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Total Asymmetric Syntheses of β-Hydroxy-δ-lactones via Umpolung with Sulfur Dioxide†

Claudia J. Exner,[‡,⊥] Sylvain Laclef,[‡,⊥] Florent Poli,[‡] Maris Turks,[§] and Pierre Vogel*[,‡]

[‡]*Laboratory of Glycochemistry and Asymmetric Synthesis (LGSA), Swiss Federal Institute of Technology Lausanne (EPFL), Batochime, CH-1015 Lausanne, Switzerland, and* [§]*Faculty of Material Science and Applied Chemistry, Riga Technical University, LV-1048 Riga, Latvia.*
[⊥]*These authors contributed equally to this work*

pierre.vogel@epfl.ch.

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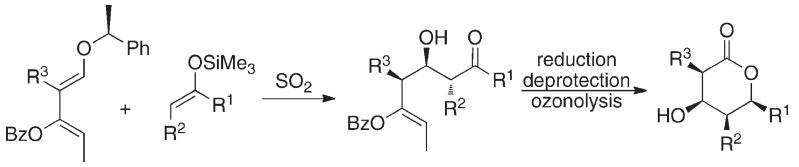

Cyclic stereotriads and stereotetrads of the β-hydroxy-δ-lactone type, e.g. prelactones B and E, common in polyketides and polypropionates, are prepared via SO_2-induced oxyallylations of enoxysilanes with (1*E*,3*Z*)-1-(1-phenylethoxy)penta-1,3-dien-3-yl carboxylates. Using (*Z*)- or (*E*)-enoxysilanes both 4,5-*cis*- or 4,5-*trans*-δ-lactones are obtained. Depending on the reduction method applied to the obtained aldol intermediates 5,6-*trans* or 5,6-*cis*-derivatives are formed. The δ-lactones can be prepared in both their enantiomeric forms depending on the (1*R*)- or (1*S*)-configuration of the starting 1-(1-phenylethoxy)penta-1,3-dienes.

Introduction

Polyketides and polypropionates represent an important class of natural compounds[1] with broad potential for pharmacological applications.[2] Their stereochemical complexity has stimulated intensive research toward the development of chemical[3,4] and biochemical methods[5] for their total synthesis. β-Hydroxy-δ-lactones like compounds **1**−**7** (Chart 1) constitute, as cyclic stereotriads and stereotetrads, a common structural motif in a large number of natural polyketides and polypropionates and are intermediates in the step-by-step biosynthesis of these compounds.[6] As such, they have been isolated from different polyketide-producing organisms.

† Dedicated to Professor Janine Cossy, ESPCI, Paris, on the occasion of being awarded the Grand Prix Achille LeBel.

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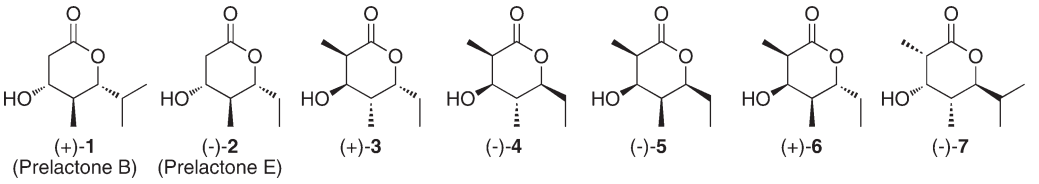
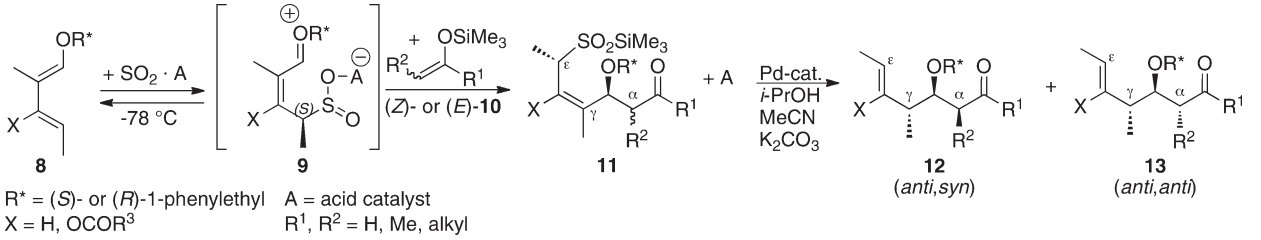
CHART 1. Different δ-Lactones 1−7, Synthesized Using SO_2-Chemistry



SCHEME 1. One-Pot Synthesis of α,β,γ-*syn*,*anti*- or *anti*,*anti*-Stereotriads through SO_2-Induced Oxyallylation of (*Z*)-or (*E*)-Enoxysilanes[a]



[a]The shown structures are obtained for R* = (*S*)-1-phenethyl.

