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Stereoselective synthesis and structure of butalactin and lactone II isolated from *Streptomyces* species

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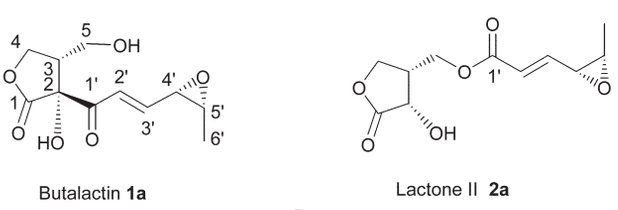
Received 24th May 2004, Accepted 21st July 2004
First published as an Advance Article on the web 23 August 2004

Butalactin (**1a**) and lactone II (**2a**) have been synthesized starting from (*S*)-malic acid and sorbic acid by a straightforward route. The absolute stereochemistry of **1a** and **2a** was unambiguously established by this synthesis.

Butalactin (**1a**) and lactone II (**2a**), which are highly functionalized γ-butyrolactones including a conjugated epoxy enone, were isolated from *Streptomyces corchorusii*[1] and *Streptomyces sp.* Go 40/10,[2] respectively. The stereochemistry of epoxide was proposed to be doubly *cis* by spectroscopic analysis; however, the relative and absolute configurations at the four stereogenic centers have not been determined. There have also been some butyrolactone autoregulators closely related to **1a**, such as A-factor,[3a] virginiae butanolides,[3b] lactone I,[2] and so forth, possessing a broad spectrum of biological activities. It is reported that **1a** exhibits moderate antibacterial activity against Gram positive bacteria, and this is the first example of the 2,3-disubstituted γ-butyrolactone showing antibiotic activity. Thus, it is very significant and indispensable to clarify the stereostructure of **1a** and **2a** for exploring structure–activity relationships among the autoregulators and **1a**. Recently, we achieved the first synthesis of **2a** and reported it as a preliminary communication.[4] Herein the synthesis and the stereochemistry of butalactin **1a** and lactone II **2a** will be described in detail. Our synthetic plan is briefly illustrated in Scheme 1.

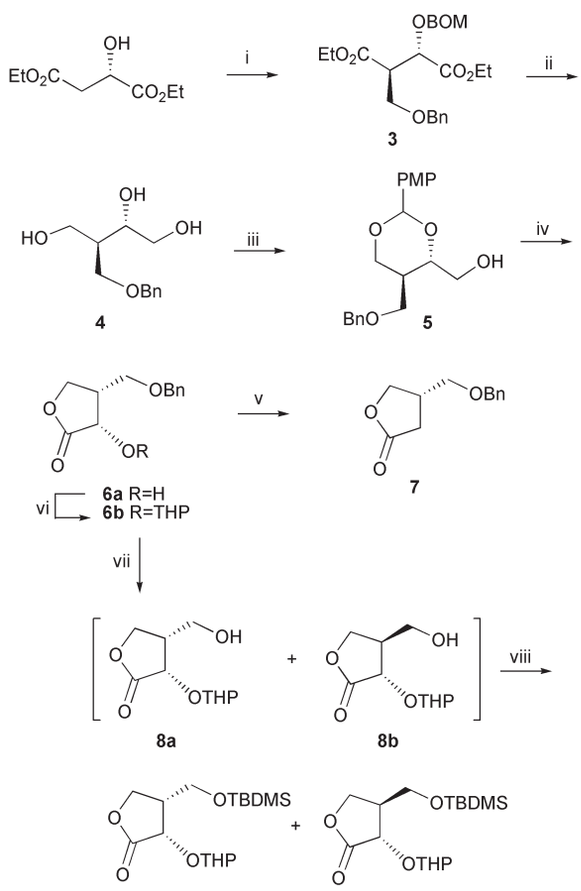


Scheme 1

Results and discussion

Synthesis of the lactone part A and the epoxy parts B and C

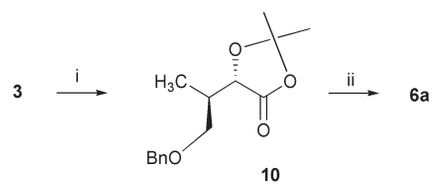
The requisite lactones **8** and **9** as coupling partners were synthesized as shown in Schemes 2 and 3. The benzyloxymethyldiester **3** was obtained by modification of the Seebach alkylation[5] of (*S*)-diethyl malate. The observed stereoselectivity was 8 : 1, and the isomers were separated by chromatography. Reduction of **3** with lithium aluminium hydride followed by acid hydrolysis gave the triol **4** (74%), which was protected with *p*-anisaldehyde to afford **5** (81%). The acetal **5** was transformed by Dess–Martin periodinane and successive sodium chlorite oxidation followed by acid-catalyzed deprotection into the γ-butyrolactone **6a** (89%). Smaller coupling constant ($J_{2,3}$ = 7.9 Hz) and larger NOE show *cis*-disposition as compared with larger coupling constant ($J_{2,3}$ = 10.2 Hz) and smaller NOE (Fig. 1). By reductive deoxygenation (*via* mesylate) of the hydroxyl group, the lactone **6a** was converted to the known compound **7**, $[\alpha]_D^{26}$ +34.6 (c, 0.9, $CHCl_3$) {ref. 6 $[\alpha]_D^{23}$ +32.5 (c, 0.9, $CHCl_3$), 95% ee for (*S*)-form}. The hydroxyl group of (2*S*, 3*S*)-**6a** was protected with dihydropyran to give separable diastereomeric isomers **6b**–**1** and **6b**–**2** (6 : 5) in 90% yield, because THP protection was, in spite of accompanying by new isomer, more successfully removed under mild conditions than MOM (methoxymethyl) protection in the final step. After separation an isomer **6b**–**1** was hydrogenolysed with palladium on carbon to yield inseparable mixture 2,3-*cis* **8a** and 2,3-*trans* **8b**: the ratio was approximately 4 : 1 by NMR. The mixture arose solely from hydrogenolytic cleavage of the benzyl group from **6b**–**1**. It is probably migrated from **8a** to **8b** *via* intramolecular translactonization. The primary hydroxyl group in **8** was protected with TBDMSCl to afford TBDMS ether **9a**



Scheme 2 Reagents, conditions and yields: (i) LDA, $ClCH_2OCH_2Ph$, HMPA, THF, −78 °C to rt, 70%; (ii) (a) $LiAlH_4$, Et_2O; (b) HCl, MeOH–H_2O, 81%; (iii) $ZnCl_2$, $MeOC_6H_4CHO$, Et_2O, MS 4A, 81%; (iv) (a) Dess–Martin periodinane, CH_2Cl_2; (b) $NaClO_2$, NaH_2PO_4, *t*-BuOH–H_2O; (c) HCl, dioxane, 89% (two steps); (v) (a) MsCl, Et_3N, CH_2Cl_2; (b) Zn, NaI, DME, 85 °C, 91%; (vi) DHP, CSA, CH_2Cl_2, 90%; (vii) H_2, Pd–C, EtOH, 100%; (viii) TBDMSCl, DMF, imidazole, rt, 93%.

DOI: 10.1039/b407820a

and **9b** (93%, 4 : 1). The stereochemistries of these compounds were confirmed by ^{1}H NMR analysis and NOE experiments (Fig. 1). The signals of H-2 appeared at δ 4.56 (J = 7.9 Hz) in **9a** and δ 4.46 (J = 9.2 Hz) in **9b**, respectively. In **9a**, a NOE was observed between H-2 and H-3, whereas a NOE was not observed in **9b**. From these results, **9a** and **9b** are presumed to be 2,3-*cis* and 2,3-*trans* isomers, respectively. An improved synthesis (shorter step and higher overall yield) of **6a** is also shown in Scheme 3.



Scheme 3 Reagents, conditions and yields: (i) (a) HCl, THF, boil, (b) aq. KOH, dioxane, 0 °C, (c) *p*-TsOH, $(MeO)_2CMe_2$, acetone, 84%; (ii) BH_3–Me_2S, THF, then HCl, 61%.

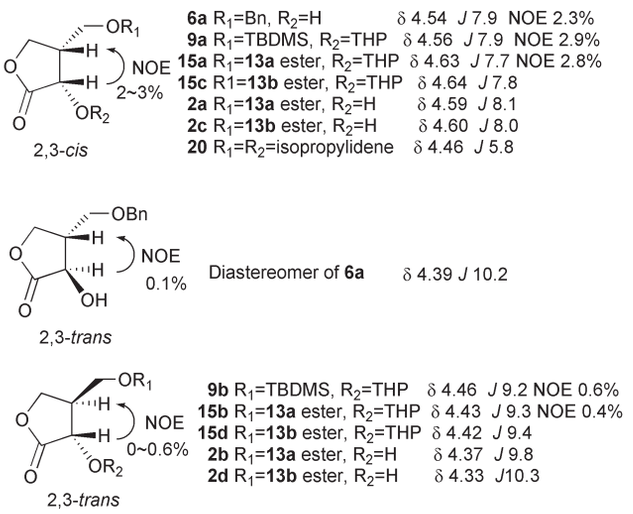
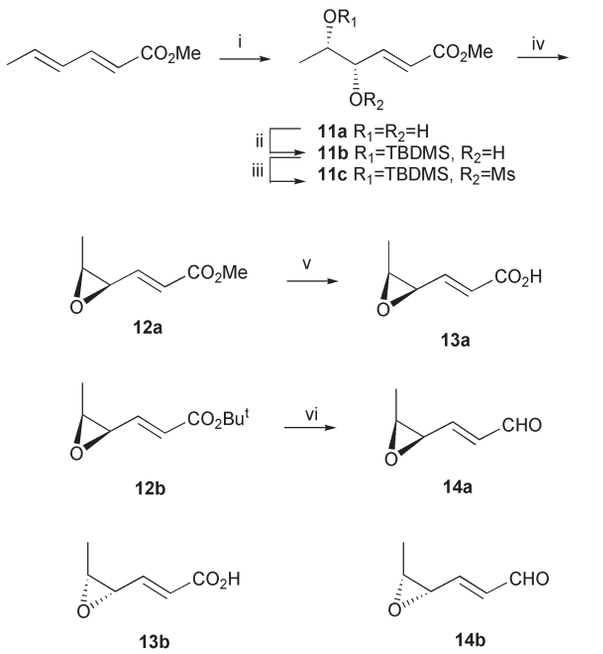


Fig. 1 Selected NOE, δ values of H-2 and $J_{2,3}$ (in Hz) of related compounds.

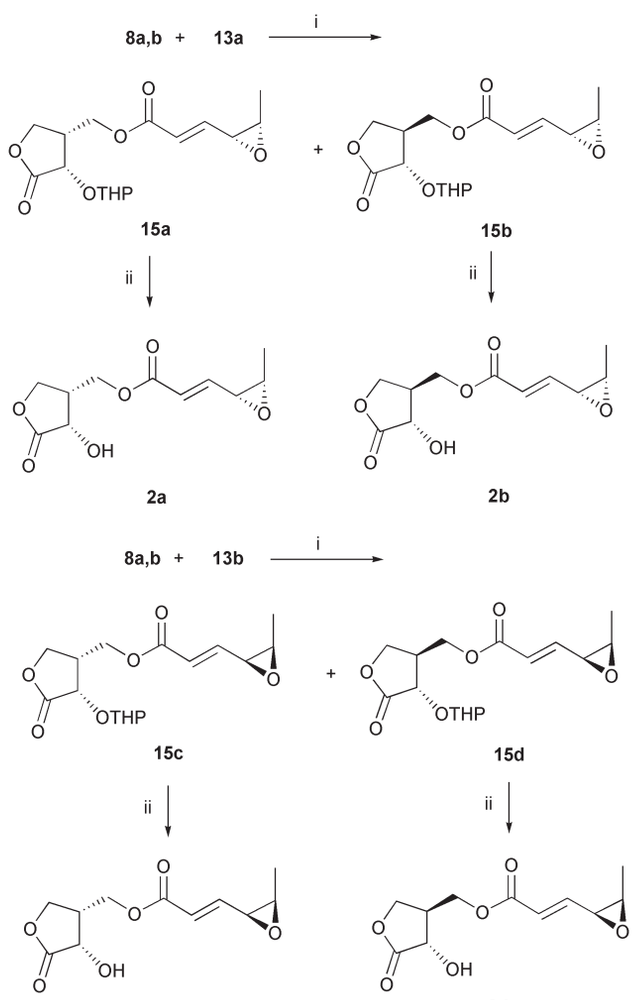
The epoxy parts (aldehyde B and acid C) were efficiently synthesized from sorbic acid according to the Sharpless method (Scheme 4). Selective protection of the hydroxyl group of the known compound **11a**[7] [prepared from methyl sorbate and AD-mix-α] with *tert*-butyldimethylsilyl triflate[8] afforded the mono hydroxy TBDMS ether **11b** (76%), which was subjected to mesylation and selective deprotection of the silyl group with TBAF to yield (4*R*,5*S*)-epoxy ester **12a** (64% from **11a**). Successful hydrolysis of **12a** with potassium trimethylsilanolate[9] afforded (4*R*,5*S*)-epoxy acid **13a** (82%) without complication. Reduction of **12a** (methyl ester) to **14a** with DIBAL-H resulted in decomposition, however, similar reaction of **12b** (*tert*-butyl ester) furnished the epoxy aldehyde **14a** as a single product. By a similar oxidation of methyl or *tert*-butyl sorbate with AD-mix-β and a subsequent series of reactions, the other isomers (4*S*,5*R*)-**13b** and (4*S*,5*R*)-**14b** were also obtained, respectively.

