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Synthesis of γ,δ-Unsaturated-β-keto Lactones via Sequential Cross Metathesis−Lactonization: A Facile Entry to Macrolide Antibiotic (−)-A26771B

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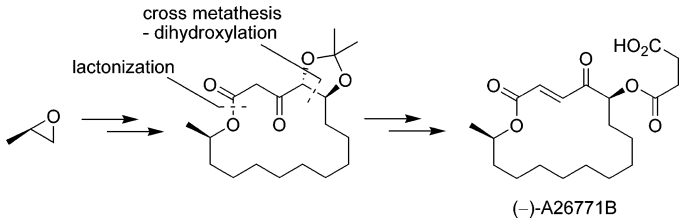


A simple access to γ,δ-unsaturated-β-keto lactones is presented, allowing a rapid total synthesis of the naturally occurring 16-membered macrolide antibiotic (−)-A26771B via cross metathesis, asymmetric dihydroxylation, and lactonization as the key steps.

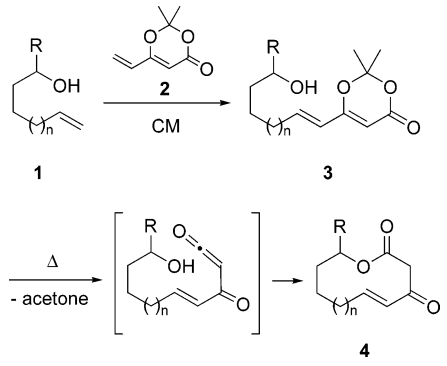
Introduction

Because of their unique biological properties and synthetically challenging structures, the development of methodology for the preparation of macrolides has received much synthetic attention during the past decades.[1] Although a mild and quite high yielding macrocyclization strategy, the thermal cycloreversion of dioxolenones followed by intramolecular ketene trapping[2] has remained rather unexploited in natural product synthesis.[3]

Intrigued by its potential we set out to combine this general lactonization method with the high efficiency of olefin metathesis.[4] Thus, selective cross metathesis (CM) of hydroxyalkenes such as **1** with the conjugated dienone **2**, followed by thermolysis under suitable high dilution conditions, was considered to conveniently deliver monomeric γ,δ-unsaturated-β-keto lactones of type **4** (Scheme 1).

Furthermore, functionalization of the CM-generated double bond as well as transformation of the β-keto lactone moiety would enable access to substituted derivatives, as demonstrated by the total synthesis of the macrolide antibiotic (−)-A26771B (Figure 1).

SCHEME 1. Concept for Synthesis of γ,δ-Unsaturated-β-keto Lactones



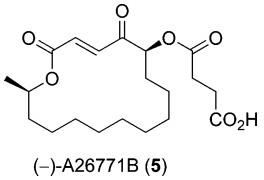


FIGURE 1. Antibiotic (−)-A26771B.

(1) Tadashi, N. In *Macrolide Antibiotics: Chemistry, Biology and Practice*, 2nd ed.; Omura, S., Ed.; Academic Press: San Diego, 2002; pp 181−284.

(2) See, for example: (a) Eisenberg, S. W. E.; Chen, C.; Wu, J.; Lebrilla, C.; Kurth, M. J. *Tetrahedron Lett.* **1996**, *37*, 7683−7686. (b) Petasis, N. A.; Patane, M. A. *J. Chem. Soc., Chem. Commun.* **1990**, *11*, 836−837. (c) Boeckman, R. K.; Perni, R. B. *J. Org. Chem.* **1986**, *51*, 5486-5489.

(3) For two recent examples, see: (a) Cramer, N.; Laschat, S.; Baro, A.; Schwalbe, H.; Richter, C. *Angew. Chem.* **2005**, *117*, 831−833. (b) Trost, B. M.; Gunzner, J. L.; Dirat, O.; Rhee, Y. H. *J. Am. Chem. Soc.* **2002**, *124*, 10396−10415.

(4) Grubbs, R. H. *Handbook of Metathesis*; Wiley-VCH: Weinheim, 2003.

