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Synthesis of Dihydroplakortin, 6-*epi*-Dihydroplakortin, and Their C10-Desethyl Analogues

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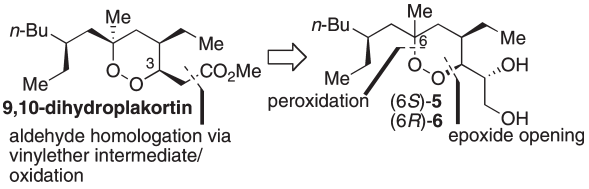

The first synthesis of the marine endoperoxide 9,10-dihydroplakortin, of its C10-desethyl analogue, and of their corresponding C6 epimers is described. Stereogenic centers at C4 and at the lateral chain have been stereoselectively synthesized through Evans' chiral auxiliary chemistry. Moreover, the reported synthesis features a one-pot three-step hydroperoxysilylation/cyclization reaction for the construction of the endoperoxide ring system. Homologation of the aldehyde resulting from diol cleavage through a Wittig-based strategy gave access to the ester-containing lateral chain at C3.

Introduction

9,10-Dihydroplakortin (**1**, Figure 1) is a polyketide isolated from the Caribbean sponge *Plakortis simplex*.[1−3] It belongs to a group of peroxide-containing natural products that have increasingly attracted the attention of medicinal chemists for their biological activities against malaria and various cancers.[4−8] Our interest in the total synthesis of natural compounds endowed with pharmacological activity[9,10] and in the field of peroxide antimalarials[2] prompted us to develop a versatile synthetic strategy to the natural product **1**. Several 1,2-dioxane-containing endoperoxides such as peroxyplakoric acids, Yingzhaosu A, Yingzhaosu C, and various plakortides and plakortolides have been isolated and structurally characterized so far, and a few syntheses have also been reported.[11−16] In general, the low stability of the O−O bond makes installation and functionalization a challenging task.[11,17] Reported procedures for the synthesis of 1,2-dioxanes involve [4 + 2]

(1) Cafieri, F.; Fattorusso, E.; Taglialatela-Scafati, O.; Ianaro, A. *Tetrahedron* **1999**, *55*, 7045–7056.
(2) Fattorusso, C.; Campiani, G.; Catalanotti, B.; Persico, M.; Basilico, N.; Parapini, S.; Taramelli, D.; Campagnuolo, C.; Fattorusso, E.; Romano, A.; Taglialatela-Scafati, O. *J. Med. Chem.* **2006**, *49*, 7088–7094.
(3) Fattorusso, E.; Parapini, S.; Campagnuolo, C.; Basilico, N.; Taglialatela-Scafati, O.; Taramelli, D. *J. Antimicrob. Chemother.* **2002**, *50*, 883–888.
(4) Efferth, T. *Drug Resist. Updates* **2005**, *8*, 85–97.
(5) Efferth, T. *Curr. Drug Targets* **2006**, *7*, 407–421.
(6) Jefford, C. W. *Drug Discovery Today* **2007**, *12*, 487–495.
(7) Tang, Y.; Dong, Y.; Vennerstrom, J. L. *Med. Res. Rev.* **2004**, *24*, 425–448.
(8) Dembitsky, V. M.; Gloriozova, T. A.; Poroikov, V. V. *Mini Rev. Med. Chem.* **2007**, *7*, 571–589.
(9) Hashimoto, M.; Liu, Y.; Fang, K.; Li, H. Y.; Campiani, G.; Nakanishi, K. *Bioorg. Med. Chem.* **1999**, *7*, 1181–1194.
(10) Kozikowski, A. P.; Campiani, G.; Sun, L.-Q.; Wang, S.; Saxena, A.; Doctor, B. P. *J. Am. Chem. Soc.* **1996**, *118*, 11357–11362.
(11) McCullough, K. J.; Nojima, M. *Curr. Org. Chem.* **2001**, *5*, 601–636.
(12) Kawanishi, M.; Kotoku, N.; Itagaki, S.; Horii, T.; Kobayashi, M. *Bioorg. Med. Chem.* **2004**, *12*, 5297–5307.
(13) Murakami, N.; Kawanishi, M.; Itagaki, S.; Horii, T.; Kobayashi, M. *Tetrahedron Lett.* **2001**, *42*, 7281–7285.
(14) Xu, X. X.; Zhu, J.; Huang, D. Z.; Zhou, W. S. *Tetrahedron Lett.* **1991**, *32*, 5785–5788.
(15) Xu, X. X.; Dong, H. Q. *J. Org. Chem.* **1995**, *60*, 3039–3044.
(16) Fattorusso, E.; Taglialatela-Scafati, O. *Mar. Drugs* **2009**, *7*, 130–152.
(17) Dussault, P. H.; Lee, H. J.; Niu, Q. J. *J. Org. Chem.* **1995**, *60*, 784–785.

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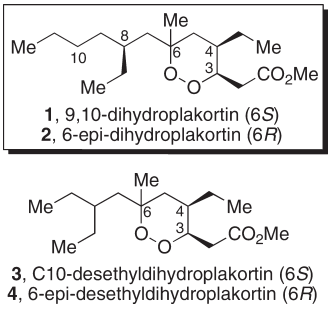
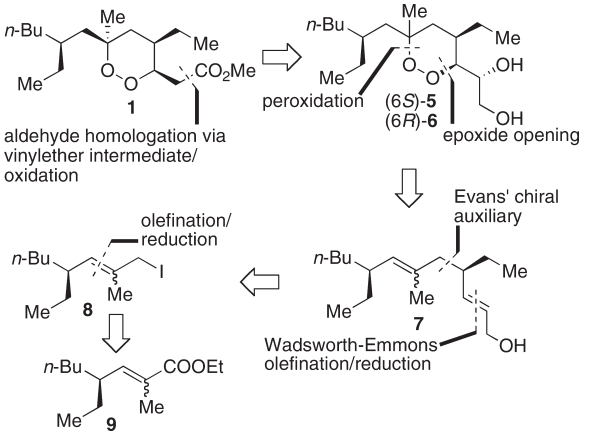


FIGURE 1. Molecular structures of 9,10-dihydroplakortin **1**, C10-desethyldihydroplakortin **3**, and their C6-epimers **2** and **4**.

SCHEME 1. Retrosynthetic Analysis for 9,10-Dihydroplakortin 1

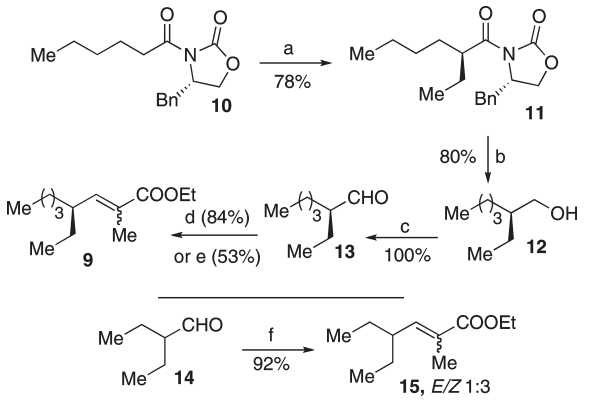


cycloadditions of oxygen to 1,3-dienes[18] or intramolecular cyclization reactions of hydroperoxides with appropriate side chains.[12,13,18−20] A drawback of these methods is the lack of stereochemical control at the newly formed stereogenic centers. One exception is the use of the peroxide as nucleophile for the intramolecular attack on epoxides, which has been exploited for the synthesis of Yingzhaousu C.[15] In this framework, the main challenge for the synthesis of 9,10-dihydroplakortin **1** is the presence of three stereogenic centers at the six-membered endoperoxide skeleton, two of them flaking the labile peroxide bond, and one of them (C6) being a quaternary carbon. Here we report the first total synthesis of **1** and of its simplified analogue **3**. The synthesis of epimers at C6 of both **1** and **3** (**2** and **4**, respectively) was also accomplished.

Results and Discussion

The retrosynthetic logic that directed the preparation of compounds **1**−**4** is illustrated in Scheme 1 for dihydroplakortin **1**. We decided to build up the 1,2-dioxane-based system of intermediates (6*S*)-**5** and (6*R*)-**6** in the latest steps of the synthetic procedure. The need of minimizing chemical operations after ring peroxide formation was dictated by the poor stability of the 1,2-dioxane system during functional group elaboration.

SCHEME 2. Synthesis of Intermediates 9 and 15[a]



[a]Reaction conditions: (a) i. NaHMDS, THF, −78 °C, 1 h; ii. EtI, −40 °C, 16 h, 78% yield, dr 99%; (b) $LiBH_4$, EtOH, Et_2O, 0 °C, 3 h, 80% yield; (c) PCC, silica gel, DCM, 25 °C, 16 h, 100% yield; (d) (carbethoxyethylidene)triphenylphosphorane, DCM, 25 °C, 16 h, 84% yield, *E*/*Z* 20:1; (e) triethyl-2-phosphonopropionate, NaH, THF, −30 °C, 4 h, 53% yield, *E*/*Z* 1:2; (f) triethyl-2-phosphonopropionate, NaH, THF, 25 °C, 3 h, 92% yield, *E*/*Z* 1:3.