For instance, β-hydroxy-δ-lactone prelactone B (**1**) has been found in the fermentation broth of *Streptomyces* producing concanamycins and bafilomycins (Chart 1),[7] which stimulated several syntheses of (+)-(**1**) and its stereoisomers using various approaches.[8] Prelactone E ((−)-**2**), a product of chemical degradation of concanolide derivatives,[9] has been synthesized recently by two groups applying Evans' aldol chemistry.[10,11] Using an L-proline-catalyzed aldol reaction Barbas and co-workers obtained lactone (+)-**3** in a two-step process with 11% ee, that could be improved by carrying out the reaction in an ionic liquid.[12,13] Lactone (−)-**4**, the 5-epimer of (+)-**3**, has been prepared by Cordova and co-workers from propanal in a three-step process with an ee >99% involving two successive L-proline- and D-proline-catalyzed aldol reactions followed by MnO_2-oxidation.[14] Compound (−)-**5** was obtained by Hoffmann and co-workers *via* enantioselective crotylboration of methacroleine followed by diastereoselective hydroboration.[17b] Chênevert and co-workers made (−)-**5** in a few steps with 58% overall yield via enzymatic desymmetrization of *meso*-(*anti*,*anti*)-2,4-dimethyl-1,3,5-pentanetriol.[15,16] δ-Lactone (+)-**6**, the 5-epimer of (−)-**5**, has been obtained only through biological synthesis applying polyketide synthase.[6a] Both lactones, (−)-**5** and (+)-**6**, contain an α,β,γ-*anti*,*anti*-stereotriad subunit, the most elusive to obtain.[17]

In this report we propose alternative syntheses of lactones (+)-**1**−(+)-**6**. Our method is general and has been applied also to the synthesis of lactone (−)-**7**, a yet unknown compound.[18]

With the use of our SO_2-reaction cascade that combines electron-rich dienes **8** and (*Z*)- or (*E*)-enoxysilanes **10** via SO_2-Umpolung, we have developed a one-pot synthesis of α,β,γ-*syn*,*anti*- and -*anti*,*anti*-stereotriads of types **12** and **13**, respectively (Scheme 1).[19,20] The starting dienes **8** are readily obtained from pentan-3-one, ethyl formate and inexpensive, enantiomerically enriched (*S*)- or (*R*)-1-phenylethanol, the source of chirality.[21]

A hetero-Diels−Alder addition between diene **8** and SO_2 followed by Lewis acid-assisted ionization gives a zwitterionic

