 H, s), 0.84 (3 H, t, J = 7 Hz), 0.88 (3 H, d, J = 7 Hz), 0.90 (9 H, s), 1.13 (3 H, d, J = 7 Hz), 1.18 (6 H, s), 4.30 (H, m), 4.34 (H, m), 4.43 (H, s), 4.61 (H, m), 5.40 (H, bs), 6.00 (H, dd, J = 6, 2 Hz).

Scheme 2



Scheme 3



s), 0.08 (3 H, s), 0.88 (9 H, s), 1.15 (3 H, s), 1.16 (3 H, s), 1.20 (3 H, d, J = 7 Hz), 2.78 (H, s), 4.28 (H, m), 4.58 (H, m), 5.30 (H, m), 5.58 (H, d, J = 10 Hz), 5.67 (H, dd, J = 10, 5 Hz). Anal. Calcd for $C_{31}H_{54}O_6Si$: C, 67.59; H, 9.88. Found: C, 67.20; H, 9.99.

6(*R*)-[2-[3-Oxo-8(*S*)-((2,2-dimethylbutyryl)oxy)-2(*S*),6(*R*)-dimethyl-1,2,3,5,6,7,8,8a(*R*)-octahydronaphth-1(*S*)-yl]ethyl]-4(*R*)-((*tert*-butyldimethylsilyl)oxy)-3,4,5,6-tetrahydro-2*H*-pyran-2-one (5). Enol **4** (7.2 g, 12 mmol) was combined with 60 mL of toluene and 25 g of pyridinium chlorochromate/aluminum oxide.[11] The mixture was stirred and heated on a steam bath for 20 min, after which time TLC showed the reaction to be complete. The mixture was cooled and filtered, and the solids were washed with warm toluene (4 × 50 mL). The solvent was evaporated to yield **5** as an amber gum (6.6 g, ~100%) (a colorless product may be obtained by dilution with toluene (100 mL) after cooling, filtering mixture through a 2 cm pad of silica followed by washing with hexane/ethyl acetate (~300 mL, 2:1/v:v) with no loss in yield). R_f = 0.23 vs 0.52 for alcohol **4** (hexane/ethyl acetate; 2:1 v:v): NMR δ 0.073 (3 H, s), 0.079 (3 H, s), 0.804 (3 H, t, J = 7 Hz), 0.881 (9 H, s), 1.026 (3 H, d, J = 6 Hz), 1.036 (3 H, d, J = 6 Hz), 1.10 (6 H, bs), 2.55–2.66 (3 H, m), 4.276 (H, m), 4.588 (H, m), 5.42 (H, m), 5.91 (H, d, J = 1.5 Hz).

6(*R*)-[2-[8(*S*)-((2,2-Dimethylbutyryl)oxy)-2(*S*),6(*R*)-dimethyl-3-((trimethylsilyl)oxy)-1,2,6,7,8,8a(*R*)-hexahydronaphth-1(*S*)-yl]ethyl]-4(*R*)-(*tert*-butyldimethylsilyl)-oxy)-3,4,5,6-tetrahydro-2*H*-pyran-2-one (6). The amber gum **5** (6.5 g, ~11.8 mmol) was dissolved in methylene chloride and cooled to 0 °C under argon. The solution was treated with triethylamine (7.2 mL, 50 mmol) followed by slow addition of trimethylsilyl trifluoromethanesulfonate (5.4 mL, 28 mmol) while maintaining the temperature below 3 °C. After stirring at 0 °C for 15 min (TLC showed the reaction to be complete by 5 min. R_f = 0.75 vs 0.23 for enone **5** (hexane/ethyl acetate, 2:1 v:v)), the dark solution was diluted with methylene chloride (100 mL), washed with satd sodium bicarbonate (100 mL), and dried, and the solvent was evaporated to give crude **6** (7.4 g, ~100%).