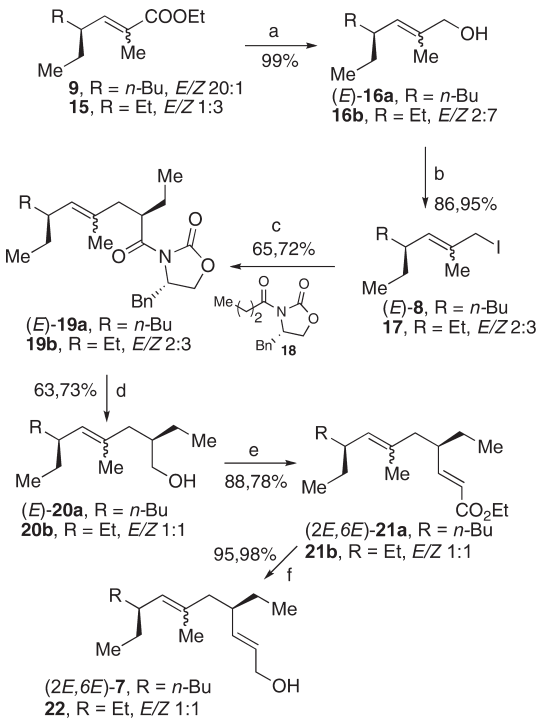
Regioselective hydroperoxysilylation reaction[21] followed by ring closure on a pre-existing epoxide was recognized as a suitable strategy for constructing the 1,2-dioxane scaffold of (6*S*)-**5** and (6*R*)-**6**.[15,22] A challenging step for the synthesis of **1** is the assembly of the ester moiety at C3. Indeed, starting from diols **5** and **6**, one approach could be the synthesis of the ester group of **1** through oxidation of the primary alcohol to the corresponding carboxylic acid, after deoxygenation of the secondary alcohol. However, this latter procedure would involve the use of hydrides or radical-forming reagents,[23] both not compatible with the peroxide functionality. This problem could be bypassed by oxidative cleavage of the 1,2-diol of **5** and **6** followed by aldehyde homologation through the synthesis of a key vinylether intermediate. 1,5-Diene **7**, necessary for the preparation of (6*S*)-**5** and (6*R*)-**6**, could be derived by the allyl iodide **8**, first introducing the ethyl chain applying Evans' chiral auxiliary chemistry and then generating the allylic double bond through the appropriate olefination protocol. Iodide **8** could be prepared starting from α,β-unsaturated ester **9**.

Following our retrosynthetic approach, ester **9** was prepared as described in Scheme 2. Reaction of the sodium enolate derived by oxazolidinone **10** with ethyl iodide afforded the corresponding α-alkylated product **11**.[24,25]

Reductive cleavage of the chiral auxiliary, accomplished by using a mixture of lithium borohydride and ethanol as the reducing system,[26] afforded alcohol **12** that was smoothly oxidized to aldehyde **13** with pyridinium chlorochromate (PCC) adsorbed on silica gel. Different oxidizing reagents

(18) Yao, G.; Steliou, K. *Org. Lett.* **2002**, *4*, 485–488.
(19) Harris, J. R.; Waetzig, S. R.; Woerpel, K. A. *Org. Lett.* **2009**, *11*, 3290–3293.
(20) Tokuyasu, T.; Kunikawa, S.; McCullough, K. J.; Masuyama, A.; Nojima, M. *J. Org. Chem.* **2005**, *70*, 251–260.
(21) O'Neill, P. M.; Hindley, S.; Pugh, M. D.; Davies, J.; Bray, P. G.; Park, B. K.; Kapu, D. S.; Ward, S. A.; Stocks, P. A. *Tetrahedron Lett.* **2003**, *44*, 8135–8138.
(22) Gemma, S.; Marti, F.; Gabellieri, E.; Campiani, G.; Novellino, E.; Butini, S. *Tetrahedron Lett.* **2009**, *50*, 5719–5722.
(23) Hudlicky, M. C. *Reductions in Organic Chemistry*, 2nd ed.; American Chemical Society: Washington, DC, 1996.
(24) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737–1739.
(25) Furuta, K.; Ashibe, K.; Shirahashi, H.; Fujita, N.; Yamashita, H.; Yamada, N.; Kuwano, E. *J. Pestic. Sci.* **2007**, *32*, 99–105.
(26) Soai, K.; Ookawa, A. *J. Org. Chem.* **1986**, *51*, 4000–4005.

SCHEME 3. Synthesis of Intermediates 8, 17 and 7, 22[a]



[a]Reagents and conditions: (a) DIBAL, DCM, −78 °C, 1.5 h; **16a**, 99% yield, **16b**, 99% yield, *E*/*Z* 2:7; (b) PPh_3, imidazole, I_2, 1:3 MeCN/Et_2O, 0 °C, 1.5 h; **8**, 65% yield, **17**, 95% yield, *E*/*Z* 2:3; (c) i. **18**, NaHMDS, THF, −78 °C, 1.5 h; ii. **8** (or **17**), THF, −35 °C, 5 h; **19a**, 65% yield, dr 99%; **19b**, 72% yield, *E*/*Z* 2:3, dr 99%; (d) $LiBH_4$, EtOH, Et_2O, 0 °C, 3 h; **20a**, 63%, **20b**, 73% yield, *E*/*Z* 1:1; (e) i. Dess−Martin periodinane, DCM, 0 °C, 4 h; ii. NaH, triethylphosphonoacetate, THF, 0 °C, 2 h; **21a**, 88% yield, **21b**, 78% yield, *E*/*Z* 1:1; (f) DIBAL, DCM, −78 °C, 1.5 h; **7**, 95%, **22**, 98% yield.

such as PCC alone, 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) and sodium hypochlorite,[27] or Dess−Martin periodinane either caused racemization of **13** or resulted in poor yields. Wadsworth−Emmons olefination of the crude aldehyde **13** with triethyl-2-phosphonopropionate and sodium hydride was performed at −30 °C to avoid racemization of the labile stereocenter and furnished the desired product **9** in 53% yield as a 1:2 *E*/*Z* isomer mixture. In order to improve the yield of **9**, aldehyde **13** was exposed to (carbethoxyethylidene)triphenylphosphorane in dichloromethane at 25 °C, providing **9** in 84% yield as a 20:1 *E*/*Z* isomer mixture. The synthesis of ester **15** (key intermediate to dihydroplakortin analogues **3** and **4**, Figure 1) was realized by using the Wadsworth−Emmons olefination protocol, starting from commercially available aldehyde **14**.

Scheme 3 outlines the synthesis of key 9,10-dihydroplakortin intermediates **8** and **7** along with intermediates **17** and **22** necessary for the synthesis of simplified analogues **3** and **4** (Figure 1). Iodides **8** and **17** (Scheme 3) were obtained by a DIBAL-mediated reduction of **9** or **15** to alcohols **16a,b** followed by treatment with I_2 in the presence of triphenylphosphine and imidazole.[28]

The alkylation of the sodium enolate of **18**[29] with **8** or **17** afforded the corresponding carboxamides **19a,b** in 63% and 73% yield, respectively. Cleavage of the chiral auxiliary to give alcohols **20a,b** was performed as described above. Exposure of alcohols **20a,b** to Dess−Martin periodinane cleanly furnished the desired aldehyde intermediates (while PCC adsorbed on silica gel resulted into racemization of the neighboring chiral center), which were immediately submitted to the Wadsworth−Emmons olefination protocol. Olefins **21a,b** presented the *E*-configuration at the newly installed double bond (*Z*-isomer not detectable at NMR). Finally, the 2*E*-allylic alcohols **7** and **22** were obtained by DIBAL-promoted reduction of the corresponding α,β-unsaturated esters.

In the next steps of the synthesis (Scheme 4), intermediates **7** and **22** were submitted to the asymmetric Sharpless epoxidation performed at −30 °C.

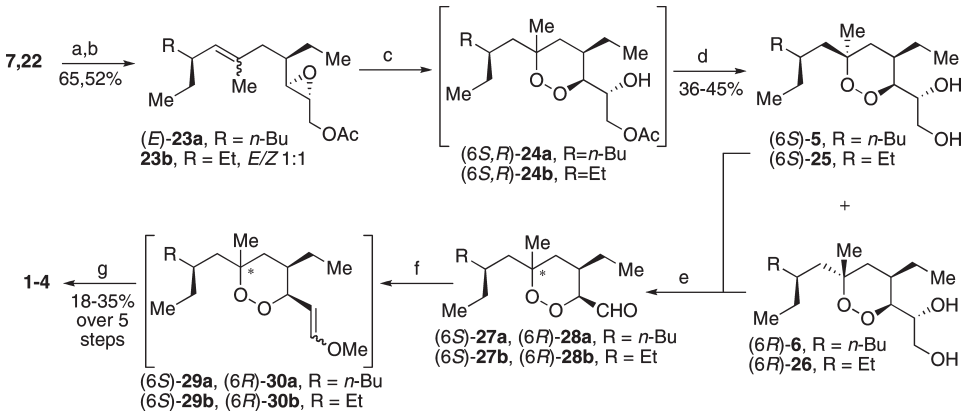
The resulting epoxides were converted into the corresponding acetates **23a,b** by treatment with acetic anhydride and pyridine. Regioselective hydroperoxysilylation reaction at the quaternary olefinic carbon was accomplished by using cobalt(II) bis[2,2,6,6-tetramethylheptane-3,5-dienoate] as the catalyst, in the presence of oxygen and triethylsilane.[21] A similar approach to an endoperoxide system was reported by Dong and co-workers for the synthesis of Yingzhaosu C. The authors used a three steps procedure to synthesize the key Yingzhaosu C 1,2-dioxane intermediate.[15] Here we successfully applied a one-pot three-step synthesis to intermediates **24a,b**. After filtration over a short pad of silica gel for removing the catalyst, crude **24a,b** were hydrolyzed to obtain the corresponding diols. The epimeric mixtures of diols thus obtained were readily separated by column chromatography affording compounds (6*S*)-**5**, (6*R*)-**6**, (6*S*)-**25**, and (6*R*)-**26** as pure isomers in 36−45% overall yield from **24a,b**. With the endoperoxides in our hand, construction of the ester at C3 was accomplished by using a Wittig-based strategy. Accordingly, oxidative cleavage of the 1,2-diols to the corresponding aldehydes **27a,b** and **28a,b** was accomplished by treatment with sodium periodate in a 1:3 mixture of water and acetonitrile. These latter aldehydes were immediately exposed to the Wittig reagent prepared from (methoxymethyl)triphenylphosphonium chloride and sodium bis(trimethylsilyl)amide. Excess of Wittig reagent and triphenylphosphine oxide were partially removed by precipitation from methyl-*tert*-butylether. The mixtures of enolethers **29a** and **29b** and the mixture of enolethers **30a** and **30b** were treated with 6 N HCl in acetone. The corresponding aldehydes were oxidized to carboxylic acids using a catalytic amount of ruthenium chloride in the presence of sodium periodate. Completion of the synthetic scheme was realized by diazomethane-promoted esterification of the crude carboxylic acid intermediates affording methyl esters **1**−**4**. Physical and spectroscopic properties of **1** are identical to those of an authentic sample of 9,10-dihydroplakortin.[1]