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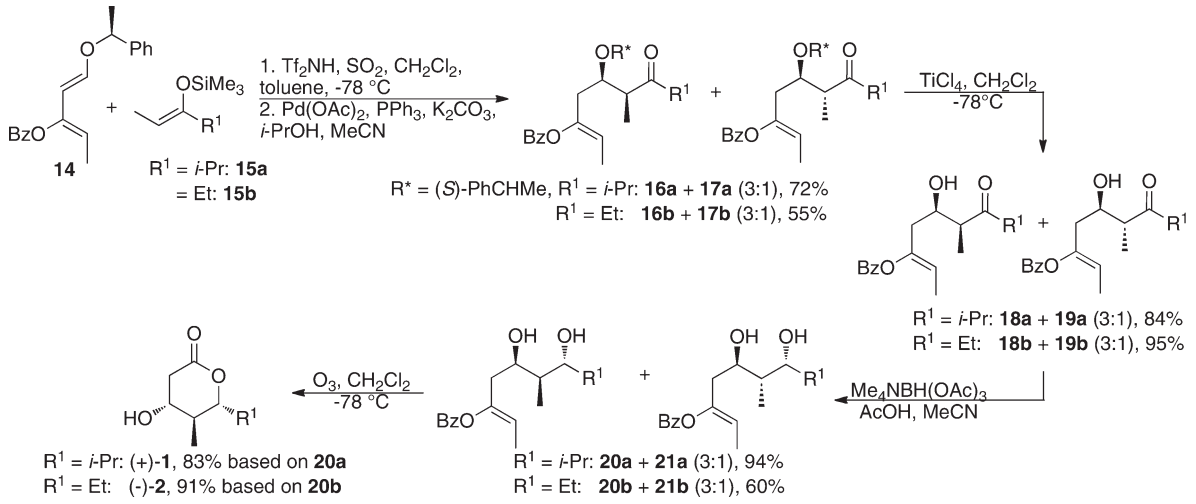
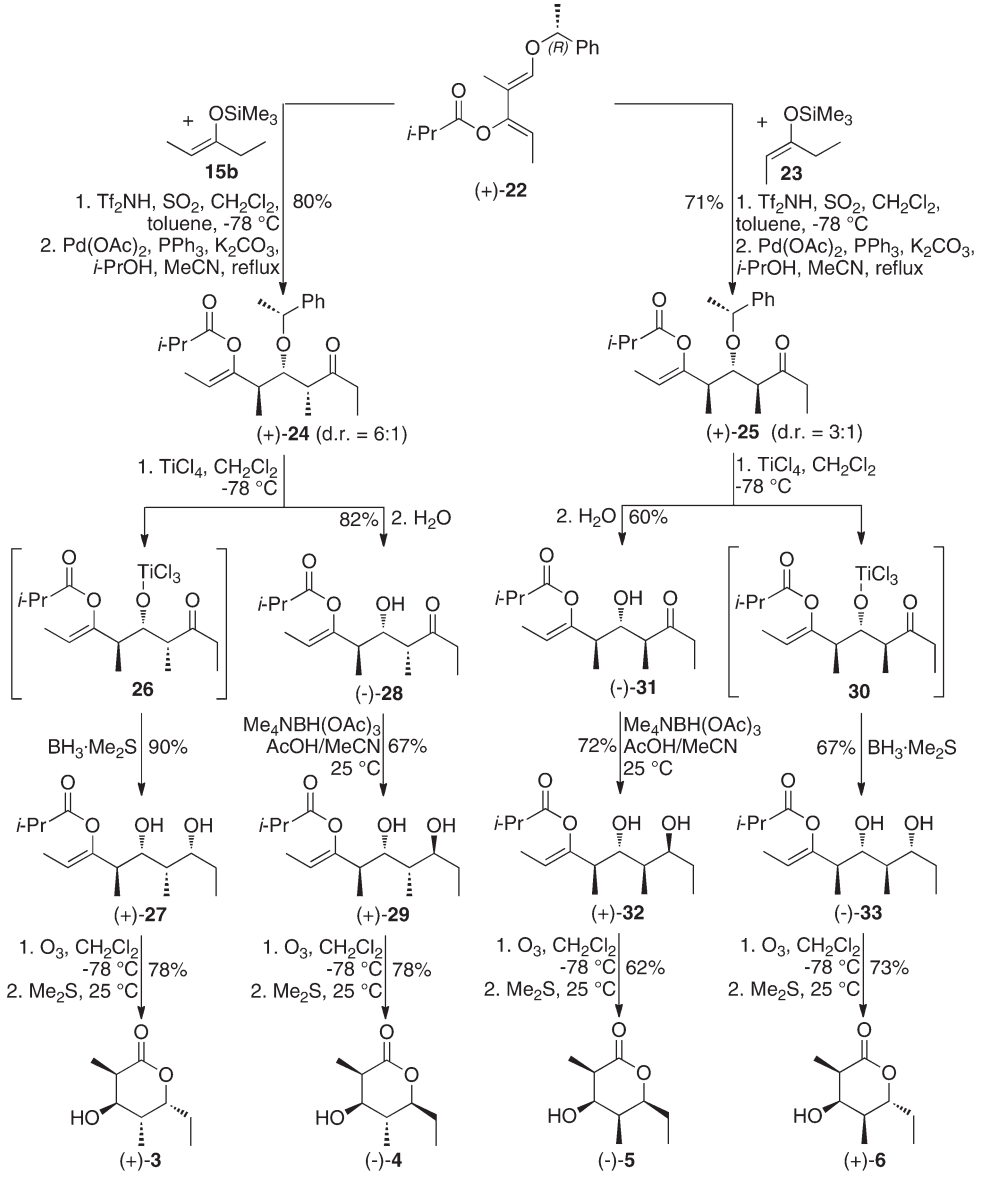
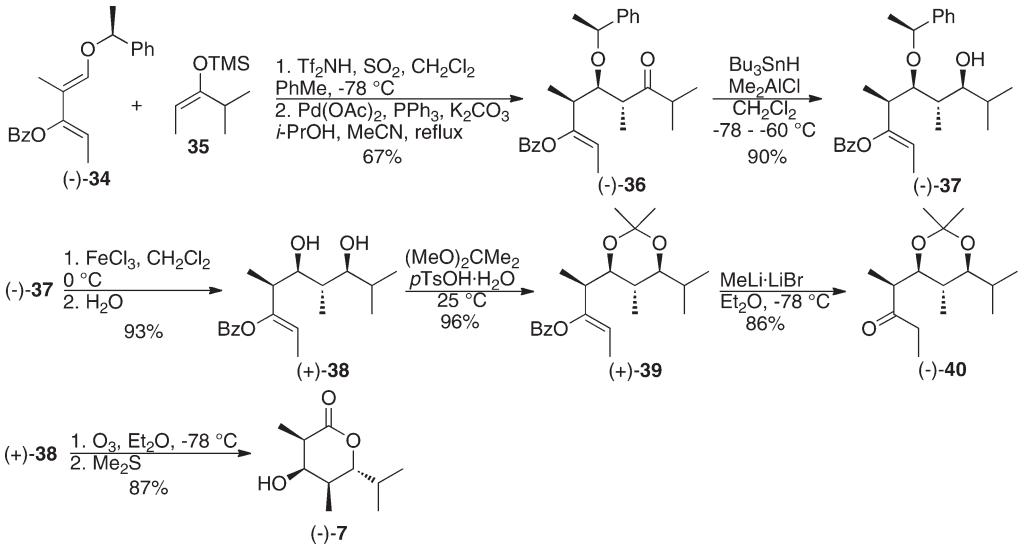
SCHEME 2. Syntheses of Prelactones B ((+)-1) and E ((−)-2)



