Enantiomeric Synthesis of the β-Lactone Precursor of the HMG-CoA Synthase Inhibitor (+)-F-(244)

Sompong Wattanasin,* Hoang D. Do, Nandkumar Bhongle, and Faizulla G. Kathawala

Sandoz Research Institute, Sandoz Pharmaceuticals Corporation, East Hanover, New Jersey 07936

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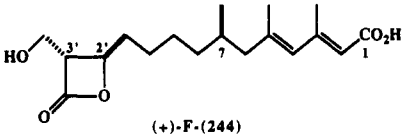
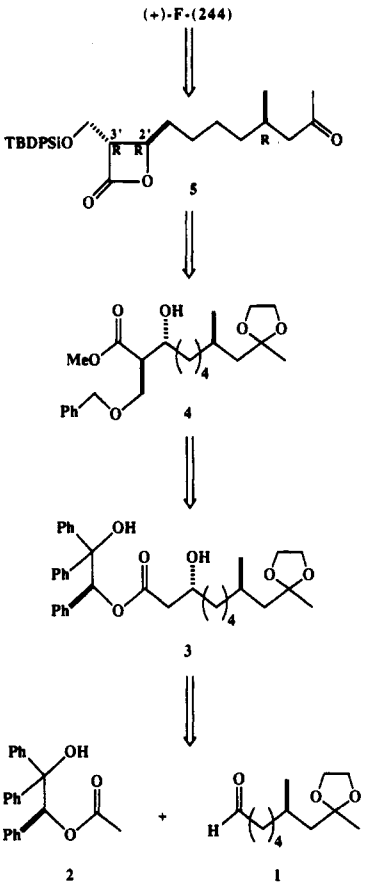
Recently there has been an increasing amount of interest in the syntheses of biologically active natural β-lactones in the literature.[1] (+)-F-(244),[2a,c] which was also known as 1233A[3] and L-659,699[2b] is the only natural β-lactone known to date that exhibits significant hypocholesterolemic activity. It had been shown[2] to specifically inhibit 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) synthase, a key regulatory enzyme in the cholesterol biosynthetic pathway.[4] (+)-F-(244) was first isolated from *Cephalosporin* sp. and identified by Turner et al. in 1971.[3] (+)-F-(244) was later discovered also from *Fusarium* sp.[2b] and *Scopulariopsis* sp.[2c] by other independent groups. The 2′*R*, 3′*R*, and 7*R* absolute configuration of the molecule was subsequently deduced by Chiang et al.[5] The first total synthesis of (+)-F-(244) was accomplished recently by the same group via the synthesis of the β-lactone **5**.[1i] This key β-lactone **5** was also derived from the natural products by a direct degradation method.[1i]



(+)-F-(244)

Herein, we wish to report an enantiospecific synthesis of the β-lactone **5** (Scheme I). The key steps in our synthesis included the asymmetric aldol condensation reaction of **1** and Braun's chiral acetate **2**[6,7] to introduce

Scheme I



the first optically active center **3** and the antidiastereoselective alkylation of **3**[8] to provide the second asymmetric center **4**.

The chiral aldehyde **1** was prepared in 9 steps (47% overall yield) from the commercially available (*R*)-(+)-citronellol by a modification of the known procedure.[1i] The synthesis of the first optically active C2′ center of the β-lactone ring was achieved by the asymmetric aldol condensation of **1** with Braun's chiral acetate **2** (S-HYTRA)[7] to give **3** in 80% yield. The chiral auxiliary was removed through the general methanolysis procedure[7a] (Scheme II) providing **6** with >99% diastereoselection. This selectivity was supported by high pressure liquid chromatography (HPLC) comparison of **6** with the diastereomeric mixture prepared from **1** and lithio enolate of methyl acetate. Alkylation of the lithioxy lithium enolate of **6** with freshly distilled benzyl chloromethyl ether (**7**) (BOMCl)[9] proceeded at −25 °C in 12 h to give **4** (35%).[10] Prolonging the reaction time did not improve the yield and warming up the reaction's temperature decomposed the starting material **6**. Transmetalation with magnesium

