An Efficient Synthesis of Antibiotic (−)-A26771B

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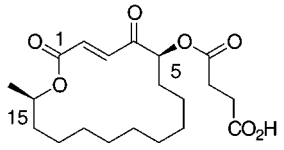
Introduction

The γ-oxygenated α,β-unsaturated carboxylic acid unit is a common structure found in some macrocyclic lactones such as cytochalasins, aspicilin, brefeldins, patulolides, pyrenophorin, and A26771B, and their biological properties as well as their structures have attracted much interest from organic chemists.[1] So far, methods for the preparation of this unit have been elaborated and used for the total syntheses. Regarding antibiotic (−)-A26771B (**1**),[2] the total syntheses, the macrocyclization, and the



(-)-A26771B (**1**)

assembly of the C(1)−C(5) unit have been published.[3−14] It is surprising, however, that the construction of the chiral centers at C(5) and C(15), the most important synthetic point, has been investigated only by the Tatsuta−Kinoshita group with success of installing a succinic moiety onto the key diol intermediate **2** regioselectively (Figure 1).[4,5] Later, the synthesis of **2** was reported

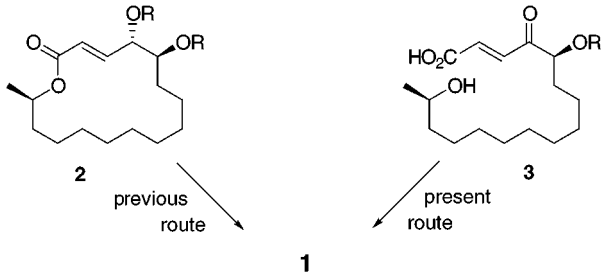
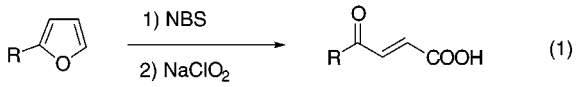


Figure 1. Two intermediates for the synthesis of **1**.

by two groups.[12,14] However, preparation of the unnecessary hydroxyl group at C(4) and its differentiation from the hydroxyl group(s) at the C(5) and/or C(15) positions make their syntheses rather lengthy.

Recently, we published the efficient protocol for conversion of 2-substituted furans into γ-oxo-α,β-unsaturated carboxylic acids (eq 1).[15] The synthetic advantage



(1)

of this oxidative conversion is that the stability of the furan ring permits a variety of reactions to be utilized for elaboration of the substituent R at C(2) of the furan ring. In addition, the high chemoselectivity of the reagents used for the furan oxidation allows common functional groups and protecting groups such as hydroxyl, carbonyl, acetal, and silyloxy groups to be involved in the substituent R. Herein we report an asymmetric synthesis of **1** that is accomplished highly efficiently utilizing the synthetic advantages mentioned above.

Results and Discussion

We envisioned a new seco acid of type **3** (Figure 1) in which the necessary C(1)−C(5) functionality is incorporated with the correct oxidation levels. Thus, installation of the succinic moiety at C(5) is a step which should be done after the macrocyclization.[16] Consequently, this would be more efficient than the previous methods if a synthesis of **1** through **3** is accomplished without epimerization at the C(5) carbon and without protection of the C(4) oxo group. We examined the route shown in Scheme 1, where the chiral center of the C(5) is secured by the kinetic resolution of racemic furfuryl alcohol *rac*-**6** with *t*-BuOOH/Ti(O-*i*-Pr)$_4$ and DIPT,[17] while the C(15) chiral center is derived from (*S*)-(+)-epichlorohydrin (**9**).

Swern oxidation of the commercially available bromo alcohol **4** afforded the aldehyde **5**,[18] which upon reaction with 2-furyllithium gave racemic furfuryl alcohol *rac*-**6** in high yield. Kinetic resolution of *rac*-**6** by using *t*-

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(16) Previously, the Hase group reported the methyl ester of A26771B through **3** (R = C(=O)(CH$_2$)$_2$CO$_2$Me).[3] The synthesis, however, suffers from low yields in some steps involved. Moreover, selective hydrolysis of the methyl succinate part to obtain acid **1** is not described.