SCHEME 3. Syntheses of δ-Lactones (+)-3, (−)-4, (−)-5, and (+)-6



SCHEME 4. Synthesis of δ-Lactone (−)-7



species **9**, which undergoes an oxyallylation reaction with alkenes **10** to silylsulfinates **11**. The latter are converted *in situ* into stereotriads **12** and **13**, respectively, in the presence of catalytic $Pd(OAc)_2/PPh_3$, involving a highly stereoselective chirality transfer from the ε-center in **11** to the γ-center in **12** respective **13** (Scheme 1).[22,23]

Results and Discussion

Our syntheses of the natural prelactones B ((+)-**1**) and E ((−)-**2**) combine diene **14**[24] with (*Z*)-enoxysilanes **15a** and **15b**, respectively. The SO_2-induced oxyallylation and concomitant desulfinylative desilylation afforded 3:1-mixtures of α,β-*syn*- and α,β-*anti*-stereodiad **16a**/**17a** (72% yield) and **16b**/**17b** (55% yield), respectively (Scheme 2). These mixtures were treated with $TiCl_4$ in CH_2Cl_2[25] to cleave the phenethyl ether moieties and provided 3:1 mixtures of the corresponding alcohols **18a**/**19a** (84%) and **18b**/**19b** (95%). Reduction of these mixtures with $Me_4NBH(OAc)_3/AcOH$[26] gave 3:1 mixtures of stereotriads **20a**/**21a** (94%) and **20b**/**21b** (60%). Ozonolysis of the latter, treatment with Me_2S, and chromatographic purification furnished (+)-**1** (83% based on **20a**) and (−)-**2** (91% based on **20b**).

This synthesis of (+)-**1** gives the final product in four steps and 35% yield based on diene (*S*)-**14** or in eight steps and 13% yield based on propionyl chloride, the starting material of diene (*S*)-**14**.[24] Prelactone E ((−)-**2**) was obtained in four steps and 21% overall yield based on diene (*S*)-**14**.

The β-hydroxy-δ-lactones (+)-**3**, (−)-**4**, (−)-**5**, and (+)-**6** (Scheme 3) were obtained by applying our oxyallylation cascade to diene (+)-**22**,[21,27] and using (*Z*)-**15b** and (*E*)-enoxysilane **23**. This generated the stereotriads (+)-**24**[27] and (+)-**25**[20] with diastereoselectivities of 6:1 and 3:1, respectively.[28] Treatment of **24** with $TiCl_4$ in CH_2Cl_2 at −78 °C afforded titanium alkoxide **26** which was reacted directly with $BH_3 \cdot Me_2S$[29] to give stereotetrad (+)-**27** in 90% yield. Ozonolysis of the enol ester of (+)-**27** followed by workup with Me_2S provided lactone (+) **3** (78%). Aqueous workup of **26** furnished alcohol (−)-**28**. Its reduction with $Me_4NBH(OAc)_3$[26] gave (+)-**29** (67%), the ozonolysis of which provided lactone (−)-**4** (78%). The same reaction sequence applied to (+)-**25** furnished stereotetrads (+)-**32** (72%) and (−)-**33** (67%), which were ozonolyzed to produce lactones (−)-**5** (62%) and (+)-**6** (73%), respectively. Structures of lactones (+)-**3**, (−)-**4**, (−)-**5**, and (+)-**6** were proven by their spectral data. Their relative configuration was established by the vicinal $^3J_{H,H}$ coupling constants in the ^1H NMR sprectra. Structures of (−)-**5** and (+)-**6** were also confirmed by single-crystal X-ray diffraction studies.[30] The diversity of our methodology is demonstrated by the synthesis of four different stereotetrads, i. e. structures (+)-**27**, (+)-**29**, (+)-**32**, and (−)-**33** (Scheme 3), all using the same diene (*R*)-**22** as starting material.