Conclusions

The synthetic methodology detailed herein led to the synthesis of the natural product 9,10-dihydroplakortin. The availability of this compound from natural sources is highly limited, also compared to the parent compound plakortin (0.1% of the sponge extract). Moreover, the

(27) Portonovo, P.; Liang, B.; Joullie, M. M. *Tetrahedron: Asymmetry* **1999**, *10*, 1451–1455.
(28) Carter, R. G.; Weldon, D. J. *Org. Lett.* **2000**, *2*, 3913–3916.
(29) Jacobsen, J. R.; Keatinge-Clay, A. T.; Cane, D. E.; Khosla, C. *Bioorg. Med. Chem.* **1998**, *6*, 1171–1177.

SCHEME 4. Synthesis Completion to Derivatives 1−4[a]



[a]Reagents and conditions: (a) 4 Å MS, $Ti(OiPr)_4$, D(−)DIPT, *t*-BuOOH, DCM, −25 °C, 48 h, (b) Ac_2O, Pyr, DMAP, DCM, 0 °C, 3 h; **23a**, 65% over two steps, dr 99%; **23b**, 52% yield, over two steps; dr 97%, *E*/*Z* 1:1, (c) i. $Co(thd)_2$, Et_3SiH, O_2, 1,2-DCE, 25 °C, 5 h; ii. Amberlyst, DCM, 25 °C, 18 h; (d) K_2CO_3, MeOH, 3 h, 0 °C; **5**, 42%, **6**, 36%, **25**, 45%, **26**, 38% yield; (e) $NaIO_4$, 3:2 MeCN/H_2O, 25 °C, 1 h; (f) i. $(MeOCH_2)PPh_3^+Cl^-$, NaHMDS, −78 → 0 °C; (g) i. 6 N HCl, acetone, 25 °C, 0.5 h; ii. $RuCl_3$, $NaIO_4$, 1:3 H_2O/MeCN, 25 °C, 1 h; iii. CH_2N_2, Et_2O, 25 °C, 0.5 h; **1**, 24%, **2**, 35%, **3**, 32%, **4**, 18% yield.

versatile synthetic approach here described paves the way to the preparation of a number of simplified plakortin analogues, differing both for the structure of the alkyl/aryl side chains and for the configuration at the stereogenic centers with the scope to improve the pharmacodynamic profile of the natural product. In vitro antimalarial evaluation of compounds **2**−**4** is currently ongoing and will be reported in due course.

Experimental Procedure

(4*S*,2′*S*)-4-Benzyl-3-(2′-ethylhexanoyl)oxazolidin-2-one (11). A solution of **10** (2.5 g, 8.9 mmol) in THF (10 mL) was added dropwise over 30 min to a solution of sodium bis(trimethylsilyl)-amide (1.0 M solution in THF, 13.4 mL, 13.4 mmol) in dry THF (20 mL) cooled to −78 °C. After 1 h, ethyl iodide (1.1 mL, 13.4 mmol) was added dropwise, and the resulting mixture was allowed to warm to −40 °C and was stirred at the same temperature for 16 h. The reaction was quenched by addition of a saturated solution of ammonium chloride at −30 °C, followed by evaporation of the solvent. The aqueous phase was extracted with chloroform, the organic extracts were dried over sodium sulfate, and the solvent was removed. The residue was purified by flash chromatography (1:5 diethyl ether/petroleum ether 40−60 °C) to afford **11** as a colorless oil (2.4 g, 78%, dr 99%). TLC R_f 0.45 (1:1 ethyl acetate/*n*-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.22 (m, 5H), 4.74−4.67 (m, 1H), 4.15 (m, 2H), 3.76−3.69 (m, 1H), 3.34 (dd, J = 2.6, 13.2 Hz, 1H), 2.71 (dd, J = 10.3, 13.2 Hz, 1H), 1.81−1.44 (m, 4H), 1.29 (m, 4H), 0.96 (t, J = 7.3 Hz, 3H), 0.89 ppm (t, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 153.4, 135.7, 129.6, 129.2, 127.5, 66.1, 55.7, 44.3, 38.3, 31.4, 29.8, 25.7, 23.0, 14.2, 11.7; MS (ESI) (*m*/*z*) 326 $(M + Na)^+$. HRMS (ESI) calcd for $C_{18}H_{25}NO_3Na$ $(M + Na)^+$ 326.1727, found 326.1728.

(*S*)-2-Ethylhexan-1-ol (12). To a mixture of **11** (1.0 g, 3.4 mmol) and ethanol (210 μL, 3.7 mmol) in dry diethylether (11 mL), cooled to 0 °C was added dropwise a 2 M solution of lithium borohydride in THF (2.0 mL, 4.0 mmol). The resulting mixture was stirred at 0 °C for 3 h and quenched by adding a 1 N solution of sodium hydroxide. The organic phase was washed with water and dried over sodium sulfate, and the solvent was removed. The crude product was purified by flash chromatography (1:1 diethylether/pentane) to afford **12** (0.35 g, 80%) as a colorless liquid. Spectroscopic and analytical data for (*S*)-**12** are identical to those reported in the literature.[30] $[\alpha]^{20}_D$ = +3.3 (*c* 4.1, $CHCl_3$); lit.[30] $[\alpha]^{20}_D$ = +3.3 (*c* 5.3, $CHCl_3$); HRMS (ESI) calcd for $C_8H_{18}ONa$ $(M + Na)^+$ 153.1250, found 153.1254

(*S*)-2-Ethylhexanal (13). To a suspension of pyridinium chlorochromate (11.2 g, 52.0 mmol) and silica gel (10.8 g) in dichloromethane (120 mL), cooled to 0 °C, was added alcohol **12** (5.6 g, 43.0 mmol) in one portion, and the reaction mixture was stirred at 25 °C for 16 h. The suspended solid was filtered off, and the filtrate was concentrated to give aldehyde **13** in quantitative yield as a colorless oil. The crude aldehyde was used in the subsequent step without further purification. Spectroscopic and analytical data for (*S*)-**13** are identical to those reported in the literature.[31] $[\alpha]^{20}_D$ = +4.5 (*c* 3.4, $CHCl_3$); lit.[31] $[\alpha]^{20}_D$ = +4.6 (*c* = 0.3, $CHCl_3$); HRMS (ESI) calcd for $C_8H_{16}ONa$ $(M + Na)^+$ 151.1093, found 151.1096.

(*S*,*Z*)-4-Ethyl-2-methyloct-2-enoic Acid Ethyl Ester ((*Z*)-9) and (*S*,*E*)-4-Ethyl-2-methyloct-2-enoic Acid Ethyl Ester ((*E*)-9). Procedure 1. To a suspension of sodium hydride (1.9 g, 47.1 mmol) in dry THF (120 mL), cooled to 0 °C, was added triethyl-2-phosphonopropionate (10.0 mL, 47.1 mmol) dropwise. After 1 h, the reaction mixture was cooled to −30 °C, and a solution of aldehyde **13** (5.5 g, 43.0 mmol) was added dropwise. After 3 h the reaction mixture was quenched with a saturated solution of ammonium chloride, the volatiles were evaporated, and the aqueous phase was extracted with chloroform. The organic extracts were dried over sodium sulfate, and the solvent was evaporated. The crude product was purified by flash chromatography (1:10 ethyl acetate/*n*-hexane) to afford ester **9** as a 1:2 mixture of *E* and *Z* isomers (5.3 g, 53%). **Procedure 2.** A mixture of crude aldehyde **13** (0.51 g, 3.9 mmol) and (carbethoxyethylidene)-triphenylphosphorane (1.6 g, 4.3 mmol) was stirred overnight at 25 °C and then concentrated. The residue was purified by column chromatography (1:50 diethyl ether/petroleum ether) to afford afford ester **9** as a 20:1 mixture of *E* and *Z* isomers (1.0 g, 84%). (*Z*)-**9**: colorless oil; R_f 0.44 (1:50 ethyl acetate/*n*-hexane); $[\alpha]^{20}_D$ = −2.3 (*c* 0.34, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.57 (d, J = 10.5 Hz, 1H), 4.18 (q, J = 7.0 Hz, 2H), 2.93 (m, 1H), 1.91 (s, 3H), 1.47−1.39 (m, 2H), 1.29 (t, J = 7.0 Hz, 3H), 1.24−1.08 (m, 6H), 0.88−0.80 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 147.4, 127.4, 60.1, 40.4, 35.1, 29.7, 28.5, 23.1,

(30) Baczko, K.; Larpent, C. *J. Chem. Soc., Perkin Trans. 2* **2000**, 521–526.

(31) Enders, D.; Wolfgang, M. *J. Chem. Soc., Chem. Commun.* **1984**, 4000–4005.