6(*R*)-[2-[8(*S*)-((2,2-Dimethylbutyryl)oxy)-2(*S*),6-dimethyl-3-oxo-1,2,3,7,8,8a(*R*)-hexahydronaphth-1(*S*)-yl]ethyl]-4(*R*)-(*tert*-butyldimethylsilyl)oxy)-3,4,5,6-tetrahydro-2*H*-pyran-2-one (7). The dark amber-colored silyl enol ether **6** (7.2 g, ~11.6 mmol) was dissolved in acetonitrile/tetrahydrofuran (60 mL, 5:1 v:v). Palladium(II) acetate (3.0 g, 13.0 mmol) was added to the mixture, and the mixture was stirred at room temperature for 22 h, at which time TLC showed the reaction to be complete. (Reaction was nearly complete in 5 h, however, after 20 h a mirror of Pd(0) forms on the flask and allows for recovery of the palladium (~1.1 g)). R_f = 0.18 vs 0.75 for silyl ether **6** (hexane/ethyl acetate, 2:1 v:v)). The mixture was filtered through a 3 cm pad of silica gel and then washed with ethyl acetate (150 mL), and the solvent was evaporated to afford **7** as a dark brown gum which may be transformed to a pale amber-yellow by redissolving in ethyl acetate (8 mL) and filtration through a 3 cm pad of silica gel, washing with hexane/ethyl acetate (5.9 g, ~94%): NMR δ 0.076 (3 H, s), 0.082 (3 H, s), 0.752 (3 H, t, J = 7 Hz), 0.883 (9 H, s), 1.033 (3 H, d, J = 7 Hz), 1.054 (3 H, s), 1.065 (3 H, s), 1.864 (3 H, s), 4.295 (H, m), 4.606 (H, m), 5.408 (H, m), 5.781 (H, bs), 6.136 (H, bs).

6(*R*)-[2-[8(*S*)-((2,2-Dimethylbutyryl)oxy)-2(*S*),6-dimethyl-3-oxo-1,2,3,7,8,8a(*R*)-hexahydronaphth-1(S)-yl]ethyl]-4(*R*)-hydroxy-3,4,5,6-tetrahydro-2*H*-furan-one (8). The dark brown gum **7** (5.8 g, ~10.6 mmol) was dissolved in tetrahydrofuran, and to this was added a mixture of tetra-*n*-butylammonium fluoride[12] (1 M in THF, 30 mL) and acetic acid (5.6 mL). The combined mixture was stirred at 50 °C for 4 h,

(11) The use of PCC was inferior in both yield and rate of reaction. For preparation of PCC absorbed on alumina, see: Cheng, Y.-S.; Liu, W.-L.; Chen, S.-H. *Synthesis* **1980**, 223.

(12) Cleavage may also be affected with CH_3CN–HF (49% aq) (95:5 v:v); reaction complete at 20 °C in 1–1.25 h. However, one should blanket the silyl ether with argon before dissolving in CH_3CN, otherwise a clear brown solution forms instead of a light yellow one. In any event, the brown color was removed by washing ether solution of the reaction mixture with saturated $NaHCO_3$.

cooled, diluted with ethyl ether (400 mL), washed with water (5 × 100 mL), and dried, and the solvent was evaporated. The residue solidified to a brown mass. The brown mass was dissolved in ethyl acetate (15 mL) and then poured on a 3 × 6 cm pad of silica gel followed by ethyl acetate washings (2 × 5 mL). The silica was then eluted with ethyl acetate/hexane (100 mL; 1:1 v:v) followed by ethyl acetate/hexane (100 mL; 3:1 v:v) and finally by ethyl acetate (250 mL). R_f = 0.14 (hexane/ethyl acetate, 1:2 v:v), mp 160–174 °C. This filtered product was then recrystallized from ethyl acetate (30 mL)–hexane (30 mL). After drying at 60 °C for 2 h under a vacuum, the dienone **8** (2.84 g, 6.57 mmol) was obtained with mp 179–180 °C: NMR δ 0.758 (3 H, t, J = 7.4 Hz), 1.035 (3 H, d, J = 7.4 Hz), 1.063 (3 H, s), 1.069 (3 H, s), 1.867 (3 H, s), 2.63 (H, ddd, J = 1.47, 3.64, 12.6 Hz), 2.749 (H, dd, J = 4.94, 12.6 Hz), 4.398 (H, m), 4.645 (H, m), 5.424 (H, m), 5.781 (H, bs), 6.138 (H, bs). Anal. Calcd for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.73; H, 8.54.

