Total Synthesis of L-659,699, a Novel Inhibitor of Cholesterol Biosynthesis

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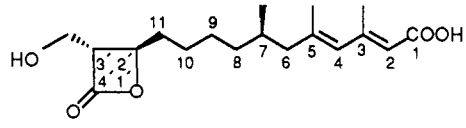
The total synthesis of (*E,E*)-11-[3′-(hydroxymethyl)-4′-oxo-2′-oxetanyl]-3,5,7-trimethyl-2,4-undecadienoic acid (L-659,699) has been accomplished from pulegone. A key step involves a highly diastereoselective aldol condensation of chiral crotonate imide to introduce the stereogenic centers at the ring carbons.

L-659,699 (also known as 1233A), a naturally occurring β-lactone isolated independently from *Fusarium* sp.,[1] *Scopulariopsis* sp.,[2] and *Cephalosporin* sp.,[3] is a potent, specific inhibitor of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A synthase (HMG-CoA synthase) and cholesterol biosynthesis in cell culture.[1,2] This compound was identified as (*E,E*)-11-[3′-(hydroxymethyl)-4′-oxo-2′-oxetanyl]-3,5,7-trimethyl-2,4-undecadienoic acid.[3] Its absolute configuration has been recently determined as 2′*R*, 3′*R*, and 7*R*.[4] Our approach to the total synthesis of L-659,699 was designed to allow rapid development of derivatives to explore the structure–activity relationships and the stereochemical requirements for HMG-CoA synthase activity. Utilizing a highly diastereoselective aldol condensation of the chiral crotonate imide developed by Evans[5] to introduce the stereogenic centers at the ring carbons, we have now accomplished the first total synthesis of L-659,699.



L-659,699

Results and Discussion

(*R*)-(+)-Pulegone was chosen as the starting material for constructing the C-2′ side chain which contains the (7*R*)-methyl. (*R*)-(+)-Pulegone (**1**), (Scheme I) was converted to (*R*)-(+)-methyl citronellate (**2**), $[\alpha]_D$ = +6.92° (*c* 3.43, MeOH), in three steps in 35% yield by using the procedure of Overberger.[6] Reduction of **2** with diisobutylaluminum hydride in toluene at −78 °C gave (*R*)-(+)-citronellal (**3**, 89%), which was exposed to methylmagnesium iodide to produce the alcohol **4** (80%). Oxidation of **4** with chromium trioxide–pyridine complex in CH_2Cl_2 yielded the methyl ketone **5** in 93% yield. Protection of **5** with ethylene glycol in the presence of a catalytic amount of *p*-toluenesulfonic acid in refluxing benzene afforded the ketal **6** (38%) along with four other unidentified products. Ozonolysis of **6** followed by Wittig extension with triethyl phosphonoacetate gave **8** in 47% yield. Hydrogenation of **8** followed by diisobutylaluminum hydride reduction in toluene provided the central piece **10** in good yield.

The key step in this total synthesis is the induction of the stereogenic centers at the ring carbons (C-2′ and C-3′). This was accomplished by employing methodology developed by Evans for highly diastereoselective aldol condensation reactions of a chiral crotonate imide.[5] Treatment of the imide **11** (Scheme II) with dibutylboron trifluoromethanesulfonate and triethylamine for 1 h at −78 °C and 15 min at 0 °C gave the boron enolate, which was reacted immediately with the aldehyde **10** for 1 h at −78 °C and 1 h at 0 °C and worked up oxidatively (30% H_2O_2, pH 7 phosphate buffer, 0 °C, 1 h) to afford the aldol adduct **12** (66%) with 94% diastereoselection.[7] Reductive removal of the chiral auxiliary was carried out by the conversion of **12** to dibutylboryl aldolate (THF, Bu_3B, AcOH, room temperature, 1.5 h). Lithium borohydride reduction and subsequent oxidative workup gave a mixture of **13a** and **13b**. Selective protection of the primary hydroxy group of the mixture of **13a** and **13b** with *tert*-butylchlorodiphenylsilane gave the corresponding diols. Hydrolysis of the ketal with 2% aqueous HCl in acetone produced **14** in 38% overall yield from **12**. The secondary hydroxy group of **14** was protected with MEMCl to give **15**, which was ozonized to yield the aldehyde intermediate. PDC oxidation[8] and subsequent methylation with diazomethane afforded the methyl ester **16**. Removal of the MEM group from **16** with zinc bromide gave the hydroxy ester **17**, which was saponified with sodium hydroxide to yield the β-hydroxy acid. Cyclization of the β-hydroxy acid with benzenesulfonyl chloride in pyridine at 0 °C provided the synthetic lactone **18**.[9] The synthetic lactone **18** was compared with material obtained from the degradation of the natural product L-659,699 as outlined in Scheme III. Ozonolysis of L-659,699 followed by silylation of the hydroxy group with *tert*-butylchlorodiphenylsilane gave the degradation product **18**, $[\alpha]_D$ +22.2° (*c* 0.59, MeOH). The optical rotation of the synthetic compound **18** was found to be $[\alpha]_D$ +21.5° (*c* 0.94, MeOH), which was in agreement with that of the degradation product **18**.

The C-2′ side chain synthesis was completed by Reformatsky reaction and subsequent dehydration. Treatment of **18** (Scheme IV) and *tert*-butyl (*E*)-4-bromo-3-methyl-

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(3) Aldridge, D. C.; Gile, D.; Turner, W. B. *J. Chem. Soc. C* **1971**, 3888–3891.