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(18) Aldehyde **5** was also prepared in 88% yield from inexpensive 9-decen-1-ol by bromination (CBr_4, PPh_3) followed by ozonolysis. See the Experimental Section for details.

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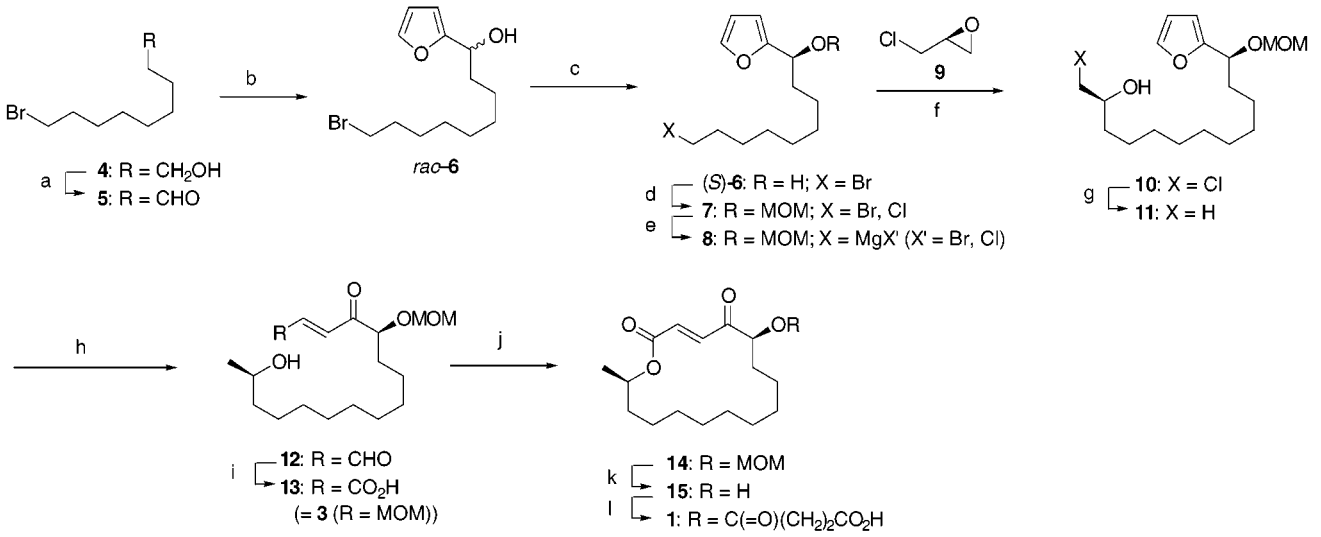
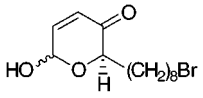
Scheme 1[a]



[a] Reagents and conditions: (a) $(COCl)_2$, DMSO, and then NEt_3 (94%); (b) 2-furyllithium, THF (91%); (c) *t*-BuOOH (0.6 equiv), $Ti(OPr)_4$ (0.2 equiv), D-(−)-DIPT (0.24 equiv), −15 °C, 15 h (36% based on *rac*-**6**); (d) MOMCl, *i*-Pr_2NEt, CH_2Cl_2 (88%); (e) Mg (3.3 equiv), $Br(CH_2)_2Br$ (0.07 equiv), THF, 45−80 °C; (f) **9**, CuCN (0.05 equiv), THF, −50 to −30 °C, 4.5 h (83%); (g) $LiAlH_4$ (96%); (h) NBS (1.2 equiv), $NaHCO_3$ (2 equiv), acetone/H_2O (10:1), −15 °C, 2.5 h; furan (3 equiv), −15 °C, 1 h; C_5H_5N (2 equiv), rt, 5 h (70%); (i) $NaClO_2$ (3 equiv), $Me_2C{=}CHMe$ (10 equiv), phosphate buffer (pH 3.6); (j) 2,4,6-$Cl_3C_6H_2COCl$, NEt_3, and then DMAP, toluene, 65−70 °C, 5 h (66% from **12**); (k) TFA, CH_2Cl_2, rt, 4 h; (l) succinic anhydride (2 equiv), DMAP (1 equiv) (63% from **14**).