Lactone (+)-**3** was synthesized in three steps and 48% overall yield from diene (+)-**22**, and (−)-**4** was obtained in four synthetic steps and 29% overall yield based on (+)-**22**. Diastereoisomers (−)-**5** and (+)-**6** were synthesized in four and three steps with 14% and 26% overall yields, respectively, starting from diene (+)-**22**.

Lactone (−)-**7** was derived in a similar way from diene (−)-**34**[27] and (*E*)-enoxysilane **35** (Scheme 4). Their SO_2-mediated condensation produced stereotriad (−)-**36**[20] (67%, dr > 10:1). Reduction of ketone (−)-**36** with Me_2AlCl/Bu_3SnH[31] in CH_2Cl_2 (workup with KF) gave stereotetrad (−)-**37**[20] in 90% yield (dr > 10:1). $FeCl_3$-induced S_N1-debenzylation of (−)-**37** provided diol (+)-**38** (93%, dr > 10:1). Its relative configuration was confirmed by the ^1H- and ^{13}C NMR

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(28) Compound **25** may be obtained with a better diastereomeric ratio of 5:1 using the *tert*-butyric ester of diene (*S*)-**14** ((1*E*,3*Z*)-2-methyl-1-((*S*)-1-phenylethoxy)penta-1,3-dien-3-yl pivalate). See also ref 20.
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spectra of the corresponding acetonide (+)-**39** obtained by treatment of (+)-**38** with $(MeO)_2CMe_2$ and catalytic TsOH·H_2O (96%). It was furthermore verified by single-crystal X-ray diffraction studies of crystalline ketone (−)-**40** obtained by treatment of (+)-**39** with MeLi·LiBr in DME/Et_2O (86%).[30] Ozonolysis of enol ester (+)-**38** and subsequent treatment with Me_2S provided crystalline lactone (−)-**7**, the structure of which was also proven by single-crystal X-ray diffraction studies.[30]

Conclusion

Fully substituted 4-hydroxy-δ-lactones containing up to four continuous stereocenters can be prepared applying the oxyallylation of enoxysilanes through SO_2−Umpolung of enantiomerically enriched (1*E*,3*Z*)-1-(1-phenylethoxy)penta-1,3-dien-3-yl carboxylates. These stereotriads and stereotetrads are common motifs in a large number of natural polyketides and polypropionates. The number of synthetic steps, yields, and availability of starting materials are comparable with other well-accepted methods. The present methodology offers an alternative approach and extends the toolbox of chemists chasing cyclic polypropionate structures. We were able to obtain lactone (+)-**6** for the first time using chemical synthesis[6a] as well as the yet unknown (−)-(3*R*,4*R*,5*S*,6*R*)-4-hydroxy-6-isopropyl-3,5-dimethyltetrahydro-2H-pyran-2-one ((−)-**7**).

Experimental Section

(+)-(3*R*,4*R*,5*S*,6*R*)-6-Ethyl-4-hydroxy-3,5-dimethyltetrahydro-2*H*-pyran-2-one ((+)-6). O_3 was bubbled into a soln of (−)-**33** (12 mg, 0.037 mmol) in CH_2Cl_2 (2 mL) at −78 °C until persistence of the blue color. After the disappearance of (−)-**33** by TLC, Me_2S (0.1 mL) was added and the mixture stirred at −78 °C for 20 min. The mixture was allowed to warm to 25 °C. Solvent evaporation and flash chromatography on silica gel (PE/EtOAc) gave (+)-**6** (5 mg, 73%) as colorless crystals (X-ray, Supporting Information). R_f = 0.23 (PE/EtOAc, 3:2). Mp 79−81 °C. $\alpha^{25}{}_D$ = +21 ($CHCl_3$, *c* = 0.16). IR (film): ν (cm^{-1}) = 3433, 2971, 2938, 2882, 1707 (s), 1461, 1380, 1212, 1172, 1119, 992, 974. ^{1}H NMR (*CDCl*$_3$, 400 MHz): (ppm) = 1.02 (t, 3H, ^3J = 7.5 Hz), 1.07 (d, 3H, ^3J = 6.5 Hz), 1.33 (d, 3H, ^3J = 7.0 Hz), 1.55 (ddq, 1H, ^3J = 7.0, 7.5 Hz), 1.82 (ddq, 1H, ^3J = 3.0, 7.0, 7.5 Hz), 1.87−1.93 (m, 1H), 2.53 (dq, 1H, ^3J = 3.0, 7.0 Hz), 3.84 (br s, 1H), 4.36 (ddd, 1H, ^3J = 3.0, 7.0, 10.5 Hz). ^{13}C NMR (*CDCl*$_3$, 100.6 MHz): δ (ppm) = 8.7, 12.9, 14.3, 26.1, 37.7, 42.6, 73.3, 82.1, 173.8. ESI-HRMS: *m*/*z* calcd for $C_9H_{17}O_3^+$ 173.1178, found 173.1175 [M + H^+].