Synthesis of lactone II

Esterification of **8** (mixture of **8a** and **8b**, 4 : 1) with **13a** was achieved by the DCC method to provide separable compounds **15a** (67%) and **15b** (13%) (Scheme 5). As mentioned on the analysis of **9a** and **9b** the stereochemistries of **15a** and **15b** were confirmed to be 2,3-*cis* and 2,3-*trans* isomers, respectively. On treatment of **15a** or **15b** with acetic acid in THF–H_2O at 50 °C to remove THP protection, the final products **2a** and **2b** were obtained in satisfactory yield, respectively. Isomers **2c** and **2d** were synthesized from **8** and (4*S*, 5*R*)-**13b** in the same manner. The compounds **2a** and **2c** have similar ^{1}H and ^{13}C NMR spectra, as do **2b** and **2d**. This is most noticeable in the C2–C3 coupling constants, because they have similar stereochemistry on the lactone ring. Of the four compounds, **2a** corresponds to the natural product, because the NMR is the closest match, but more importantly, because the specific rotations match the most closely (Fig. 1 and experimental section). From these results, the absolute configuration of lactone II was determined as 2*S*,3*S*,4′*R*,5′*S*.



Scheme 4 Reagents, conditions and yields: (i) ref. 7; (ii) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 76%; (iii) MsCl, CH_2Cl_2, Et_3N, rt, 92%; (iv) TBAF, THF, rt, 92%; (v) TMSOK, THF, 82%; (vi) DIBAL, Et_2O, −78 °C, 54%.



Scheme 5 Reagents, conditions and yields: (i) DCC, DMAP, CH_2Cl_2, rt, 24 h, 88%; (ii) AcOH, THF–H_2O, 50 °C, 3 h, 63% for **2a**, 69% for **2b**, 58% for **2c** and 43% for **2d**.

Synthesis of butalactin

The aldol reaction of the lithium enolate of (2*S*, 3*R*)-**9a** with (4*S*, 5*R*)-**14b** afforded **17a** as an inseparable mixture of four diastereomers (Scheme 6). Although a multitude of isomers is formed, in the light of the subsequent steps this factor is of minor significance. Successive treatment of **17a** with Dess–Martin periodinane provided **18a** and **18b** (75%, 12 : 1) as a separable mixture. A NOE was observed between H-3 and H-2′ for the major isomer, but not for the minor isomer (Fig. 2). From these results, **18a** and **18b** are presumed to be 2,3-*trans* and 2,3-*cis* isomers, respectively. In stepwise removal of the protecting group in **18a**, the THP group was firstly removed by treatment with acetic acid in THF–H_2O at 40 °C to give **19a** (48%) along with **1a** (11%). Secondly, the treatment of **19a** with tetrabutylammonium fluoride (TBAF) in THF at 0 °C yielded surprisingly the unexpected esters **2d**, ***ent*-2a** (enantiomer of **2a**) and decomposition products (Scheme 6). Similarly, deprotection treatment of **19b** with TBAF gave the esters **2c** and ***ent*-2b** (enantiomer of **2b**). The products were identical with the samples synthesized according to the procedure mentioned above, *i.e.* 2*S* esters (**2c** and **2d**) and 2*R* esters (***ent*-2a** and ***ent*-2b**) were prepared from (*S*)- or (*R*)-malic acid and **13b**, respectively. A proposed mechanism of the rearrangement (*via* intramolecular double esterification) is shown in Scheme 7. The detailed process is currently under investigation and will be reported in due course.

Concurrent removal of the THP and TBDMS groups in **18a** with acetic acid in THF–H_2O at 60 °C gave **1a** (α-epoxide) in 27% yield along with cleavage of the epoxide (Scheme 6). It was impossible to isolate the polar decomposition products. Successive stereoselective synthesis of **1a** was achieved by the following procedures (Scheme 8).

The Seebach alkylation of the acetonide **20** [prepared from **6a**] with the epoxy aldehyde **14b** and subsequent treatment of the Dess–Martin oxidation afforded the ketone **21** (68%, 2 steps) as a single diastereoisomer. The stereochemistry of **21** was determined to be 2,3-*trans* configuration by NOE experiment. The final deprotection of the acetonide group using acetic acid–THF–H_2O at 40 °C furnished **1a** in 66% yield. The synthetic **1a** was identical with the natural product by comparing the optical rotation, ^{1}H and ^{13}C NMR spectra with those reported.[1] Thus, it has been found that the absolute configuration of butalactin is assigned to 2*R*, 3*S*, 4′*S*, 5′*R*. Although another isomer **1b** (β-epoxide) was, in the same way (Scheme 6), synthesized from **9a** and the aldehyde **14a**, this was not identical with the natural product.

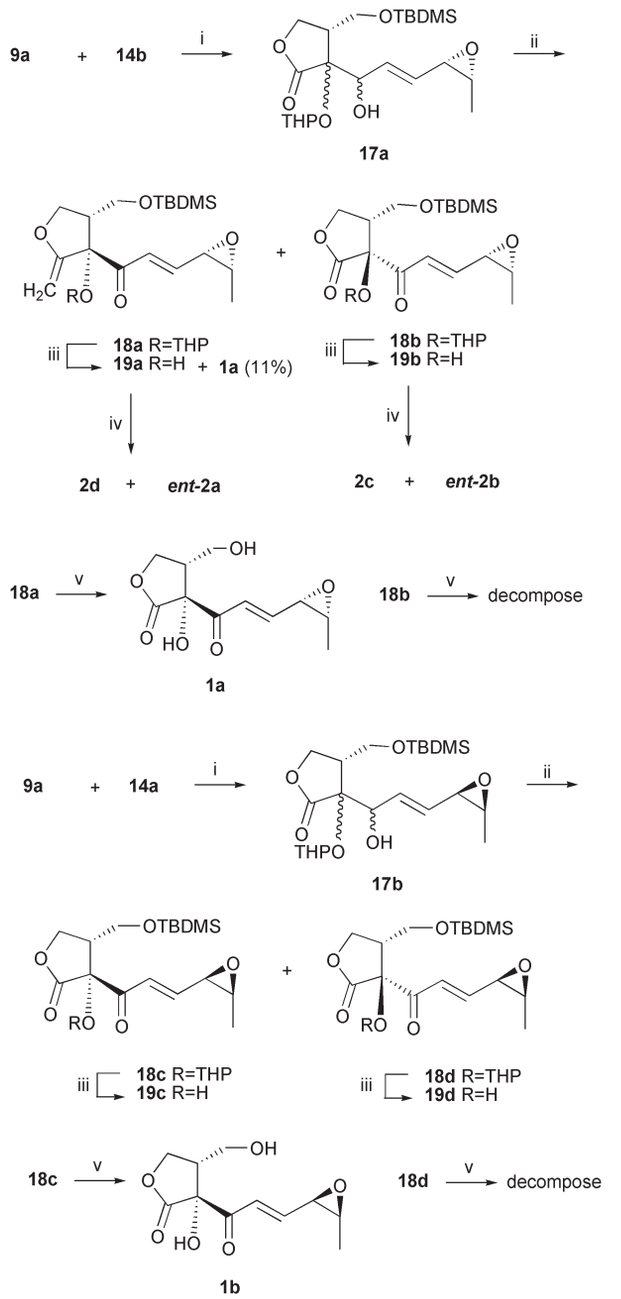
On the contrary, the same deprotection procedure for both 2,3-*cis* **18b** and 2,3-*cis* **18d** resulted in decomposition. Unfortunately, the *cis* isomers corresponding to butalactin could not be obtained. However, while a NOE between H-3 and H-2′ was observed in the 2,3-*trans* isomers (**18a**, **19a**, **18c**, **19c**, **1a**, **1b** and natural butalactin), no NOE was observed in the 2,3-*cis* isomers (**18b**, **19b**, **18d** and **19d**) (Fig. 2). Moreover, the optical rotations showed the following tendency: positive sign for the *trans* **19a**, **19c** and butalactin, and negative sign for the *cis* **19b** and **19d**. These results suppose that 2,3-*cis* derivatives might be non-natural. Judging from the fact that 3-oxymethyl anion of **1a** caused intramolecular double migration to yield **2d** and **ent-2a**, it might be assumed that neither butalactin is the precursor of lactone II in biogenesis nor lactone II is the artifact of butalactin in working-up.

Conclusion

In conclusion, we have achieved the first stereoselective synthesis of butalactin and lactone II from (*S*)-malic acid and sorbic acid, and determined their absolute configurations. The interesting rearrangement *via* intramolecular double esterification of 3-oxymethyl anion, generated from 2,3-*trans*-3-silyloxymethyl-1′-ketoalkyl-4-butanolides, was first observed.

Experimental

Melting points were measured with a Yanagimoto MP apparatus and are uncorrected. Specific rotations were measured with



Scheme 6 Reagents, conditions and yields: (i) LDA, THF, HMPA, −78 °C; (ii) Dess–Martin periodinane, CH_2Cl_2, 75% for **18a** and **18b**, 57% for **18c** and **18d** (two steps); (iii) AcOH, THF, H_2O, 40 °C, 14 h, 48% for **19a** and 22% for **19b**; (iv) Tetrabutylammonium fluoride (TBAF), THF, 0 °C, (v) AcOH, THF, H_2O, 60 °C, 14 h, 27% for **1a** and 28% for **1b**.

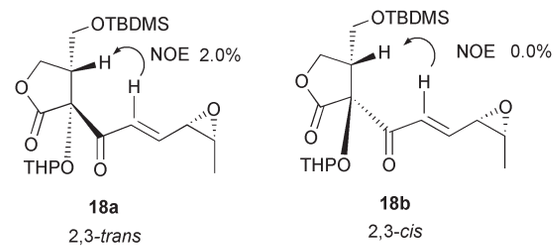
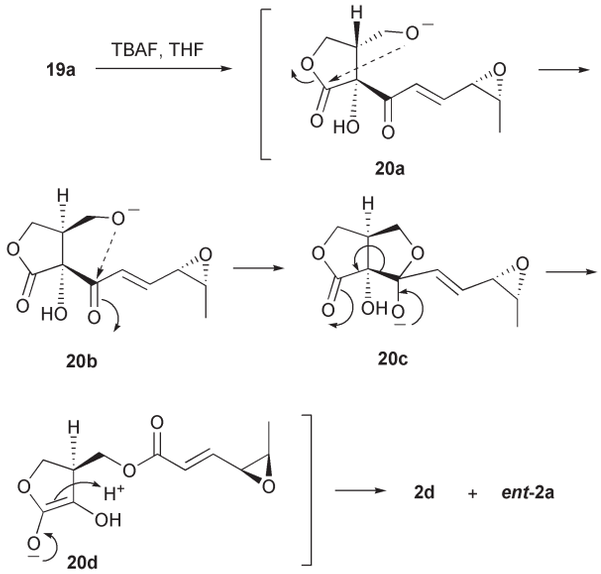
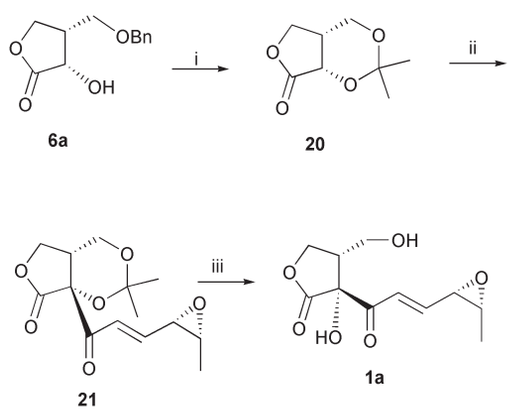


Fig. 2 NOE of **18a** and **18b**.

a JASCO Model DIP-370 polarimeter ($[\alpha]_D$-values are in units of 10^{-1} ° cm^2 g^{-1}). IR spectra were taken on a JASCO A-102 infrared spectrophotometer. ^{1}H and ^{13}C nmr spectra were recorded on a JEOL LA-300 (300 MHz) and LA-400 (400 MHz) in deuteriochloroform solution, unless stated otherwise. Chemical shifts (in ppm) are given downfield of tetramethylsilane. Mass spectra were determined on a JEOL AX-500 spectrometer.