BuOOH (0.6 equiv), Ti(O-*i*-Pr)$_4$ (0.2 equiv), and D-(−)-DIPT (0.24 equiv) at −15 °C for 15 h gave a mixture of pyran **16**, optically active alcohol (*S*)-**6**, and D-(−)-DIPT



16

after the usual workup. Since **16** is not useful in the synthesis any more, the mixture was treated with aqueous NaOH to convert both **16** and DIPT into water-soluble compounds according to the literature,[17] and thus purification of (*S*)-**6** (>95% ee)[19] by chromatography was carried out quite easily in 36% yield. Although the yield of (*S*)-**6** does not exceed the theoretical yield of 50% based on *rac*-**6**, the present method is efficient enough for practical use due to the operational simplicity of the steps and the adaptability to large-scale production of (*S*)-**6**. Protection of (*S*)-**6** with MOMCl unexpectedly afforded a mixture of bromide and chloride **7** (X = Br, Cl) in a ratio of 2:3−7 which was determined by ^{1}H NMR spectroscopy. Without separation, both halides were converted into Grignard reagent **8** under forcing conditions, keeping the higher temperature of 45−80 °C (bath temperature). Reaction of epoxide **9** (98.9% ee) with **8** (1.5 equiv) proceeded well in the presence of CuCN (0.05 equiv) to afford **10**, which upon reduction with $LiAlH_4$ furnished the alcohol **11** in good yield.

Oxidation of furan **11** with NBS under the reported conditions[15] proceeded efficiently with 70% yield, and further oxidation of aldehyde **12** with $NaClO_2$ furnished crude seco acid **13** (=**3** (R = MOM) in Figure 1). Macrocyclization of **13** was carried out by the Yamaguchi method[20] at 65−70 °C and proceeded successfully to afford lactone **14** in 66% yield from **12**. Comparison of the ^{1}H NMR spectrum (300 MHz) of **14** with that of a mixture[21] of **14** and its C(5) epimer[22] confirmed that <5% epimerization at the C(5) carbon took place during the macrocyclization. Finally, deprotection of MOM group with CF_3CO_2H followed by esterification with succinic anhydride furnished **1** in 63% yield without epimerization. The ^{1}H and ^{13}C NMR spectra and $[\alpha]_D$ value of **1** thus synthesized were identical with those previously reported ($[\alpha]^{26}_D$ −13.7 (*c* 0.19, MeOH); lit. $[\alpha]_D$ −13 to −14 (MeOH)).[2,4,12]

In summary, the efficient and short-step synthesis of antibiotic A26771B was achieved through the new seco acid **3** (R = MOM).[23]

Experimental Section

General Methods. Infrared (IR) spectra are reported in wavenumbers (cm^{-1}). Unless otherwise noted, ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were measured in $CDCl_3$ using $SiMe_4$ (δ = 0 ppm) and the center line of the $CDCl_3$ triplet (δ = 77.1 ppm) as internal standards, respectively. The following solvents were distilled before use: THF (from Na/benzophenone), Et_2O (from Na/benzophenone), and CH_2Cl_2 (from CaH_2). (*S*)-Epichlorohydrin (**9**) (98.9% ee) was kindly offered by Daiso, Japan. The phosphate buffer of pH 3.6 was prepared by mixing $Na_2HPO_4{\cdot}12H_2O$ (2.31 g), citric acid (1.31 g), and H_2O (98.6 g). Routinely, organic extracts were concentrated using a rotary evaporator, and residues were purified by chromatography on silica gel.

9-Bromononanal (5) from 9-Bromo-1-nonanol (4). To a solution of $(COCl)_2$ (1.41 mL, 16.2 mmol) in CH_2Cl_2 (35 mL) was

(19) Determined by comparing the ^{1}H NMR spectrum of the MTPA ester of (*S*)-**6** with that of *rac*-**6**.

(20) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989−1993.