21.1, 14.5, 14.2, 11.9; MS (ESI) (m/z) 326 (M + Na)$^+$. HRMS (ESI) calcd for $C_{13}H_{24}O_2Na$ (M + Na)$^+$ 235.1669, found 235.1670. (*E*)-**9**: colorless oil; $[\alpha]^{20}_D = -2.5$ (*c* 0.16, $CHCl_3$); R_f 0.36 (1:50 ethyl acetate/*n*-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.47 (d, J = 10.5 Hz, 1H), 4.17 (q, J = 7.0 Hz, 2H), 2.25−2.19 (m, 1H),1.82 (s, 3H), 1.46−1.39 (m, 2H), 1.31−1.16 (m, 9H), 0.87−0.79 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 147.5, 127.7, 60.6, 40.8, 34.9, 29.9, 28.3, 23.1, 14.5, 14.3, 13.1, 12.1; MS (ESI) (m/z) 235 (M + Na)$^+$. HRMS (ESI) calcd for $C_{13}H_{24}O_2Na$ (M + Na)$^+$ 235.1669, found 235.1669.

(*Z*)-4-Ethyl-2-methylhex-2-enoic Acid Ethyl Ester ((*Z*)-15) and (*E*)-4-Ethyl-2-methylhex-2-enoic Acid Ethyl Ester ((*E*)-15). Starting from the commercially available aldehyde **14** and following the procedure described for the synthesis of **9** (procedure 1), the title compound was obtained in 92% yield and as a 3:1 mixture of *Z* and *E* isomers. (*Z*)-**15**: colorless oil; TLC R_f 0.79 (1:10 ethyl acetate/*n*-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.49 (d, J = 10.6 Hz, 1H), 4.11 (q, J = 7.0 Hz, 2H), 2.83−2.77 (m, 1H), 1.85 (s, 3H), 1.43−1.32 (m, 2H), 1.25−1.10 (m, 5H), 0.77 (t, J = 7.3 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 147.0, 127.7, 60.0, 42.0, 28.1, 21.0, 14.4, 11.8; MS (ESI) (m/z) 207 (M + Na)$^+$. HRMS (ESI) calcd for $C_{11}H_{20}O_2Na$ (M + Na)$^+$ 207.1356, found 207.1351. (*E*)-**15**: colorless oil; TLC R_f 0.74 (1:10 ethyl acetate/*n*-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.45 (d, J = 10.5 Hz, 1H), 4.15 (q, J = 7.0 Hz, 2H), 2.21−2.13 (m, 1H), 1.80 (s, 3H), 1.51−1.40 (m, 2H),1.30−1.19 (m, 5H), 0.80 (t, J = 7.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 147.0, 128.0, 60.5, 42.5, 27.9, 14.5, 13.1, 12.0; MS (ESI) (m/z) 207 (M + Na)$^+$. HRMS (ESI) calcd for $C_{11}H_{20}O_2Na$ (M + Na)$^+$ 207.1356, found 207.1355.

(*S*,*E*)-4-Ethyl-2-methyloct-2-en-1-ol (16a). To a solution of **9** (5.3 g, 25 mmol) in dry dichloromethane (120 mL), cooled to −78 °C, was added dropwise a 1 M solution of diisobutylaluminum hydride (50 mL, 50 mmol) within 30 min. After 1 h, the reaction mixture was quenched with a saturated solution of ammonium chloride, and the mixture was allowed to warm to 25 °C. The white precipitate was filtered off, the layers were separated, and the aqueous phase was extracted with dichloromethane. The combined organic extracts were dried over sodium sulfate, and the solvent was removed. The residue was purified by flash chromatography (1:10 ethyl acetate/*n*-hexane) to afford **16a** (4.2 g, 99%) as a 16:1 mixture of *E* and *Z* isomers. $[\alpha]^{20}_D = -2.4$ (*c* 2.1, $CHCl_3$); R_f 0.17 (1:6 diethyl ether/petroleum ether 40−60 °C); ^{1}H NMR (300 MHz, $CDCl_3$, signals reported for the major isomer only) δ 4.96 (d, 1H, J = 10.3 Hz), 4.11 (s, 2H), 2.19−2.10 (m, 1H), 1.82 (s, 3H), 1.47−1.28 (m, 2H), 1.26−1.11 (m, 7H), 0.87 (t, J = 6.5 Hz, 3H), 0.81 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, signals reported for the major isomer only) δ 134.3, 134.2, 62.4, 39.7, 35.6, 30.0, 28.9, 23.1, 21.6, 14.3, 12.2; MS (ESI) (m/z) 193 (M + Na)$^+$. HRMS (ESI) calcd for $C_{11}H_{22}ONa$ (M + Na)$^+$ 193.1563, found 193.1563.

(*Z*)-4-Ethyl-2-methylhex-2-en-1-ol and (*E*)-4-Ethyl-2-methylhex-2-en-1-ol (16b). The title compound was obtained from **15** in 99% yield and as a 7:2 mixture of *Z*/*E* isomers as described for the synthesis of **16a**. R_f 0.35 (1:20 ethyl acetate/*n*-hexane); ^{1}H NMR (300 MHz, $CDCl_3$, signals reported for the major isomer only) δ 4.90 (d, J = 10.0 Hz, 1H), 4.11 (s, 2H), 2.10−2.03 (m, 1H), 1.82 (s, 3H), 1.47−1.09 (m, 5H), 0.81 (t, J = 7.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, signals reported for the major isomer only) δ 134.6, 133.8, 62.4, 41.4, 28.6, 21.6, 12.2; MS (ESI) (m/z) 165 (M + Na)$^+$. HRMS (ESI) calcd for $C_9H_{18}ONa$ (M + Na)$^+$ 165.1250, found 165.1254.

(*S*,*E*)-4-Ethyl-1-iodo-2-methyloct-2-ene (8). A mixture of triphenylphosphine (20.2 g, 77.0 mmol) and imidazole (5.7 g, 84.6 mmol) in 1:3 acetonitrile/diethyl ether (140 mL) was cooled to 0 °C, and afterward iodine (10.5 g, 77 mmol) was added in two portions. The resulting mixture was stirred at 0 °C for 1 h, when a yellow precipitate was formed. Alcohol **16a** (4.4 g, 25.6 mmol) was subsequently added and stirred at 0 °C for 30 min. A 1:6 mixture of diethyl ether/*n*-hexane (390 mL) was added, and the resulting precipitate was filtered off. The filtrate was concentrated under vacuum, and the crude product was purified by flash chromatography (1:100 ethyl acetate/*n*-hexane) to afford **8** (6.3 g, 86%) as a pale yellow oil containing trace impurities of the *Z* isomer. R_f 0.90 (1:20 diethyl ether/petroleum ether 40−60 °C); $[\alpha]^{20}_D = -2.6$ (*c* 0.8, in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.07 (d, J = 10.3 Hz, 1H), 3.92 (s, 2H), 2.19−2.07 (m, 1H), 1.87 (s, 3H), 1.54−1.32 (m, 2H), 1.30−1.13 (m, 6H), 0.90−0.82 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1, 132.1, 40.8, 35.0, 29.9, 28.3, 23.2, 22.7, 14.3, 12.2, 8.2; MS (ESI) (m/z) 303 (M + Na)$^+$. HRMS (ESI) calcd for $C_{11}H_{21}INa$ (M + Na)$^+$ 303.0580, found 303.0579.

(*Z*)-4-Ethyl-1-iodo-2-methylhex-2-ene and (*E*)-4-Ethyl-1-iodo-2-methylhex-2-ene (17). The title compound was obtained from **16b** in 95% yield and as a 3:2 mixture of *Z*/*E* isomers as described for the synthesis of **8**. R_f 0.80 (1:50 ethyl acetate/*n*-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.39 (d, 1H, J = 10.0 Hz), 5.07 (d, 1H, J = 10.3 Hz), 3.97 (s, 2H), 3.93 (s, 2H), 2.17−1.98 (m, 2H), 1.87 (s, 3H), 1.78 (s, 3H), 1.53−1.38 (m, 4H), 1.23−1.11 (m, 4H), 0.90−0.80 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7, 135.4, 133.3, 132.5, 42.5, 42.2, 31.8, 28.2, 27.9, 22.9, 22.6, 17.4, 16.2, 14.3, 12.2, 11.9; MS (ESI) (m/z) 275 (M + Na)$^+$. HRMS (ESI) calcd for $C_9H_{17}INa$ (M + Na)$^+$ 275.0267, found 275.0270.

(*S*)-4-Benzyl-3-[(2*R*,6*S*,*Z*)-2,6-diethyl-4-methyldec-4-enoyl]-oxazolidin-2-one (19a). To a mixture of sodium bis(trimethylsilyl)amide (1.0 M in THF, 24.3 mL, 24.3 mmol) and THF (60 mL), cooled to −78 °C, was added dropwise a solution of **18**[29] (6.0 g, 24.3 mmol) in THF (20 mL) within 30 min. After 1 h, a solution of **8** (6.2 g, 22.1 mmol) in THF (20 mL) was added dropwise within 30 min. The reaction mixture was allowed to warm to −35 °C, and was stirred at the same temperature for 5 h. A saturated solution of ammonium chloride was added to the reaction mixture, which was subsequently allowed to warm to 25 °C. The volatiles were removed, and the aqueous phase was extracted with diethyl ether. The organic extracts were dried over sodium sulfate, and the solvent was removed. The residue was purified by flash chromatography (1:6 diethylether/*n*-hexane) to afford **19a** (5.7 g, 65%, dr 99%) as a colorless thick oil. $[\alpha]^{20}_D = +51.0$ (*c* 0.38, $CHCl_3$); R_f 0.58 (1:4 ethyl acetate/*n*-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.21 (m, 5H), 4.92 (d, J = 10.0 Hz, 1H), 4.71−4.64 (m, 1H), 4.20−4.12 (m, 2H), 4.00−3.94 (m, 1H), 3.34 (dd, J = 3.1, 13.3 Hz, 1H), 2.64 (dd, J = 10.3, 13.2 Hz, 1H), 2.52 (dd, J = 6.7, 13.8 Hz, 1H), 2.17−2.10 (m, 2H), 1.66 (s, 3H), 1.60−1.51 (m, 1H), 1.43−1.09 (m, 9H), 0.91 (t, J = 7.3 Hz, 3H), 0.86 (t, J = 6.9 Hz, 3H), 0.80 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8, 153.4, 135.8, 133.2, 132.0, 129.6, 129.2, 127.5, 66.1, 55.8, 42.7, 42.5, 39.8, 38.3, 35.6, 30.0, 29.0, 24.8, 23.1, 16.6, 14.4, 12.2, 11.9; MS (ESI) (m/z) 422 (M + Na)$^+$ HRMS (ESI) calcd for $C_{25}H_{37}NO_3Na$ (M + Na)$^+$ 422.2666, found 422.2664.