Scheme 7 Proposed pathway leading to esters.



Scheme 8 Reagents, conditions and yields: (i) (a) H_2, Pd–C, EtOAc, (b) 2,2-dimethoxypropane, CSA, CH_2Cl_2, 67% (two steps); (ii) (a) LDA, THF, HMPA, **14b**, −78 °C; (b) Dess–Martin periodinane, CH_2Cl_2, 63% (two steps); (iii) AcOH, THF, H_2O, 40 °C, 66%.

Elemental analyses were performed with a JMS AX-500 elemental analyzer by the staff at our Instrumental Measurement Center. Thin-layer chromatography (TLC) was performed with a glass plate coated Kieselgel 60 GF_{254} (Merck). Column chromatography was carried out on silica gel 60 (Merck No. 7734; 63–200 μm). Solvents were dried (drying agent in parenthesis) and distilled prior to use: THF, diethyl ether and DME (sodium/benzophenone ketyl), DMF (CaH_2), and dichloromethane (P_2O_5). Organic solutions were dried over anhydrous Na_2SO_4. Hexane and ether refer to *n*-hexane and diethyl ether, respectively.

Diethyl (2*S*,3*R*)-3-benzyloxymethyl-2-benzyloxymethoxy-succinate 3

To a solution of lithium diisopropylamide, prepared from diisopropylamine (9.05 cm^3, 64.6 mmol) in dry THF (100 cm^3) and *n*-butyllithium (1.6 M in hexane, 36.64 cm^3, 59.2 mmol), was added a solution of diethyl (*S*)-malate (5.11 g, 26.9 mmol) in dry THF (5 cm^3) at −78 °C under nitrogen, and the mixture was stirred for 30 min, and then at −20 °C for 1 h. To the cooled (−78 °C) solution was added benzyl chloromethyl methyl ether (11.1 cm^3, 80.7 mmol) in HMPA (23 cm^3) over 20 minutes, and the mixture was stirred at −78 °C for 6 h, then at room temperature for 12 h. After quenching by addition of a solution of glacial acetic acid (7.5 cm^3) in ether (10 cm^3) at 0 °C, the mixture was poured into water, and extracted with ether. The extract was washed with water, saturated aqueous $NaHCO_3$ and brine, dried, and concentrated under reduced pressure. The residue was purified by column chromatography (hexane–ethyl acetate, 8 : 1) to give **3** (7.96 g, 70%) as a pale yellow oil; $[\alpha]_D^{25}$ −34.1 (c, 1.28, $CHCl_3$); [Found: $(M + H)^+$, 431.2078. $C_{24}H_{31}O_7$ requires M + H, 431.2070]; ν_{max}(film)/cm^{-1} 1732, 1456 and 1371; δ_H (300 MHz, $CDCl_3$) 1.16 (3H, t, *J* 7.0), 1.18 (3H, t, *J* 7.0), 3.23–3.29 (1H, m), 3.66 (1H, dd, *J* 7.7 and 9.7), 3.75 (1H, dd, *J* 6.2 and 9.7), 4.04–4.14 (4H, m), 4.43 (2H, s), 4.54 (1H, d, *J* 5.3), 4.56 (2H, s), 4.75 (1H, d, *J* 7.1), 4.80 (1H, d, *J* 7.1) and 7.18–7.28 (10H, m); δ_C (75 MHz, $CDCl_3$) 14.00 (q), 14.02 (q), 48.6 (d), 60.9 (t), 61.1 (t), 66.6 (t), 70.1 (t), 73.2 (t), 73.8 (d), 94.6 (t), 127.6 (d), 127.8 (d), 128.3 (d), 137.5 (s), 137.7 (s), 170.1 (s) and 170.9 (s).

(2*S*,3*R*)-3-Benzyloxymethyl-1,2,4-butanetriol 4

To a solution of **3** (1.277 g, 2.97 mmol) in dry ether (20 cm^3) was added LAH (1.0 *M* in ether, 5.94 cm^3, 5.94 mmol), and the mixture was boiled for 6 h. A small amount of water was slowly added to decompose excess LAH, and the precipitate was filtered off through Celite and washed with ethyl acetate. The filtrate was dried, and concentrated under reduced pressure. The residue was purified by chromatography (hexane–ethyl acetate, 8 : 1) to give (2*S*,3*R*)-3-benzyloxymethyl-2-benzyloxy–methoxy-1,4-butanediol (834 mg, 81%) as a colorless oil; $[\alpha]_D^{25}$ +13.2 (c, 0.98, $CHCl_3$); [Found: $(M + H)^+$, 347.1882. $C_{20}H_{27}O_5$ requires M + H, 347.1859]; ν_{max}(film)/cm^{-1} 3400, 1497, 1456 and 1367; δ_C (75 MHz, $CDCl_3$) 43.3 (d), 61.4 (t), 63.2 (t), 69.4 (t), 70.0 (t), 73.2 (t), 79.6 (d), 95.0 (t), 127.55 (d), 127.62 (d), 127.7 (d), 127.8 (d), 128.3 (d), 128.4 (d), 137.1 (s) and 137.7 (s).

To a solution of the diol (834 mg, 2.41 mmol) in MeOH (3 cm^3) and H_2O (1 cm^3) was added concentrated HCl (0.5 cm^3), and the mixture was stirred at 55 °C for 2 h. The reaction mixture was neutralized with solid $NaHCO_3$, filtered, and washed with methanol. The filtrate was concentrated under reduced pressure. The residue was purified by chromatography (EtOAc–MeOH, 10 : 1) to give the triol **4** (544 mg, 100%) as a colorless viscous oil; $[\alpha]_D^{26}$ +1.82 (c, 0.94, $CHCl_3$); [Found: $(M + H)^+$, 227.1267. $C_{12}H_{19}O_4$ requires M + H, 227.1284]; ν_{max}(film)/cm^{-1} 3234; δ_C (75 MHz, $CDCl_3$) 43.7 (d), 62.1 (t), 64.9 (t), 70.5 (t), 72.5 (d), 73.6 (t), 127.7 (d), 127.9 (d), 128.5 (d) and 137.6 (s).

(2*S*,3*S*)-3-Benzyloxymethyl-2,4-(4-methoxybenzylidenedioxy)-butane-1-ol 5

To a suspension of **4** (2.3 g, 10.2 mmol) and 4 Å molecular sieve (3.5 g) in 4-methoxybenzaldehyde (15 cm^3) was added a solution of zinc chloride (2.77 g, 20.4 mmol) in dry ether (20 cm^3). After stirring at room temperature for 17 h, the reaction mixture was diluted with ethyl acetate and the organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried, and concentrated under reduced pressure. The residue was purified by chromatography (hexane–ethyl acetate, 2 : 1) to give the benzylidene acetal **5** (2.85 g, 81%) as a colorless oil; $[\alpha]_D^{25}$ +4.5 (c, 2.3, $CHCl_3$); [Found: M^+, 344.1598. $C_{20}H_{24}O_5$ requires M, 344.1624]; ν_{max}(film)/cm^{-1} 3441, 1616, 1518 and 1248; δ_H (300 MHz, $CDCl_3$) 2.22–2.34 (1H, m), 2.41 (1H, br s, OH), 3.38 (2H, d, *J* 5.3), 3.65–3.77 (2H, m), 3.79 (3H, s), 3.85–3.91 (2H, m), 4.23 (1H, dd, *J* 5.0 and 11.4), 4.45 (1H, d, *J* 11.9), 4.51 (1H, d, *J* 11.9), 5.46 (1H, s), 6.89 (2H, d, *J* 8.6), 7.28–7.39 (5H, m) and 7.41 (2H, d, *J* 8.6), δ_C (75 MHz, $CDCl_3$) 36.1 (d), 55.3 (q), 63.8 (t), 67.8 (t), 68.8 (t), 73.4 (t), 80.1 (d), 101.0 (d), 113.6 (d), 127.4 (d), 127.6 (d), 127.9 (s), 128.5 (d), 130.7 (d), 137.6 (s) and 160.0 (s).

(2*S*,3*S*)-3-Benzyloxymethyl-2-hydroxy-4-butanolide 6a

To a solution of **5** (577.5 mg, 1.67 mmol) in dry dichloromethane (30 cm^3) was added Dess–Martin periodinane (4.08 g, 9.62 mmol), and the mixture was stirred at room temperature for 1 h. After quenching by addition of saturated aqueous $NaHCO_3$ and aqueous sodium thiosulfate, the mixture was extracted with dichloromethane. The extract was washed with water and brine, dried, and concentrated under reduced pressure. The residue was purified

by chromatography to afford (2*S*,3*S*)-3-benzyloxymethyl-2,4-(4-methoxybenzylidenedioxy)butanal, (551 mg, 96%) as white needles; mp 62.5–63 °C; $[\alpha]_D^{25}$ −16.7 (c, 0.83, $CHCl_3$); [Found: M^+, 342.1472. $C_{20}H_{22}O_5$ requires M, 342.1467]; δ_H (300 MHz, $CDCl_3$) 2.35–2.41 (1H, m), 3.70 (1H, dd, *J* 6.2 and 9.3), 3.79 (3H, s), 3.97 (1H, t, *J* 9.3), 4.05 (1H, dd, *J* 2.6 and 11.7), 4.21 (1H, d, *J* 11.0), 4.41 (1H, d, *J* 2.6), 4.46 (1H, d, *J* 11.9), 4.50 (1H, d, *J* 11.9), 5.52 (1H, s), 6.90 (2H, d, *J* 8.6), 7.25–7.37 (5H, m), 7.41 (2H, d, *J* 8.6) and 9.62 (1H, s); δ_C (75 MHz, $CDCl_3$) 37.1 (d), 55.2 (q), 66.9 (t), 68.3 (t), 73.1 (t), 82.4 (d), 101.8 (d), 113.6 (d), 127.5 (d), 127.61 (d), 127.65 (d), 128.3 (d), 130.0 (s), 137.7 (s), 160.2 (s) and 198.8 (d).

To a solution of the aldehyde in *t*-butanol (20 cm^3) and 2-methyl-2-butene (20 cm^3) were added sodium chlorite ($NaClO_2$) (1.9 g, 16.8 mmol) and sodium dihydrogenphosphate (NaH_2PO_4) (1.4 g, 13 mmol) in water (20 cm^3). After stirring for 1 h, the reaction mixture was quenched with water and extracted with ethyl acetate. The extract was washed with water and brine, dried, and concentrated under reduced pressure to give (2*S*,3*S*)-3-benzyloxymethyl-2,4-(4-methoxybenzylidenedioxy)butanoic acid as a white wax. The crude acid was, without further purification, hydrolyzed with concentrated hydrochloric acid (0.5 cm^3) in 1,4-dioxane (8 cm^3) at room temperature with stirring for 36 h. The reaction mixture was diluted with water and extracted with ether. The extract was washed with water and brine, dried and concentrated under reduced pressure. The residue was purified by chromatography (hexane–ethyl acetate, 2 : 1) to give **6a** (333 mg, 89% from **5**) as a pale yellow solid, which was recrystallized twice from ether-hexane to furnish white microcrystalline; mp 85–86 °C; $[\alpha]_D^{29}$ +44.1 (c, 0.99, $CHCl_3$); (Found: C, 64.64; H, 6.42%. Calc. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35%); [Found: M^+, 222.0878. $C_{12}H_{14}O_4$ requires M, 222.0892]; ν_{max}(nujol)/cm^{-1} 3396, 1759, 1456 and 1207; δ_H (300 MHz, $CDCl_3$) 2.95–3.02 (1H, m), 3.16 (1H, br s, OH), 3.63 (1H, d, *J* 9.9), 3.68 (1H, d, *J* 9.9), 4.28 (1H, dd, *J* 5.7 and 9.3), 4.34 (1H, dd, *J* 2.0 and 9.3), 4.49 (1H, d, *J* 12.1), 4.52 (1H, d, *J* 12.1), 4.54 (1H, d, *J* 7.9) and 7.27–7.37 (5H, m); δ_C (75 MHz, $CDCl_3$) 39.4 (d), 66.8 (t), 68.0 (d), 68.2 (t), 73.4 (t), 127.5 (d), 127.7 (d), 128.4 (d), 137.5 (s) and 177.3 (s).