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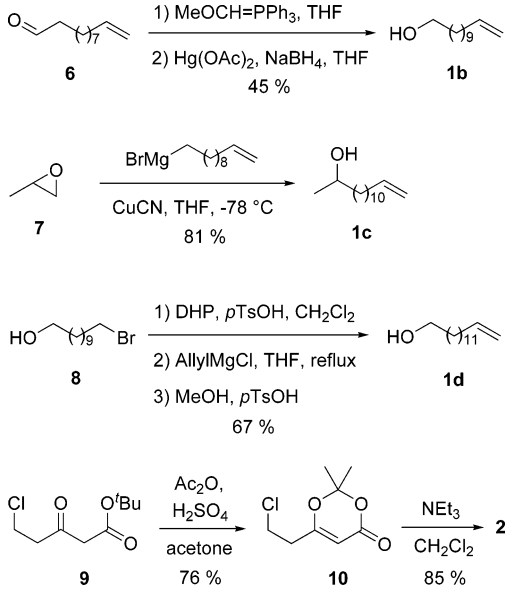
SCHEME 2. Synthesis of CM Precursors



Results and Discussion

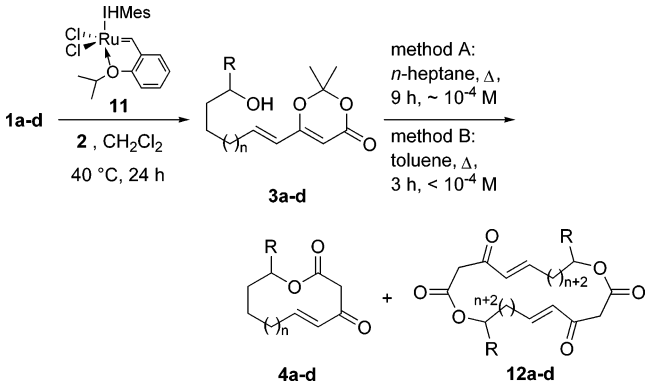
The intramolecular trapping of hydroxyalkylketenes derived from substrates such as **3** is quite sensitive to transition-state conformational effects manifested by ring size.[5] Whereas the preparation of saturated eight-membered β-keto lactones worked well,[2b] the cyclization to corresponding 10- and 11-membered analogues failed even under high dilution conditions ($<10^{-4}$ M).[2a] For this reason and with respect to the additional unsaturation in the starting material lowering the conformational flexibility, we focused our investigations on the synthesis of simple 14- to 18-membered macrolactones.

In addition to purchasable 9-decen-1-ol (**1a**), the long-chain alcohols **1b**−**d** were favored as adequate substrates because they can be easily derived from commercially available compounds (Scheme 2). While dodecenol **1b**[6] and tetradecenol **1c**[7] could be prepared according to literature procedures, the direct conversion of 11-bromo-1-undecanol (**8**) with allylmagnesium bromide in the presence of CuI produced significant amounts of byproduct. However, refluxing the corresponding THP ether with excess allylmagnesium chloride[8] in THF gave the known tetradecenol **1d**[9] in 67% overall yield after deprotection.

Concerning the synthesis of dienone **2**, acetonization of the known β-keto ester **9**[10] and subsequent chloride elimination were found to be an efficient strategy, which at the same time should allow access to various substituted congeners.

The results and conditions of the CM reactions and subsequent lactonizations are presented in Table 1. As indicated, the CM reactions between alcohols **1a**−**d** and dienone **2** were preferentially carried out stoichiometrically in the presence of

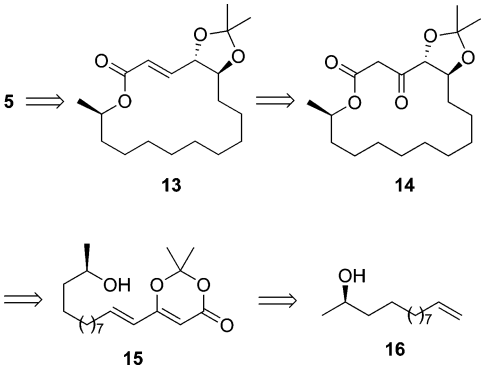
TABLE 1. Results and Conditions of CM Reactions and Subsequent Lactonizations



alcohol	*n*	R	equiv **2**	mol % **11**	yield **3** (%)	yield **4** (%)	yield **12** (%)
1a	5	H	1	5	71		71[a]
1b	7	H	1	5	75	44[a]/78[b]	*c*
1c	8	Me	1	5	78	82[a]	
1d	9	H	1	5	77	85[a]	

[a] Method A. [b] Method B. [c] Not isolated.