(21) A mixture of **14** and the epimer at C(5) was synthesized by the method of Scheme 1 using racemic alcohol *rac*-**6** as the C(1)−C(13) part.

(22) Diagnostic peaks in the ^{1}H NMR spectrum of the epimer: δ 4.36 (t, *J* = 6 Hz, 1 H), 6.75 (d, *J* = 16 Hz, 1 H), 7.24 (d, *J* = 16 Hz, 1 H).

(23) The synthesis was achieved with 12 steps in 6.3% overall yield.

added a solution of DMSO (2.55 mL, 36.0 mmol) in CH_2Cl_2 (7.6 mL) at −55 °C. After 5 min, **4** (1.67 g, 17.5 mmol) dissolved in CH_2Cl_2 (7.5 mL) was added over 5 min. The mixture was stirred at the same temperature for 15 min, and then NEt_3 (5.2 mL, 37 mmol) was added. The mixture was allowed to warm to 0 °C over 40 min with vigorous stirring and poured into brine. Product was extracted with Et_2O two times, and the combined extracts were dried over $MgSO_4$ and concentrated. The residue was purified by chromatography (hexane/Et_2O) to afford **5** (1.55 g) in 94% yield: IR (neat) 1724, 1269 cm^{-1}; ^1H NMR δ 1.26−1.48 (m, 8 H), 1.58−1.68 (m, 2 H), 1.85 (quintet, J = 7 Hz, 2 H), 2.42 (dt, J = 2, 7 Hz, 2 H), 3.40 (t, J = 7 Hz, 2 H), 9.77 (t, J = 2 Hz, 1 H).

9-Bromononanal (5) from 9-Decen-1-ol. To an ice cold solution of 9-decen-1-ol (9.92 mL, 55.6 mmol) and CBr_4 (20.8 g, 62.7 mmol) in CH_2Cl_2 (84 mL) was added PPh_3 (9.60 g, 74.7 mmol) portionwise. The mixture was stirred at 0 °C for 2 h and then at room temperature overnight. Most of the volatile material was removed by using a rotary evaporator, and the residue was diluted with hexane. The resulting mixture was filtered through a pad of Celite with hexane, and the filtrate was concentrated to give crude 1-bromo-9-decene, which was used for the next reaction without further purification: ^1H NMR δ 1.24−1.48 (m, 10 H), 1.85 (quintet, J = 7 Hz, 2 H), 2.03 (q, J = 7 Hz, 2 H), 3.40 (t, J = 7 Hz, 2 H), 4.93 (ddt, J = 10, 2, 1 Hz, 1 H), 4.99 (ddt, J = 17, 2, 2 Hz, 1 H), 5.81 (ddt, J = 17, 10, 7 Hz, 1 H).

To a solution of the above bromide and NEt_3 (2.5 mL, 17.9 mmol) in EtOH (80 mL) was gently bubbled ozone gas at −70 °C for 2 h. To remove excess ozone, argon gas was bubbled for 1 h, during which time the solution was allowed to warm to room temperature, and then SMe_2 (16 mL, 218 mmol) was added to it. The solution was stirred overnight and concentrated to give an oil, which was purified by chromatography (hexane/Et_2O) to afford **5** (10.84 g) in 88% yield.