(2*R*,3*S*)-3-Benzyloxymethyl-2-hydroxy-4-butanolide: Isomer of 6a

This compound was obtained from the minor diastereomer of **3** in the same manner as described above. Colorless oil; δ_H (300 MHz, $CDCl_3$) 2.71–2.83 (1H, m), 3.05 (1H, d, *J* 3.4, OH), 3.66 (1H, dd, *J* 4.2 and 7.2), 3.68 (1H, dd, *J* 3.3 and 7.2), 4.12 (1H, dd, *J* 2.1 and 9.2), 4.39 (1H, dd, *J* 3.4, and 10.2), 4.43 (1H, dd, *J* 2.0 and 8.7), 4.55 (2H, s) and 7.30–7.39 (5H, m); δ_C (75 MHz, $CDCl_3$) 44.0 (d), 67.2 (t), 67.4 (d), 68.9 (t), 73.4 (t), 127.7 (d), 127.9 (d), 128.5 (d), 137.5 (s) and 177.4 (s).

(3*S*)-3-Benzyloxymethyl-4-butanolide 7

To a solution of **6a** (37 mg, 0.17 mmol) in dry dichloromethane (2 cm^3) were added triethylamine (0.12 cm^3, 0.83 mmol) and methanesulfonyl chloride (0.02 cm^3, 0.32 mmol) at 0 °C, and the mixture was stirred at room temperature for 15 h. The mixture was quenched with water and extracted with dichloromethane. The extract was washed with water and brine, dried, and concentrated under reduced pressure. The residue was purified by chromatography (hexane/ethyl acetate; 2/1) to afford (2*S*, 2*S*)-3-benzyloxymethyl-2-methanesulfonyl-4-butanolide (50 mg, 100%) as white plates; mp 102.5–103 °C; $[\alpha]_D^{25}$ +24.7 (c, 1.4, $CHCl_3$); (Found: C, 52.02; H, 5.39%. Calc. for $C_{13}H_{16}O_6S$: C, 51.99; H, 5.37%); [Found: M^+, 300.0663. $C_{13}H_{16}O_6S$ requires M, 300.0668]; ν_{max}(nujol)/cm^{-1} 1782, 1456, 1367 and 1178; δ_H (300 MHz, $CDCl_3$) 2.97–3.03 (1H, m), 3.24 (3H, s), 3.64 (1H, dd, *J* 3.3 and 9.7), 3.64 (1H, dd, *J* 7.3 and 9.7), 4.39 (1H, dd, *J* 5.9 and 9.5), 4.45 (1H, dd, *J* 2.4 and 9.5), 4.52 (2H, s), 5.37 (1H, d, *J* 8.3) and 7.27–7.36 (5H, m); δ_C (75 MHz, $CDCl_3$) 38.9 (d), 39.7 (q), 66.0 (t), 68.4 (t), 73.5 (d), 73.6 (t), 127.6 (d), 127.9 (d), 128.5 (d), 137.4 (s) and 170.1 (s).

To a solution of the mesylate (53.9 mg, 0.18 mmol) in dry DME (5 cm^3) were added sodium iodide (62 mg, 0.41 mmol) and freshly activated zinc powder (54 mg, 0.83 mmol) [wash several times with 5% hydrochloric acid, wash in turn with water, methanol, and ether, and dry],[10] and the mixture was stirred at 85 °C for 24 h. The mixture was filtered, and the filtrate was acidified (pH 2) with 1.0 M hydrochloric acid and stirred for 5 h. The reaction mixture was diluted with water and extracted with ether. The extract was washed with aqueous sodium thiosulfate and water, dried, and concentrated under reduced pressure. The residue was purified by chromatography (hexane–ethyl acetate, 3 : 1) to give **7** (33.7 mg, 91%) as a colorless oil; $[\alpha]_D^{26}$ +34.6 (c, 0.6, $CHCl_3$); lit:[6] $[\alpha]_D$ +32.5 (c, 0.9, $CHCl_3$, ee = 95%); [Found: M^+, 206.0917. $C_{12}H_{14}O_3$ requires M, 206.0943]; ν_{max}(film)/cm^{-1} 2862, 1771, 1367, 1175, 1101, 1024, 743 and 700; δ_H (300 MHz, $CDCl_3$) 2.37 (1H, dd, *J* 6.2 and 17.6), 2.60 (1H, dd, *J* 9.0 and 17.6), 2.77–2.90 (1H, m), 3.45 (1H, dd, *J* 6.7 and 9.2), 3.49 (1H, dd, *J* 5.9 and 9.2), 4.18 (1H, dd, *J* 5.5 and 9.2), 4.39 (1H, dd, *J* 7.5 and 9.2), 4.52 (2H, s) and 7.27–7.39 (5H, m); δ_C (75 MHz, $CDCl_3$) 31.1 (d), 35.3 (t), 70.3 (t), 70.7 (t), 73.3 (t), 127.6 (d), 127.8 (d), 128.4 (d), 137.5 (s) and 176.8 (s).

(2*S*,3*S*)-3-Benzyloxymethyl-2-tetrahydropyranyloxy-4-butanolide 6b

To a solution of **6a** (470 mg, 2.12 mmol) and 3,4-dihydro-2*H*-pyran (267 mg, 3.2 mmol) in dry dichloromethane (15 cm^3) was added camphorsulfonic acid (CSA) (5.2 mg), and the mixture was stirred at room temperature for 18 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with dichloromethane. The extract was washed with saturated aqueous $NaHCO_3$ and brine, dried, and concentrated under reduced pressure. The residue was purified by chromatography (hexane–ethyl acetate, 8 : 1) to afford **6b–1** (327 mg, 50%) and **6b–2** (266 mg, 41%).

Compound 6b–1. White plates; mp 112–113 °C, $[\alpha]_D^{31}$ −54.3 (c, 1.11, $CHCl_3$); (Found: C, 66.60; H, 7.32%. Calc. for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24%); [Found: $(M + H)^+$, 307.1546. $C_{17}H_{23}O_5$ requires M + H, 307.1546]; ν_{max}(nujol)/cm^{-1} 1790, 1456 and 1375; δ_H (300 MHz, $CDCl_3$) 1.51–1.83 (6H, m), 2.79–2.85 (1H, m), 3.40 (1H, dd, *J* 7.3 and 9.5), 3.42–3.48 (1H, m), 3.51 (1H, dd, *J* 5.0 and 9.5), 4.02 (1H, dd, *J* 2.8 and 10.8), 4.17 (1H, dd, *J* 5.9 and 9.3), 4.30 (1H, dd, *J* 2.4 and 9.3), 4.42 (1H, d, *J* 11.9), 4.46 (1H, d, *J* 11.9), 4.58 (1H, d, *J* 7.5), 4.68 (1H, t, *J* 2.8) and 7.22–7.27 (5H, m); δ_C (75 MHz, $CDCl_3$) 19.2 (t), 25.2 (t), 30.1 (t), 39.9 (d), 62.9 (t), 66.5 (t), 68.0 (t), 69.8 (d), 73.5 (t), 98.2 (d), 127.6 (d), 127.7 (d), 128.4 (d), 137.9 (s) and 170.5 (s).

Compound 6b–2. A colorless oil, $[\alpha]_D^{24}$ +117.5 (c, 0.56, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 1.50–1.68 (6H, m), 2.76–2.86 (1H, m), 3.45 (1H, dd, *J* 7.9 and 9.5), 3.49 (1H, dd, *J* 5.8 and 9.5), 3.48–3.53 (1H, m), 4.07 (1H, dd, *J* 7.4 and 10.8), 4.24 (1H, dd, *J* 5.9 and 9.5), 4.36 (1H, dd, *J* 2.5 and 9.5), 4.52 (1H, d, *J* 12.1), 4.64 (1H, d, *J* 7.5), 4.74 (1H, t, *J* 2.8), 4.82 (1H, d, *J* 12.1) and 7.27–7.35 (5H, m); δ_C (75 MHz, $CDCl_3$) 18.0 (t), 25.1 (t), 29.7 (t), 38.7 (d), 61.3 (t), 66.4 (t), 67.5 (t), 69.9 (d), 73.5 (t), 97.0 (d), 127.7 (d), 127.8 (d), 128.4 (d), 137.6 (s) and 174.2 (s);

(2*S*,3*R*)- and (2*S*,3*S*)-3-*tert*-Butyldimethylsiloxymethyl-2-tetrahydropyranyloxy-4-butanolide, 9a and 9b

A mixture of **6b–1** (100 mg, 0.327 mmol) and 10% palladium on carbon (30 mg) in 95% ethanol (15 cm^3) was stirred under an atmosphere of hydrogen at room temperature for 16 h. The mixture was filtered, and the filtrate was concentrated under reduced pressure to give a mixture of alcohol. To a solution of the crude alcohol in dry DMF (5 cm^3) was added imidazole (139 mg, 2.05 mmol) and *tert*-butyldimethylsilylchloride (154 mg, 1.03 mmol), and the mixture was stirred at room temperature for 24 h and diluted with ether. The organic layer was washed with water and brine, dried, and concentrated under reduced pressure. The residue was purified by

chromatography (hexane–ethyl acetate, 8 : 1) to give **9a** (85.5 mg, 79%) and **9b** (15 mg, 14%).

Compound 9a. A colorless oil, $[\alpha]_D^{23}$ −17.8 (*c*, 0.97, $CHCl_3$); [Found: $(M + H)^+$, 331.1944. $C_{16}H_{31}O_5Si$ requires M + H, 331.1941]; δ_H (300 MHz, $CDCl_3$) 0.03 (6H, s), 0.85 (9H, s), 1.51–1.83 (6H, m), 2.69–2.71 (1H, m), 3.48–3.56 (1H, m), 3.75–3.79 (1H, m), 3.77 (1H, dd, *J* 6.5 and 10.3), 3.78 (1H, dd, *J* 6.5 and 10.3), 4.25 (1H, dd, *J* 5.9 and 9.2), 4.35 (1H, dd, *J* 2.2 and 9.2), 4.56 (1H, d, *J* 7.9) and 5.07 (1H, dd, *J* 2.0 and 4.4); δ_C (75 MHz, $CDCl_3$) −5.6 (q), 18.2 (s), 19.4 (t), 25.2 (t), 25.7 (q), 30.2 (t), 41.3 (d), 59.7 (t), 63.0 (t), 67.7 (t), 69.6 (d), 98.4 (d) and 175.1 (s).

Compound 9b. A colorless oil, [Found: $(M + H)^+$, 331.1969. $C_{16}H_{31}O_5Si$ requires M + H, 331.1941]; ν_{max}(film)/cm^{-1} 2856, 1790 and 1256; $[\alpha]_D^{25}$ −117.6 (*c*, 0.98, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 0.03 (3H, s), 0.04 (3H, s), 0.86 (9H, s), 1.50–1.79 (6H, m), 2.64–2.68 (1H, m), 3.47–3.54 (1H, m), 3.77–3.84 (1H, m), 3.71 (1H, dd, *J* 3.3 and 10.4), 3.80 (1H, dd, *J* 4.8 and 10.4), 4.11 (1H, t, *J* 9.0), 4.35 (1H, t, *J* 8.6), 4.46 (1H, d, *J* 9.2) and 5.11 (1H, t, *J* 2.0); δ_C (75 MHz, $CDCl_3$) −5.6 (q), −3.6 (q), 18.1 (s), 19.2 (t), 25.5 (t), 25.7 (q), 30.2 (t), 44.3 (d), 59.8 (t), 62.6 (t), 67.0 (t), 70.5 (d), 98.1 (d) and 175.8 (s).