(*S*)-4-Benzyl-3-[(*R*,*Z*)-2,6-diethyl-4-methyloct-4-enoyl]oxazolidin-2-one (19b). The title compound was obtained from **18** and **17** in 72% yield (99% dr) and as a 2:3 mixture of *E*/*Z* isomers as described for the synthesis of **19a**. R_f 0.39 (1:10 ethyl acetate/*n*-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.20 (m, 10H), 4.95 (d, J = 10.0 Hz, 1H), 4.87 (d, J = 9.7 Hz, 1H), 4.67−4.61 (m, 2H), 4.19−4.11 (m, 4H), 4.03−3.94 (m, 2H), 3.48−3.24 (m, 2H), 2.82−2.74 (m, 2H), 2.48 (dd, J = 6.7, 13.2 Hz, 1H), 2.35−2.30 (m, 1H), 2.15−2.00 (m, 4H), 1.72 (s, 3H), 1.62 (s, 3H), 1.56 (bs, 1H), 1.45−1.28 (m, 4H + 3H), 1.20−1.06 (m, 10H), 0.87−0.76 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5, 177.4, 135.6, 135.5, 133.7, 132.9, 132.3, 131.8, 129.7, 129.6, 129.2, 129.1, 127.5, 66.2, 55.7, 55.6, 44.0, 41.6, 40.9, 38.1, 36.1, 35.8, 28.7, 28.6 (2C), 23.4, 17.0, 16.8, 16.6, 12.1, 12.0, 11.9; MS (ESI) (m/z) 394 (M + Na)$^+$. HRMS (ESI) calcd for $C_{23}H_{33}NO_3Na$ (M + Na)$^+$ 394.2353, found 394.2352.

(2*R*,6*S*,*E*)-2,6-Diethyl-4-methyldec-4-en-1-ol (20a). The title compound was obtained from **19a** in 63% yield as described for the synthesis of **12**. R_f 0.72 (1:1 diethyl ether/ petroleum ether 40−60 °C); $[\alpha]^{20}_D$ = +8.8 (*c* 0.57, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.87 (d, *J* = 10.8 Hz, 1H), 3.56 (d, *J* = 7.2 Hz, 2H), 2.12−2.04 (m, 1H), 2.01 (d, *J* = 8.0 Hz, 2H), 1.68−1.59 (m, 1H), 1.61 (s, 3H), 1.56−1.09 (m, 11H), 0.91 (t, *J* = 7.3 Hz, 3H), 0.86−0.79 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.7, 132.5, 65.8, 42.5, 40.0, 39.8, 35.7, 29.9, 29.0, 23.9, 23.1, 16.7, 14.4, 12.2, 11.4; MS (ESI) (*m*/*z*) 249 (M + Na)$^+$. HRMS (ESI) calcd for $C_{15}H_{30}ONa$ (M + Na)$^+$ 249.2189, found 249.2186.

(*R*,*Z*)-2,6-Diethyl-4-methyloct-4-en-1-ol and (*R*,*E*)-2,6-Diethyl-4-methyloct-4-en-1-ol (20b). The title compound was obtained from **19b** in 73% yield as a 1:1 mixture of *E*/*Z* isomers as described for the synthesis of **12**. R_f 0.40 (1:4 ethyl acetate/*n*-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.92 (d, *J* = 10.0 Hz, 1H), 4.87 (d, *J* = 9.7 Hz, 1H), 3.56−3.52 (m, 4H), 2.12−1.95 (m, 6H), 1.72 (s, 3H), 1.69−1.63 (m, 2H), 1.61 (s, 3H), 1.45−1.31 (m, 10H), 1.21−1.09 (m, 4H), 0.95−0.89 (m, 6H), 0.86−0.79 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.1, 133.8, 132.6, 132.1, 65.9, 65.8, 42.5, 41.6, 40.9, 40.5, 40.0, 34.5, 28.7, 28.62, 24.0, 23.9, 23.8, 16.7, 12.2, 12.1, 12.0, 11.9, 11.6, 11.4; MS (ESI) (*m*/*z*) 221 (M + Na)$^+$. HRMS (ESI) calcd for $C_{13}H_{26}ONa$ (M + Na)$^+$ 221.1876, found 221.1872.

(2*E*,4*R*,6*Z*,8*S*)-4,8-Diethyl-6-methyldodeca-2,6-dienoic Acid Ethyl Ester (21a). A mixture of alcohol **20a** (2.6 g, 11.5 mmol) and Dess−Martin periodinane (7.3 g, 17.2 mmol) in dicholoromethane (60 mL) was stirred at 0 °C for 4 h. The cold organic phase was washed with a saturated solution of sodium dithionite and a saturated solution of sodium bicarbonate. The organic phase was dried over sodium sulfate, and the solvent was removed. The crude aldehyde thus obtained was immediately used in the next step. Accordingly, to an ice-cold suspension of sodium hydride (430 mg, 10.7 mmol) in THF (20 mL) was added triethylphosphonoacetate (2.1 mL, 10.7 mmol) dropwise. The suspension was stirred for 1 h, and to the clear solution formed was added a solution of above aldehyde in THF (20 mL). The reaction mixture was stirred at 0 °C for 1 h, and afterward a saturated solution of ammonium chloride was added. The volatiles were removed, and the aqueous phase was extracted with chloroform. The organic extracts were washed with brine and dried over sodium sulfate, and the solvent was removed. The residue was purified by flash chromatography (1:20 diethyl ether/*n*-hexane) to afford **21a** (2.3 g, 88%) as a colorless oil. R_f 0.90 (1:10 ethyl acetate/*n*-hexane); $[\alpha]^{20}_D$ = +68.2 (*c* 0.44, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.65 (dd, *J* = 8.9, 15.7 Hz, 1H), 5.67 (d, *J* = 15.7 Hz, 1H), 4.72 (d, *J* = 10.0 Hz, 1H), 4.08 (q, *J* = 7.0 Hz, 2H), 2.21−2.09 (m, 1H), 2.06−1.91 (m, 3H), 1.47 (s, 3H), 1.45−1.30 (m, 1H), 1.28−0.97 (m, 12H), 0.79 (t, *J* = 7.3 Hz, 6H), 0.69 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 153.4, 133.0, 132.1, 121.2, 60.3, 45.3, 42.6, 39.8, 35.8, 31.2, 29.0, 27.0, 23.1, 16.7, 14.5, 14.4, 12.0, 11.9; MS (ESI) (*m*/*z*) 317 (M + Na)$^+$. HRMS (ESI) calcd for $C_{19}H_{34}O_2Na$ (M + Na)$^+$ 317.2451, found 317.2456.

(*R*,2*E*,6*Z*)-4,8-Diethyl-6-methyldeca-2,6-dienoic Acid Ethyl Ester ((6*Z*)-21b) and (*R*,2*E*,6*E*)-4,8-Diethyl-6-methyldeca-2,6-dienoic Acid Ethyl Ester ((6*E*)-21b). The title compound was obtained from **20b** in 78% yield as a 1:1 mixture of *E*/*Z* isomers as described for the synthesis of **21a**. R_f 0.85 (1:10 ethyl acetate/*n*-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.76−6.66 (m, 2H), 5.76 (d, *J* = 15.5 Hz, 1H), 5.75 (d, *J* = 15.6 Hz, 1H), 4.87 (d, *J* = 10.0 Hz, 1H), 4.78 (d, *J* = 9.7 Hz, 1H), 4.05 (q, *J* = 7.0 Hz, 4H), 2.27−1.98 (m, 8H), 1.65 (s, 3H), 1.53 (s, 3H), 1.53−1.42 (m, 2H), 1.38−1.23 (m, 12H), 1.95−1.02 (m, 4H), 0.87−0.72 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 153.4, 153.1, 132.8, 132.7, 132.4, 121.2, 60.3, 60.2, 45.3, 43.0, 42.6, 41.6, 41.0, 37.4, 28.8, 28.7, 28.6, 28.5, 27.2, 27.0, 24.0, 16.7, 14.5, 12.1 (2C), 12.0 (2C), 11.9; MS (ESI) (*m*/*z*) 289 (M + Na)$^+$. HRMS (ESI) calcd for $C_{17}H_{30}O_2Na$ (M + Na)$^+$ 289.2138, found 289.2136.