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(5) (a) Evans, D. A.; Sjogren, E. B.; Bartroli, J.; Dow, R. L. *Tetrahedron Lett.* **1986**, *27*, 4957–4960. (b) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099–3111. (c) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129.

(6) Overberger, C. G.; Weise, J. K. *J. Am. Chem. Soc.* **1968**, *90*, 3525–3531.

(7) The diastereoselection was determined by GC analysis of the silylated aldol adduct. The silylated compound was prepared by treating **12** with *tert*-butyldimethylsilyl chloride and imidazole in DMF. GC analysis was carried out on a Perkin-Elmer Instrument (Model Sigma 2000) employing a 30 m × 0.32 mm SPB5 column.

(8) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399–402.

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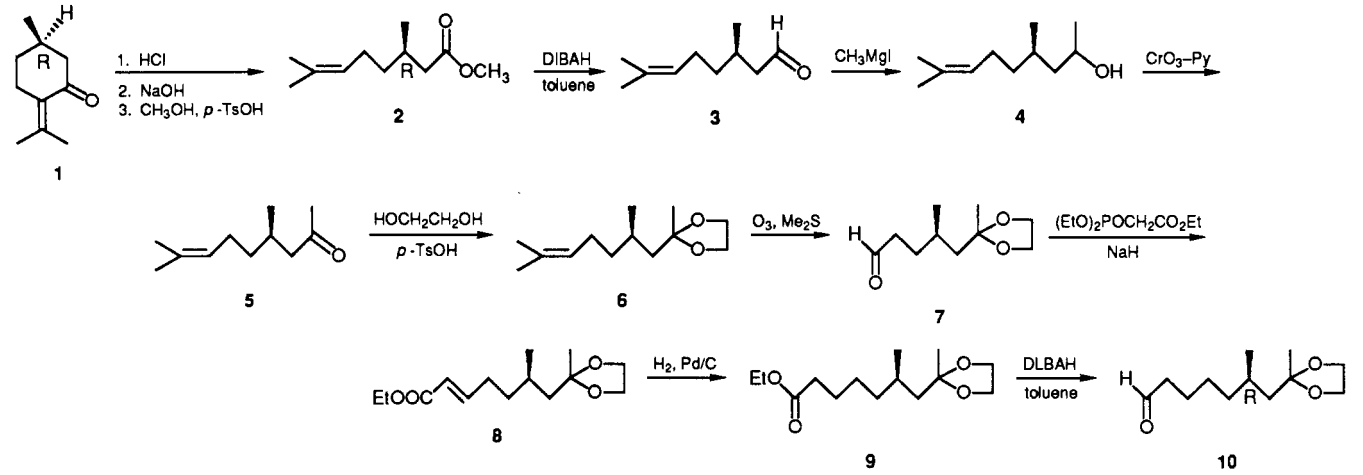
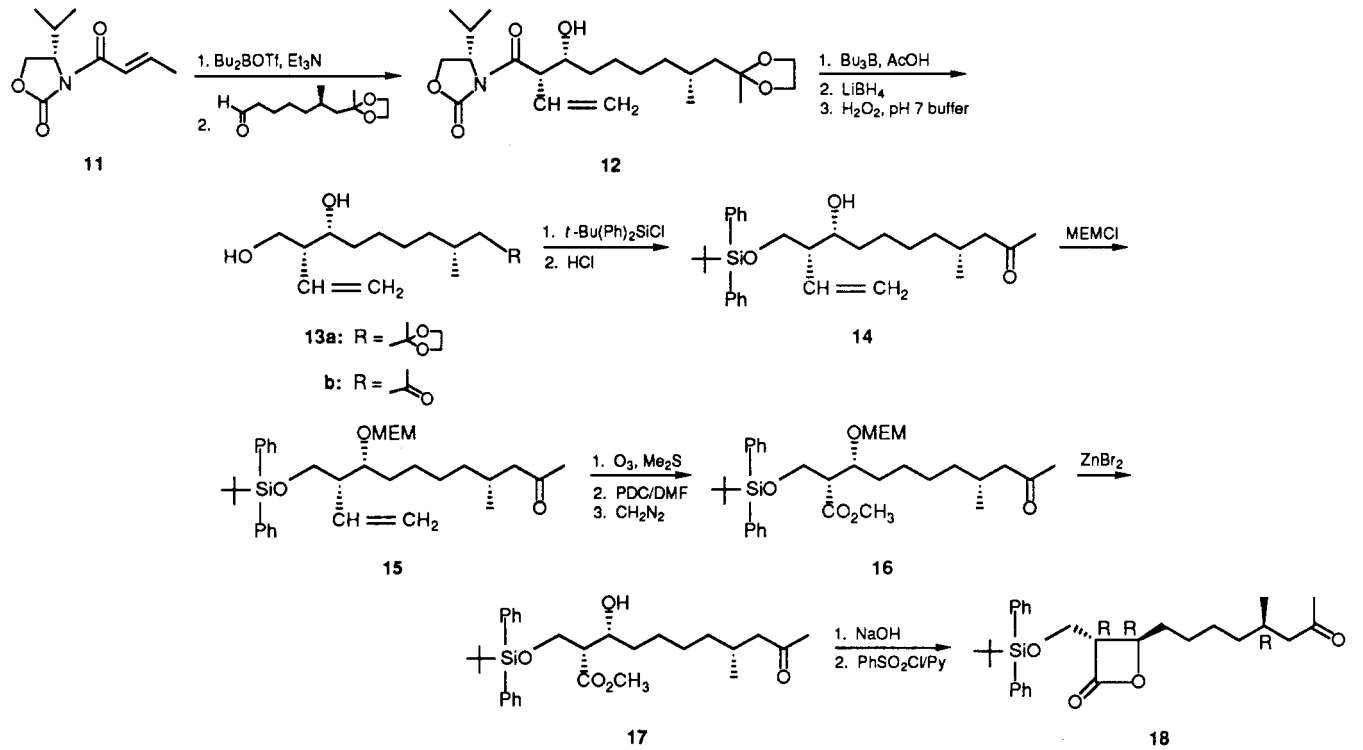
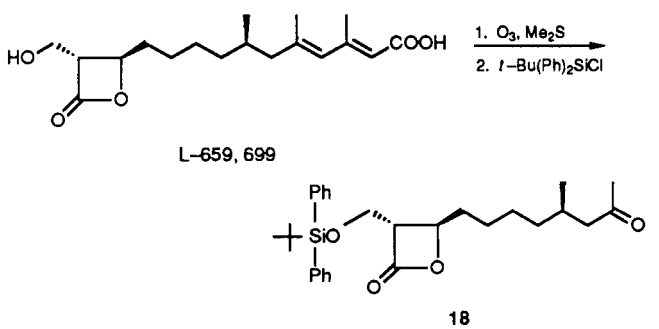
Scheme I