SCHEME 3. Retrosynthetic Analysis of (−)-A26771B



5 mol % of the commercial ruthenium catalyst **11**[11] under standardized conditions (CH_2Cl_2, 40 °C, 24 h). In this manner, the desired hydroxyalkenyldioxolenones **3a**−**d** were obtained with high *E*-selectivity (*E*/*Z* > 20:1) in good yields after column chromatographic separation from some amount of partially homodimerized alcohol.

The subsequent lactonizations were initially performed on a 0.1 mmol scale by refluxing a dilute solution ($\sim 10^{-4}$ M) of the cyclization precursors in *n*-heptane for 9 h (method A). Although the use of toluene resulted in shorter reaction times (3 h), the crude products contained significant amounts of solvent-derived byproducts, complicating their column chromatographical purification.

Whereas the formation of 14-membered lactones by ring-closing metathesis is usually easy,[12] FAB mass spectrometry revealed that the main product obtained upon thermal cyclization of **3a** was the 28-membered diolide **12a** and no monomeric

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(6) Crouch, D. R.; Mehlmann, J. F.; Herb, B. R.; Mitten, J. V.; Dai, G. H. *Synthesis* **1999**, *4*, 559−561.
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(8) Taber, D. F.; Green, J. H.; Geremia, J. M. *J. Org. Chem.* **1997**, *62*, 9342−9344.
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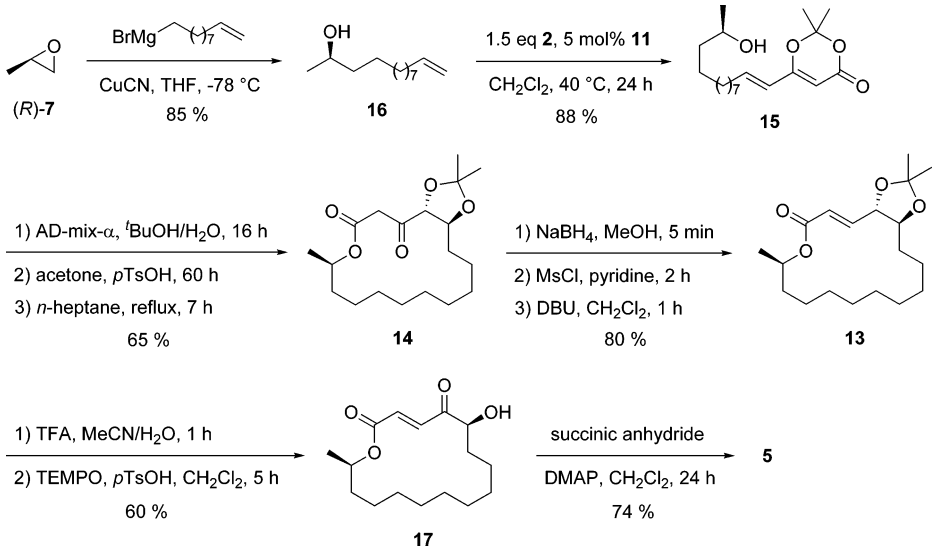
(11) For a short review on its unique activity, see: (a) Hoveyda, A. H.; Gillingham, D. G.; Van Veldhuizen, J. J.; Kataoka, O.; Garber, S. B.; Kingsbury, J. S.; Harrity, J. P. A. *Org. Biomol. Chem.* **2004**, *2*, 8−23. (b) Connon, S. J.; Blechert, S. *Angew. Chem.* **2003**, *115*, 1944−1968.
(12) See, for example: (a) Lee, C. W.; Grubbs, R. H. *Org. Lett.* **2000**, *2*, 2145−2147. (b) Fürstner, A.; Langemann, K. *Synthesis* **1997**, *7*, 792−803.