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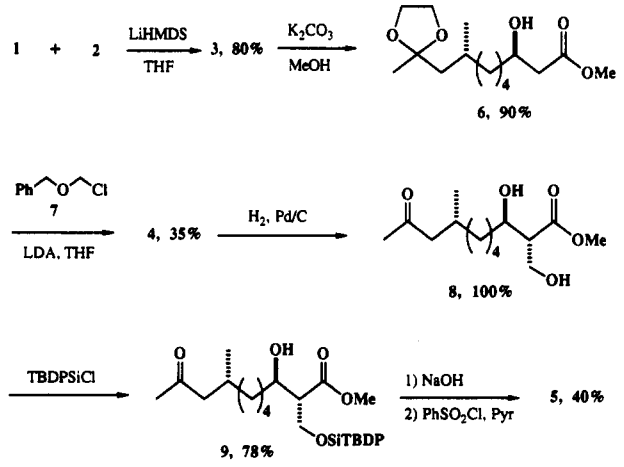
0022-3263/93/1958-1610$04.00/0

Scheme II



bromide etherate ($MgBr_2$–Et_2O)[6a] and chlorotitanium triisopropoxide (i-PrO)$_3$TiCl[11] did not enhance the yield. Also, use of hexamethylphosphoramide (HMPA) as cosolvent had no effect on the yield. Paraformaldehyde cracked at 150 °C as an alternate source of formaldehyde as electrophile furnished a similar yield but gave no control over the diastereoselectivity in the condensation reaction. A 1:1 mixture of 8 and its syn diastereomer was obtained. Trimethylsilyl chloromethyl ether ($(CH_3)_3SiOCH_2Cl$)[12] was too unreactive and did not alkylate the enolate of 6 at all. We found that[13] the cyclic ketal was susceptible to cleavage in the hydrogenation reaction using palladium over carbon as the catalyst in methanol. Hence, the cyclic ketal and benzyl groups of 4 were simultaneously deprotected under catalytic hydrogenation conditions to afford the diol 8 (100%), which was selectively reprotected with *tert*-butylchlorodiphenylsilane (TBDPSi) to produce 9 (78%).[1i] Analysis of compound 9 revealed that the alkylation of 6 had progressed to provide a 98:2 (anti:syn) diastereoselection. This well precedented anti selectivity[8] was confirmed by NMR and HPLC studies. Saponification of ester 9 followed by cyclization via the well-established Adam procedure[1i,14] provided known chiral β-lactone 5 in 40% yield. Its HPLC analysis suggested a 97:3 diastereomeric mixture. The NMR spectrum of 5 was indistinguishable from the same compound previously reported.[15]

In summary, the β-lactone 5 has been synthesized from commercially available (*R*)-(+)-citronellol and S-HYTRA in an enantiospecific manner. The overall yield of 5 is 7.9% from the aldehyde 1. Since 5 has been converted to the natural product, our procedure constitutes an improved and a much shorter formal total synthesis of (+)-F-(244).

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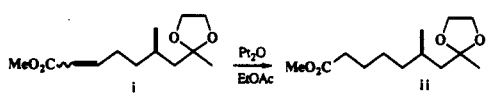
(12) Trimethylsilyl chloromethyl ether was prepared by refluxing a mixture of trimethylsilyl chloride (1.18 equiv), paraformaldehyde (1.00 equiv), and a catalytic amount of zinc chloride (0.0093 equiv) for 14 h at 60 °C, a procedure offered by Professor R. K. Boeckman, Jr.
(13) Hydrogenation of i using palladium over carbon in methanol gave the ketone of ii as the sole product. Quantitative hydrogenation of i to ii can be achieved in ethyl acetate by either using palladium over carbon and a few drops of triethylamine or using platinum oxide as the catalyst.



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(15) We thank Dr. Y.-C. P. Chiang of Merck Sharp & Dohme Research Laboratories, Rahway, NJ, for providing important NMR spectra.

Experimental Section

General Methods. Proton and carbon nuclear magnetic resonance (NMR) spectra were obtained from a JEOL FX 300 spectrometer. NMR data of compound 5 were collected from a Bruker AM 500 instrument. Spectra were recorded in deuteriochlorofrom ($CDCl_3$) solution with tetramethylsilane (TMS) as internal standard (δ 0.00). NMR signals are described in terms of chemical shift in parts per million from TMS. Coupling constants are reported in hertz, and multiplicities are described by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Infrared (IR) spectra were recorded on an Analect Instrument FTIR FX 6260 spectrometer either as neat or potassium bromide (KBr) samples. The abbreviation br is used to describe broad stretches in the IR spectra. A Thomas-Hoover melting point apparatus was used to determine melting points, which are uncorrected. Elemental analyses were performed by members of the Physical Chemistry Department, Sandoz. Fast atom bombardment (FAB) mass spectral determinations were obtained on the Finigan MAT TSQ70 mass spectrometer. A Perkin Elmer 241 MC polarimeter was used to measure optical rotations.