Scheme II



Scheme III



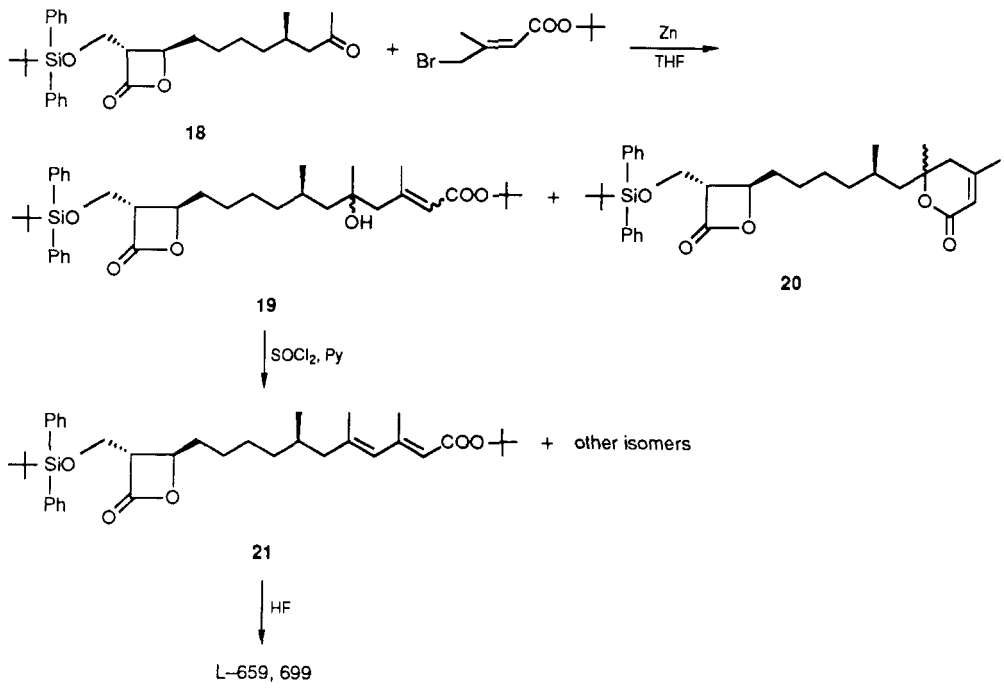
2-butenoate with activated zinc dust in refluxing THF gave **19** (a mixture of four isomers) in 44% yield along with 32% of the δ-lactone **20**. Dehydration of **19** with thionyl chloride in the presence of pyridine in refluxing CH_2Cl_2 afforded **21** (30%) and other isomers. The protected compound **21** was converted to the target compound, L-659,699, by deblocking the *tert*-butyldiphenylsilyl group and the *tert*-butyl ester with hydrofluoric acid simultaneously. Spectral (^1H NMR, mass, IR) properties of the synthetic L-659,699 were identical with those of the natural product. The optical rotation of the synthetic compound was found to be $[\alpha]_D$ +27.4° (*c* 0.45, $CHCl_3$), which was in agreement with that of the naturally occurring material, $[\alpha]_D$ +28.6° (*c* 0.62, $CHCl_3$).

Experimental Section

General Procedures. Proton nuclear magnetic resonance spectra were recorded on a Varian XL-200 or XL-300 NMR spectrometer with tetramethylsilane as an internal standard. Mass spectra were determined on a Varian MAT 731 mass spectrometer. IR spectra were recorded on a Perkin-Elmer 283B infrared spectrophotometer. Silica gel 60 (230–400 mesh, EM Reagents) and silica gel GF plates purchased from Analtech, Newark, DE, were used for flash column chromatography and preparative TLC.