SCHEME 4. Synthesis of (−)-A26771B



lactone could be isolated. Somewhat surprised at this outcome, we continued with the 16-membered ring precursor **3b**. In this case two lactones in a ratio of about 1:1 (determined by ^{1}H NMR) were obtained of which the less polar one (SiO_2; 1% acetone in CH_2Cl_2) appeared to be the known β-keto lactone **4b**.[13] In an attempt to favor its formation, the macrocyclization was conducted by slow addition of a dilute toluene solution of **3b** to refluxing toluene over 4 h and additional stirring for 3 h (method B). Under these conditions, the concentration of dioxolenone was always $<10^{-4}$ M and only trace amounts of dimeric lactone were observed, affording **4b** in a considerably improved yield of 78%. Pleased by these results, we turned to the last two substrates **3c** and **3d**. Interestingly, in both cases application of method A led to the exclusive formation of the corresponding monomeric lactones **4c** and **4d**.

Regarding a first application of our methodology to natural product synthesis, the 16-membered macrolide antibiotic (−)-A26771B (**5**) was considered a suitable target (Figure 1). Isolated from the fungus *Penicillium turbatum*,[14] its unique antimicrobial profile has generated tremendous interest among organic chemists. Of numerous enantioselective approaches,[15] two more recent ones aimed at the asymmetric synthesis of lactone **13**,[15c,d] whose successful transformation into **5** has already been reported (Scheme 3).[15e,f] Since the conversion of β-keto esters into α,β-unsaturated derivatives is easy,[16] the β-keto lactone **14** represents a useful intermediate that should in turn be readily available from enantiopure CM product **15** via chemoselective asymmetric dihydroxylation, diol protection, and lactonization.

Accordingly, our intended total synthesis began with the preparation of the homochiral tridecenol **16** by ring opening of commercially available (*R*)-methyloxirane (Scheme 4). To avoid homodimerization, the following CM of **16** was carried out with 1.5 equiv of **2**, affording the desired cyclization precursor **15** in excellent yield (E/Z > 20:1). Asymmetric dihydroxylation of **15** using a modified AD-mix-α[17] and ^{t}BuOH/H_2O as solvent occurred smoothly and with high chemoselectivity over 16 h at room temperature. Protection of the crude diol and direct thermolysis (method A) of the reaction mixture furnished the β-keto lactone **14** in 65% yield as a single diastereoisomer that appeared to be partially enolized. As expected, mesylation of the diastereoisomeric alcohols obtained upon $NaBH_4$ reduction of **14**, followed by treatment with DBU, finally furnished in high overall yield the lactone **13**, whose spectral and physical data {$[\alpha]^{20}_D$ +5.4 (*c* 1.0, $CHCl_3$)} agreed with that reported.[15e,f]

As previously reported attempts to selectively oxidize the allylic hydroxy group of the diol derived from **13** were unsuccessful, a regioselective monosuccinylation followed by Swern oxidation of the remaining allylic alcohol afforded the natural product in 48% overall yield from **13**.[15f] In our search for an appropriate reagent allowing the selective oxidation, we were encouraged to find that a similar TEMPO-mediated oxidation has recently been employed in the synthesis of grahamimycin A.[18]

In this case, deprotection of **13** and treatment of the crude diol with 2 equiv of TEMPO and *p*TsOH in CH_2Cl_2 produced the hydroxyketone **17** in moderate yield. As its corresponding MOM ether has already been converted into **5** without epimerization in 63% yield via deprotection and succinylation in the prescence of DMAP,[15b] esterification of **17** under analogous conditions gave in 74% yield (−)-A26771B (**5**), which showed spectral and physical data consistent with the literature {$[\alpha]^{20}_D$ −13.2 (*c* 0.19, MeOH)}.[15e,f]

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(14) Michel, K. H.; Demarco, P. V.; Nagarajan, R. *J. Antibiot.* **1977**, *30*, 571−575.

