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Erythrulose derivatives as functionalized chiral d^3 and d^4 synthons†

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Abstract—Protected erythrulose derivatives have been shown to undergo highly stereoselective dicyclohexylboron chloride-mediated aldol reactions. After suitable synthetic manipulation of the resulting aldol adducts, chiral polyoxygenated molecules can be obtained in which either three or all four carbon atoms of the starting erythrulose molecule have been incorporated. Erythrulose derivatives may therefore behave, according to convenience, as chiral, functionalized d^3 or d^4 synthons. As an example, this methodology has been applied to a stereoselective synthesis of the naturally occurring, pharmacologically active lactone (+)-boronolide.

1. Introduction

Over the last few years we have investigated the enolization of protected L-erythrulose derivatives having general formula **1** (Scheme 1, P^1–P^3 = protecting groups) and the subsequent addition of the resulting enolates to aldehydes.[1] As shown in Scheme 1, further manipulation of the key aldol adduct **2** through carbonyl reduction and oxidative cleavage of C–C bonds **a** or **b** should yield protected α,β-dihydroxy aldehydes **3** (X = H) or α,β,γ-trihydroxy aldehydes **4** (X = H), respectively, with high selectivity. The corresponding acid derivatives (X = heteroatom) should be similarly obtained through oxidative cleavage of the same bonds without prior carbonyl reduction. Compounds **1** should thus be potential equivalents of the d^2 and d^3 chiral synthons depicted in Scheme 1. We have recently confirmed this[1] in the case of the hydroxyacetic acid enolate, a well-precedented d^2 type chiron.[2] However, counterparts for the functionalized d^3 synthon α,β-dihydroxy propanal homoenolate (Scheme 1) are yet to be reported in the literature.[3] Furthermore, the interesting possibility that, if no oxidative C–C bond cleavage is performed, derivatives **1** can also act as an α,β,γ-trihydroxy butanal bishomoenolate equivalent (cf. **5**), also lacks any literature precedent. This possibility is particularly interesting as **1** would then function as a hitherto unprecedented chiral d^4 synthon type with no loss of carbon, thus maximizing atom economy.[4] All aforementioned chirons, most particularly the d^3 and d^4 types, may be extremely useful for the stereoselective synthesis of natural, polyhydroxylated compounds such as long-chain sugars, macrolide and polyether polyketides,[5] etc. Furthermore, a combination of these aldol reactions with appropriate nucleophilic substitution reactions should open a way to aza analogues of the aforementioned compounds, including the biologically significant amino polyols and amino sugars.

2. Results and discussion

As alluded to above, some of the aforementioned ideas have recently been brought into practice. For practical reasons (mainly the ease of preparation),[6] the most convenient derivatives **1** are those having an acetal moiety joining the hydroxyl groups at C-3 and C-4 (Scheme 1, P^1, $P^2 = CR_2$) and a silylated hydroxyl function at C-1. As a matter of fact, ketone **6** has been shown to undergo dicyclohexylboron chloride (Chx_2BCl)-mediated aldol reactions with achiral aldehydes to yield aldol condensation products **7** with very high diastereoselectivity (Scheme 2).[1,7] Oxidative cleavage of bond C_2–C_3 in the latter compounds (which

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† Dedicated to Professor Emanuel Vogel, former Director of the Institute of Organic Chemistry at the University of Cologne, on the occasion of his 75th birthday.