(1*R*)- and (1*S*)-9-Bromo-1-(2-furyl)nonan-1-ol (*rac*-6). To an ice cold solution of furan (10 mL, 137 mmol) and bipyridine (ca 10 mg) in THF (50 mL) was added *n*-BuLi (50 mL, 2.46 M in hexane, 123 mmol) dropwise. After being stirred for 3 h at 0 °C, the solution was cooled to −70 °C, and **5** (10.84 g, 49.0 mmol) dissolved in THF (30 mL) was added slowly. The solution was stirred between −70 and −60 °C for 4 h and poured into a mixture of Et_2O and saturated NH_4Cl with vigorous stirring. The phases were separated, and the aqueous phase was extracted with Et_2O. The combined extracts were dried over $MgSO_4$ and concentrated to give an oil, which was purified by chromatography (hexane/EtOAc) to afford *rac*-**6** (12.93 g) in 91% yield: IR (neat) 3369, 1504, 1149, 737 cm^{-1}; ^1H NMR δ 1.28−1.48 (m, 10 H), 1.79−1.89 (m, 5 H), 3.40 (t, J = 7 Hz, 2 H), 4.66 (t, J = 7 Hz, 1 H), 6.23 (d, J = 3 Hz, 1 H), 6.33 (dd, J = 3, 2 Hz, 1 H), 7.37 (dd, J = 2, 1 Hz, 1 H); ^{13}C NMR δ 157.1, 142.1, 110.3, 105.9, 67.9, 35.5, 34.0, 32.8, 29.28, 29.25, 28.6, 28.1, 25.4. Anal. Calcd for $C_{13}H_{21}BrO_2$: C, 53.99; H, 7.32. Found: C, 53.78; H, 7.31.

(1*S*)-9-Bromo-1-(2-furyl)nonan-1-ol ((*S*)-6). To a mixture of 4 Å molecular sieves (5 g) and Ti(O-*i*-Pr)$_4$ (2.44 mL, 8.27 mmol) in CH_2Cl_2 (34 mL) was added D-(−)-DIPT (2.11 mL, 9.94 mmol) at −20 °C. The mixture was stirred at −20 °C for 10 min, and then *rac*-**6** (11.97 g, 41.4 mmol) in CH_2Cl_2 (7 mL) and, after 30 min, *t*-BuOOH in CH_2Cl_2 (5.3 mL, 4.72 M, 25 mmol) were added at −20 °C. The mixture was stirred at −15 °C for 15 h, and the reaction was quenched by addition of SMe_2 (1.8 mL, 24.5 mmol). After 30 min of stirring at −20 °C, the cooling bath was removed, and aqueous tartaric acid (1.7 mL, 10% solution), Et_2O (34 mL), NaF (10 g, 240 mmol), and Celite (10 g) were added successively. The resulting mixture was stirred at room temperature for 2 h and filtered through a pad of Celite with Et_2O. The filtrate was concentrated to afford a mixture of (*S*)-**6**, pyran **16**, and D-(−)-DIPT.

To the above mixture dissolved in Et_2O (70 mL) was added 3 N NaOH (30 mL, 90 mmol) at 0 °C. The mixture was stirred vigorously for 30 min and diluted with Et_2O and brine. The resulting mixture was filtered through a pad of Celite with Et_2O. The filtrates were separated, and the aqueous layer was extracted with Et_2O two times. The combined ethereal solutions were dried over $MgSO_4$ and concentrated to give an oil, which was purified by chromatography (hexane/Et_2O) to afford (*S*)-**6** (4.29 g, 36% based on *rac*-**6**). The enantiomeric excess of (*S*)-**6** thus obtained was >95% by ^1H NMR spectroscopy of the MTPA ester: $[\alpha]^{28}_D$ −8.49 (*c* 0.47, $CHCl_3$).

(*S*)-2-[(9-Halo-1-methoxymethoxy)nonanyl]furan (7, X = Br, Cl). A solution of (*S*)-**6** (7.83 g, 27.1 mmol), *i*-Pr_2NEt (19 mL, 109 mmol), and MOMCl (4.1 mL, 54 mmol) in CH_2Cl_2 (90 mL) was stirred at room temperature overnight and poured into a mixture of EtOAc and saturated $NaHCO_3$. The resulting mixture was stirred for 30 min vigorously, the layers were separated, and the aqueous layer was extracted with EtOAc. The combined extracts were dried over $MgSO_4$ and concentrated to furnish an oil, which was purified by chromatography (hexane/EtOAc) to give **7** (7.31 g). The ^1H NMR spectrum of the product showed it to be a mixture of **7** (X = Br) and **7** (X = Cl) in a ratio of 2:3, and hence the yield was calculated to be 88%. Compound **7** (X = Br, Cl) thus obtained was distilled for the next reaction without separation: bp 140 °C (1 Torr); IR (neat) 3120, 1504, 1032, 738 cm^{-1}; ^1H NMR δ 1.20−1.46 (m, 10 H), 1.70−1.93 (m, 4 H), 3.36 (s, 3 H), 3.40 (t, J = 7 Hz, 0.8 H), 3.52 (t, J = 7 Hz, 1.2 H), 4.53 (d, J = 7 Hz, 1 H), 4.58 (t, J = 7 Hz, 1 H), 4.61 (d, J = 7 Hz, 1 H), 6.26 (dd, J = 3, 1 Hz, 1 H), 6.32 (dd, J = 3, 2 Hz, 1 H), 7.38 (dd, J = 2, 1 Hz, 1 H).