(*R*)-(+)-Citronellal (3). The starting material, (*R*)-(+)-methyl citronellate (**2**), $[\alpha]_D$ +6.92° (*c* 3.43, MeOH), was prepared from (*R*)-(+)-pulegone according to a literature procedure.[6] To a −78

Scheme IV



°C solution of 24.85 g (0.135 mol) of **2** in 600 mL of toluene was added 89.35 mL (0.134 mol) of diisobutylaluminum hydride (1.5 M in toluene) dropwise over 0.5 h. After stirring for 0.5 h at −78 °C, the solution was added dropwise 20 mL of methanol and the mixture was poured into a 0 °C stirred solution of Rochelle salt (100 mL of saturated aqueous solution diluted with 300 mL of H_2O). The mixture was stirred for 1 h at 0 °C and filtered through Celite, and the solids were washed with 3 × 60 mL of ether. The aqueous phase was extracted with 3 × 200 mL of ether, and the combined organic phases were dried, filtered, and concentrated. The product was purified by flash column chromatography (R_f 0.61, 8% EtOAc in hexane) to give 18.51 g (89%) of air-sensitive product **3**: ^{1}H NMR ($CDCl_3$) δ 0.96 (d, 3 H), 1.17–1.43 (m, 2 H), 1.60 (s, 3 H), 1.68 (s, 3 H), 1.89–2.13 (m, 3 H), 2.14–2.49 (m, 2 H), 5.09 (td, 1 H), 9.74 (t, 1 H).

(6*R*)-2,6-Dimethyl-2-nonen-8-ol (4). The secondary alcohol **4** was prepared in 84% yield from **3** according to a literature procedure.[4]

(4*R*)-4,8-Dimethyl-7-nonen-2-one (5). Chromium trioxide, 130 g (1.30 mol), was added to a stirred solution of 210.3 g (2.66 mol) of pyridine in 800 mL of CH_2Cl_2 at 0 °C. The resulting deep burgundy solution was stirred for 0.5 h at room temperature, and then a solution of 36.6 g (0.218 mol) of **4** in 50 mL of CH_2Cl_2 was added in one portion. A black tarry solid precipitated immediately. After stirring for 15 h at room temperature, the solution was decanted from the residue, which was washed with 2 × 200 mL of ether. The combined organic phases were washed with 3 × 250 mL of 5% aqueous NaOH solution, 300 mL of 5% aqueous HCl, 250 mL of 5% aqueous sodium bicarbonate solution, and 250 mL of brine, dried, and filtered. The filtrate was concentrated, and the product was purified by flash column chromatography (R_f 0.46, 5% acetone in hexane) to afford 34 g (93%) of **5**: ^{1}H NMR ($CDCl_3$) δ 0.89 (d, 3 H), 1.08–1.42 (m, 2 H), 1.59 (s, 3 H), 1.67 (s, 3 H), 1.86–2.07 (m, 3 H), 2.11 (s, 3 H), 2.16–2.48 (m, 2 H), 5.09 (t, 1 H); mass spectrum, *m/e* 168 (M^+). Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.21; H, 12.09.

(6*R*)-2,6-Dimethyl-8,8-(ethylenedioxy)-2-nonene (6). To a solution of 6.2 g (37 mmol) of **5** in 50 mL of benzene were added 6.8 g (110 mmol) of ethylene glycol and 0.3 g (16 mmol) of *p*-toluenesulfonic acid monohydrate. The resulting solution was heated to reflux, and water was removed by using a Dean–Stark trap. After being refluxed for 4 h, the solution was concentrated. The product was purified by flash column chromatography (R_f 0.56, 5% acetone in hexane) to yield 2.95 g (38%) of **6** along with four other unidentified products. Spectral data of **6** were as follows: ^{1}H NMR ($CDCl_3$) δ 0.96 (d, 3 H), 1.06–1.76 (m + 3 s, 14 H), 1.89–2.06 (m, 2 H), 3.93 (s, 4 H), 5.0 (t, 1 H); mass spectrum, *m/e* 212 (M^+). Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 73.79; H, 11.69.

(4*R*)-4-Methyl-6,6-(ethylenedioxy)heptanal (7). Ozone was introduced to a solution of 3.4 g (16 mmol) of **6** in 200 mL of CH_2Cl_2 at −78 °C until a faint blue color persisted. After this stirred for 1 h at −78 °C and 0.5 h at room temperature, 5 mL of dimethyl sulfide was added. The resulting mixture was stirred for 1 h at room temperature and concentrated in vacuo. The air-sensitive crude product was used in the next step without further purification. The spectral data of **7** were as follows: ^{1}H NMR ($CDCl_3$) δ 0.96 (d, 3 H), 1.30 (s, 3 H), 1.40–1.86 (m, 5 H), 2.36–2.52 (m, 2 H), 3.92 (s, 4 H), 9.75 (t, 1 H).

(6*R*)-Ethyl 6-Methyl-8,8-(ethylenedioxy)-2-nonenoate (8). To a slurry of 0.69 g (28.1 mmol) of sodium hydride in 40 mL of THF was added dropwise 5.69 mL (28.1 mmol) of triethyl phosphonoacetate in 30 mL of THF. Temperature was kept < 20 °C during the addition and vigorous evolution of hydrogen was noted. The resulting mixture was stirred for 15 min until the solution turned clear, to which 3 g of **7** in 30 mL of THF was added dropwise. After this stirred for 4 h at room temperature, the solvent was removed, and the residue was purified by flash column chromatography (R_f 0.33, 15% EtOAC in hexane) to afford 1.81 g (46% from **6**) of **8**: ^{1}H NMR ($CDCl_3$) δ 0.95 (d, 3 H), 1.24–1.74 (s + t + m, 11 H), 2.06–2.28 (m, 2 H), 3.91 (s, 4 H), 4.18 (q, 2 H), 5.82 (d, 1 H, J = 15 Hz), 6.96 (dt, 1 H, J = 15 Hz, 7 Hz); mass spectrum, *m/e* 241 (M^+ − 15). Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.41; H, 9.67.