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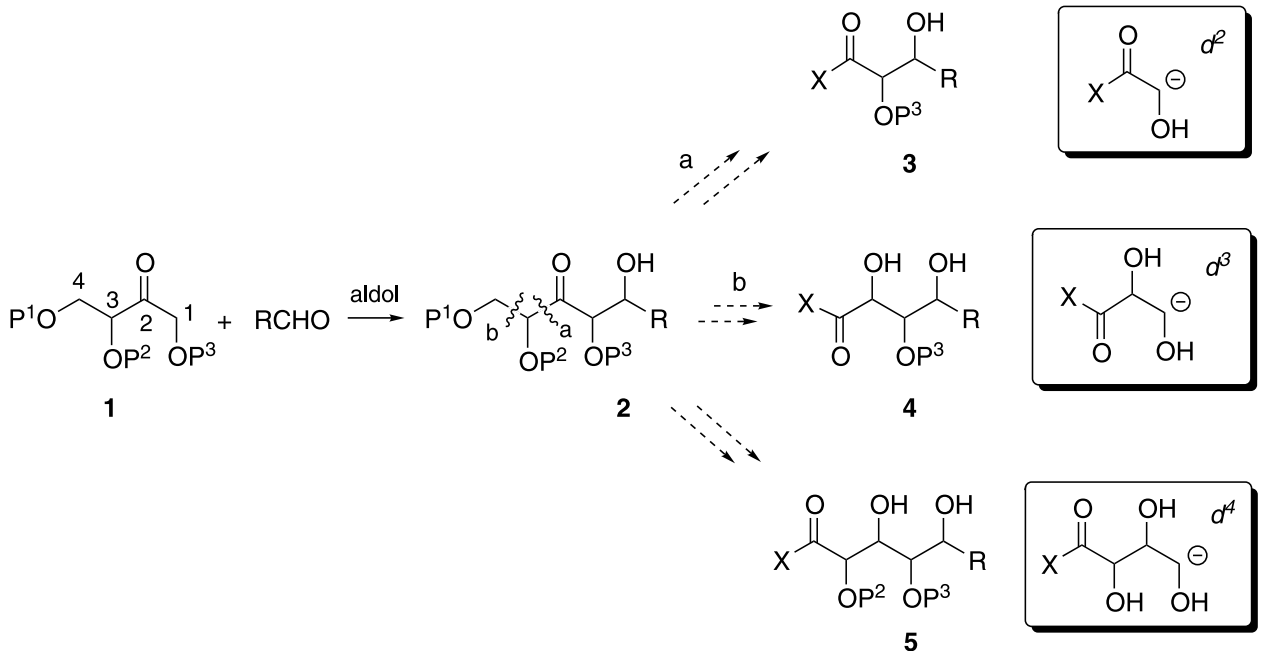
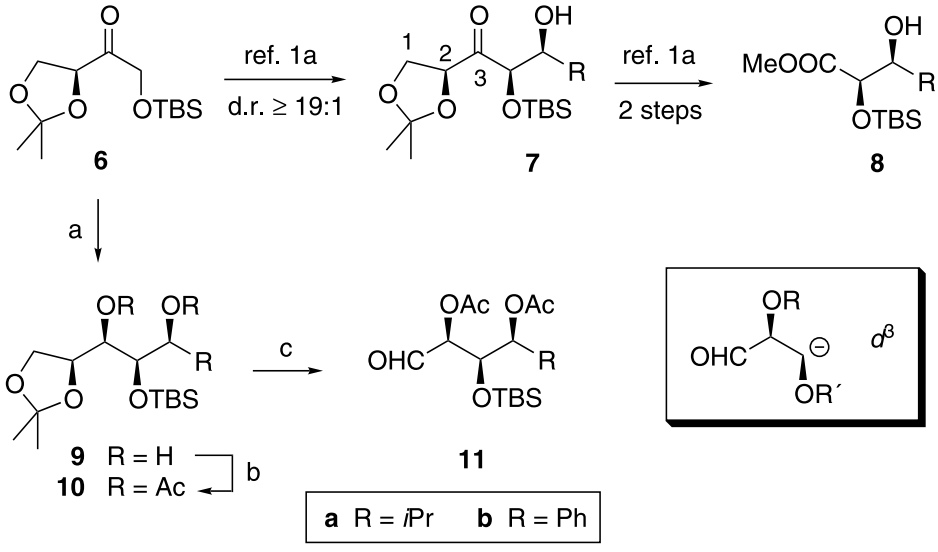


Scheme 1. Erythrulose derivatives as chiral, functionalized synthons of various types.