(2*E*,4*R*,6*Z*,8*S*)-4,8-Diethyl-6-methyldodeca-2,6-dien-1-ol (7). To a solution of **21a** (2.7 g, 9.2 mmol) in dry dichloromethane (30 mL), cooled to −78 °C was added dropwise a 1 M solution of diisobutylaluminum hydride (18.4 mL, 18.4 mmol) within 30 min. After 1 h, to the reaction mixture was added a saturated solution of ammonium chloride, and the mixture was allowed to warm to 25 °C. The white precipitate was filtered off, the layers were separated, and the aqueous phase was extracted with dichloromethane. The combined organic extracts were dried over sodium sulfate, and the solvent was removed. The crude product was purified by flash chromatography (1:5 ethyl acetate/*n*-hexane) to afford **7** (2.2 g, 95%) as a colorless oil. R_f 0.52 (1:2 ethyl acetate/*n*-hexane); $[\alpha]^{20}_D$ = +26.9 (*c* 0.16, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.58 (dt, *J* = 5.9, 15.2 Hz, 1H), 5.41 (dd, *J* = 8.2, 15.2 Hz, 1H), 4.84 (d, *J* = 10.0 Hz, 1H), 4.05 (d, *J* = 5.9 Hz, 2H), 2.15−1.94 (m, 4H), 1.65 (s, 3H), 1.50−1.03 (m, 11H), 0.91−0.75 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5, 133.1, 132.5, 128.9, 64.1, 42.7, 39.4, 38.0, 35.8, 30.0, 29.0, 27.6, 24.1, 23.3, 14.4, 12.1, 12.0; MS (ESI) (*m*/*z*) 275 (M + Na)$^+$. HRMS (ESI) calcd for $C_{17}H_{32}ONa$ (M + Na)$^+$ 275.2345, found 275.2341.

(*R*,2*E*,6*Z*)-4,8-Diethyl-6-methyldeca-2,6-dien-1-ol ((6*Z*)-22) and (*R*,2*E*,6*E*)-4,8-Diethyl-6-methyldeca-2,6-dien-1-ol ((6*E*)-22). The title compound was obtained from **21b** in 98% yield as a 1:1 mixture of *E*/*Z* isomers as described for the synthesis of **7**. R_f 0.45 (1:3 ethyl acetate/*n*-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.61−5.50 (m, 2H), 5.43−5.35 (m, 2H), 4.83 (d, *J* = 10.0 Hz, 1H), 4.74 (d, *J* = 10.0 Hz, 1H), 4.05−4.03 (m, 4H), 2.11−1.92 (m, 8H), 1.66 (s, 3H), 1.65 (bs, 2H), 1.53 (s, 3H), 1.46−1.30 (m, 6H), 1.24−1.03 (m, 6H), 0.86−0.75 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.4, 137.3, 133.4, 132.1, 131.9, 128.9, 64.0, 46.0, 42.6, 42.2, 41.6, 40.9, 28.8, 28.7 (2C), 27.6, 27.5, 26.1, 16.8, 12.1, 12.0, 11.8; MS (ESI) (*m*/*z*) 247 (M + Na)$^+$. HRMS (ESI) calcd for $C_{15}H_{28}ONa$ (M + Na)$^+$ 247.2032, found 247.2033.

(2*R*,3*R*,4*R*,8*S*,*Z*)-4,8-Diethyl-6-methyl-2,3-epoxydodec-6-ene-1-yl Acetate (23a). A mixture of 4 Å molecular sieves (3.7 g), titanium(IV) isopropoxide (1.3 mL, 4.3 mmol), and D-(−)-diisopropyl tartrate (1.3 mL, 6.2 mmol) in dichloromethane (55 mL) was cooled to −25 °C and allowed to stir for 1 h. Subsequently, a solution of **7** (2.2 g, 8.7 mmol) in dichloromethane (10 mL) was added, followed by addition of *tert*-butyl hydroperoxide (5.5 M in nonane, 3.2 mL, 17.5 mmol). The reaction mixture was stirred at −25 °C for 48 h, and afterward a 1 M solution of sodium hydroxide was carefully added. The layers were separated, and the organic phase was washed with 1 m sodium hydroxide and water. The organic layer was dried over sodium sulfate, and the solvent was removed. The residue was purified by flash chromatography (1:7 ethyl acetate/petroleum ether 40−60 °C) to afford (2*R*,3R,4*R*,8*S*,*Z*)-4,8-diethyl-6-methyl-2,3-epoxydodec-6-ene-1-ol (1.5 g, 65%, dr 99%) as a thick colorless oil. $[\alpha]^{20}_D$ = +15.1 (*c* 0.007, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.93 (d, *J* = 10.0 Hz, 1H), 3.92 (dd, *J* = 2.5, 12.4 Hz, 1H), 3.63 (dd, *J* = 4.1, 12.6 Hz, 1H), 2.99−2.96 (m, 1H), 2.72 (d, *J* = 2.3, 7.9 Hz, 1H), 2.16 (d, *J* = 7.0 Hz, 2H), 2.13−2.07 (m, 1H), 1.68 (s, 3H), 1.56 (bs, 1H), 1.48−1.08 (m, 11H), 0.91 (t, *J* = 7.3 Hz, 3H), 0.88−0.79 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.1, 132.4, 61.9, 59.8, 58.5, 41.1, 39.4, 35.7, 35.4, 29.8, 29.0, 24.2, 23.9, 23.3, 14.4, 12.3, 12.1; MS (ESI) (*m*/*z*) 291 (M + Na)$^+$. HRMS (ESI) calcd for $C_{17}H_{32}O_2Na$ (M + Na)$^+$ 291.2295, found 291.2297. A mixture of the above compound (0.15 g, 0.57 mmol), pyridine (0.30 mL, 3.7 mmol), acetic anhydride (0.17 mL, 1.8 mmol), and a catalytic amount of *N*,*N*-dimethylaminopyridine in dichloromethane (40 mL) was stirred at 0 °C for 3 h. The organic phase was washed with a saturated solution of sodium bicarbonate, with 1 N hydrochloric acid, and

with brine. The organic extracts were dried over sodium sulfate, and the solvent was removed. The residue was purified by flash chromathography (1:20 ethyl acetate/*n*-hexane) to afford **23a** (0.17 g, 99%) as a colorless oil. R_f 0.79 (1:2 diethyl ether/petroleum ether 40−60 °C); $[\alpha]^{20}_D$ = +28.0 (*c* 0.14, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.84 (d, *J* = 9.7 Hz, 1H), 4.34 (dd, *J* = 3.5, 12.3 Hz, 1H), 3.94 (dd, *J* = 6.5, 12.3 Hz, 1H), 3.05−3.01 (m, 1H), 2.64 (dd, *J* = 2.3, 7.6 Hz, 1H), 2.25 (dd, *J* = 4.7, 13.2 Hz, 1H), 2.13−2.06 (m, 1H), 2.08 (s, 3H), 2.00 (dd, *J* = 8.5, 14.0 Hz, 1H), 1.56 (s, 3H), 1.45−1.06 (m, 11H), 0.91 (t, *J* = 7.3 Hz, 3H), 0.88−0.79 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 132.9, 132.2, 65.1, 60.3, 55.2, 42.9, 40.4, 39.8, 35.7, 29.9, 29.0, 23.6, 23.1, 21.0, 16.7, 14.4, 12.1, 11.9; MS (ESI) (*m*/*z*) 333 $(M + Na)^+$. HRMS (ESI) calcd for $C_{19}H_{34}O_3Na$ $(M + Na)^+$ 333.2400, found 333.2400.

(2*R*,3R,4*R*,*Z*)-4,8-Diethyl-6-methyl-2,3-epoxydec-6-ene-1-yl Acetate ((6*Z*)-23b) and (2*R*,3R,4*R*,*E*)-4,8-Diethyl-6-methyl-2,3-epoxydec-6-ene-1-yl Acetate ((6*E*)-23b). The title compound was obtained from **22** in 52% yield as a 1:1 mixture of *E*/*Z* isomers as described for the synthesis of **23a**. (2*R*,3R,4*R*,*Z*)-4,8-Diethyl-6-methyl-2,3-epoxydec-6-ene-1-ol and (2*R*,3R,4*R*,*E*)-4,8-diethyl-6-methyl-2,3-epoxydec-6-ene-1-ol (dr 97%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.88 (d, *J* = 10.0 Hz, 1H), 4.79 (d, *J* = 9.7 Hz, 1H), 3.84 (d, *J* = 11.5 Hz, 2H), 3.55−3.43 (m, 2H), 2.98−2.94 (m, 4H), 2.72−2.59 (m, 2H), 2.26−2.12 (m, 4H), 2.04−1.92 (m, 4H), 1.65 (s, 3H), 1.53 (s, 3H), 1.45−1.26 (m, 8H), 1.24−1.06 (m, 4H), 0.87 (t, *J* = 7.3 Hz, 6H), 0.80−0.64 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.8, 132.7, 132.6, 132.4, 62.1, 62.0, 59.9, 59.7, 58.9, 43.0, 41.6, 41.0, 40.9, 40.4, 35.3, 28.8, 28.7, 28.6, 28.5, 24.0, 23.9, 23.6, 16.7, 12.3, 12.2, 12.0, 11.9; MS (ESI) (*m*/*z*) 263 $(M + Na)^+$. HRMS (ESI) calcd for $C_{15}H_{28}O_2Na$ $(M + Na)^+$ 263.1982, found 263.1987. (*Z*)-**23b** and (*E*)-**23b**: R_f 0.83 (1:5 diethyl ether/petroleum ether 40−60 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.84 (d, *J* = 10.0 Hz, 1H), 4.76 (d, *J* = 9.4 Hz, 1H), 4.27 (dd, *J* = 3.2, 12.3 Hz, 2H), 3.86 (dd, *J* = 6.3, 12.3 Hz, 2H), 3.00−2.94 (m, 2H), 2.58−2.53 (m, 2H), 2.19−2.07 (m, 4H), 2.00 (s, 6H), 1.99−1.90 (m, 2H), 1.60 (s, 3H), 1.49 (s, 3H), 1.48−1.01 (m, 16H), 0.84 (t, *J* = 7.3 Hz, 6H), 0.76−0.71 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 132.7, 132.6, 132.5, 132.4, 65.0, 64.8, 60.3, 60.2, 55.3, 55.2, 42.9, 41.6, 41.0, 40.3, 35.2, 28.7, 28.6, 24.0, 23.8, 23.6, 20.8, 16.6, 12.1 (2C), 12.0 (2C), 11.9, 11.8; MS (ESI) (*m*/*z*) 263 $(M + Na)^+$. HRMS (ESI) calcd for $C_{17}H_{30}O_3Na$ $(M + Na)^+$ 305.2087, found 305.2090.