(5*S*,1′*R*)-2,2-Dimethyl-5-(1′-benzyloxymethylcarboxymethyl)-1,3-dioxolan-4-one 10

To a solution of the ester **3** (531 mg, 1.23 mmol) in 1,4-dioxane (10 cm^3) was added concentrated hydrochloric acid (0.5 cm^3), and the mixture was stirred at 60 °C for 62 h. The reaction mixture was diluted with water and extracted with ether. The extract was washed with brine, dried, and concentrated under reduced pressure to give a diethyl ester (305.6 mg, 80%) as a pale yellow oil. To a solution of the diethyl ester (120.9 mg, 0.39 mmol) in 1,4-dioxane (3 cm^3) was added the solution of potassium hydroxide (64 mg, 0.98 mmol) in water (1 cm^3), and the mixture was stirred at room temperature for 5 h. After removal of 1,4-dioxane under reduced pressure, the residue was dissolved in water and extracted with ether. The aqueous layer was acidified (pH 2) with 1.0 *M* hydrochloric acid and saturated with solid sodium chloride. The aqueous solution was successively extracted with ether. The extract was dried, and concentrated under reduced pressure to give a diacid (91 mg, 92%) as a colorless oil; $[\alpha]_D^{31}$ −5.2 (c, 0.96, $CHCl_3$); δ_C (75 MHz, CD_3OD) 50.4 (d), 68.2 (t), 69.6 (t), 74.2 (d), 128.7 (d), 128.8 (d), 129.3 (d), 139.4 (s), 174.0 (s) and 176.6 (s).

To a solution of the diacid (40 mg, 0.16 mmol) in 2,2-dimethoxypropane (2 cm^3) was added a catalytic amount of *p*-TsOH, and the mixture was stirred at room temperature for 17 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$, and acidified (pH 4) with aqueous citric acid and extracted with ether. The extract was washed with water and brine, dried, and concentrated under reduced pressure to give the acetonide **10** (41.7 mg, 91%) as a colorless oil; [Found: M^+, 294.1077. $C_{15}H_{18}O_6$ requires M, 294.1103]; δ_H (400 MHz, $CDCl_3$) 1.54 (3H, s), 1.57 (3H, s), 3.35 (1H, ddd, *J* 3.2, 6.3 and 8.6), 3.78 (1H, dd, *J* 8.7 and 9.5), 3.96 (1H, dd, *J* 6.3 and 9.5), 4.57 (1H, d, *J* 12.1), 4.61 (1H, d, *J* 12.1), 4.73 (1H, d, *J* 3.2) and 7.26–7.38 (5H, m); δ_C (100 MHz, $CDCl_3$) 26.0 (q), 26.3 (q), 46.7 (d), 65.8 (t), 71.3 (d), 73.2 (t), 111.2 (s), 127.6 (d), 127.8 (d), 128.4 (d), 137.4 (s), 171.9 (s) and 174.3 (s).

Lactone 6a

To a solution of **10** (328 mg, 1.12 mmol) in dry THF (10 cm^3) was added BH_3–DMS complex (1.0 *M* in THF, 0.11 cm^3, 1.17 mmol) at 0 °C, and the mixture was stirred at room temperature for 21 h. After being acidified (pH 1) with 1.0 *M* hydrochloric acid, the mixture was stirred for 5 h and diluted with water, and extracted with ether. The extract was washed with saturated aqueous sodium thiosulfate and brine, dried, and concentrated under reduced pressure. The residue was purified by chromatography (hexane–ethyl acetate, 3 : 1) to give **6a** (151.5 mg, 61%) as white needles.

Methyl (4*S*,5*S*,2*E*)-5-*tert*-butyldimethylsilyloxy-4-hydroxyhexenoate 11b

To a solution of the diol **11a**[7] (164 mg, 1.03 mmol) in dry dichloromethane (15 cm^3) were added 2,6-lutidine (0.36 cm^3, 3.08 mmol) and *tert*-butyldimethylsilyl triflate (TBDMSOTf) (0.23 cm^3, 1.03 mmol) at −78 °C. After stirring at −78 °C for 1 h, the reaction mixture was quenched with water and extracted with dichloromethane. The organic layer was washed with 0.3 *M* $KHSO_4$, water, and brine, dried, and concentrated under reduced pressure. The residue was purified by chromatography (hexane–ethyl acetate, 10 : 1) to afford **11b** (230.3 mg, 82%) as a colorless oil; $[\alpha]_D^{25}$ +6.6 (c, 0.90, $CHCl_3$); [Found: $(M + H)^+$, 275.1703. $C_{13}H_{27}O_4Si$ requires M + H, 275.1679]; ν_{max}(film)/cm^{-1} 3477, 1705 and 1663; δ_H (300 MHz, $CDCl_3$) 0.02 (3H, s), 0.04 (3H, s), 0.84 (9H, s), 1.16 (3H, d, *J* 6.2), 2.62 (1H, d, *J* 5.5), 3.70 (3H, s), 3.71–3.77 (1H, m), 3.99 (1H, ddd, *J* 1.6, 6.4 and 9.7), 6.09 (1H, dd, *J* 1.8 and 15.6) and 6.88 (1H, dd, *J* 4.4 and 15.6); δ_C (75 MHz, $CDCl_3$) −5.1 (q), −4.7 (q), 17.8 (s), 19.6 (q), 25.5 (q), 51.3 (q), 70.8 (d), 74.8 (d), 121.1 (d), 147.6 (d) and 166.6 (s).

Methyl (4*S*,5*S*,2*E*)-5-*tert*-butyldimethylsilyloxy-4-methanesulfonyloxyhexenoate 11c

To a solution of the alcohol **11b** (652 mg, 2.38 mmol) in dry dichloromethane (20 cm^3) were added triethylamine (1.66 cm^3, 11.9 mmol) and methanesulfonyl chloride (0.28 cm^3, 3.56 mmol) at 0 °C. After stirring at room temperature for 17 h, the reaction mixture was quenched with water and extracted with dichloromethane. The organic layer was washed with brine, dried, and concentrated under reduced pressure. The residue was purified by chromatography (hexane–ethyl acetate, 4 : 1) to afford **11c** (806 mg, 96%) as a pale yellow viscous oil; $[\alpha]_D^{24}$ −10.4 (*c*, 1.10, $CHCl_3$); [Found: $(M - H)^+$, 351.1294. $C_{14}H_{27}O_6SSi$ requires M − H, 351.1297]; ν_{max}(film)/cm^{-1} 1728, 1666 and 1364; δ_H (300 MHz, $CDCl_3$) 0.06 (3H, s), 0.07 (3H, s), 0.86 (9H, s), 1.12 (3H, d, *J* 4.6), 3.00 (3H, s), 3.74 (3H, s), 4.03 (1H, dt, *J* 4.0 and 4.6), 4.99 (1H, dt, *J* 1.3 and 4.0), 6.11 (1H, dd, *J* 1.3 and 15.8) and 6.91 (1H, dd, *J* 4.0 and 15.8); δ_C (75 MHz, $CDCl_3$) −4.9 (q), −4.8 (q), 17.9 (s), 18.6 (q), 25.7 (q), 38.7 (q), 51.9 (q), 69.2 (d), 82.3 (d), 124.1 (d), 140.7 (d) and 165.7 (s).

Methyl (4*R*,5*S*,2*E*)-4,5-epoxyhexenoate 12a

To a solution of the mesylate **11c** (770 mg, 2.19 mmol) in THF (20 cm^3) were added tetra-*n*-butylammmonium fluoride (TBAF) (1.0 *M* in THF, 4.38 cm^3, 4.38 mmol) at 0 °C, and the mixture was stirred at room temperature for 3 h. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl, and extracted with ether. The organic layer was washed with brine, dried, and concentrated. The residue was purified by chromatography (hexane–ether, 5/1) to afford **12a** (285 mg, 92%) as a colorless oil; bp 80–83 °C at 60 mmHg (Kugelrohr); $[\alpha]_D^{31}$ −66.5 (c, 0.9, $CHCl_3$); ν_{max}(film)/cm^{-1} 2999, 2955, 1724, 1661, 1437 and 1252; δ_H (300 MHz, $CDCl_3$) 1.30 (3H, d, *J* 5.3), 3.32 (1H, dq, *J* 4.4 and 5.4), 3.52 (1H, ddd, *J* 1.0, 4.4 and 6.6), 3.76 (3H, s), 6.14 (1H, dd, *J* 1.0 and 15.9) and 6.83 (1H, dd, *J* 6.6 and 15.9); δ_C (75 MHz, $CDCl_3$) 25.6 (q), 51.7 (q), 55.2 (d), 55.3 (d), 124.9 (d), 142.1 (d) and 166.0 (s).

(4*R*,5*S*,2*E*)- and (4*S*,5*R*,2*E*)-4,5-Epoxyhexenoic acid, 13a and 13b

To a solution of the ester **12a** (15.4 mg, 0.108 mmol) in THF (4 cm^3) was added potassium trimethylsilanolate (Me_3SiOK) (17 mg, 0.12 mmol), the mixture was stirred for 3 h. Aqueous citric acid (0.5 M, 1 cm^3) was added, and after a further 1.5 h, the mixture was washed with water, dried, and concentrated under reduced pressure. The residue was purified by chromatography (hexane–ether, 1/3) to give **13a** (11.3 mg, 82%) as white microcrystalline; mp 93–93.5 °C [hygroscopic]. $[\alpha]_D^{21}$ −70.0 (c, 0.50, $CHCl_3$); [Found: $(M - H)^+$, 127.0390. $C_6H_7O_3$ requires M − H, 127.0394]; ν_{max}(nujol)/cm^{-1} 1717, 1456, 1377 and 1285; δ_H (300 MHz, $CDCl_3$) 1.31 (3H, dd, *J* 1.1 and 5.3), 3.36 (1H, ddq, *J* 1.1, 4.4 and 5.3), 3.55 (1H, ddd, *J* 0.9,

4.4 and 6.4), 6.15 (1H, d, *J* 15.6) and 6.94 (1H, ddd, *J* 0.9, 6.4 and 15.6); δ_C (75 MHz, $CDCl_3$) 13.1 (q), 55.1 (d), 55.5 (d), 124.5 (d), 144.6 (d) and 170.5 (s).

Compound **13b** was obtained from **11b** (enantiomer of **11a**) in 53% yield (four steps) as white microcrystalline; mp 94–95.5 °C; $[\alpha]_D^{24}$ +72.8 (c, 0.5, $CHCl_3$).

(4*R*,5*S*,2*E*)- and (4*S*,5*R*,2*E*)-4,5-Epoxyhexenal, 14a and 14b

To a solution of **12b** (bp 85–87 °C/60 mmHg (Kugelrohr), $[\alpha]_D^{29}$ −36.8 (*c*, 1.0, $CHCl_3$) (48.6 mg, 0.26 mmol) in dry ether (4 cm^3) was added DIBAL-H (1.5 *M* in toluene, 0.39 cm^3, 0.58 mmol) at −78 °C for 15 min. After the reaction mixture was quenched by addition of water, the precipitate was removed by filtration through Celite. The filtrate was washed with brine, dried, and concentrated. The residue was purified by chromatography (hexane–ether, 8 : 1) to give **14a** (16 mg, 54%) as a colorless oil; bp 70–75 °C/45 mmHg (Kugelrohr); $[\alpha]_D^{26}$ −82.5 (c, 1.5, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 1.32 (3H, d, *J* 5.5), 3.41 (1H, dq, *J* 4.4 and 5.5), 3.63 (1H, ddd, *J* 0.9, 4.4 and 6.4), 6.40 (1H, ddd, *J* 0.9, 7.7 and 15.8), 6.80 (1H, dd, *J* 6.4 and 15.8) and 9.60 (1H, d, *J* 7.7); δ_C (75 MHz, $CDCl_3$) 13.1 (q), 55.1 (d), 55.7 (d), 135.3 (d), 150.1 (d) and 192.2 (d).

Compound **14b** was obtained from *tert*-butylsorbate in 39% yield (five steps); $\alpha]_D^{23}$ +83.0 (c, 1.7, $CHCl_3$).