Scheme 2. *Reaction conditions*: (a) Chx_2BCl, base; RCHO; $LiBH_4$, 0°C (75–80%). (b) Ac_2O, pyridine, cat. DMAP, rt (83–87%). (c) H_5IO_6, EtOAc, rt (79–81%). For abbreviations, see Section 3.

corresponds to bond **a** in **2**, Scheme 1) furnishes protected α,β-dihydroxy esters **8** (loss of *two* of the erythrulose carbon atoms) in good yields,[1a] thus showing the ability of ketone **6** to behave as a chiral, functionalized d^2 synthon. In order to unveil the potential nature of **6** as a d^3 synthon (loss of *one* of the erythrulose carbon atoms), it is necessary to oxidatively cleave the bond connecting C_1 and C_2 (bond **b** in **2**, Scheme 1). It is not possible to do this in **7** until the carbonyl function has been reduced and protected. It is possible to perform direct in situ reduction of the ketone function in the boron aldolate formed after the aldolization step and this one-pot aldolization/reduction procedure[8] yields *syn* 1,3-diols **9** with very high stereoselectivity (2-methylpropanal and benzaldehyde were used here as standard achiral aldehydes). Suitable protection of the two free hydroxyl groups, for example as acetate esters,[9] gives compounds **10**, amenable to oxidative cleavage of the C_1–C_2 bond. In fact, treatment of **10** with periodic acid hydrate in ethyl acetate[10] provides α,β,γ-trioxygenated aldehydes **11** with good yields (Scheme 2). Compounds **11** contain three differently protected hydroxyl groups and a carbonyl function, structural features which permit many additional syn-

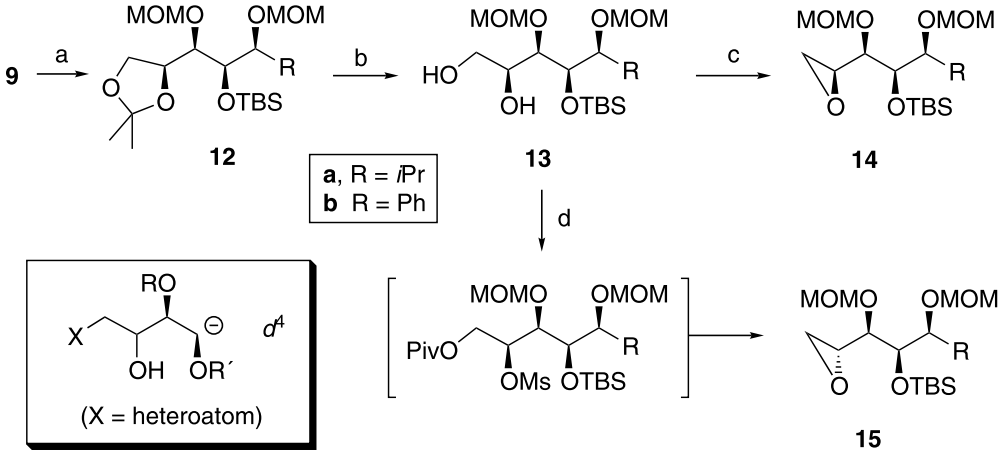
thetic manipulations to give various polyfunctionalized, chiral molecules. Ketone **6** therefore behaves as an equivalent of the depicted chiral d^3 synthon.

The previous reaction sequence furnishes all-*syn* α,β,γ-trioxygenated aldehydes **11** because $LiBH_4$ was used as an in situ aldol reducing agent. We also tried to obtain compounds with different relative configurations through *anti* reduction of the isolated aldol **7**. However, we have not been successful thus far: using tetramethylammonium triacetoxyborohydride, a reagent which usually reduces β-hydroxy ketones to *anti*-1,3-diols with high stereoselectivity,[11] afforded only a 3:7 mixture of **9** (minor) and its desired *anti* diastereoisomer. A great deal of other reagents, including reductive Tishchenko procedures, were investigated but no success was met with.[12]