(15) See, for example: (a) Lee, W.; Shin, H. J.; Chang, S. *Tetrahedron: Asymmetry* **2001**, *12*, 29−31. (b) Kobayashi, Y.; Okui, H. *J. Org. Chem.* **2000**, *65*, 612−615. (c) Nagarajan, M. *Tetrahedron Lett.* **1999**, *40*, 1207−1210. (d) Sinha, S. C.; Sinha-Bagchi, A.; Keinan, E. *J. Org. Chem.* **1993**, *58*, 7789−7796. (e) Quinkert, G.; Kueber, F.; Knauf, W.; Wacker, M.; Koch, U.; Becker, H.; Nestler, H. P.; Dürner, G.; Zimmermann, G.; Bats, J. W.; Egert, E. *Helv. Chim. Acta* **1991**, *74*, 1853−1923. (f) Tatsuta, K.; Amemiya, Y.; Kanemura, Y.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3248−3253.

(16) See, for example: (a) Taber, D. F.; Neubert, T. D. *J. Org. Chem.* **2001**, *66*, 143−147. (b) Kimura, Y.; Atarashi, S.; Takahashi, M.; Hayakawa, I. *Chem. Pharm. Bull.* **1994**, *42*, 1442−1454.

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(18) Hunter, T. J.; O'Doherty, G. A. *Org. Lett.* **2002**, *4*, 4447−4450.

Conclusion

In summary, we have described an efficient synthesis of γ,δ-unsaturated-β-keto lactones via sequential CM−lactonization resulting in a concise total synthesis of the macrolide antibiotic (−)-A26771B {17% overall yield from commercial (*R*)-methyloxirane}. Furthermore, the simple choice of starting material and AD-mix enables access to all nonnatural isomers, of which the (5*R*,15*R*)-diastereomer proved to be twice as active as the natural product.[15f]

Experimental Section

6-(2-Chloro-ethyl)-2,2-dimethyl-[1,3]dioxin-4-one (10). To a solution of **9** (1.03 g, 5 mmol) and Ac_2O (1.5 g, 15 mmol) in acetone (10 mmol, 0.75 mL) was added concentrated H_2SO_4 (5 mmol, 0.28 mL) dropwise at 0 °C. The mixture was stirred at room temperature for 16 h, diluted with H_2O (50 mL), and extracted with CH_2Cl_2 (3 × 50 mL). Drying of the combined organic phases (Na_2SO_4), evaporation of the solvent, and purification by flash chromatography (SiO_2; MTB/hexane = 1:2) afforded 730 mg (76%) of **10** as a yellow liquid: R_f = 0.14 (MTB/hexane = 1:2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.36 (s, 1H), 3.69 (t, *J* = 6.4 Hz, 2H), 2.70 (t, *J* = 6.4 Hz, 2H), 1.71 (s, 6H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.1, 160.8, 107.0, 95.8, 39.4, 36.6, 25.1 ppm; IR (ATR) ν 2999, 1728, 1638, 1392, 1273, 1203, 1016, 901 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_8H_{11}ClO_3$ (M^+) 190.0397, found 190.0388.

2,2-Dimethyl-6-vinyl-[1,3]dioxin-4-one (2). To a solution of **10** (720 mg, 3.8 mmol) in CH_2Cl_2 (10 mL) was added NEt_3 (764 mg, 7.55 mmol) dropwise at room temperature. The mixture was stirred at room temperature for 3 h, diluted with CH_2Cl_2 (70 mL) and washed with 1 N HCl (20 mL). Drying of the organic phase (Na_2SO_4), evaporation of the solvent and purification by flash chromatography (SiO_2; MTB/hexane = 1:2) afforded 500 mg (85%) of **2** as a yellow liquid: R_f = 0.26 (MTB/hexane = 1:2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.20 (dd, *J* = 17.2, 10.7 Hz, 1H), 6.01 (d, *J* = 17.2 Hz, 1H), 5.59 (d, *J* = 10.7 Hz, 1H), 5.34 (s, 1H), 1.71 (s, 6H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.9, 161.8, 129.4, 123.9, 106.6, 95.3, 25.1 ppm; IR (ATR) ν 2999, 1728, 1645, 1581, 1391, 1273, 1205, 1045, 999, 903 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_8H_{10}O_3$ (M^+) 154.0630, found 154.0631.