(6*R*)-Ethyl 6-Methyl-8,8-(ethylenedioxy)nonanoate (9). A solution of 1.5 g (5.9 mmol) of **8** in 15 mL of EtOAc and 0.15 g of 10% palladium on carbon was hydrogenated at room temperature for 0.5 h under 40 psi of hydrogen. The solution was filtered and concentrated to give 1.5 g (98%) of **9**: ^{1}H NMR ($CDCl_3$) δ 0.94 (d, 3 H), 1.10–1.70 (s + t + m, 15 H), 2.30 (t, 2 H), 3.94 (s, 4 H), 4.13 (q, 2 H); mass spectrum, *m/e* 243 (M^+ − 15). Anal. Calcd for $C_{14}H_{26}O_4$: C, 65.09; H, 10.14. Found: C, 65.39; H, 10.43.

(6*R*)-6-Methyl-8,8-(ethylenedioxy)nonanal (10). (6*R*)-6-Methyl-8,8-(ethylenedioxy)nonanal (**10**) was obtained in 90% yield from **9** according to the method described for **3**. Spectral data of **10** were as follows: ^{1}H NMR ($CDCl_3$) δ 0.93 (d, 3 H), 1.08–1.72 (s + m, 12 H), 2.25–2.48 (m, 2 H), 3.91 (s, 4 H), 9.74 (t, 1 H).

(4*R*,2′*S*,3′*R*,8′*R*)-3-[2′-Vinyl-3′-hydroxy-8′-methyl-10′,10′-(ethylenedioxy)undecanoyl]-4-isopropyl-2-oxazolidinone (12). To a solution of 0.57 g (2.9 mmol) of **11** in 13 mL of CH_2Cl_2 stirred at −78 °C were added 3.16 mL (3.2 mmol) of

dibutylboron trifluoromethanesulfonate (1 M in CH_2Cl_2) and 0.41 g (4.1 mmol) of triethylamine. After being stirred for 1 h at −78 °C and 15 min at 0 °C, the solution was recooled to −78 °C and treated dropwise with 0.8 g (3.7 mmol) of **10** in 2 mL of CH_2Cl_2. The solution was stirred for 1 h at −78 °C and 1 h at 0 °C and then partitioned between 150 mL each of 1 M aqueous $NaHSO_4$ and hexane–EtOAc (1:1). The organic phase was washed with 100 mL of brine and concentrated to an oil, which was dissolved in 20 mL of ether, cooled to 0 °C, and treated with 4 mL each of pH 7 phosphate buffer and 30% H_2O_2. After stirring for 1 h at 0 °C, the mixture was partitioned between 150 mL each of water and hexane–EtOAc (1:1). The organic phase was washed with saturated aqueous $NaHCO_3$ solution and brine, then dried, and concentrated to an oil. The product was purified by preparative TLC (R_f 0.26, 30% EtOAc in hexane) to give 0.782 g (66%) of **12** with 94% diastereoselection:[7] $[\alpha]_D$ −0.69° (*c* 0.73, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.8–1.02 (m, 9 H), 1.06–1.74 (s + m, 14 H), 2.36 (m, 1 H), 3.12 (s, 1 H), 3.88–4.02 (s + m, 5 H), 4.16–4.36 (m, 2 H), 4.44–4.64 (m, 2 H), 5.34–5.46 (m, 2 H), 5.88–6.08 (m, 1 H); FAB mass spectrum, *m/e* 412 (M^+ + 1). Anal. Calcd for $C_{22}H_{37}NO_6$: C, 64.21; H, 9.06; N, 3.40. Found: C, 63.94; H, 9.21; N, 3.28.

(3*R*,4*R*,9*R*)-3-(Hydroxymethyl)-4-hydroxy-9-methyl-11,11-(ethylenedioxy)-1-dodecene (13a) and (3*R*,4*R*,9*R*)-3-(Hydroxymethyl)-4-hydroxy-9-methyl-1-dodecen-11-one (13b). To a solution of 0.45 g (1.09 mmol) of **12** in 4.3 mL of THF at room temperature were added 1.2 mL (1.2 mmol) of tributylborane (1 M in THF) and 94 μL (1.64 mmol) of glacial acetic acid. After stirring at room temperature for 1.5 h, the solution was cooled to 0 °C and treated with 1.09 mL (2.18 mmol) of lithium borohydride (2 M in THF). The mixture was stirred for 1 h at 0 °C and then 4 mL each of 30% H_2O_2 and pH 7 phosphate buffer were added. The mixture was stirred for 2 h at room temperature and partitioned between 100 mL each of water and EtOAc. The organic phase was washed with saturated aqueous $NaHCO_3$ solution and brine, dried, and concentrated to give a crude mixture of **13a** and **13b**. The residue was used in the next step without further purification.

(3*R*,4*R*,9*R*)-3-[((*tert*-Butyldiphenylsilyl)oxy)methyl]-4-hydroxy-9-methyl-1-dodecen-11-one (14). The crude mixture of **13a** and **13b** from the previous step was dissolved in 4 mL of DMF and treated with 0.15 g (2.2 mmol) of imidazole and 0.41 g (1.50 mmol) of *tert*-butylchlorodiphenylsilane. After stirring for 3 h at room temperature, the mixture was poured into 50 mL of ice water and extracted with 3 × 30 mL of ether. The combined ether phases were dried and concentrated. The product was purified by preparative TLC (R_f 0.63, 30% EtOAc in hexane) to yield a mixture of 0.146 g (28% from **12**) of 14 and 0.08 g of silyl ketal. The silyl ketal was then deprotected by treatment with 2 mL of a 4% aqueous HCl in 10 mL of acetone to afford an additional 0.053 g of **14** (total yield 0.199 g, 38%): ^1H NMR ($CDCl_3$) δ 0.89 (d, 3 H), 1.06 (s, 9 H), 1.12–1.52 (m, 10 H), 1.88–2.05 (m, 1 H), 2.13 (s, 3 H), 2.15–2.48 (m, 2 H), 3.83 (d, 2 H), 3.90 (m, 1 H), 5.02–5.20 (m, 2 H), 5.84–5.97 (m, 1 H), 7.34–7.50 (m, 6 H), 7.62–7.74 (m, 4 H); FAB mass spectrum, *m/e* 481 (M^+ + 1). Anal. Calcd for $C_{30}H_{44}O_3Si$: C, 74.95; H. 9.22. Found: C, 74.85; H, 9.15.