6(*R*)-[2-[5(*S*)-Chloro-3-oxo-8(*S*)-((2,2-dimethylbutyryl)-oxy)-2(*S*),6(*R*)-dimethyl-1,2,3,5,6,7,8,8a(*R*)-octahydronaphth-1(*S*)-yl]ethyl]-4(*R*)-((*tert*-butyldimethylsilyl)-oxy)-3,4,5,6-tetrahydro-2*H*-pyran-2-one (9). Chlorohydrin **3** (3.25 g, 5.4 mmol) was combined with 50 mL of toluene and pyridinium chlorochromate/aluminum oxide (20 g). The mixture was stirred and heated on a steam bath for 8 h. The mixture was cooled and filtered, and the solids were washed with warm toluene (4 × 5 mL). The solvent was evaporated to yield **9** as an amber gum (3 g, 95%), R_f = 0.47 for **9** vs 0.53 for alcohol **3** (hexane/ethyl acetate; 2:1 v:v): NMR δ 0.069 (3 H, s), 0.076 (3 H, s), 0.804 (3 H, t, J = 7 Hz), 0.879 (9 H, s), 1.049 (3 H, d, J = 7 Hz), 1.094 (3 H, s), 1.099 (3 H, s), 1.135 (3 H, d, J = 7 Hz), 2.56–2.60 (H, m), 2.70 (H, m), 2.92 (H, m), 4.288 (H, m), 4.505 (H, bs), 4.584 (H, m), 5.43 (H, m), 6.06 (H, d, J = ~1 Hz); high-resolution MS calcd for $C_{31}H_{52}ClO_6Si$ (M + H)$^+$ 583.3221, found 583.3232.

6(*R*)-[2-[5(*S*)-Chloro-8(*S*)-((2,2-dimethylbutyryl)oxy)-2(*S*),6(*R*)-dimethyl-1,2,3,5,6,7,8,8a(*R*)-octahydronaphth-1(*S*)-yl]ethyl]-4(*R*)-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran-2-one (10). The amber gum **9** (1.92 g 3.3 mmol) was dissolved in acetonitrile (20 mL). After cooling the solution to ~5 °C, 49% aqueous hydrofluoric acid (1 mL) was added and the nearly colorless solution was stirred at 20 °C for 1.5 h. The reaction mixture was diluted with ether (150 mL), washed with satd sodium bicarbonate solution (3 × 25 mL), dried ($MgSO_4$), and evaporated: TLC, R_f = 0.32 for **9** vs 0.13 for dienone **8** (hexane/ethyl acetate; 1:2 v:v); NMR δ 0.820 (3 H, t, J = 7 Hz), 1.050 (3 H, d, J = 7 Hz), 1.110 (6 H, s), 1.150 (3 H, d, J = 7 Hz), 2.3–2.5 (2 H, m), 2.63 (H, ddd, J = 1.47, 3.64, 12.6 Hz), 2.749 (H, dd, J = 4.94, 12.6 Hz), 2.93 (H, m), 4.385 (H, m), 4.625 (H, m), 5.45 (H, m), 6.060 (H, d, J = 1 Hz).