(2*R*,12*S*)-1-Chloro-12-(2-furyl)-12-methoxymethoxydodecan-2-ol (10). To a mixture of Mg (0.95 g, 0.040 mol) and THF (5 mL) was added 1,2-dibromoethane (0.07 mL, 0.81 mmol) to activate Mg. Exothermic reaction occurred immediately, and then halide **7** (X = Br and Cl in a mole ratio of 2:7) (3.57 g, 12.0 mmol) dissolved in THF (6 mL) was added to it. After the addition, the mixture was heated to 45 °C (bath temperature) for 3.5 h and then to 80 °C for 2.5 h, and cooled to room temperature. The Grignard reagent **8** thus prepared was used for the next reaction without titration.

To a flask containing CuCN (36 mg, 0.402 mmol) at −50 °C were added the above Grignard reagent **8** and epoxide **9** (98.9% ee, 0.63 mL, 8.05 mmol) dissolved in THF (5 mL). After the addition, the mixture was warmed to −30 °C over 4.5 h and poured into a mixture of Et_2O and saturated NH_4Cl with vigorous stirring. The organic layer was separated, and the aqueous layer was extracted with Et_2O two times. The combined extracts were dried over $MgSO_4$ and concentrated to give an oil, which was purified by chromatography (hexane/EtOAc) to furnish **10** (2.30 g) in 83% yield: IR (neat) 3446, 1504, 1034, 741 cm^{-1}; ^1H NMR δ 1.20−1.55 (m, 16 H), 1.75−1.98 (m, 2 H), 2.12 (d, J = 5 Hz, 1 H), 3.36 (s, 3 H), 3.47 (dd, J = 11, 7 Hz, 1 H), 3.63 (dd, J = 11, 3 Hz, 1 H), 3.74−3.84 (m, 1 H), 4.53 (d, J = 7 Hz, 1 H), 4.58 (t, J = 7 Hz, 1 H), 4.61 (d, J = 7 Hz, 1 H), 6.26 (dd, J = 3, 1 Hz, 1 H), 6.32 (dd, J = 3, 2 Hz, 1 H), 7.38 (dd, J = 2, 1 Hz, 1 H); ^{13}C NMR δ 154.4, 142.4, 110.1, 108.1, 94.1, 71.5, 71.0, 55.6, 50.6, 34.2, 34.0, 29.4, 29.3, 25.7, 25.5.

(2*R*,12*S*)-12-(2-Furyl)-12-methoxymethoxydodecan-2-ol (11). To an ice cold solution of **10** (1.97 g, 5.67 mmol) dissolved in THF (11 mL) was added $LiAlH_4$ (215 mg, 5.67 mmol) slowly. The resulting mixture was stirred at room temperature overnight and cooled to 0 °C. Excess hydride was destroyed by addition of EtOAc (6 mL, 61 mmol) and H_2O (0.51 mL, 28 mmol). After the mixture was stirred for 10 min at room temperature, NaF (1.18 g, 28 mmol) and EtOAc (4 mL) were added, and the resulting mixture was stirred at room temperature for 2 h and filtered through a pad of Celite with EtOAc. The filtrate was concentrated to give an oil, which was purified by chromatography (hexane/EtOAc) to furnish **11** (1.71 g) in 96% yield: $[\alpha]^{27}_D$ −111 (*c* 0.506, $CHCl_3$); IR (neat) 3417, 1504, 1034, 739 cm^{-1}; ^1H NMR δ 1.18 (d, J = 6 Hz, 3 H), 1.20−1.46 (m, 17 H), 1.74−1.98 (m, 2 H), 3.36 (s, 3 H), 3.72−3.83 (m, 1 H), 4.53 (d, J = 7 Hz, 1 H), 4.57 (t, J = 7 Hz, 1 H), 4.61 (d, J = 7 Hz, 1 H), 6.26 (dd, J = 3, 1 Hz, 1 H), 6.31 (dd, J = 3, 2 Hz, 1 H), 7.38 (dd, J = 2, 1 Hz, 1 H); ^{13}C NMR δ 154.5, 142.4, 110.0, 108.1, 94.1, 71.0, 68.2, 55.5, 39.4, 34.0, 29.55, 29.60, 29.5, 29.3, 25.74, 25.66, 23.5. Anal. Calcd for $C_{18}H_{32}O_4$: C, 69.19; H, 10.32. Found: C, 69.06; H, 10.55.