(*R*)-Tridec-12-en-2-ol (16). A solution of 9-decenylmagnesium bromide [freshly prepared from 10-bromo-1-decene (510 mg, 2.3 mmol) and Mg (62 mg, 2.55 mmol) in THF (3 mL)] was added over 30 min to a stirred suspension of (*R*)-methyloxirane (90 mg, 1.55 mmol) and CuCN (7 mg, 78 μmol) in THF (2 mL) at −78 °C. The mixture was allowed to warm to room temperature over 2 h, quenched with 1 N HCl (10 mL), and extracted with MTB (3 × 10 mL). Drying of the combined organic phases (Na_2SO_4), evaporation of the solvent, and purification by flash chromatography (SiO_2; MTB/hexane = 1:4) afforded 260 mg (85%) of **16** as a colorless liquid: R_f = 0.15 (MTB/hexane = 1:4); $[\alpha]^{20}_D$ = −6.2 (*c* = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.80 (m, 1H), 4.90−5.00 (m, 2H), 3.79 (m, 1H), 2.04 (m, 2H), 1.25−1.45 (m, 17H), 1.18 (d, *J* = 6.2 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 139.3, 114.2, 68.3, 39.4, 33.9, 29.7, 29.65, 29.6, 29.5, 29.2, 29.0, 25.8, 23.6 ppm; IR (ATR) ν 3349 (br), 2925, 2854, 1641, 1465, 1373, 909 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_{13}H_{26}O$ (M^+) 198.1984, found 198.1980.

6-[(*E*,*R*)-12-Hydroxy-tridec-1-enyl]-2,2-dimethyl-[1,3]dioxin-4-one (15). A solution of **16** (100 mg, 0.5 mmol), **2** (116 mg, 0.75 mmol), and catalyst **11** (16 mg, 0.025 mmol) in dry CH_2Cl_2 (5 mL) under nitrogen was stirred at 40 °C for 24 h. Evaporation of the solvent and purification by flash chromatography (SiO_2; 5% AcMe/CH_2Cl_2) afforded 142 mg (88%) of **15** as a light brown viscous oil: R_f = 0.16 (5% AcMe/CH_2Cl_2); $[\alpha]^{20}_D$ = −4.2 (*c* = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.55 (dt, *J* = 15.5, 7.0 Hz, 1H), 5.88 (d, *J* = 15.5 Hz, 1H), 5.23 (s, 1H), 3.78 (m, 1H), 2.19 (m, 2H), 1.70 (s, 6H), 1.35−1.45 (m, 5H), 1.25−1.35 (m, 12H), 1.18 (d, *J* = 6.2 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.5, 162.2, 142.8, 122.5, 106.3, 93.3, 68.2, 39.4, 32.8, 29.7, 29.6, 29.5, 29.4, 29.3, 28.4, 25.8, 25.1, 23.6 ppm; IR (ATR) ν 3429 (br), 2926, 2854, 1725, 1653, 1592, 1390, 1274, 1205, 1019, 903 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_{19}H_{32}O_4$ (M^+) 324.2301, found 324.2306; Anal. Calcd for $C_{19}H_{32}O_4$: C, 70.34; H, 9.94. Found: C, 69.97; H, 9.86.