(−)-(3*S*,4*S*,5*R*,6*S*)-4-Hydroxy-6-isopropyl-3,5-dimethyltetrahydro-2*H*-pyran-2-one ((−)-7). O_3 was bubbled through a soln of (−)-**38** (200 mg, 0.62 mmol) in CH_2Cl_2 (5 mL) at −78 °C until persistence of the blue color, then O_2 was bubbled. After the disappearance of (−)-**38** by TLC, Me_2S (0.25 mL) was added and the mixture was allowed to warm to 25 °C overnight. Water (10 mL) was added and the aq phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine (2 × 10 mL) and dried (Na_2SO_4), and the solvent was evaporated. Flash chromatography on silica gel (CH_2Cl_2/EtOAc) gave pure (−)-**7** (110 mg, 87%), that was recrystallized from hexane (X-ray, Supporting Information). R_f = 0.45 (PE/EtOAc, 7:3). Mp 92−95 °C. $\alpha^{25}{}_D$ = −28 ($CHCl_3$, *c* = 0.40). IR (film): ν (cm^{-1}) = 3370, 3260, 2970, 2920, 1725, 1695, 1465, 1370, 1345, 1220, 1195, 1170, 1120, 990. ^{1}H NMR (*CDCl*$_3$, 400 MHz): (ppm) = 0.89 (d, 3H, ^3J = 7.1 Hz), 1.06, 1.11 (2d, 6H, ^3J = 7.0 Hz), 1.32 (d, 3H, ^3J = 7.1 Hz), 1.87 (sept, 1H, ^3J = 7.0 Hz), 1.95 (dq, 1H, ^3J = 6.6, 10.7 Hz), 2.51 (q, 1H, ^3J = 7.1 Hz), 3.85 (s, 1H), 4.29 (d, 1H, ^3J = 10.7 Hz). ^{13}C NMR (*CDCl*$_3$, 100.6 MHz): δ (ppm) = 12.7, 14.0, 10.0, 28.9, 36.0, 42.3, 73.2, 84.8, 173.9. ESI-HRMS: *m*/*z* calcd for $C_{10}H_{19}O_3^+$ 187.1334, found 187.1336 [M + H^+].

(2*Z*,4*R*,5*R*,6*R*,7*R*)-5,7-Dihydroxy-4,6-dimethylnon-2-en-3-yl 2-methylpropanoate ((−)-33). One molar $TiCl_4$ in CH_2Cl_2 (3 mL, 3.0 mmol) was added quickly to a stirred soln of (+)-(1*Z*,2*R*,3*S*,4*S*)-1-ethylidene-2,4-dimethyl-5-oxo-3-[(1*R*)-1-phenylethoxy]-heptyl-2-methylpropanoate ((+)-**25**) (550 mg, 1.47 mmol). After stirring at −78 °C for 1 h, 1 M BH_3·Me_2S in CH_2Cl_2 (6.7 mL, 6.7 mmol) was added, and the mixture was stirred at −78 °C for two more hours. The reaction mixture was quenched with a sat. aq soln of $NaHCO_3$ (15 mL). The mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (15 mL) and dried ($MgSO_4$). Solvent evaporation and flash chromatography on silica gel (PE/EtOAc) gave (−)-**33** (269 mg, 67%) as colorless oil. R_f = 0.29 (PE/EtOAc, 4:1). $\alpha^{25}{}_D$ = −26 ($CHCl_3$, *c* = 0.58). IR (*film*): ν (cm^{-1}) = 3438, 2970, 2935, 2876, 1746 (s), 1691, 1459, 1408, 1337, 1240, 1138, 968. ^{1}H NMR (*CDCl*$_3$, 400 MHz): (ppm) = 0.93 (d, 3H, ^3J = 7.0 Hz), 0.97 (t, 3H, ^3J = 7.5 Hz), 1.08 (d, 3H, ^3J = 6.5 Hz), 1.26 (d, 6 H, ^3J = 7.0 Hz), 1.34−1.49 (m, 1H), 1.46 (d, 3H, ^3J = 6.5 Hz), 1.58−1.78 (m, 2H), 2.64−2.76 (m, 2H), 3.19 (dd, 1H, ^3J = 5.0 Hz, ^3J = 7.5 Hz), 3.51−3.61 (m, 1H), 5.25 (q, 1H, ^3J = 7.0 Hz). ^{13}C NMR (*CDCl*$_3$, 100.6 MHz): (ppm) = 10.1, 10.9, 15.3, 16.6, 19.2, 19.3, 27.9, 34.3, 40.1, 44.4, 76.5, 78.5, 114.6, 149.0, 176.2. ESI-HRMS: calcd for $C_{15}H_{29}O_4^+$ 273.2066, found 273.2059 [M + H^+].