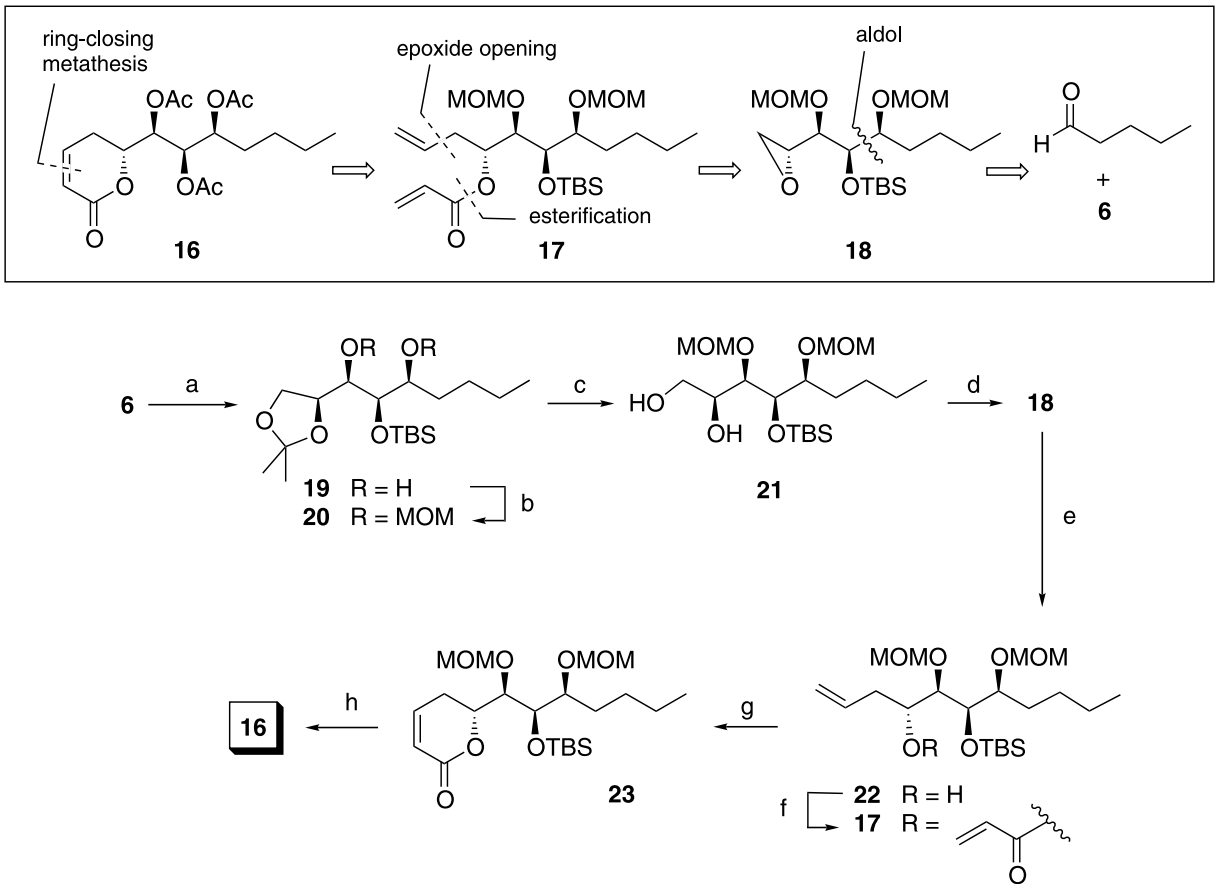
Synthetic applications of erythrulose derivative **6** as a chiral d^4 synthon demand a hydrolytic, non-oxidative cleavage of the acetal ring in protected derivatives of **9**. We have found that the success of this hydrolytic cleavage is closely related to the nature of the hydroxyl protecting groups. For instance, we were not able to find suitable reaction conditions when *only* silyl protecting groups were present.[9] In contrast, when one or two of the hydroxyl groups were protected, for example, as their MOM derivatives **12**,[13] hydrolytic cleavage of the acetal occurred smoothly (Scheme 3). Compounds **12** were then transformed in a straightforward manner into epoxides **14** through diols **13**. The diastereoisomeric epoxides **15** were also readily obtained through a minor variation in the reaction sequence (Scheme 3), where closure of the epoxide ring takes place via internal nucleophilic substitution in a secondary mesylate. These reaction sequences show therefore that ketone **6** is equivalent to the depicted chiral d^4 synthon—a specific case of the general d^4 synthon shown in Scheme 1.