(2*S*,3*S*,4′*R*,5′*S*,2′*E*)- and (2*S*,3*R*,4′*R*,5′*S*,2′*E*)-3-(4′,5′-Epoxy-1′-oxohexenyloxymethyl)-2-tetrahydropyranyloxy-4-butanolide, 15a and 15b

To a solution of the alcohol **8** (mixture of **8a** and **8b**) (121.5 mg, 0.56 mmol) and the acid **13a** (60 mg, 0.47 mmol) in dry dichloromethane (10 cm^3) were added DMAP (68.7 mg, 0.56 mmol) and DCC (116.0 mg, 0.56 mmol) at 0 °C, and the mixture was stirred at room temperature for 24 h. After concentration under reduced pressure, the residue was purified by chromatography (hexane–ethyl acetate, 2 : 1) to give **15a** (117.5 mg, 77%) and **15b** (16.8 mg, 11%).

Compound 15a. A colorless oil, $[\alpha]_D^{25}$ −66.0 (c, 0.89, $CHCl_3$); [Found: $(M + H)^+$, 327.1448. $C_{16}H_{23}O_7$ requires M + H, 327.1445]; δ_H (300 MHz, $CDCl_3$) 1.30 (3H, d, *J* 5.3), 1.51–1.81 (6H, m), 2.94–2.96 (1H, m), 3.32 (1H, dq, *J* 4.4 and 5.3), 3.51 (1H, dd, *J* 4.4 and 6.4), 3.50–3.55 (1H, m), 3.75–3.78 (1H, m), 4.29–4.40 (3H, m), 4.48 (1H, dd, *J* 4.4 and 11.6), 4.63 (1H, d, *J* 7.7), 5.10 (1H, dd, *J* 2.3 and 4.3), 6.08 (1H, d, *J* 15.6) and 6.82 (1H, dd, *J* 6.4 and 15.6); δ_C (75 MHz, $CDCl_3$) 13.0 (q), 19.1 (t), 25.1 (t), 30.0 (t), 38.8 (d), 55.2 (d), 55.4 (d), 61.3 (t), 62.9 (t), 67.7 (t), 69.3 (d), 98.2 (d), 124.4 (d), 143.1 (d), 165.1 (s) and 174.4 (s).

Compound 15b. A colorless oil, $[\alpha]_D^{25}$ −170.5 (c, 1.10, $CHCl_3$); [Found: $(M + H)^+$, 327.1459. $C_{16}H_{23}O_7$ requires M + H, 327.1445]; ν_{max}(film)/cm^{-1} 1790, 1724, 1655 and 1391; δ_H (300 MHz, $CDCl_3$) 1.30 (3H, d, *J* 5.5), 1.52–1.83 (6H, m), 2.87–2.99 (1H, m), 3.34 (1H, dq, *J* 4.4 and 5.5), 3.53 (1H, ddd, *J* 1.1, 4.4 and 6.2), 3.56–3.58 (1H, m), 3.77–3.85 (1H, m), 4.08 (1H, t, *J* 9.3), 4.33 (1H, dd, *J* 6.4 and 11.7), 4.43 (1H, d, *J* 9.3), 4.44 (1H, dd, *J* 4.0 and 11.7), 4.48 (1H, dd, *J* 6.3 and 9.3), 5.16 (1H, dd, *J* 2.3 and 3.5), 6.14 (1H, dd, *J* 1.1 and 15.8) and 6.86 (1H, dd, *J* 6.4 and 15.8); δ_C (75 MHz, $CDCl_3$) 13.0 (q), 18.9 (t), 25.1 (t), 30.0 (t), 41.6 (d), 55.0 (d), 55.4 (d), 62.0 (t), 62.5 (t), 67.0 (t), 70.7 (d), 97.9 (d), 124.0 (d), 143.3 (d), 164.9 (s) and 174.5 (s).

(2*S*,3*S*,4′*S*,5′*R*,2′*E*)- and (2*S*,3*R*,4′*S*,5′*R*,2′*E*)-3-(4′,5′-Epoxy-1′-oxohexenyloxymethyl)-2-tetrahydropyranyloxy-4-butanolide, 15c and 15d

In the same manner as described above, the reaction of **8** with **13b** gave **15c** (128 mg, 54%) and **15d** (55.6 mg, 24%).

Compound 15c. A colorless oil, $[\alpha]_D^{26}$ −4.3 (c, 1.10, $CHCl_3$); [Found: $(M + H)^+$, 327.1465. $C_{16}H_{23}O_7$ requires M + H, 327.1445]; ν_{max}(film)/cm^{-1} 1778, 1713, 1651, 1391 and 1362; δ_H (300 MHz, $CDCl_3$) 1.30 (3H, d, *J* 5.5), 1.51–1.80 (6H, m), 2.97–3.05 (1H, m), 3.32 (1H, dq, *J* 4.4 and 5.5), 3.51 (1H, ddd, *J* 0.9, 4.4 and 6.6), 3.55–3.59 (1H, m), 3.78–3.85 (1H, m), 4.32 (1H, dd, J 2.9 and 9.9), 4.34–4.44 (2H, m), 4.45 (1H, dd, *J* 4.5 and 11.5), 4.64 (1H, d, *J* 7.8), 5.09 (1H, dd, J 2.2 and 3.8), 6.11 (1H, dd, *J* 0.9 and 15.7) and 6.80 (1H, dd, *J* 6.6 and 15.7); δ_C (75 MHz, $CDCl_3$) 12.8 (q), 18.9 (t), 24.9 (t), 29.8 (t), 38.5 (d), 54.9 (d), 55.2 (d), 61.2 (t), 62.6 (t), 67.5 (t), 69.1 (d), 98.0 (d), 124.2 (d), 142.8 (d), 164.8 (s) and 174.2 (s).

Compound 15d. A colorless oil, $[\alpha]_D^{25}$ −121.0 (c, 1.04, $CHCl_3$); [Found: $(M + H)^+$, 327.1450. $C_{16}H_{23}O_7$ requires M + H, 327.1445]; δ_H (300 MHz, $CDCl_3$) 1.29 (3H, d, *J* 5.5), 1.55–1.82 (6H, m), 2.90–2.99 (1H, m), 3.34 (1H, dq, *J* 4.5 and 5.5), 3.54 (1H, dd, *J* 4.5 and 6.4), 3.78–3.85 (1H, m), 4.07 (1H, t, *J* 9.1), 4.34 (1H, dd, *J* 6.3 and 11.7), 4.42 (1H, d, *J* 9.4), 4.43 (1H, dd, *J* 3.9 and 11.7), 4.47 (1H, t, *J* 9.1), 5.16 (1H, br. s), 6.14 (1H, d, *J* 15.8) and 6.86 (1H, dd, *J* 6.4 and 15.8); δ_C (75 MHz, $CDCl_3$) 13.1 (q), 19.0 (t), 25.2 (t), 30.1 (t), 41.7 (d), 55.1 (d), 55.5 (d), 62.1 (t), 62.6 (t), 67.1 (t), 70.8 (d), 98.0 (d), 124.0 (d), 143.4 (d), 165.0 (s) and 174.5 (s).

(2*S*,3*S*,4′*R*,5′*S*,2′*E*)-3-(4′,5′-Epoxy-1′-oxohexenyloxymethyl)-2-hydroxy-4-butanolide 2a: lactone II

A solution of **15a** (15.8 mg, 0.048 mmol) in acetic acid (2 cm^3), THF (1 cm^3), and water (0.5 cm^3) was stirred at 50 °C for 3 h. After concentration under reduced pressure, the residue was purified by chromatography (hexane–ethyl acetate, 1 : 1) to give **2a** (7.4 mg, 63%) as white needles; mp 74–75 °C; $[\alpha]_D^{21}$ +38.8 (c, 0.1, MeOH); δ_H (300 MHz, DMSO) 1.23 (3H, d, *J* 5.5), 2.83–2.91 (1H, m), 3.33 (1H, dq, *J* 4.4 and 5.5), 3.62 (1H, ddd, *J* 0.8, 4.4 and 7.1), 4.13 (1H, dd, *J* 5.4 and 11.0), 4.19 (1H, dd, *J* 2.0 and 9.3), 4.27 (1H, dd, *J* 3.9 and 11.0), 4.33 (1H, dd, *J* 6.2 and 9.3), 4.56 (1H, dd, *J* 6.0 and 8.0), 6.12 (1H, dd, *J* 0.8 and 15.7), 6.13 (1H, d, *J* 5.9, OH) and 6.67 (1H, dd, *J* 7.1 and 15.7); δ_H (300 MHz, $CDCl_3$) 1.30 (3H, d, *J* 5.5), 2.95–3.03 (m, 1H), 2.99 (1H, br.s, OH), 3.33 (1H, dq, *J* 4.6 and 5.5), 3.51 (1H, ddd, *J* 0.9, 4.4 and 6.6), 4.33 (1H, dd, J 5.5 and 11.7), 4.35–4.43 (2H, m), 4.49 (1H, dd, *J* 3.8 and 11.7), 4.59 (1H, d, *J* 8.1), 6.11 (1H, dd, *J* 0.5 and 15.8) and 6.81 (1H, dd, *J* 6.4 and 15.8); δ_C (75 MHz, $CDCl_3$) 13.1 (q), 38.9 (d), 55.2 (d), 55.5 (d), 61.0 (t), 67.6 (t), 67.8 (d), 124.2 (d), 143.5 (d), 165.2 (s) and 176.5 (s).

(2*S*,3*R*,4′*R*,5′*S*,2′*E*)-3-(4′,5′-Epoxy-1′-oxohexenyloxymethyl)-2-hydroxy-4-butanolide 2b

In the same manner as described above, **15b** was converted to **2b** in 69% yield as a colorless oil; $[\alpha]_D^{21}$ −78.5 (c, 0.11, MeOH); [Found: M^+, 242.0779. $C_{11}H_{14}O_6$ requires M, 242.0790]; δ_H (300 MHz, $CDCl_3$) 1.30 (3H, d, *J* 5.3), 2.83–2.96 (1H, m), 3.35 (1H, dq, *J* 4.5 and 5.3), 3.55 (1H, ddd, *J* 0.9, 4.5 and 6.3), 4.00 (1H, br.s, OH), 4.07 (1H, dd, *J* 9.7 and 9.9), 4.37 (1H, d, *J* 9.8), 4.36 (1H, dd, *J* 3.8 and 10.2), 4.45 (1H, dd, *J* 4.3 and 11.6), 4.47 (1H, dd, *J* 7.9 and 9.9), 6.15 (1H, dd, *J* 0.9 and 15.7) and 6.87 (1H, dd, *J* 6.3 and 15.7); δ_C (75 MHz, $CDCl_3$) 13.0 (q), 43.1 (d), 55.1 (d), 55.5 (d), 61.9 (t), 66.9 (d), 68.8 (t), 124.0 (d), 143.4 (d), 165.2 (s) and 176.7 (s).

(2*S*,3*S*,4′*S*,5′*R*,2′*E*)-3-(4′,5′-Epoxy-1′-oxohexenyloxymethyl)-2-hydroxy-4-butanolide 2c

In the same manner as described above, **15c** was converted to **2c** in 58% yield as white microcrystalline; mp 94–95 °C; $[\alpha]_D^{20}$ +121.0 (c, 0.11, MeOH); [Found: M^+, 242.0785. $C_{11}H_{14}O_6$ requires M, 242.0790]; δ_H (300 MHz, DMSO) 1.23 (3H, d, *J* 5.5), 2.82–2.91 (1H, m), 3.33 (1H, dq, *J* 4.4 and 5.5), 3.61 (1H, dd, *J* 4.4 and 7.1), 4.15 (1H, dd, *J* 5.3 and 11.2), 4.20 (1H, dd, *J* 2.0 and 9.3), 4.25 (1H, dd, *J* 3.8 and 11.2), 4.34 (1H, dd, *J* 6.2 and 9.3), 4.56 (1H, dd, *J* 5.7 and 7.9), 6.12 (1H, d, *J* 5.7, OH), 6.13 (1H, d, *J* 15.6) and 6.66 (1H, dd, *J* 7.1 and 15.6); δ_H (300 MHz, $CDCl_3$) 1.31 (3H, d, *J* 5.5), 2.95–3.03 (1H, m), 3.18 (1H, br s, OH), 3.33 (1H, dq, *J* 4.6 and 5.3), 3.51 (1H, ddd, *J* 0.9, 4.4 and 6.5), 4.34 (1H, dd, J 5.3 and 11.4), 4.34–4.42 (2H, m), 4.46 (1H, dd, *J* 3.8 and 11.4), 4.60 (1H, d, *J* 8.0), 6.11 (1H, dd, *J* 0.9 and 15.7) and 6.80 (1H, dd, *J* 6.5

and 15.7); δ_C (75 MHz, $CDCl_3$) 13.1 (q), 38.9 (d), 55.2 (d), 55.5 (d), 61.1 (t), 67.5 (d), 67.8 (t), 124.3 (d), 143.5 (d), 165.1 (s) and 176.6 (s).