(2*E*,5*S*,15*R*)-15-Hydroxy-5-methoxymethoxy-4-oxo-2-hexadecenal (12). To a mixture of **11** (726 mg, 2.32 mmol) and $NaHCO_3$ (390 mg, 4.64 mmol) in acetone/H_2O (10:1, 10 mL) was added NBS (496 mg, 2.79 mmol) dissolved in acetone/H_2O (10:1, 5.5 mL) at −15 °C. The mixture was stirred for 2.5 h, and furan (0.50 mL, 6.9 mmol) was added to destroy excess NBS. After 1 h at −15 °C, pyridine (0.37 mL, 4.6 mmol) was added, and the cooling bath was removed. The mixture was stirred at

room temperature for 5 h and poured into the phosphate buffer (pH 3.6) with EtOAc. The phases were separated, and the aqueous phase was extracted with EtOAc. The combined organic phases were dried over $MgSO_4$ and concentrated to give the residue, which was purified by chromatography (hexane/EtOAc) to afford **12** (530 mg) in 70% yield: IR (neat) 3448, 1715, 1695, 1039, 920 cm^{-1}; ^1H NMR δ 1.18 (d, J = 6 Hz, 3 H), 1.22−1.50 (m, 16 H), 1.60−1.81 (m, 3 H), 3.35 (s, 3 H), 3.73−3.84 (m, 1 H), 4.18 (dd, J = 8, 6 Hz, 1 H), 4.68 (br s, 2 H), 6.94 (dd, J = 16, 8 Hz, 1 H), 7.28 (d, J = 16 Hz, 1 H), 9.8 (d, J = 8 Hz, 1 H); ^{13}C NMR δ 200.1, 193.3, 140.8, 138.3, 96.8, 82.4, 68.0, 56.2, 39.2, 31.9, 29.5, 29.4, 29.3, 29.23, 29.19, 25.6, 24.9, 23.4.

(2*E*,5*S*,15*R*)-5-Methoxymethoxyhexadec-2-en-15-olide (14). To a solution of **12** (197 mg, 0.60 mmol) and 2-methyl-2-butene (0.64 mL, 6.04 mmol) in *t*-BuOH (3 mL) and the phosphate buffer (pH 3.6, 1.5 mL) was added $NaClO_2$ (204 mg, purity 80%, 1.80 mmol) dissolved in H_2O (1.5 mL), and the resulting mixture was stirred for 3 h at room temperature. Most of the solvents were removed by using a vacuum pump, and the residue was diluted with EtOAc and the phosphate buffer (pH 3.6). The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated to leave crude **13**, which was used for the next reaction without further purification: IR (neat) 3421, 1720, 1701, 1036 cm^{-1}; ^1H NMR δ 1.19 (d, J = 6 Hz, 3 H), 1.20−1.50 (m, 17 H), 1.58−1.78 (m, 2 H), 3.35 (s, 3 H), 3.76−3.87 (m, 1 H), 4.15 (dd, J = 7, 6 Hz, 1 H), 4.64 (d, J = 7 Hz, 1 H), 4.67 (d, J = 7 Hz, 1 H), 5.4 (br peak, 1 H), 6.80 (d, J = 16 Hz, 1 H), 7.45 (d, J = 16 Hz, 1 H).