(+)-(2*Z*,4*S*,5*S*,6*S*,7*S*)-5,7-Dihydroxy-4,6,8-trimethylnon-2-en-3-yl benzoate ((+)-38). To a soln of (2*Z*,4*S*,5*S*,6*S*,7*S*)-7-hydroxy-4,6,8-trimethyl-5-[(1*S*)-1-phenylethoxy]non-2-en-3-yl benzoate ((−)-**37**) (277 mg, 0.65 mmol) in CH_2Cl_2 (50 mL) was added a solution of $FeCl_3$ (0.2 g, 1.3 mmol) in 20 mL of CH_2Cl_2. The resulting mixture was stirred vigorously for 10 min at 25 °C, and H_2O was added. The aq phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4), filtered, and evaporated. Flash chromatography on silica gel (PE/EtOAc, 9:1) gave (+)-38 (195 mg, 93%) as colorless oil. R_f = 0.48 (PE/AcOEt, 8:2). $\alpha^{25}{}_D$ = +16 ($CHCl_3$, *c* = 0.22). IR (*film*): ν (cm^{-1}) = 3441, 3063, 2963, 2930, 2875, 1722, 1715, 1694, 1601, 1462, 1453, 1261, 1176, 1165, 1142, 1105, 1069, 1026. ^{1}H NMR (*CDCl*$_3$, 400 MHz): (ppm) = 0.88, 0.88 (2d, 6H, ^3J = 6.8 Hz), 1.00, 1.19 (2d, 6H, ^3J = 6.8 Hz), 1.53 (d, 3H, ^3J = 6.8 Hz), 1.79−1.90 (m, 2H), 2.91 (quint, 1H, ^3J = 7.4 Hz), 3.32 (dd, 1H, ^3J = 7.4, 4.3 Hz), 3.50 (dd, 1H, ^3J = 8.6, 3.1 Hz), 5.38 (q, 1H, ^3J = 7.4 Hz), 7.51 (t, 2H, ^3J = 7.4 Hz), 7.64 (t, 1H, ^3J = 7.4 Hz), 8.13 (d, 2H, ^3J = 8.0 Hz). ^{13}C NMR (*CDCl*$_3$, 100.6 MHz): (ppm) = 11.1, 14.7, 15.4, 16.9, 20.4, 30.2, 37.6, 44.2, 78.7, 79.7, 114.9, 128.7, 129.1, 130.2, 133.8, 149.3, 165.5. ESI-HRMS: calcd for $C_{19}H_{28}O_4Na^+$ 343.1885; found 343.1895 [M + Na^+].