(2*R*)-2-{(3*S*,4*R*)-4-Ethyl-6-[(*S*)-2-ethylhexyl]-6-methyl-1,2-dioxan-3-yl}-2-hydroxyethyl Acetate (24a). To a solution of **23a** (0.17 g, 0.55 mmol) and $Co(thd)_2$ (0.14 g, 0.33 mmol) in 1,2-dichloroethane (9.0 mL), stirred under an oxygen atmosphere, was added triethylsilane (0.18 mL, 1.2 mmol), together with a drop of *tert*-butylhydroperoxide (catalytic, 5.5 M in nonane). The resulting green mixture was stirred at 25 °C for 5 h, until consumption of the starting material. Amberlyst-15 (20 mg) was subsequently added, and the resulting mixture was stirred at 25 °C for 18 h. After evaporation of the solvent, the cyclization product **24a** was separated from the catalyst by filtering through a short pad of silica gel affording an inseparable mixture of C6-epimers (0.11 g, 57%) and a byproduct probably resulting from the reduction of the peroxide bond to the corresponding tetrahydrofuran derivative MS (ESI) (*m*/*z*) 367 $(M + Na)^+$.

(2*R*)-2-[(3*S*,4*R*)-4-Ethyl-6-(2-ethylbutyl)-6-methyl-1,2-dioxan-3-yl]-2-hydroxyethyl Acetate (24b). The title compound was obtained from **23b** in 62% yield as a mixture C6-epimers as described for the synthesis of **24a**. MS (ESI) (*m*/*z*) 339 $(M + Na)^+$.

(*R*)-1-{(3*S*,4*R*,6*S*)-4-Ethyl-6-[(*S*)-2-ethylhexyl]-6-methyl-1,2-dioxan-3-yl}ethane-1,2-diol (5) and (*R*)-1-{(3*S*,4*R*,6*S*)-4-Ethyl-6-[(*R*)-2-ethylhexyl]-6-methyl-1,2-dioxan-3-yl}ethane-1,2-diol (6). A mixture of **24a** (0.11 g, 0.32 mmol) and potassium carbonate (2.2 mg) in methanol (5 mL) was stirred ad 0 °C for 3 h. Water was added to the reaction mixture, the volatiles were removed, and the aqueous phase was washed with chloroform. Compounds (6*S*)-**5** and (6*R*)-**6** were separated by flash chromatography (1:5 ethyl acetate/*n*-hexane). (6*S*)-**5** (41 mg, 42%): $[\alpha]^{20}_D$ = +57.5 (*c* 0.006, $CHCl_3$); R_f 0.15 (1:4 ethyl acetate/*n*-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.10−4.04 (m, 1H), 3.96−3.83 (m, 3H), 2.50 (bs, 2H), 2.27−2.03 (m, 1H), 1.60−1.39 (m, 4H), 1.36 (s, 3H), 1.33−1.20 (m, 11H), 0.95 (t, *J* = 7.3 Hz, 3H), 0.88 (t, *J* = 6.9 Hz, 3H), 0.81 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 82.7, 81.9, 69.7, 64.9, 45.6, 36.2, 35.3, 34.7, 34.2, 29.1, 27.5, 24.8, 23.3, 21.5, 14.3, 12.1, 10.7; MS (ESI) (*m*/*z*) 325 $(M + Na)^+$. HRMS (ESI) calcd for $C_{17}H_{34}O_4Na$ $(M + Na)^+$ 325.2349, found 325.2351. (6*R*)-**6** (35 mg, 36%): $[\alpha]^{20}_D$ = +92.6 (*c* 0.05, $CHCl_3$); R_f 0.10 (1:4 ethyl acetate/*n*-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.04 (bs, 1H), 3.95−3.72 (m, 3H), 2.66 (bs, 1H), 2.46 (bs, 1H), 2.21−2.13 (m, 1H), 1.76 (dd, *J* = 3.5, 11.4 Hz; 1H), 1.68 (dd, *J* = 4.4, 13.8 Hz, 1H), 1.62−1.40 (m, 3H), 1.39−1.18 (m, 10H), 1.11 (s, 3H), 0.95 (t, *J* = 7.3 Hz, 3H), 0.90−0.82 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 82.7, 81.6, 69.7, 65.0, 39.3, 36.4, 35.1, 34.9, 34.0, 28.8, 27.6, 25.4, 24.4, 23.3, 14.4, 12.1, 11.0; MS (ESI) (*m*/*z*) 325 $(M + Na)^+$. HRMS (ESI) calcd for $C_{17}H_{34}O_4Na$ $(M + Na)^+$ 325.2349, found 325.2354.

(*R*)-1-((3*S*,4*R*,6*S*)-4-Ethyl-6-(2-ethylbutyl)-6-methyl-1,2-dioxan-3-yl]ethane-1,2-diol (25) and (*R*)-1-[(3*S*,4*R*,6*R*)-4-Ethyl-6-(2-ethylbutyl)-6-methyl-1,2-dioxan-3-yl]ethane-1,2-diol (26). The title compounds were obtained from **24b** in 45% and 38% yield, respectively as white low melting solids. (6*S*)-**25**: $[\alpha]^{20}_D$ = +142 (*c* 0.33, $CHCl_3$); R_f 0.22 (1:3 ethyl acetate/*n*-hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.03 (m, 1H, H-2), 3.89 (dd, *J* = 5.0, 7.0 Hz, 1H, H-3), 3.84 (m, 2H, H-1), 2.63 (bs, 2H, OH), 2.20 (m, 1H, H-4), 1.61 (m, 1H, H-8), 1.56 (m, 1H, H-14a), 1.42 (overlapped, 5H, H-5a, H_2-9, H_2-11), 1.35 (s, 3H, H-13), 1.36 (m, 1H, H-5b), 1.25 (m, 1H, H-14b), 1.22 (2H, m, H-7), 0.94 (t, *J* = 7.3 Hz, 3H, H-15), 0.79 (t, *J* = 7.3 Hz, 6H, H-10, H-12); ^{13}C NMR (125 MHz, $CDCl_3$) δ 82.7 (C-6), 81.9 (C-3), 69.7 (C-2), 64.9 (C-1), 45.1 (C-7), 36.4 (C-8), 35.9 (C-5), 35.3 (C-4), 27.3 (C-9), 27.0 (C-11), 24.8 (C-14), 21.5 (C-13), 12.1 (C-15), 11.1 (C-10), 10.8 (C-12); MS (ESI) (*m*/*z*) 297 $(M + Na)^+$. HRMS (ESI) calcd for $C_{15}H_{30}O_4Na$ $(M + Na)^+$ 297.2036, found 297.2040. (6*R*)-**26**: $[\alpha]^{20}_D$ = +150 (*c* 0.30, $CHCl_3$); R_f 0.15 (1:3 ethyl acetate/*n*-hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.04 (bs, 1H, H-2), 3.92 (dd, *J* = 5.0, 7.0 Hz, 1H, H-3), 3.85 (m, 2H, H-1), 2.58 (bs, 1H, OH), 2.39 (bs, 1H, OH), 2.20 (m, 1H, H-4), 1.82 (dd, *J* = 4.2, 14.4 Hz, 1H, H-8), 1.68 (dd, *J* = 4.7, 13.8 Hz, 1H, H-5a), 1.59 (m, 1H, H-14a), 1.50−1.37 (m, 3H, H-9a, H-11a, H-5b), 1.31−1.22 (m, 5H, H_2-7, H-9b, H-11b,H-14b), 1.11 (s, 3H, H-13), 0.95 (t, *J* = 7.4 Hz, 3H, H-15), 0.85 (t, *J* = 7.4 Hz, 6H, H-10, H-12); ^{13}C NMR (125 MHz, $CDCl_3$) δ 82.7 (C-6), 81.6 (C-3), 69.7 (C-2), 65.0 (C-1), 38.8 (C-7), 36.6 (C-5), 36.3 (C-8), 35.1 (C-4), 27.1 (C-9), 26.5 (C-11), 25.4 (C-14), 21.4 (C-13), 12.1 (C-15), 11.1 (C-10), 10.8 (C-12); MS (ESI) (*m*/*z*) 297 $(M + Na)^+$. HRMS (ESI) calcd for $C_{15}H_{30}O_4Na$ $(M + Na)^+$ 297.2036, found 297.2033.

(3*S*,4*R*,6*S*)-4-Ethyl-6-[(*S*)-2-ethylhexyl]-6-methyl-1,2-dioxane-3-carbaldehyde (27a). A solution of (6*S*)-**5** (45 mg, 0.15 mmol) and sodium periodate (36 mg, 0.16 mmol) in a 3:2 mixture of acetonitrile and water (2.0 mL) was stirred at 25 °C for 1 h. After this time, the resulting white precipitate was filtered off, the volatiles were removed, and the aqueous phase was extracted with dichloromethane. The organic extracts were dried over sodium sulfate, and the solvent was removed. The crude aldehyde **27a** (40 mg, 99%) was immediately reacted in the next step. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.02 (s, 1H), 4.25 (d, 1H, *J* = 5.3 Hz), 2.27−2.21 (m, 1H), 1.73−1.61 (m, 1H), 1.57−1.48 (m, 3H), 1.45−1.38 (m, 1H), 1.43 (s, 3H), 1.35−1.22 (m, 10H), 0.96 (t, 3H, *J* = 7.4 Hz), 0.88 (t, 3H, *J* = 6.9 Hz), 0.81 (t, 3H, *J* = 7.3 Hz); MS (ESI) (*m*/*z*) 293 $(M + Na)^+$.