(5*S*,6*S*,16*R*)-5,6-(Isopropylidendioxy)-16-methyl-oxacyclohexadeca-2,4-dione (14). A solution of **15** (65 mg, 0.2 mmol) in ^{t}BuOH/H_2O (1:1, 1.0 mL) was added to a vigorously stirred suspension of AD-mix-α (280 mg), K_2OsO_2 (0.44 mg), $NaHCO_3$ (50 mg, 0.6 mmol), and $MeSO_2NH_2$ (19 mg, 0.2 mmol) in ^{t}BuOH/H_2O (1:1, 1.0 mL) at 0 °C. After 16 h at room temperature the mixture was quenched with a dilute Na_2SO_3 solution (5 mL) and extracted with MTB (4 × 5 mL). Drying of the combined organic phases (Na_2SO_4) and evaporation of the solvent gave a residue that was dissolved in acetone (4 mL) and treated with *p*TsOH (3.8 mg, 0.02 mmol). After being stirred for 60 h at room temperature, the mixture was diluted with *n*-heptane (1600 mL) and refluxed for 7 h under nitrogen. Evaporation of the solvent and purification by flash chromatography (SiO_2; MTB/hexane = 1:10) afforded 44 mg (65%) of **14** as a colorless viscous oil: R_f = 0.18 (MTB/hexane = 1:10); $[\alpha]^{20}_D$ = +14.5 (*c* = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz, keto-/enol-form = 2:1) δ 11.9 (s, 1H, enol-form), 5.23 (s, 1H, enol-form), 5.20 (m, 1H, enol-form), 4.94 (m, 1H, keto-form), 4.24 (m, 1H, keto- and enol-form), 4.09 (d, *J* = 7.0 Hz, 1H, keto-form), 3.85 (d, *J* = 8.5 Hz, 1H, enol-form), 3.70 (d, *J* = 15 Hz, 1H, keto-form) 3.60 (d, *J* = 15 Hz, 1H, keto-form), 1.20−1.80 (m, 27H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz, keto- and enol-form) δ 202.0, 172.1, 171.8, 166.4, 110.3, 110.0, 93.4, 85.4, 82.5, 77.7, 77.3, 77.1, 76.8, 76.7, 73.0, 70.2, 45.9, 35.6, 32.1, 32.09, 28.1, 27.4, 27.3, 27.0, 26.9, 26.85, 26.8, 26.4, 26.0, 25.9, 25.8, 24.5, 23.5, 23.3, 23.0, 20.1 ppm; IR (ATR) ν 2985, 2932, 2859, 1747, 1721, 1651, 1460, 1381, 1235, 1063, 868, 804 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_{19}H_{32}O_5$ (M^+) 340.2250, found 340.2252. Anal. Calcd for $C_{19}H_{32}O_5$: C, 67.03; H, 9.47. Found: C, 66.71; H, 9.11.

(*E*,5*S*,6*S*,16*R*)-5,6-(Isopropylidendioxy)-16-methyl-oxacyclohexadec-3-en-2-one (13). To a stirred solution of **14** (34 mg, 0.1 mmol) in MeOH (1.0 mL) was added $NaBH_4$ (3.8 mg, 0.1 mmol) at room temperature. After 5 min the mixture was quenched with a saturated NaCl solution (5 mL) and extracted with Et_2O (3 × 5 mL). Drying of the combined organic phases (Na_2SO_4) and evaporation of the solvent gave a 2:1 mixture of two diastereomeric alcohols that was dissolved in pyridine (1 mL) and treated with MsCl (23 mg, 0.2 mmol). After being stirred for 2 h at room temperature the mixture was diluted with H_2O (5 mL) and extracted with CH_2Cl_2 (3 × 5 mL). Drying of the combined organic phases (Na_2SO_4) and evaporation of the solvent gave a residue that was dissolved in CH_2Cl_2 (1 mL), treated with DBU (30 mg, 0.2 mmol) and stirred for 1 h at room temperature. Evaporation of the solvent and purification by flash chromatography (SiO_2; MTB/hexane = 1:10) afforded 26 mg (80%) of **13** as a white solid: R_f = 0.21 (MTB/hexane = 1:10); mp 71−72 °C; $[\alpha]^{20}_D$ = +5.4 (*c* = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.88 (dd, *J* = 15.7, 6.8 Hz, 1H), 6.12 (d, *J* = 15.7 Hz, 1H), 5.03 (m, 1H), 4.13 (t, *J* = 7.5 Hz, 1H), 3.75 (m, 1H), 1.80 (m, 1H), 1.63 (m, 2H), 1.35−1.50 (m, 2H) 1.43 (s, 3H), 1.42 (s, 3H), 1.15−1.35 (m, 13H), 1.25 (d, *J* = 6.3 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.6, 144.4, 123.7, 109.3, 80.9, 80.2, 71.2, 35.4, 31.1, 27.9, 27.4, 27.37, 27.3, 27.1, 26.7, 26.6, 24.9, 23.4, 20.6 ppm; IR (ATR) ν 2986, 2929, 2858, 1709, 1661, 1458, 1369, 1257, 1182, 1055, 990, 862 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_{19}H_{32}O_4$ (M^+) 324.2301, found 324.2297.