(3*R*,4*R*,9*R*)-3-[((*tert*-Butyldiphenylsilyl)oxy)methyl]-4-[(2-methoxyethoxy)methoxy]-9-methyl-1-dodecen-11-one (15). To a 0 °C solution of 256 mg (0.53 mmol) of **14** in 12 mL of CH_2Cl_2 was added 0.40 mg (3.1 mmol) of *N,N*-diisopropylethylamine. The mixture was stirred for 10 min at 0 °C, and then 400 μL (3.5 mmol) of (2-methoxyethoxy)methyl chloride was added. After stirring for 19 h at room temperature, the solution was concentrated, and the product was purified by preparative TLC (R_f 0.51, 30% EtOAc in hexane) to give 238 mg (79%) of **15**: ^1H NMR ($CDCl_3$) δ 0.89 (d, 3 H), 1.04 (s, 9 H), 1.14–1.62 (m, 9 H), 1.88–2.04 (m, 1 H), 2.12 (s, 3 H), 2.22–2.42 (m, 2 H), 3.36 (s, 3 H), 3.44–3.56 (m, 2 H), 3.58–3.70 (m, 3 H), 3.72–3.86 (m, 2 H), 4.73 (s, 2 H), 4.98–5.14 (m, 2 H), 5.63–5.81 (m, 1 H), 7.32–7.48 (m, 6 H), 7.62–7.72 (m, 4 H); FAB mass spectrum, *m/e* 481 (M^+ − 88). Anal. Calcd for $C_{34}H_{52}O_5Si$: C, 71.79; H, 9.21. Found: C, 71.98; H, 9.13.

(2*R*,3*R*,8*R*)-Methyl 2-[((-*tert*-Butyldiphenylsilyl)oxy)methyl]-3-[(2-methoxyethoxy)methoxy]-8-methyl-10-oxoundecanoate (16). A −78 °C solution of 238 mg (0.376 mmol) of **15** in 30 mL of CH_2Cl_2 was treated with ozone until the solution turned blue. After being stirred for 0.5 h at −78 °C and 0.5 h at room temperature, 0.8 g (12.9 mmol) of methyl sulfide was added. The resulting solution was stirred for 10 min at 0 °C and then 1 h at room temperature, concentrated, and redissolved in 3 mL of DMF to which was added 1 g (3.87 mmol) of pyridinium dichromate. The mixture was stirred for 17 h at room temperature, poured into 30 mL of ice water, and treated with 70 mL of diazomethane[10] in ether. After this stirred for 1 h at room temperature, the organic phase was separated, the aqueous phase was extracted with 2 × 30 mL of ether, and the combined organic phases were dried and concentrated. The product was purified by preparative TLC (R_f 0.34, 30% EtOAc in hexane) to give 122 mg (54%) of **16**: ^1H NMR ($CDCl_3$) δ 0.86 (d, 3 H), 1.01 (s, 9 H), 1.06–1.64 (m, 9 H), 1.86–2.04 (m, 1 H), 2.11 (s, 3 H), 2.21–2.42 (m, 2 H), 2.88 (q, 1 H), 3.36 (s, 3 H), 3.46–3.52 (m, 2 H), 3.58–3.66 (m, 2 H), 3.71 (s, 3 H), 3.74–4.02 (m, 2 H), 4.68 (s, 2 H), 7.32–7.46 (m, 6 H), 7.62–7.72 (m, 4 H); FAB mass spectrum, *m/e* 525 (M^+ − 75). Anal. Calcd for $C_{34}H_{52}O_7Si$: C, 67.96; H, 8.72. Found: C, 68.26; H, 8.87.

(2*R*,3*R*,8*R*)-Methyl 2-[((*tert*-Butyldiphenylsilyl)oxy)methyl]-3-hydroxy-8-methyl-10-oxoundecanoate (17). To a solution of 122 mg (0.20 mmol) of **16** in 8 mL of CH_2Cl_2 was added 300 mg (1.33 mmol) of zinc bromide. After stirring for 3 h at room temperature, the solution was filtered, dried, and concentrated. The product was purified by preparative TLC (R_f 0.32, 30% EtOAc in hexane) to afford 75 mg (72%) of **17**: ^1H NMR ($CDCl_3$) δ 0.88 (d, 3 H), 1.03 (s, 9 H), 1.10–1.50 (m, 8 H), 1.62 (m, 1 H), 1.96 (m, 1 H), 2.12 (s, 3 H), 2.14–2.44 (m, 2 H), 2.70 (q, 1 H), 3.71 (s, 3 H), 3.84–4.00 (d + m, 3 H), 7.32–7.48 (m, 6 H), 7.58–7.70 (m, 4 H); FAB mass spectrum, *m/e* 513 (M^+ + 1). Anal. Calcd for $C_{30}H_{44}O_5Si \cdot {}^3/_4H_2O$: C, 68.47; H, 8.71. Found: C, 68.68, H, 8.88.