(+)-(2*Z*,4*S*)-4-[(4*S*,5*S*,6*S*)-2,2,5-Trimethyl-6-(propan-2-yl)-1,3-dioxan-4-yl]pent-2-en-3-yl benzoate ((+)-39). To a soln of diol (+)-**38** (190 mg, 0.59 mmol) in dimethoxypropane (2 mL) was added *p*-TsOH·H_2O (5.6 mg, 0.03 mmol). The mixture was stirred for 1 h at 25 °C, then neutralized by adding solid $NaHCO_3$, filtered, and evaporated. Flash chromatography on silica gel (PE/EtOAc, 9:1) gave (+)-**39** (200 mg, 96%) as a colorless oil. $\alpha^{25}{}_D$ = +6 ($CHCl_3$, *c* = 0.30). IR (*film*): ν (cm^{-1}) = 2964, 2930, 2875, 2849, 1738, 1687, 1602, 1492, 1453, 1390, 1378, 1261, 1201, 1174, 1154, 1133, 1105, 1026. ^{1}H NMR (*CDCl*$_3$, 400 MHz): (ppm) = 0.72 (d, 3H, ^3J = 6.5 Hz), 0.88, 0.93 (2d, 6H, ^3J = 6.4 Hz), 1.18 (s, 3H), 1.21 (d, 3H, ^3J = 7.1 Hz), 1.30 (s, 3H), 1.54 (d, 3H, ^3J = 6.8 Hz), 1.80−1.90 (m, 2H), 2.68 (qd, 1H, ^3J = 7.4, 1.8 Hz), 3.32 (dd, 1H, ^3J = 10.4, 1.8 Hz), 3.40 (dd, 1H, ^3J = 9.8, 2.4 Hz), 5.33 (q, 1H, ^3J = 6.8 Hz), 7.48 (t, 2H, ^3J = 7.4 Hz), 7.58 (t, 1H, ^3J = 7.4 Hz), 8.13 (d, 2H, ^3J = 8.0 Hz). ^{13}C NMR (*CDCl*$_3$, 100.6 MHz): (ppm) = 10.8, 11.4, 14.1, 15.7, 18.8, 19.8, 27.8, 29.5, 29.7, 32.6, 39.1, 76.4, 77.0, 97.3, 112.7, 128.0, 129.7, 132.6, 148.8, 163.5. ESI-HRMS: calcd for $C_{22}H_{32}O_4K^+$ 399.1938; found 399.1937 [M + K^+]. Anal. calcd for $C_{22}H_{32}O_4$ (360.49): C, 73.30%; H, 8.95%; O, 17.75%. Found C, 73.22%; H, 8.85%; O, 17.74%.

(−)-(**4*S*,5*S*,6*S*,7*S*)-5,7-Isopropylidendioxy-4,6,8-trimethylnona-3-one** (−)-**40.** A soln of (+)-**39** (1.00 g, 2.78 mmol) in DME (15 mL) was added to a soln of MeLi·LiBr (2.1 M in Et_2O, 6.6 mL, 13.9 mmol) in Et_2O (10 mL) at −78 °C. The mixture was stirred at −78 °C for 5 h, poured into an ice-cold sat. aq soln of NH_4Cl (30 mL). The aq phase was extracted with Et_2O (4 × 20 mL). The organic layers were washed with brine (20 mL), dried (Na_2SO_4), and evaporated. The residue was purified by recrystallization from hexane, giving (−)-**40** (615 mg, 86%) as colorless crystals. R_f = 0.52 (PE/AcOEt, 9:1). Mp = 89−92 °C. α^{25}_D = −20 ($CHCl_3$, *c* = 0.15). IR (*film*): ν (cm^{-1}) = 2975, 2959, 2938, 2875, 2841, 1693, 1458, 1412, 1378, 1358, 1346, 1249, 1198, 1164, 1152, 1130, 1101, 1048. ^{1}H NMR (*$CDCl_3$*, 400 MHz): (ppm) = 0.75, 0.80 (2d, 6H, ^3J = 6.7 Hz), 0.91 (d, 3H, ^3J = 6.9 Hz), 1.01 (t, 3H, ^3J = 7.1 Hz), 1.19 (d, 3H, ^3J = 7.3 Hz), 1.31, 1.36 (2s, 6H), 1.44 (m, 1H), 1.85 (sept, 1H, ^3J = 6.6 Hz), 2.45, 2.59 (2qd, 2H, ^2J = 18.1 Hz, ^3J = 7.2 Hz), 2.71 (m, 1H), 3.27 (d, 1H, ^3J = 10.0 Hz), 3.56 (d, 1H, ^3J = 10.3 Hz). ^{13}C NMR (*$CDCl_3$*, 100.6 MHz): (ppm) = 7.4, 7.6, 11.7, 13.7, 14.2, 19.1, 20.1, 27.9, 29.9, 34.1, 49.7, 76.9, 77.6, 97.8, 214.2. ESI-HRMS: *m*/*z* calcd for $C_{15}H_{28}O_3Na^+$ 279.1936, found 279.1939 [M + Na^+].

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Supporting Information Available: Further complete experimental procedures and compound characterization data for (+)-**1**, (−)-**2**, (+)-**3**, (−)-**4**, (−)-**5**, **16a**, **16b**, **18a**, **18b**, **20a**, **20b**, (+)-**27**, **28**, (+)-**29**, (−)-**31**, (+)-**32**, (−)-**33** as well as copies of ^{1}H and ^{13}C NMR spectra for all newly reported compounds. X-ray data for (−)-**5**, (+)-**6**, (−)-**7**, and (−)-**40** have been deposited at the Cambridge crystallographic database. This material is available free of charge via the Internet at http://pubs.acs.org.