(*E*,6*S*,16*R*)-6-Hydroxy-16-methyl-oxacyclohexadec-3-en-2,5-dione (17). To a stirred solution of **13** (25 mg, 0.077 mmol) in MeCN/H_2O (2:1, 0.9 mL) was added TFA (0.6 mL) dropwise at 0 °C. The mixture was allowed to warm to room temperature over 1 h, diluted with CH_2Cl_2 (60 mL), and washed with a saturated $NaHCO_3$ solution (30 mL). Drying of the organic phase (Na_2SO_4)

and evaporation of the solvent gave a yellow solid that was dissolved in dry CH_2Cl_2 (3 mL) and treated with *p*TsOH (29 mg, 0.15 mmol) and TEMPO (24 mg, 0.15 mmol) at 0 °C. After being stirred for 5 h at room temperature the solvent was evaporated, and the resulting residue was purified by flash chromatography (SiO_2; MTB/hexane = 1:4). Recrystallization from hexane afforded 13 mg (60%) of **17** as a white solid: R_f = 0.11 (MTB/hexane = 1:4); mp 84−85 °C; $[\alpha]^{20}_D$ = +22.4 (*c* = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.25 (d, *J* = 15.7, 1H), 6.79 (d, *J* = 15.7 Hz, 1H), 5.18 (m, 1H), 4.54 (m, 1H), 3.45 (br. s, 1H), 1.85 (m, 2H), 1.73 (m, 1H), 1.52 (m, 3H) 1.05−1.45 (m, 14H), 1.30 (d, *J* = 6.2 Hz, 3H), 0.98 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 201.5, 165.1, 135.0, 132.6, 76.5, 72.7, 34.3, 31.2, 28.2, 28.1, 27.4, 27.1, 26.9, 23.5, 20.7, 19.7 ppm; IR (ATR) ν 3490 (br), 2928, 2856, 1714, 1697, 1642, 1460, 1354, 1287, 1191, 1059, 983 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_{16}H_{27}O_4$ (MH^+) 283.1909, found 283.1914.

Mono[(*E*,6*S*,16*R*)-16-methyl-2,5-dioxooxacyclohexadec-3-en-6-yl]succinate (A26771B) (5). A solution of **17** (5 mg, 17.7 μmol), succinic anhydride (3.5 mg, 35 μmol), and DMAP (2.4 mg, 20 μmol) in CH_2Cl_2 (0.3 mL) was stirred for 24 h at room temperature. Evaporation of the solvent and purification by flash chromatography (SiO_2; 5% MeOH/CH_2Cl_2) afforded 5 mg (74%) of **5** as a white solid: R_f = 0.21 (5% MeOH/CH_2Cl_2); mp 121−122 °C; $[\alpha]^{20}_D$ = −13.2 (*c* = 0.19, MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.22 (d, *J* = 15.8, 1H), 6.75 (d, *J* = 15.8 Hz, 1H), 5.32 (t, *J* = 5.4 Hz, 1H), 5.14 (m, 1H), 2.73 (m, 4H), 1.90 (m, 2H), 1.68 (m, 1H), 1.55 (m, 1H) 1.10−1.50 (m, 15H), 1.30 (d, *J* = 6.3 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 195.5, 176.2, 171.5, 164.9, 135.3, 132.6, 78.0, 72.6, 34.6, 28.9, 28.7, 28.6, 28.0, 27.9, 27.3, 27.1, 27.0, 23.6, 22.3, 19.9 ppm; IR (ATR) ν 2928, 2857, 1742, 1703, 1381, 1300, 1196, 1165 cm^{-1}; MS (FAB) *m*/*z* calcd for $C_{20}H_{31}O_7$ (MH^+) 383, found 383.

Supporting Information Available: General experimental details and characterization data for the products from Table 1 and ^{1}H NMR spectra for the compounds **2**, **5**, **10**, and **13**−**17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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