(2′*R*,3′*R*,4*R*)-8-[3′-[((*tert*-Butyldiphenylsilyl)oxy)methyl]-4′-oxo-2′-oxetanyl]-4-methyl-2-octanone (18). To a solution of 75 mg (0.15 mmol) of **17** in 3 mL of isopropyl alcohol was added 12 mg (0.30 mmol) of sodium hydroxide in 1 mL of H_2O. After being heated for 0.5 h at 60 °C, the solution was poured into 40 mL of ether/H_2O (1:1) and acidified with 2 mL of 1 N HCl. The aqueous phase was extracted with 3 × 15 mL of ether, and the combined organic phases were dried and concentrated to give 70 mg (96%) of the β-hydroxy acid, which was used in the next step without further purification. To a 0 °C solution of 70 mg (0.14 mmol) of the β-hydroxy acid in 2 mL of pyridine was added 49.5 mg (0.28 mmol) of benzenesulfonyl chloride dropwise. After the mixture was kept in the freezer overnight, the solution was poured into 40 mL of 1:1 (v/v) ether/H_2O. The aqueous phase was extracted with 3 × 20 mL of ether, and the ether extracts were combined, washed with brine, dried, and concentrated. The product was purified by preparative TLC (R_f 0.60, 30% EtOAc in hexane) to give 32.1 mg (48%) of **18**: ^1H NMR ($CDCl_3$), δ 0.89 (d, 3 H), 1.05 (s, 9 H), 1.14–1.44 (m, 6 H), 1.60–2.04 (m, 3 H), 2.12 (s, 3 H), 2.16–2.45 (m, 2 H), 3.33 (q, 1 H), 3.81 (dd, 1 H), 4.02 (dd, 1 H), 4.57 (m, 1 H), 7.30–7.46 (m, 6 H), 7.56–7.76 (m, 4 H); FAB mass spectrum, *m/e* 481 (M^+ + 1); IR ($CDCl_3$) 1825 cm^{-1} (β-lactone); $[\alpha]_D$ +21.49° (*c* 0.94, MeOH). Anal. Calcd for $C_{29}H_{40}O_4Si$: C, 72.46; H, 8.39. Found: C, 72.34; H, 8.65.

(2′*R*,3′*R*,5*RS*,7*R*)-*tert*-Butyl 11-[3′-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-4′-oxo-2′-oxetanyl]-5-hydroxy-3,5,7-trimethyl-2-undecenoate (19). To a solution of 72 mg of zinc dust in 4.0 mL of dry THF under N_2 was added 9.6 μL (0.11 mmol) of dibromoethane. The mixture was refluxed under N_2 for 0.5 h, and then were added dropwise a solution of 240 mg (0.5 mmol) of **18** and 216 mg (1.2 mmol) of *tert*-butyl (*E*)-4-bromo-3-methyl-2-butenoate in 2.0 mL of THF during 3 min. The reaction mixture was heated under reflux for 67 min and then purified by preparative TLC (R_f 0.24, 20% EtOAc in hexane) to give 102 mg (44% based on the reacted starting material) of **19** along with 65 mg of **20** and 66 mg of the recovered starting material **18**. The NMR spectrum showed that **19** is a mixture of four isomers, which was used in the next step without further separation. Spectral data of **20** were as follows: ^1H NMR ($CDCl_3$) δ 0.99 (d, 3 H), 1.07 (s, 9 H), 1.26–1.94 (s + m, 13 H), 1.97 (s, 3

(10) Arndt, F. *Org. Synth.* **1943**, Coll. Vol. 2, 165.

H), 2.18-2.46 (m, 3 H), 3.34 (m, 1 H), 3.83 (dd, 1 H), 4.03 (dd, 1 H), 4.60 (m, 1 H), 5.72 (s, 1 H), 7.34-7.48 (m, 6 H), 7.61-7.68 (m, 4 H); FAB mass spectrum, m/e 563 ($M^+ + 1$); IR (CH_2Cl_2) 1823 (β-lactone), 1705 cm^{-1} (α,β-unsaturated δ-lactone).

(2′*R*,3′*R*,7*R*)-(*E*,*E*)-*tert*-Butyl 11-[3′-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-4′-oxo-2′-oxetanyl]-3,5,7-trimethyl-2,4-undecadienoate (21). To a refluxing solution of 16 mg (0.025 mmol) of **19** in 3 mL of CH_2Cl_2 in the presence of 100 μL (1.23 mmol) of pyridine was added dropwise a solution of 50 μL (0.69 mmol) of thionyl chloride in 1 mL of CH_2Cl_2 during 3 min. The mixture was then stirred for 5 min at refluxing temperature. The product was purified by preparative TLC (R_f 0.63, 20% EtOAc in hexane) to afford 14 mg (90%) of a mixture, which was then purified again via repeated development seven times on preparative TLC plates to give 4.2 mg (30%) of **21** (bottom band, top band was a mixture of other isomers): $[\alpha]_D$ +3.38° (c 0.65, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.83 (d, 3 H), 1.07 (s, 9 H), 1.19-1.57 (s + m, 15 H), 1.58-2.00 (s + m, 7 H), 2.09 (dd, 1 H), 2.10 (s, 3 H), 3.34 (q, 1 H), 3.83 (dd, 1 H), 4.04 (dd, 1 H), 4.60 (m, 1 H), 5.59 (s, 1 H), 5.68 (s, 1 H), 7.34-7.53 (m, 6 H), 7.60-7.70 (m, 4 H); FAB mass spectrum, m/e 619 ($M^+ + 1$); IR (CH_2Cl_2) 1820 cm^{-1} (β-lactone). Anal. Calcd for $C_{38}H_{54}O_5Si$: C, 73.75; H, 8.79. Found: C, 73.45; H, 8.70.