A solution of the above acid **13** and NEt_3 (0.42 mL, 3.01 mmol) in THF (3 mL) was stirred at room temperature for 20 min, and 2,4,6-trichlorobenzoyl chloride (0.14 mL, 0.896 mmol) in THF (3 mL) was added. The solution was stirred at room temperature for a further 2 h. The resulting white precipitate (triethylamine hydrochloride) was removed by dilution with toluene (100 mL) followed by filtration through a pad of Celite with additional toluene. The filtrate, after further dilution with toluene (total 300 mL), was divided into three equal portions, while three solutions of DMAP (each 98 mg, 0.802 mmol) in toluene (each 30 mL) were prepared. Each toluene solution of the mixed anhydride was added to each solution of DMAP at 65−70 °C over 5 h. After the addition, the solutions were stirred for a further 30 min and cooled to room temperature. The combined solutions were washed with saturated $NaHCO_3$ and with brine. The layers were separated, and the aqueous layer was washed with Et_2O. The toluene and ether extracts were combined, dried over $MgSO_4$, and concentrated to afford a residue, which was purified by chromatography (hexane/EtOAc) to afford lactone **14** (130 mg) in 66% yield from **12**: $[\alpha]^{27}_D$ −49 (*c* 0.282, $CHCl_3$); IR (neat) 1725, 1715, 1630, 920 cm^{-1}; ^1H NMR δ 1.30 (d, J = 6 Hz, 1 H), 1.06−1.66 (m, 16 H), 3.35 (s, 3 H), 4.23 (dd, J = 7, 5 Hz, 1 H), 4.65 (d, J = 7 Hz, 1 H), 4.68 (d, J = 7 Hz, 1 H), 5.04−5.15 (m, 1 H), 6.77 (d, J = 16 Hz, 1 H), 7.32 (d, J = 16 Hz, 1 H); ^{13}C NMR δ 199.3, 165.2, 135.1, 132.1, 96.3, 81.9, 72.6, 56.1, 34.8, 30.5, 27.7, 27.64, 27.56, 26.7, 26.4, 23.6, 21.9, 20.1. Anal. Calcd for $C_{18}H_{30}O_5$: C, 66.23; H, 9.26. Found: C, 66.04; H, 9.40.

(−)-A26771B (1). To an ice cold solution of **14** (64 mg, 0.196 mmol) in CH_2Cl_2 (10 mL) was added CF_3CO_2H (0.65 mL). The cooling bath was removed, and the solution was stirred at room temperature for 4 h. The volatile compounds were removed by using a vacuum pump, and the residue was filtered through a short column of silica gel with EtOAc to afford **15**, which was used for the next reaction without further purification: ^1H NMR (selected peaks) δ 1.30 (d, J = 7 Hz, 3 H), 4.50−4.57 (m, 1 H), 5.12−5.23 (m, 1 H), 6.80 (d, J = 16 Hz, 1 H), 7.26 (d, J = 16 Hz, 1 H).

A solution of the above **15**, succinic anhydride (39 mg, 0.39 mmol), and DMAP (24 mg, 0.20 mmol) in CH_2Cl_2 (3 mL) was stirred at room temperature for 6 h and poured into a mixture of EtOAc and the phosphate buffer (pH 3.6) with vigorous stirring. The layers were separated, and the aqueous layer was extracted with EtOAc two times. The combined extracts were dried over $MgSO_4$ and concentrated to leave an oil, which was purified by chromatography (benzene/acetone) to afford **1** (47 mg, 63% from **14**): $[\alpha]^{26}_D$ −13.7 (*c* 0.188, MeOH); lit.[2,4,12] −13 to −14 (MeOH). The ^1H NMR and ^{13}C NMR spectra of **1** were identical with those reported in the literature.[2,4,12]

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Supporting Information Available: Copies of NMR spectra for **5**, **7**, **10**, **12**, **13**, **14**, and a mixture of **14** and the epimer of **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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