Thin layer chromatography (TLC) was performed on 0.25-mm E. Merck precoated silica gel plates (60F-254). Preparative thick-layer chromatography (Preparative TLC) was performed on 1-mm × 20-cm × 20-cm Analtech precoated silica gel plates (Silica gel GF). Flash chromatography was done using silica gel 60 (230–400 mesh) supplied by Merck. High pressure liquid chromatography (HPLC) was performed using a Rainin instrument, Beckman 110 UV or Varex light scattering detector, and a 4.5-mm × 250-mm Daicel Chiracel OD column.

All moisture-sensitive reactions were run under an argon atmosphere. All organic extracts were dried with anhydrous magnesium sulfate ($MgSO_4$), filtered, and rotoevaporated on a Buchi Rotavapor. Tetrahydrofuran (THF) was distilled under argon from sodium benzophenone ketyl. Triethylamine (Et_3N), methylene chloride (CH_2Cl_2), dimethylformamide (DMF), diisopropylamine, and hexamethyldisilazane were distilled from calcium hydride (CaH_2). Pyridine was dried with solid potassium hydroxide followed by fractional distillation. Benzyl chloromethyl ester was freshly distilled over calcium chloride before each use. Benzenesulfonyl chloride was distilled before use. All other solvents were anhydrous, high purity grade and were used as received.

(3*R*,8*R*)-2-Hydroxy-1,2,2-triphenylethyl 3-Hydroxy-8-methyl-10,10-(ethylenedioxy)undecanoate (3). To a −35 °C tetrahydrofuran solution (32 mL) of freshly prepared lithium bis(trimethylsilyl)amide (2.99 g, 17.87 mmol) was added 2(*S*)-acetoxy-1,1,2-triphenylethanol (2) (1.65 g, 4.96 mmol) in portions. The reaction mixture was gradually warmed to −10 °C and stirred for 45 min to observe a yellow dianion solution. The solution was cooled to −100 °C to which a tetrahydrofuran solution (12.8 mL) of 1 (0.85 g, 3.97 mmol) was added dropwise. The reaction solution was stirred for 1.25 h and then quenched with saturated ammonium chloride solution (31 mL) followed by ethyl acetate (13 mL). Layers were separated and the organic phase was washed with saturated ammonium chloride (2 × 25 mL) and then with saturated sodium chloride (10 mL). The resulting organic layer was dried and concentrated to a solid. The solid was washed with pentane to contain the crude product, which was purified by flash chromatography (30% ethyl acetate–petroleum ether) to give pure 3 as a white solid (1.74 g, 80%): mp 98–99 °C; ^{1}H NMR ($CDCl_3$) δ 0.93 (d, 3 H, J = 6.55), 1.05–1.66 (m, 12 H), 1.31 (s, 3 H), 2.30–2.39 (m, 2 H), 2.83 (s, 1 H), 3.75–3.86 (m, 1 H), 3.89–3.93 (m, 4 H), 6.72 (s, 1 H), 7.04–7.20 (m, 10 H), 7.28–7.31 (m, 1 H), 7.33–7.39 (m, 2 H), 7.55–7.59 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 20.92, 24.11, 25.63, 26.71, 28.90, 36.37, 37.93, 41.80, 45.59, 64.24, 64.42, 68.02, 78.91, 80.27, 110.49, 126.20, 126.26, 127.15, 127.49, 127.59, 127.87, 128.08, 128.40, 128.42, 135.51, 142.51, 144.58, 171.45 ppm; IR (KBr) 3460 (br), 3061, 3032, 2981, 2931, 2858, 1719, 1495, 1450, 1377, 1339, 1284, 1250, 1222, 1066, 1034, 992, 949, 893, 760, 751, 733, 698, 644, 617, 534 cm^{-1}; $[\alpha]_D$ −107.25° (*c* 0.87, MeOH). Anal. Calcd for $C_{34}H_{42}O_6$: C, 74.70; H, 7.74. Found: C, 74.55; H, 7.76.