(3*S*,4*R*,6*S*)-4-Ethyl-6-(2-ethylbutyl)-6-methyl-1,2-dioxane-3-carbaldehyde (27b). The title compound was obtained from

(6*S*)-**25** in quantitative yield as described for the synthesis of (6*S*)-**27a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.00 (s, 1H), 4.25 (d, J = 5.3 Hz, 1H), 2.25−2.18 (m, 1H), 1.72−1.62 (m, 1H), 1.56−1.44 (m, 2H), 1.42 (s, 3H), 1.38−1.19 (m, 7H), 0.95 (t, J=7.4 Hz, 3H), 0.80 (t, J = 7.2 Hz, 6H); MS (ESI) (m/z) 265 $(M + Na)^+$.

(3*S*,4*R*,6*R*)-4-Ethyl-6-[(*S*)-2-ethylhexyl]-6-methyl-1,2-dioxane-3-carbaldehyde (28a). The title compound was obtained from (6*R*)-**6** in quantitative yield as described for the synthesis of (6*S*)-**27a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.03 (s, 1H), 4.26 (d, J = 5.3 Hz, 1H), 2.27−2.14 (m, 1H), 1.94 (dd, J = 4.8, 14.5 Hz, 1H), 1.72−1.62 (m, 2H), 1.55−1.20 (m, 12H), 1.10 (s, 3H), 0.95 (t, J = 7.4 Hz, 3H), 0.90−0.84 (m, 6H); MS (ESI) (m/z) 293 $(M + Na)^+$.

(3*S*,4*R*,6*R*)-4-Ethyl-6-(2-ethylbutyl)-6-methyl-1,2-dioxane-3-carbaldehyde (28b). The title compound was obtained from (6*R*)-**26** in quantitative yield as described for the synthesis of (6S)-**27a**. MS (ESI) (m/z) 265 $(M + Na)^+$.

2-{(3*R*,4*R*,6*S*)-4-Ethyl-6-[(*S*)-2-ethylhexyl]-6-methyl-1,2-dioxan-3-yl}acetic Acid Methyl Ester (1). To a suspension of methoxymethyl(triphenyl)phosphonium chloride (48.0 mg, 0.14 mmol) in dry THF (2.0 mL), cooled to −78 °C, was added sodium bis(trimethylsily)amide (1.0 M solution in THF, 130 μL, 0.13 mmol) dropwise, and the resulting red solution was stirred at 0 °C for 1 h. The Wittig reagent prepared was cooled to −78 °C, and a solution of aldehyde (6*S*)-**27a** (20 mg, 0.07 mmol) in THF (1.0 mL) was added dropwise. The reaction mixture was allowed to warm to 0 °C over 1 h and then was quenched by addition of methy-*tert*-butylether. The white precipitate was filtered off, and the filtrate was concentrated. The crude product was dissolved in acetone (2.0 mL) containing 100 μL of 6 N hydrochloric acid and stirred for 30 min. Afterward the solution was neutralized by addition of a saturated solution of sodium bicarbonate, the volatiles were removed, and the aqueous phase was extracted with dichloromethane. The organic extracts were dried over sodium sulfate and concentrated. The crude aldehyde (11 mg, 0.04 mmol) was dissolved in acetonitrile (0.5 mL) and added to a solution of sodium periodate (34.0 mg, 0.16 mmol) and ruthenium(III) chloride (catalytic amount) in 1:3 water/acetonitrile (1.0 mL). The reaction mixture was stirred at 25 °C for 1 h; afterward diethyl ether (5 mL) was added, and the dark precipitate was filtered off. The filtrate was dried over sodium sulfate and concentrated. The crude carboxylic acid was dissolved in diethyl ether, and a freshly prepared solution of diazomethane was added until disappearance of the carboxylic acid as monitored by TLC (1:5 ethyl acetate/*n*-hexane). The solvent was finally removed, and the residue was purified by flash chromatography to afford (6*S*)-**1** (5.3 mg, 24%) as a colorless oil. Analytical and spectral data are identical to those reported in the literature.[1] $[\alpha]^{20}_D$ = +32 (c 0.001, $CHCl_3$); lit.[1] +49 (c 0.002, $CHCl_3$); MS (ESI) (m/z) 337 $(M + Na)^+$. HRMS (ESI) calcd for $C_{18}H_{34}O_4Na$ $(M + Na)^+$ 337.2349, found 337.2350.

2-{(3*R*,4*R*,6*R*)-4-Ethyl-6-[(*S*)-2-ethylhexyl]-6-methyl-1,2-dioxan-3-yl}acetic Acid Methyl Ester (2). The title compound was obtained from (6*R*)-**28a** in 35% yield as described for the synthesis of (6*S*)-**1**. $[\alpha]^{20}_D$ = +143 (c 0.001, $CHCl_3$) R_f 0.24 (1:40 diethyl ether/*n*-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.53−4.47 (m, 1H, H-3), 3.71 (s, 3H, COOMe), 3.02 (dd, J = 9.4, 15.8 Hz, 1H, H-2a), 2.38 (dd, J = 3.7, 15.7 Hz, 1H, H-2b), 2.20−2.10 (m, 1H, H-4), 1.84 (dd, J = 4.5, 14.5 Hz, 1H, 7a), 1.64−1.56 (m, 1H, 5a), 1.48−1.14 (m, 13H), 1.12 (s, 3H,), 0.94−0.80 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ172.4 (C-1), 81.1 (C-6), 78.7 (C-3), 52.0 (C-18), 38.2 (C-7), 36.0 (C-5), 34.6 (C-4), 34.5 (C-8), 33.8 (C-9), 31.2 (C-2), 28.5 (C-10), 27.2 (C-13), 27.3 (C-15), 25.0 (C-16), 22.4 (C-11), 14.1 (C-12), 10.3 (C-17), 10.1 (C-14); MS (ESI) (m/z) 337 $(M + Na)^+$. HRMS (ESI) calcd for $C_{18}H_{34}O_4Na$ $(M + Na)^+$ 337.2349, found 337.2346.

2-((3*R*,4*R*,6*S*)-4-Ethyl-6-(2-ethylbutyl)-6-methyl-1,2-dioxan-3-yl]acetic Acid Methyl Ester (3). The title compound was obtained from (6*S*)-**27b** in 32% yield as described for the synthesis of (6*S*)-**1**. $[\alpha]^{20}_D$ = +194 (c 0.01, $CHCl_3$); R_f 0.25 (1:30 ethyl acetate/*n*-hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.53−4.47 (m, 1H, H-3), 3.71 (s, 3H, COOMe), 3.00 (dd, J = 9.4, 15.5 Hz, 1H, H-2a), 2.37 (dd, J = 3.5, 15.5 Hz, 1H, H-2b), 2.21 (m, 1H, H-4), 1.45 (dd, J = 4.7, 13.5 Hz, 1H, H-5a), 1.37 (s, 3H, H-13), 1.36 (overlapped,1H, H-14a), 1.35 (overlapped, 1H, H-8), 1.30 (m, 3H, H_2-7, H-14b), 1.24 (m, 2H, H-9a, H-11a), 1.20 (overlapped,1H, H-5b), 1.16 (overlapped, 2H, H-9b, H-11b), 0.91 (t, J = 7.3 Hz, 3H, H-10), 0.84 (t, J = 7.3 Hz, 6H, H-12, H-15); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4 (C-1), 81.5 (C-6), 78.8 (C-3), 52.0 (COOMe), 45.1 (C-7), 35.8 (C-5), 35.6 (C-4), 35.1 (C-8), 31.6 (C-2), 27.3 (C-14), 25.3 (C-9, C-11), 21.6 (C-13), 11.3 (C-15), 11.1 (C-10), 10.8 (C-12); MS (ESI) (m/z) 309 $(M + Na)^+$. HRMS (ESI) calcd for $C_{16}H_{30}O_4Na$ $(M + Na)^+$ 309.2036, found 309.2037.

2-[(3*R*,4*R*,6*R*)-4-Ethyl-6-(2-ethylbutyl)-6-methyl-1,2-dioxan-3-yl]acetic Acid Methyl Ester (4). The title compound was obtained from (6*R*)-**28b** in 18% yield as described for the synthesis of (6*S*)-**1**. $[\alpha]^{20}_D$ = +180 (c 0.02, $CHCl_3$); R_f 0.25 (1:30 ethyl acetate/*n*-hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.52 (m, 1H, H-3), 3.71 (s, 3H, COOMe), 3.05 (dd, J = 9.4, 15.5 Hz, 1H, H-2a), 2.40 (dd, J = 3.5, 15.5 Hz, 1H, H-2b), 2.19 (m, 1H, H-4), 1.91 (dd, J = 4.2, 14.2 Hz, 1H, H-8), 1.62 (dd, J = 4.7, 13.5 Hz, 1H, H-5a), 1.49 (m, 2H, H-9a, H-11a), 1.35 (overlapped, 2H, H-9b, H-11b), 1.28 (overlapped,1H, H-5b), 1.22 (m, 3H, H_2-7, H-14a), 1.18 (overlapped,1H, H-14b), 1.12 (s, 3H, H-13), 0.91 (t, J = 7.3 Hz, 3H, H-15), 0.84 (t, J = 7.3 Hz, 6H, H-10, H-12); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5 (C-1), 81.2 (C-6), 78.8 (C-3), 52.1 (COOMe), 38.4 (C-7), 36.4 (C-5), 36.3 (C-8), 35.1 (C-4), 31.6 (C-2), 27.1 (C-9, C-11), 25.3 (C-14), 21.6 (C-13), 11.3 (C-15), 11.1 (C-10), 10.8 (C-12); MS (ESI) (m/z) 309 $(M + Na)^+$. HRMS (ESI) calcd for $C_{16}H_{30}O_4Na$ $(M + Na)^+$ 309.2036, found 309.2031.

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Supporting Information Available: General experimental methods and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.