8 from 10. Chlorohydrin **10** was dissolved in 2-butanone (25 mL), sodium iodide (1.0 g, 6.7 mmol) was added, the system was purged with argon, and the mixture stirred for 48 h. Additional sodium iodide (1.0 g) was added, and the reaction was continued for an additional 24 h. The orange-brown mixture, was cooled, diluted with ethyl acetate (100 mL), and washed with dilute sodium sulfite to expel the color of iodine (TLC showed only a trace of **10** present). The colorless organic layer was then washed with water (2 × 100 mL), dried ($MgSO_4$), and evaporated to yield crude **8** (1.2 g), which upon crystallization from ethanol (4 mL) and hexane (6 mL) gave **8** (1.0 g, 2.3 mmol), mp 175–177 °C, 70% yield from chloro enone **9**.

6(*R*)-[2-[8(*S*)-((2,2-Dimethylbutyryl)oxy)-2(*S*),6,6-trimethyl-3-oxo-1,2,3,5,6,7,8,8a(*R*)-octahydronaphth-1(*S*)-yl]-ethyl]-4(*R*)-((*tert*-butyldimethylsilyl)oxy)-3,4,5,6-tetrahydro-2*H*-pyran-2-one (11). Methyl magnesium bromide (1.4 M in tetrahydrofuran, 1.1 mL, 1.54 mmol) was added to a suspension of cuprous bromide–dimethyl sulfide (150 mg, 0.73 mmol) in dry tetrahydrofuran (10 mL) at −20 °C under argon. After 15 min, the clear faint tan solution was cooled to −78 °C and treated with a cold (−60 °C) solution of dienone **7** (400 mg, 0.73 mmol) and boron trifluoride etherate (300 μL, 2.2 mmol) in dry tetrahydrofuran (5 mL). After the yellow reaction mixture was stirred at −78 °C for 15 min, the flask was placed in a cooling bath at −20 °C and stirring was continued for 1 ½ h. The now nearly colorless mixture was quenched with saturated ammonium chloride solution and extracted into ether. The ether was dried and evaporated, and the residue was purified by flash chromatography on a silica gel column. Elution with hexane/ethyl acetate (4:1 v:v) provided enone **11** (283 mg, 0.503 mmol, 69%), mp 102–104 °C, R_f = 0.23 vs 0.18 for dienone **7** (hexane/ethyl acetate, 2:1 v:v): NMR δ 0.066 (3 H, s), 0.075 (3 H, s), 0.803 (3 H, t, J = 7 Hz), 0.877 (9 H, s), 0.983 (3 H, s), 1.015 (3 H, d, J = 7 Hz), 1.027 (3 H, s), 1.097 (3 H, s), 1.105 (3 H, s), 4.286 (H, m), 4.585 (H, m), 5.426 (H, m), 5.886 (H, m). Anal. Calcd for $C_{32}H_{54}O_6Si$: C, 68.29; H, 9.67. Found: C, 68.51; H, 9.58.

6(*R*)-[2-[3(*R*)-Hydroxy-8(*S*)-((2,2-dimethylbutyryl)oxy)-2(*S*),6,6-trimethyl-1,2,3,5,6,7,8,8a(*R*)-octahydronaphth-1(*S*)-yl]ethyl]-4(R)-((*tert*-butyldimethylsilyl)oxy)-3,4,5,6-tetrahydro-2*H*-pyran-2-one (12). Sodium borohydride (11 mg, 0.28 mmol) was added to a cold (−78 °C) solution of enone **11** (160 mg, 0.28 mmol) and ceric chloride heptahydrate (100 mg, 0.28 mmol) in methanol (10 mL). After 30 min, the reaction mixture was quenched with acetone (0.5 mL) and distributed between ethyl acetate and saturated ammonium chloride, dried, and evaporated. The residue was purified by flash chromatography on a silica gel column. Elution with hexane/ethyl acetate (2:1 v:v) provided enol **12** (89 mg, 0.158 mmol, 56% yield), R_f = 0.55 vs 0.63 for enone **11** (hexane/ethyl acetate, 1:1 v:v): NMR δ 0.065 (3 H, s), 0.075 (3 H, s), 0.743 (3 H, d, J = 7 Hz), 0.816 (3 H, t, J = 7Hz), 0.884 (9 H, s), 0.939 (3 H, s), 0.949 (3 H, s), 1.116 (3 H, s), 1.126 (3 H, s), 4.3 (2 H, m), 4.6 (H, m), 5.305 (H, m), 5.35 (H, s). Anal. Calcd for $C_{32}H_{56}O_6Si$: C, 68.04; H, 9.99. Found: C, 68.28; H, 9.92.