(3*R*,8*R*)-Methyl 3-Hydroxy-8-methyl-10,10-(ethylenedioxy)undecanoate (6). A methanol solution (21 mL) containing

3 (1.4 g, 2.56 mmol) and potassium carbonate (0.19 g, 1.36 mmol) was stirred at room temperature for 3.0 h. The reaction mixture was poured into a mixture of saturated solution of ammonium chloride (18 mL) and ethyl acetate (50 mL) and the resulting solution was then stirred for 10 min. Layers were separated and the organic phase was washed with water (23 mL) and then with saturated aqueous sodium chloride solution (23 mL). Following the usual workup procedure, the crude product oil was subjected to flash chromatography (10% acetone–methylene chloride) to provide pure clear oil **6** with >99% diastereoselectivity by chiral HPLC analysis (0.67 g, 90%): ^{1}H NMR ($CDCl_3$) δ 0.94 (d, 3 H, J = 6.60), 1.11–1.68 (m, 11 H), 1.31 (s, 3 H), 2.41 (dd, 1 H, J = 8.79, 16.38), 2.52 (dd, 1 H, J = 3.37, 16.38), 2.84 (br s, 1 H), 3.71 (s, 3 H), 3.90–3.94 (m, 4 H), 3.96–4.05 (m, 1 H); ^{13}C NMR ($CDCl_3$) 20.93, 24.11, 25.69, 26.81, 28.92, 36.57, 37.96, 41.15, 45.61, 51.72, 64.24, 64.42, 68.01, 110.51, 173.47 ppm; IR (neat) 3504 (br), 2982, 2933, 1739, 1438, 1377, 1252, 1196, 1169, 1091, 1041, 948, 888, 849, 813, 648 cm^{-1}; $[\alpha]_D$ −7.91°, (c 1.04, $CHCl_3$). Anal. Calcd for $C_{15}H_{28}O_5$: C, 62.47; H, 9.79. Found: C, 62.53; H, 9.88.

(2*R*,3*R*,8*R*)-Methyl 2-(Hydroxymethyl)-3-hydroxy-8-methyl-10-oxoundecanoate (8). To a −78 °C tetrahydrofuran solution (3 mL) containing freshly prepared lithium diisopropylamide (0.33 g, 3.08 mmol) was added dropwise a tetrahydrofuran solution (1.2 mL) of **13** (0.35 g, 1.21 mmol). The reaction solution was stirred for 1.0 h followed by dropwise addition of benzyl chloromethyl ether (**7**) (0.21 g, 1.34 mmol). The reaction solution was stirred while warming up to −25 °C over the course of 4.0 h and remained at this temperature for an additional 12.0 h. The reaction was quenched with a saturated solution of ammonium chloride (2 mL), followed by the usual workup procedure. Flash chromatography (5% acetone–methylene chloride) provided (2*R*,3*R*,8*R*)-methyl 2-[(benzyloxy)methyl]-3-hydroxy-8-methyl-10,10-(ethylenedioxy)undecanoate (**4**) (0.17 g, 35%) as a clear oil: ^{1}H NMR ($CDCl_3$) δ 0.94 (d, 3 H, J = 6.58), 1.10–1.50 (m, 9 H), 1.31 (s, 3 H), 1.50–1.67 (m, 2 H), 2.62 (d, 1 H, J = 8.11), 2.82 (dt, 1 H, J = 4.67, 6.55), 3.72 (s, 3 H), 3.76 (d, 1 H, J = 6.89), 3.77 (d, 1 H, J = 6.25), 3.84–3.93 (m, 5 H), 4.50 (d, 2 H, J = 1.16), 7.25–7.37 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 20.89, 24.09, 25.93, 26.76, 28.88, 35.30, 37.93, 45.59, 51.08, 51.81, 64.20, 64.39, 68.88, 70.33, 73.34, 110.47, 127.63, 127.72, 128.39, 137.81, 173.79 ppm. An ethyl acetate solution (1 mL) containing **4** (0.056 g, 0.14 mmol) and 7 mg of 10% paladium on carbon was hydrogenated at 50 psi for 1.0 h to produce a quantitative amount of **8**: ^{1}H NMR ($CDCl_3$) δ 0.89 (d, 3 H, J = 6.47), 1.10–1.63 (m, 8 H), 1.99 (m, 1 H), 2.12 (s, 3 H), 2.23 (dd, 1 H, J = 7.72, 15.90), 2.39 (dd, 1 H, J = 5.99, 15.90), 2.46 (t, 1 H, J = 6.25), 2.65 (m, 1 H), 2.75 (d, 1 H, J = 7.58), 3.76 (s, 3 H), 3.87–4.06 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 19.83, 25.91, 26.75, 29.16, 30.44, 35.41, 36.74, 51.28, 51.85, 51.91, 62.99, 71.95, 173.98, 208.94 ppm. Anal. Calcd for $C_{14}H_{26}O_5$: C, 61.29; H, 9.55. Found: C, 60.89; H, 9.41.