(2*S*,3*R*,4′*S*,5′*R*,2′*E*)-3-(4′,5′-Epoxy-1′-oxohexenyloxymethyl)-2-hydroxy-4-butanolide 2d

In the same manner as described above, **15d** was converted to **2d** in 43% yield as a colorless oil; $[\alpha]_D^{21}$ −23.6 (*c*, 0.19, MeOH); [Found: M^+, 242.0771. $C_{11}H_{14}O_6$ requires M, 242.0790]; δ_H (300 MHz, $CDCl_3$) 1.30 (3H, d, *J* 5.5), 2.82–2.95 (1H, m), 3.35 (1H, dq, *J* 4.5 and 5.5), 3.54 (1H, ddd, *J* 0.9, 4.5 and 6.2), 4.07 (1H, dd, *J* 9.4 and 10.2), 4.33 (1H, d, *J* 10.3), 4.38 (1H, dd, *J* 6.0 and 11.7), 4.43 (1H, dd, *J* 5.4 and 11.7), 4.47 (1H, dd, *J* 8.4 and 10.2), 6.15 (1H, dd, *J* 0.9 and 15.6) and 6.88 (1H, dd, *J* 6.2 and 15.6); δ_C (75 MHz, $CDCl_3$) 13.1 (q), 43.2 (d), 55.1 (d), 55.5 (d), 61.8 (t), 66.8 (d), 68.9 (t), 124.0 (d), 143.6 (d), 165.2 (s) and 176.3 (s).

(2*R*,3*S*,4′*S*,5′*R*,2′*E*)- and (2*S*,3*S*,4′*S*,5′*R*,2′*E*)-2-(4′,5′-Epoxyhexen)oyl-2-tetrahydro-pyranyloxy-3-tert-butyldimethylsilyloxy-4-butanolide, 18a and 18b

To a solution of lithium diisopropylamide, prepared from diisopropylamine (0.17 cm^3, 1.18 mmol) in dry THF (10 cm^3) and *n*-butyllithum (1.6 M in hexane, 0.73 cm^3, 1.18 mmol), was added a solution of the lactone **9a** (156 mg, 0.47 mmol) in dry THF (1 cm^3) at −78 °C, and the mixture was stirred for 45 min. The aldehyde **14b** (65 mg, 0.58 mmol) and HMPA (0.05 cm^3) in dry THF (1 cm^3) was added over 5 min, and stirred at −78 °C for 1.5 h. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl (2 cm^3) at −78 °C, and extracted with ethyl acetate. The extract was washed with water and brine, dried, and concentrated under reduced pressure. The residue was purified by chromatography (hexane–ethyl acetate, 20 : 1) to give **17a** as an oil. A mixture of **17a** and Dess–Martin periodinane (400 mg, 0.95 mmol) in dichloromethane (15 cm^3) was stirred at 0 °C for 1 h. The reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$ (10 cm^3) and saturated aqueous sodium thiosulfate (10 cm^3). After removal of the precipitate, the filtrate was extracted with dichloromethane. The organic layer was washed with water and brine, dried, and concentrated under reduced pressure. The residue was purified by chromatography (hexane–ethyl acetate, 4/1) to give **18a** (143.8 mg, 69%) and **18b** (12.0 mg, 6%).

Compound 18a. A colorless oil, $[\alpha]_D^{23}$ +19.9 (c, 0.93, $CHCl_3$); [Found: $(M + H)^+$, 441.2325. $C_{22}H_{37}O_7Si$ requires M + H, 441.2309]; δ_H (300 MHz, $CDCl_3$) 0.03 (6H, s), 0.86 (9H, s), 1.29 (3H, d, *J* 5.4), 1.46–1.56 (6H, m), 2.81–2.87 (1H, m), 3.32 (1H, dq, *J* 4.4 and 5.4), 3.40 (1H, dd, *J* 5.8 and 10.3), 3.52 (1H, dd, *J* 4.4 and 7.2), 3.82 (1H, dd, *J* 6.4 and 10.3), 3.80–3.91 (2H, m), 4.17 (1H, dd, *J* 6.0 and 9.2), 4.28 (1H, dd, *J* 2.8 and 9.2), 5.07 (1H, d, *J* 5.3), 6.88 (1H, dd, *J* 7.2 and 15.5) and 7.05 (1H, d, *J* 15.5); δ_C (75 MHz, $CDCl_3$) −5.6 (q), 13.4 (q), 18.1 (s), 20.6 (t), 24.9 (t), 25.9 (q), 31.3 (t), 45.1 (d), 55.7 (d), 55.8 (d), 59.8 (t), 65.0 (t), 67.5 (t), 85.1 (s), 98.1 (d), 127.9 (d), 142.1 (d), 171.6 (s) and 192.6 (s).

Compound 18b. A colorless oil, $[\alpha]_D^{24}$ −10.9 (*c*, 0.75, CHCl3); [Found: $(M + H)^+$, 441.2315. $C_{22}H_{37}O_7Si$ requires M + H, 441.2309]; δ_H (300 MHz, $CDCl_3$) 0.02 (6H, s), 0.85 (9H, s), 1.29 (3H, d, *J* 5.5), 1.74–1.86 (6H, m), 3.31–3.40 (1H, m), 3.36 (1H, dq, *J* 4.6 and 5.4), 3.56 (1H, dd, *J* 4.5 and 4.8), 3.52–3.59 (1H, m), 3.69 (1H, dd, *J* 7.4 and 10.4), 3.77 (1H, dd, *J* 5.4 and 10.4), 3.95–4.04 (1H, m), 4.21 (1H, dd, *J* 8.8 and 9.7), 4.46 (1H, dd, *J* 8.2 and 9.7), 4.86 (1H, dd, *J* 2.6 and 5.0), 6.88 (1H, dd, *J* 5.4 and 15.5) and 6.99 (1H, d, *J* 15.5); δ_C (75 MHz, $CDCl_3$) −5.65 (q), −5.63 (q), 13.4 (q), 18.1 (s), 19.9 (t), 25.0 (t), 25.7 (q), 31.2 (t), 47.1 (d), 55.71 (d), 55.73 (d), 59.6 (t), 63.7 (t), 68.4 (t), 87.7 (s), 97.4 (d), 127.7 (d), 143.1 (d), 172.3 (s) and 193.5 (s).

(2*R*,3*S*,4′*S*,5′*R*,2′*E*)-2-(4′,5′-Epoxyhexen)oyl-2-hydroxy-3-hydroxymethyl-4-butanolide 1a and (2*R*,3*S*,4′*S*,5′*R*,2′*E*)-2-(4′,5′-epoxyhexen)oyl-2-hydroxy-3-tert-butyldimethylsilyloxy-4-butanolide 19a

A solution of **18a** (27.5 mg, 0.062 mmol) in acetic acid (2 cm^3), THF (1 cm^3), and water (0.5 cm^3) was stirred at 40 °C for 14 h. After concentration under reduced pressure, the residue was purified by chromatography (hexane–ethyl acetate, 1 : 1) to give **19a** (10.7 mg, 48%) and **1a** (1.7 mg, 11%).

Compound 19a. A colorless oil, $[\alpha]_D^{24}$ +55.8 (c, 0.145, $CHCl_3$); [Found: $(M + H)^+$, 357.1739. $C_{17}H_{29}O_6Si$ requires M + H, 357.1733]; δ_H (300 MHz, $CDCl_3$) 0.06 (6H, s), 0.86 (9H, s), 1.29 (3H, d, *J* 5.3), 2.98–3.02 (1H, m), 3.36 (1H, dq, *J* 4.4 and 5.3), 3.57 (1H, ddd, *J* 0.8, 4.4 and 5.3), 3.80 (1H, dd, *J* 5.1 and 10.2), 3.85 (1H, dd, *J* 4.4 and 10.2), 4.17 (1H, br s, OH), 4.26 (1H, dd, *J* 5.0 and 9.0), 4.55 (1H, dd, *J* 7.4 and 9.0), 6.92 (1H, d, *J* 15.6) and 7.00 (1H, dd, *J* 5.5 and 15.6).

Compound 1a (butalactin). A colorless oil, $[\alpha]_D^{28}$ +47.2 (c, 0.37, MeOH); [Found: $(M + H)^+$, 243.0859. $C_{11}H_{15}O_6$ requires M + H, 243.0869]; δ_H (400 MHz, $CDCl_3$) 1.28 (3H, d, *J* 5.4), 2.90–3.00 (1H, m), 3.37 (1H, dq, *J* 4.4 and 5.4), 3.57 (1H, ddd, *J* 1.0, 4.6 and 6.2), 3.87 (2H, br. s), 4.39 (1H, dd, *J* 4.9 and 9.0), 4.53 (1H, br. s), 4.57 (1H, dd, *J* 7.8 and 9.0), 6.80 (1H, dd, *J* 1.0 and 15.4) and 7.07 (1H, dd, *J* 6.2 and 15.4); δ_C (100 MHz, $CDCl_3$) 13.2 (q), 43.9 (d), 55.5 (d), 56.1 (d), 60.0 (t), 68.9 (t), 81.6 (s), 124.9 (d), 145.8 (d), 173.4 (s) and 192.8 (s).

(2*S*,3*S*,4′*S*,5′*R*,2′*E*)-2-(4′,5′-Epoxyhexen)oyl-2-hydroxy-3-tert-butyldimethylsilyloxy-4-butanolide 19b

In the same manner as described above, **18b** was converted to **19b** in 12% yield as a single product: a colorless oil; $[\alpha]_D^{23}$ −2.76 (*c*, 0.17, $CHCl_3$); [Found: $(M + H)^+$, 357.1744. $C_{17}H_{29}O_6Si$ requires M + H, 357.1733]; δ_H (400 MHz, $CDCl_3$) 0.02 (6H, s), 0.86 (9H, s), 1.30 (3H, d, *J* 5.4), 2.98–3.03 (1H, m), 3.36 (1H, dq, *J* 4.5 and 5.4), 3.53 (1H, ddd, *J* 0.8, 4.5 and 5.8), 3.73 (1H, dd, *J* 6.1 and 13.9), 3.76 (1H, dd, *J* 5.8 and 13.9), 3.95 (1H, br. s, OH), 4.31 (1H, dd, *J* 9.4 and 10.3), 4.53 (1H, dd, *J* 8.5 and 10.3), 6.86 (1H, dd, *J* 0.8 and 15.5) and 6.94 (1H, dd, *J* 6.1 and 15.5); δ_C (100 MHz, $CDCl_3$) −5.7 (q), 13.3 (q), 18.1 (s), 25.7 (q), 50.6 (d), 55.5 (d), 55.9 (d), 58.9 (t), 67.6 (t), 82.2 (s), 127.0 (d), 144.0 (d), 174.2 (s) and 193.9 (s).

Rearrangement of 19a and 19b using TBAF

To a solution of **19a** (36 mg, 0.1 mmol) in THF (3 cm^3) was added TBAF (1 M in THF, 0.21 cm^3) at 0 °C. After stirring for 45 min, the reaction mixture was quenched with aqueous NH_4Cl and extracted with ethyl acetate. The extract was washed with water and brine, dried, and concentrated under reduced pressure. The residue was purified by chromatography (hexane–ethyl acetate, 1 : 1) to give **2d** (5.8 mg, $[\alpha]_D^{22}$ −20.5 (c, 0.1, MeOH) and ***ent*-2a** (3.0 mg, $[\alpha]_D^{22}$ −35.2 (c, 0.1, MeOH). The ^1H NMR spectra of these compounds were in agreement with those of authentic samples **2d** and **2a**, respectively.