(2′*R*,3′*R*,7*R*)-(*E*,*E*)-11-[3′-(Hydroxymethyl)-4′-oxo-2′-oxetanyl]-3,5,7-trimethyl-2,4-undecadienoic Acid (L-659,699). To a solution of 10 mg (0.016 mmol) of **21** in 0.1 mL of THF was added 0.14 mL of 50% aqueous hydrofluoric acid. After stirring for 18 h at room temperature, the mixture was neutralized with saturated $NaHCO_3$ solution and then extracted with 3 × 10 mL of CH_2Cl_2. The organic phases were combined, dried and concentrated. The product was purified by preparative TLC to afford 4 mg (76%) of the synthetic L-659,699: $[\alpha]_D$ +27.4° (c 0.45, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.84 (d, 3 H), 1.10-1.57 (m, 6 H), 1.58-1.99 (s + m, 7 H), 2.10 (dd, 1 H), 2.25 (s, 3 H), 3.41 (q, 1 H), 4.00 (dd, 1 H), 4.07 (dd, 1 H), 4.61 (m, 1 H), 5.71 (s, 1 H), 5.75 (s, 1 H); FAB mass spectrum, m/e 325 ($M^+ + 1$); IR (CH_2Cl_2) 1815 cm^{-1} (β-lactone). Anal. Calcd for $C_{18}H_{28}O_5$: C, 66.64; H, 8.70. Found: C, 66.59; H, 8.59.

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A New General Synthetic Approach to Diterpenes: Application to Syntheses of (±)-Taxodione and (±)-Royleanone

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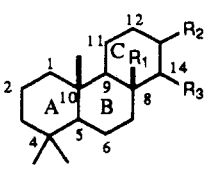
High-pressure Diels-Alder reactions of 1,3,3-trimethyl-2-vinyl-1-cyclohexenes **3a,b,i** with substituted 1,4-benzoquinones afford, in good yield, highly functionalized tricyclic ring systems which are found in many classes of naturally occurring terpenes. Notably, the reactions of **3a** are highly regio- and stereoselective. Efficient, formal syntheses of the antitumor diterpenes (±)-taxodione and (±)-royleanone are reported, which demonstrate the practical application of this new strategy for the preparation of varied terpene systems. Of particular interest is that the high-pressure reactions are accelerated by mild Lewis acids and the regio- and stereoselectivity of these reactions is also improved under the combined high-pressure/Lewis acid conditions in comparison to the high-pressure conditions alone. Indeed, in the reaction of **3a** with 2-methoxy-5-methyl-1,4-benzoquinone, $ZnBr_2$ is required to effect the Diels-Alder reaction even at 12 kbar, and endo adduct **12c** is formed stereoselectively in ≥90% yield. In contrast, low-temperature Ti(IV)-catalyzed reactions of diene **3a** with methoxy-substituted 1,4-benzoquinones at atmospheric pressure regioselectively produce dihydrobenzofurans **19** and **20**, apparently via alkylation of the quinone Ti(IV) complex by the diene followed by ring closure.

Introduction

The 4,4,10-trimethyl- and 4,4,8,10-tetramethylperhydrophenanthrene[1a] ring systems **1** and **2** form all, or part of, the basic carbocyclic framework of several classes of terpenes.[1] In addition, the B and C rings in many of the natural products incorporate carbonyl, hydroxyl, epoxide, and/or olefin moieties at various positions. Strategies for total synthesis of these terpenes most commonly employ consecutive Robinson annulation reactions or cation-olefin/arene cyclization reactions. An alternate, albeit obvious, strategy to molecules incorporating structures **1**/**2** with oxidized B/C rings is a Diels-Alder reaction of 1,3,3-trimethyl-2-vinylcyclohexene **3** with an appropriately substituted 1,4-benzoquinone (Scheme I). However, cycloaddition reactions of **3** are difficult to effect with many dienophiles, probably due to steric hindrance provided by three methyl groups on the diene, and relatively few synthetic approaches to natural products using this strategy have been reported.[2,3]



1, R_1=H, R_2,R_3=H or alkyl
2, R_1=CH_3, R_2,R_3=H or alkyl

† Lilly Grantee, 1989-1991.

(1) (a) In the interest of clarity, the standard terpene numbering scheme for **1** and **2** and derivatives is used in the Introduction and Results and Discussion sections. However, the systematic *Chemical Abstracts* names and numbering scheme are used in the Experimental Section, as recommended by the Editor. For reviews of structures and syntheses of di-, sester-, and triterpene ring systems, see: (b) Hanson, J. R. *Nat. Prod. Rep.* **1988**, *5*, 211. (c) Hanson, J. R. *Ibid.* **1986**, *3*, 123. (d) Connolly, J. D.; Hill, R. A. *Ibid.* **1985**, *2*, 1. (e) ApSimon, J. W.; Fyfe, K. E.; Greaves, A. M. In *The Total Synthesis of Natural Products*; ApSimon, J. W., Ed.; Wiley-Interscience: New York, 1984; Vol. 6, p 85. (f) Nakanishi, K.; Goto, T.; Ito, S.; Natori, S.; Noze, S. *Natural Products Chemistry*; Academic Press: New York, 1974; Vol. 1. (g) Hanson, J. R. *Terpenoids and Steroids-Specialist Periodical Report of the Royal Society of Chemistry*; The Royal Society of Chemistry: London, 1971-1983; Vol. 1-12 and references cited in the above.

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