6(*R*)-[2-[8(*S*)-((2,2-Dimethylbutyryl)oxy)-2(*S*),6,6-trimethyl-1,2,6,7,8,8a(*R*)-hexahydronaphth-1(*S*)-yl]ethyl]-4(*R*)-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran-2-one (13). The enol (**12**, 74 mg, 0.13 mmol) was dissolved in acetonitrile (5 mL) and added to aqueous hydrofluoric acid (49%, 0.25 mL), and reaction mixture was stirred at 50 °C for 30 min. The reaction mixture was diluted with ethyl acetate, washed with saturated sodium bicarbonate, dried, and evaporated. The residue was purified by flash chromatography on a silica gel column. Elution with hexane/ethyl acetate (1:2 v:v) provided diene **13** (30 mg, 0.069 mmol, 53% yield), mp 100–110 °C, as an amorphous white solid: R_f = 0.39 (coincident with **1**) (hexane/ethyl acetate, 1:2 v:v); HPLC t_R 14.17 min vs 13.70 min for **1**; NMR δ 0.829 (3 H, t, J = 7 Hz), 0.889 (3 H, d, J = 7 Hz), 1.018 (3 H, s), 1.054 (3 H, s), 1.123 (3 H, s), 1.131 (3 H, s), 2.63 (H, ddd, J = 1.47, 3.64, 12.6 Hz), 2.745 (H, dd, J = 4.94, 12.6 Hz), 4.376 (H, m), 4.618 (H, m), 5.339 (2 H, m), 5.779 (H, dd, J = 6.6, 10.5 Hz), 5.969 (H, d, J = 10.5 Hz); High-resolution MS calcd for $C_{26}H_{41}O_5$ (M + H)$^+$ 433.2954, found 433.2948. Anal. Calcd for $C_{26}H_{40}O_5$: C, 72.19; H, 9.32. Found: C, 72.71; H, 9.58.

6(*R*)-[2-[8(*S*)-((2,2-Dimethylbutyryl)oxy)-2(*S*),6,6-trimethyl-3-oxo-1,2,3,5,6,7,8,8a(*R*)-octahydronaphth-1(*S*)-yl]-ethyl]-4(*R*)-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran-2-one (14). The enone (**11**, 95 mg, 0.165 mmol) was treated identically to enol **12** to give enone **14** (65 mg, 0.145 mmol, 88% yield), mp 158-161 °C, as an amorphous white solid: R_f = 0.12 vs 0.39 for diene **13** (hexane/ethyl acetate, 1:2 v:v); HPLC t_R 11.68 min vs 10.85 min for **8**; NMR δ 0.808 (3 H, t, J = 7 Hz), 0.991 (3 H, s), 1.015 (3 H, d, J = 7 Hz), 1.027 (3 H, s), 1.101 (3 H, s), 1.106 (3 H, s), 2.64 (H, ddd, J = 1.5, 3.6, 12.6 Hz), 2.74 (H, dd, J = 4.9, 12.6 Hz), 4.377 (H, m), 4.62 (H, m), 5.445 (H, m), 5.887 (H, s). Anal. Calcd for $C_{26}H_{40}O_6$: C, 69.61; H, 8.99. Found: C, 69.53; H, 8.94.

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