A similar reaction of **19b** afforded **2c** and ***ent*-2b** which were identical with the authentic samples.

(2*R*,3*S*,4′*S*,5′*R*,2′*E*)- and (2*S*,3*S*,4′*S*,5′*R*,2′*E*)-2-(4′,5′-Epoxyhexen)oyl-2-tetrahydro-pyranyloxy-3-*tert*-butyldimethylsilyloxy-4-butanolide, 18c and 18d

The β-epoxy aldehyde isomer **14a** and the lactone **9a** were treated as in the synthesis of **18a** and **18b** to give **18c** (275.1 mg, 53%) and **18d** (21.2 mg, 4%).

Compound 18c. A colorless oil, $[\alpha]_D^{21}$ −27.0 (*c*, 0.93, $CHCl_3$); [Found: $(M + H)^+$, 441.2333. $C_{22}H_{37}O_7Si$ requires M + H, 441.2309]; δ_H (300 MHz, $CDCl_3$) 0.06 (6H, s), 0.88 (9H, s), 1.29 (3H, d, *J* 5.5), 1.50–1.80 (6H, m), 2.76–2.82 (1H, m), 3.29–3.44 (1H, m), 3.58

(1H, dd, *J* 4.4 and 7.1), 3.78–3.91 (2H, m), 3.81 (1H, dd, *J* 6.4 and 10.1), 3.87 (1H, dd, *J* 4.7 and 10.1), 4.17 (1H, dd, *J* 6.1 and 9.2), 4.28 (1H, dd, *J* 3.0 and 9.2), 5.15 (1H, d, *J* 6.0), 6.83 (1H, dd, *J* 7.3 and 15.8) and 7.05 (1H, d, *J* 15.8); δ_C (75 MHz, $CDCl_3$) −5.59 (q), −5.55 (q), 13.4 (q), 18.1 (s), 20.6 (t), 24.9 (t), 25.7 (q), 31.3 (t), 45.1 (d), 55.69 (d), 55.74 (d), 59.8 (t), 64.9 (t), 67.5 (t), 85.1 (s), 98.1 (d), 127.9 (d), 142.1 (d), 171.6 (s) and 192.6 (s).

Compound 18d. A colorless oil, [Found: $(M + H)^+$, 441.2322. $C_{22}H_{37}O_7Si$ requires M + H, 441.2309]; δ_H (300 MHz, $CDCl_3$) 0.02 (6H, s), 0.85 (9H, s), 1.29 (3H, d, *J* 5.5), 1.58–1.86 (6H, m), 3.29–3.41 (1H, m), 3.38–3.43 (1H, m), 3.36 (1H, dq, *J* 4.4 and 7.0), 3.55 (1H, dd, *J* 4.4 and 7.0), 3.65 (1H, dd, *J* 8.0 and 10.2), 3.78 (1H, dd, *J* 5.3 and 10.2), 3.94–4.01 (1H, m), 4.22 (1H, dd, *J* 8.8 and 9.7), 4.48 (1H, dd, *J* 8.2 and 9.7), 4.85 (1H, dd, *J* 2.7 and 5.5), 6.83 (1H, dd, *J* 7.1 and 15.6) and 7.05 (1H, d, *J* 15.6); δ_C (75 MHz, $CDCl_3$) −5.7 (q), −5.6 (q), 13.4 (q), 18.1 (s), 19.9 (t), 25.0 (t), 25.7 (q), 31.2 (t), 47.1 (d), 55.71 (d), 55.73 (d), 59.6 (t), 63.7 (t), 68.4 (t), 87.7 (s), 97,4 (d), 127.7 (d), 143.1 (d), 172.3 (s) and 193.5 (s).

(2*R*,3*S*,4′*R*,5′*S*,2′*E*)-2-(4′,5′-Epoxyhexen)oyl-2-hydroxy-3-hydroxymethyl-4-butanolide 1b and (2*R*,3*S*,4′*R*,5′*S*,2′*E*)-2-(4′,5′-epoxyhexen)oyl-2-hydroxy-3-*tert*-butyldimethylsilyloxy-4-butanolide 19c

To a solution of **18c** (51.5 mg, 0.117 mmol) in acetic acid (4 cm^3), THF (2 cm^3), and water (1 cm^3) was stirred at 60 °C for 4 h, and concentrated under reduced pressure. The residue was purified by chromatography (hexane–ethyl acetate, 1/1) to give **1b** (8.0 mg, 28%) and **19c** (8.5 mg, 20%).

Compound 1b. A colorless oil, $[\alpha]_D^{19}$ +14.1 (c, 0.66, MeOH); [Found: $(M + H)^+$, 243.0861. $C_{11}H_{15}O_6$ requires M + H, 243.0869]; δ_H (400 MHz, $CDCl_3$) 1.27 (3H, d, *J* 5.6), 2.95–3.03 (1H, m), 3.39 (1H, dq, *J* 4.6 and 5.4), 3.61 (1H, ddd, *J* 1.0, 4.6 and 5.6), 3.83–3.91 (2H, m), 4.41 (1H, dd, *J* 5.1 and 9.3), 4.60 (1H, dd, *J* 7.6 and 9.3), 6.78 (1H, dd, *J* 1.0 and 15.4) and 7.10 (1H, dd, *J* 5.6 and 15.4); δ_C (100 MHz, $CDCl_3$) 13.0 (q), 43.9 (d), 55.5 (d), 56.3 (d), 59.9 (t), 68.9 (t), 81.7 (s), 124.7 (d), 145.6 (d), 173.5 (s) and 193.0 (s).

Compound 19c. A colorless oil, $[\alpha]_D^{23}$ +11.5 (c, 0.43, $CHCl_3$); [Found: $(M + H)^+$, 357.1734. $C_{17}H_{29}O_6Si$ requires M + H, 357.1733]; δ_H (300 MHz, $CDCl_3$) 0.06 (6H, s), 0.86 (9H, s), 1.29 (3H, d, *J* 5.5), 2.99–3.01 (1H, m), 3.35 (1H, dq, *J* 4.4 and 5.5), 3.58 (1H, dd, *J* 4.4 and 5.9), 3.81 (1H, dd, *J* 5.0 and 10.2), 3.86 (1H, dd, *J* 4.2 and 10.2), 4.14 (1H, br. s, OH), 4.26 (1H, dd, *J* 4.8 and 9.0), 4.55 (1H, dd, *J* 7.3 and 9.0), 6.90 (1H, d, *J* 15.5) and 7.03 (1H, dd, *J* 5.9, 15.5); δ_C (75 MHz, $CDCl_3$) −5.8 (q), 13.1 (q), 18.0 (s), 25.6 (q), 44.4 (d), 55.6 (d), 56.0 (d), 60.4 (t), 69.2 (t), 81.3 (s), 125.7 (d), 144.6 (d), 173.4 (s) and 193.1 (s).

(2*S*,3*S*,4′*R*,5′*S*,2′*E*)-2-(4′,5′-Epoxyhexen)oyl-2-hydroxy-3-*tert*-butyldimethylsilyloxy-4-butanolide 19d

In the same manner as described above, **18d** was converted to **19d** in 27% yield as a colorless oil; $[\alpha]_D^{25}$ −42.3 (c, 0.10, $CHCl_3$); [Found: $(M + H)^+$, 357.1756. $C_{17}H_{29}O_6Si$ requires M + H, 357.1733]; δ_H (400 MHz, $CDCl_3$) 0.02 (6H, s), 0.86 (9H, s), 1.27 (3H, d, *J* 5.5), 2.98–3.03 (1H, m), 3.35 (1H, dq, *J* 4.4 and 5.3), 3.55 (1H, ddd, *J* 0.8, 4.4 and 5.1), 3.71 (1H, dd, *J* 6.2 and 10.6), 3.77 (1H, dd, *J* 5.9 and 10.6), 3.98 (1H, br s, OH), 4.34 (1H, dd, *J* 9.2 and 10.6), 4.53 (1H, dd, *J* 8.6 and 10.0), 6.81 (1H, dd, *J* 0.8 and 15.4) and 6.96 (1H, ddd, *J* 1.0, 5.9 and 15.4); δ_C (75 MHz, $CDCl_3$) −5.7 (q), 13.3 (q), 18.0 (s), 25.7 (q), 50.6 (d), 55.5 (d), 55.9 (d), 58.9 (t), 67.6 (t), 82.2 (s), 127.0 (d), 144.0 (d), 172.4 (s) and 193.9 (s).

(2*S*,3*S*)-2-Hydroxy-3-hydroxymethyl-4-butanolide-2,5-acetonide 20

The benzyl lactone **6a** (596 mg, 2.68 mmol) was treated in ethyl acetate as in the preparation of **8** to give an oil of the diol. To a solution of the crude diol in dry dichloromethane (15 cm^3) was added 2,2-dimethoxypropane (3 cm^3) and camphorsulfonic acid (10 mg), and the mixture was stirred at room temperature for 3 h. After neutralization with saturated aqueous $NaHCO_3$, the mixture was extracted with dichloromethane. The organic layer was washed with water and brine, dried, and concentrated under reduced pressure. The residue was purified by chromatography (hexane–ethyl acetate, 2 : 1) to give **20** (311 mg, 67%) as white needles; mp 70–72°; $[\alpha]_D^{20}$ +31.4 (c, 0.10, $CHCl_3$); [Found: $(M + H)^+$, 173.0821. $C_8H_{13}O_4$ requires M + H, 173.0815]; ν_{max}(nujol)/cm^{-1} 2980, 1717, 1653, 1393, 1367 and 1155; δ_H (400 MHz, $CDCl_3$) 1.43 (3H, s), 1.50 (3H, s), 2.44–2.53 (1H, m), 3.72 (1H, dd, *J* 2.8 and 12.7), 4.17 (1H, dd, *J* 4.4 and 12.7), 4.41 (1H, dd, *J* 8.0 and 8.6), 4.46 (1H, d, *J* 5.8) and 4.49 (1H, dd, *J* 8.8 and 9.5); δ_C (75 MHz, $CDCl_3$) 20.2 (q), 27.8 (q), 33.2 (d), 56.9 (t), 67.1 (d), 68.6 (t), 98.6 (s) and 175.1 (s).

(2*R*,3*S*,4′*S*,5′*R*,2′*E*)-2-(4′,5′-Epoxyhexen)oyl-2-hydroxy-3-hydroxymethyl-4-butanolide-2,5-acetonide 21

The α-epoxy aldehyde **14b** and the acetonide **20** were treated as in the synthesis of **18** to give **21** in 63% yield as a colorless oil; $[\alpha]_D^{20}$ +80.8 (*c*, 0.98, $CHCl_3$); [Found: $(M + H)^+$, 283.1184. $C_{14}H_{19}O_6$ requires M + H, 283.1182]; ν_{max}(film)/cm^{-1} 2995, 1774, 1734, 1693, 1628, 1458 and 1202; δ_H (300 MHz, $CDCl_3$) 1.31 (3H, dd, *J* 0.6 and 5.5), 1.40 (3H, s), 1.48 (3H, s), 3.11 (1H, m), 3.38 (1H, dq, *J* 4.9 and 5.5), 3.61 (1H, dd, *J* 4.4 and 4.9), 3.74 (1H, dd, *J* 4.7 and 12.5), 4.08 (1H, dd, *J* 5.0 and 12.5), 4.32 (1H, dd, *J* 5.9 and 9.0), 4.49 (1H, dd, *J* 8.0 and 8.8), 6.98 (1H, dd, *J* 5.7 and 15.8) and 7.09 (1H, d, *J* 15.8); δ_C (75 MHz, $CDCl_3$) 12.9 (q), 24.7 (q), 26.5 (q), 33.1 (d), 55.4 (d), 56.0 (d), 57.7 (t), 68.1 (t), 79.8 (s), 100.3 (s), 126.6 (d), 143.6 (d), 171.9 (s) and 193.6 (s).

Butalactin 1a

A solution of **21** (17 mg, 0.06 mmol) in acetic acid (2 cm^3), THF (1 cm^3) and water (0.5 cm^3) was stirred at 40 °C for 48 h. After cooling the solvents were evaporated under reduced pressure to give an oil. The residue was purified by chromatography (hexane–ethyl acetate, 1 : 2) to afford **1a** (9.7 mg, 66%) as a colorless oil.

Acknowledgements

T. Ueki thanks Osaka City University for the OCU Grant for Graduate Course Students.

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