(2*R*,3*R*,8*R*)-Methyl 2-[((*tert*-Butyldiphenylsilyl)oxy)-methyl]-3-hydroxy-8-methyl-10-oxoundecanoate (9).[11] To a vial containing **8** (0.038 g, 0.14 mmol) dissolved in dimethylformamide (0.4 mL) were added imidazole (0.018 g, 0.26 mmol) and *tert*-butylchlorodiphenylsilane (0.052 g, 0.19 mmol), and the solution was stirred for 3.0 h. The reaction mixture was added to ice water (13 mL), extracted with diethyl ether (3 × 5 mL), and worked up in the usual manner. Preparative thick layer chromatography (30% ethyl acetate–petroleum ether) provided pure clear oil **9** (0.056 g, 78%). HPLC analysis provided a diastereoselectivity ratio of 98:2: ^{1}H NMR ($CDCl_3$) δ 0.88 (d, 3 H, J = 6.62), 1.03 (s, 9 H), 1.10–1.50 (m, 9 H), 1.97 (m, 1 H), 2.11 (s, 3 H), 2.21 (dd, 1 H, J = 8.09, 15.90), 2.39 (dd, 1 H, J = 5.74, 15.90), 2.70 (m, 1 H), 3.71 (s, 3 H), 3.85–3.94 (m, 1 H), 3.95 (d, 1 H, J = 2.57), 3.97 (d, 1 H, J = 3.16), 7.35–7.46 (m, 6 H), 7.61–7.67 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 19.17, 19.76, 25.77, 26.71, 26.82, 29.20, 30.39, 35.14, 36.79, 51.24, 51.67, 53.16, 62.88, 69.78, 127.73, 129.79, 133.10, 135.53, 135.56, 174.03, 208.98 ppm; $[\alpha]_D$ +13.41° (c 0.41, $CHCl_3$); FAB mass spectrum, m/e 513 (M^+ + 1), 435 (M^+ − phenyl).

(2′*R*,3′*R*,4*R*)-8-[3-[((*tert*-Butyldiphenylsilyl)oxy)methyl]-4-oxo-2-oxetanyl]-4-methyl-2-octanone (5).[11] In a vial containing **9** (0.025 g, 0.049 mmol) in isopropyl alcohol (1.0 mL) was placed 0.3 N sodium hydroxide (0.3 mL), and the vial was then placed into a preheated oil bath at 60 °C for 0.5 h. After cooling to ambient temperature, the reaction solution was pipetted into a 1:1 mixture of diethyl ether–water (12 mL) and then acidified with 1 N hydrochloric acid (0.6 mL). The organic phase was separated and the aqueous phase was extracted with diethyl ether (2 × 4 mL). The combined organic phase was dried ($MgSO_4$) and concentrated to the crude β-hydroxy acid (0.024 g, 100%), which was used in the next step without further purification. The β-hydroxy acid (0.024 g, 0.049 mmol) was transferred into a vial with pyridine (1 mL) and then placed in an ice bath. Benzenesulfonyl chloride (0.017 g, 0.098 mmol) was added and the reaction stirred for 1.0 h at 0 °C and then 12.0 h at −25 °C. The reaction solution was poured into a 1:1 mixture of diethyl ether–water (12 mL). The organic phase was separated and the aqueous phase was extracted with diethyl ether (3 × 1 mL). The combined organic phase was washed with brine and evaporated to an oil. Preparative thick layer chromatography (30% ethyl acetate–petroleum ether) gave pure clear oil **5** (9.60 mg, 40%). HPLC analysis provided a diastereoselectivity ratio of 97:3: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90 (d, 3 H, J = 6.65), 1.07 (s, 9 H), 1.14–1.45 (m, 6 H), 1.73 (m, 1 H), 1.88 (m, 1 H), 1.99 (m, 1 H), 2.12 (s, 3 H), 2.24 (dd, 1 H, J = 7.76, 16.05), 2.39 (dd, 1 H, J = 5.93, 16.05), 3.33 (m, 1 H), 3.83 (dd, 1 H, J = 3.23, 11.09), 4.03 (dd, 1 H, J = 4.79, 11.09), 4.57 (dt, 1 H, J = 4.03, 6.72), 7.38–7.47 (m, 6 H), 7.63–7.66 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 19.25, 19.77, 25.10, 26.56, 26.63, 26.72, 29.03, 30.50, 33.96, 36.59, 51.14, 58.75, 58.99, 74.75, 127.87, 129.97, 132.92, 135.52, 135.66, 169.38, 208.82 ppm; $[\alpha]_D$ +15.32° (c 0.47, MeOH); FAB mass spectrum, m/e 481 (M^+ + 1), 403 (M^+ − phenyl).

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