The potential reactivity of the epoxide ring in molecules **14** and **15** offers many additional possibilities, which can be exploited synthetically in a number of ways. We now show one of these possibilities in a stereoselective synthesis of the naturally occurring, pharmacologically active lactone (+)-boronolide **16**. This compound was first found in extracts of bark and branches of *Tetradenia fruticosa* Benth., a shrub which grows in Madagascar and is widely used there for various medicinal purposes.[14] Total syntheses of **16** have been reported in the literature in recent years.[15] In the synthesis planned here (Scheme 4), we make use of the d^4 synthon hidden in erythrulose derivative **6**. Retrosynthetic disconnection of the target molecule through an olefin ring-closing metathesis and an epoxide opening leads to compound **18** (≡**15**, R = *n*-C_4H_{11}) via acrylate ester **17**. Thus, the synthesis was carried out as depicted in Scheme 3. Erythrulose **6** was subjected to aldol addition with *n*-pentanal followed by in situ reduction with $LiBH_4$ to yield *syn*-1,3-diol **19**. Protection of the latter as its bis-MOM derivative **20** followed by conversion into epoxide **18** was performed as described above in Scheme 3. Epoxide opening with a vinyl copper reagent[16] afforded alcohol **22**, subsequently acylated to ester **17**. Ring-closing metathesis of the latter compound was performed with Grubbs's catalyst[17] PhCH=$RuCl_2(PCy_3)_2$ and furnished conjugated lactone **23** with a good yield. Cleavage of all protecting groups and peracetylation (six steps altogether, 46% overall yield) provided synthetic boronolide **16**, with physical and spectroscopic properties identical to literature data.[15a,c]

In summary, we have described various synthetic protocols according to which erythrulose derivatives can be manipulated to act as chiral, functionalized d^3 or d^4 synthons. As a demonstration of the practical application of the latter synthon type, we have described a stereoselective synthesis of a pharmacologically active, naturally occurring product. Further applications of this methodology are currently being investigated within our group and will be reported in the near future.



Scheme 3. *Reaction conditions*: (a) MOMCl, DIPEA, CH_2Cl_2, Δ (78–80%). (b) PPTS, MeOH, rt (83–85%). (c) *p*-TsCl, Et_3N, cat. Bu_2SnO, rt, then K_2CO_3, MeOH, rt (65–66%). (d) PivCl, NEt_3, cat. DMAP, rt, then MsCl, Et_3N, DMAP, rt, then K_2CO_3, MeOH, rt (60–61%). For abbreviations, see Section 3.



Scheme 4. Retrosynthetic scheme and actual synthetic path for (+)-boronolide **16**. *Reaction conditions*: (a) Chx_2BCl, base; n-C_4H_9CHO; $LiBH_4$, 0°C (83%). (b) MOM chloride, DIPEA, CH_2Cl_2, Δ (82%). (c) PPTS, MeOH, rt (81%). (d) PivCl, Et_3N, cat. DMAP, CH_2Cl_2, rt, then MsCl, Et_3N, cat. DMAP, CH_2Cl_2, rt, then K_2CO_3, MeOH, rt (60%). (e) VinylMgBr, CuI, THF, −30°C (89%). (f) Acryloyl chloride, Et_3N, cat. DMAP, CH_2Cl_2, rt (84%). (g) 10% $PhCH{=}RuCl_2(PCy_3)_2$, CH_2Cl_2, Δ (83%). (h) BF_3, SMe_2, −30°C, then aq HF, MeCN, rt, then Ac_2O, Et_3N, cat. DMAP, CH_2Cl_2, rt (46% overall). For abbreviations, see Section 3.

3. Experimental

3.1. General methods

^1H NMR spectra (400 or 500 MHz) and ^{13}C NMR spectra (100 or 125 MHz) were measured at 22°C. The signals of the deuterated solvent ($CDCl_3$) were taken as the reference (the singlet at δ 7.25 for ^1H NMR and the triplet centered at 77.00 ppm for ^{13}C NMR data). Multiplicity assignments of ^{13}C NMR signals were made with the DEPT pulse sequence. Mass spectra were run in a VG AutoSpec mass spectrometer using either the electron impact (EIMS, 70 eV), the chemical ionization (CIMS, CH_4) or the fast atom bombardment mode (FAB MS, *m*-nitrobenzyl alcohol matrix). Samples for IR spectroscopic measurements were prepared as oily films on NaCl plates (oils) or KBr pellets (solids). Optical rotations were measured at 25°C.

Column chromatography (CC) was performed on silica gel Süd-Chemie AG (60–200 μm). Experiments which required an inert atmosphere were carried out under dry argon (Ar) in a flame-dried glassware. THF and Et_2O were freshly distilled from sodium/benzophenone ketyl and were transferred via syringe. Toluene was freshly distilled from sodium wire. Methylene chloride was freshly distilled from CaH_2. Tertiary amines were freshly distilled from KOH. Commercially available reagents were used as received. Chx_2BCl was prepared according to the described procedure,[18] distilled and used as the neat liquid. If not detailed otherwise, the work-up of the reactions was consistently performed in the following manner: the reaction mixture was poured into brine and extracted twice with solvent (Et_2O or CH_2Cl_2), the organic layer was washed with diluted aq NH_4Cl and then washed again with brine, the organic layer was dried over anhydrous $MgSO_4$ or Na_2SO_4, and the solvent was eliminated with a rotary evaporator at aspirator pressure. Abbreviations used throughout the text: TBS, *t*-butyldimethylsilyl; MOM, methoxymethyl; DMAP, 4-dimethylaminopyridine; DIPEA, *N*,*N*-diisopropyl ethylamine; PPTS, pyridinium *p*-toluenesulphonate; PivCl, pivaloyl chloride.

3.2. General experimental procedure for the one-pot aldolization–reduction protocol

Ketone **6** (1 mmol) dissolved in anhydrous ether (5 mL) was added at 0°C to a stirred solution prepared by dissolving Chx_2BCl (neat, 395 μL, ca. 1.8 mmol) and

Et_3N (280 μL, 2 mmol) in anhydrous Et_2O (5 mL). After stirring for 30 min at this temperature, a solution of the appropriate aldehyde (1.5 mmol) in anhydrous ether (6 mL) was added, and the reaction mixture was stirred at the same temperature for 4 h. A solution of $LiBH_4$ in THF (2 M, 1.5 mL, 3 mmol) was then added via syringe and stirring was continued at 0°C for 2 h. The reaction was quenched with aqueous phosphate buffer (pH 7 6 mL) and MeOH (6 mL), followed by a 30% aq H_2O_2 solution (3 mL). After stirring for 1 h at room temperature, the mixture was poured into satd. aq $NaHCO_3$ and extracted with Et_2O. The organic layer was washed with brine and dried on anhydrous Na_2SO_4. Solvent removal in vacuo afforded an oily residue which was chromatographed on silica gel (hexanes–EtOAc, 9:1 and 4:1) to yield *syn*-1,3-diols of general formula **9**. Overall chemical yields of the aldolization–reduction sequence were: **9a**, 75%; **9b**, 80%.

3.3. (4*S*)-2,2-Dimethyl-4-[(1*R*,2*R*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-1,3-dihydroxy-4-methylpentyl]-1,3-dioxolane, 9a

Oil: $[\alpha]_D^{22}$ −23.7 (*c* 6.8, $CHCl_3$). ^1H NMR (400 MHz) δ 4.30 (1H, *dt*, $J=5.5$, 6.5 Hz), 4.02 (1H, *dd*, $J=8.4$, 6.5 Hz), 3.84 (1H, *dd*, $J=8.4$, 6.5 Hz), 3.82 (1H, *dd*, $J=4.5$, 1.5 Hz), 3.55 (1H, *dt*, $J=4.5$, 5.5 Hz), 3.22 (1H, *td*, $J=9$, 1.5 Hz), 2.40 (1H, *d*, $J=5.5$ Hz, OH), 2.20 (1H, *d*, $J=9$ Hz, OH), 1.65 (1H, *br m*), 1.42 (3H, *s*), 1.34 (3H, *s*), 0.99 (3H, *d*, $J=6.5$ Hz), 0.90 (9H, *s*), 0.88 (3H, *d*, $J=6.5$ Hz), 0.14 (3H, *s*), 0.11 (3H, *s*). ^{13}C NMR (100 MHz) δ 109.0, 18.3 (C), 76.1, 75.0, 73.4, 73.0, 31.1 (CH), 66.4 (CH_2), 26.7, 26.0, 25.3, 19.4, 18.8, −3.9, −4.7 (CH_3). IR ν_{max} 3400 (br), 1215, 1066, 756, 700 cm^{-1}. HR CIMS *m*/*z* 349.2398 ($M+H^+$). Calcd for $C_{17}H_{37}O_5Si$, 349.2410. Anal. calcd for $C_{17}H_{36}O_5Si$: C, 58.58; H, 10.41. Found C, 58.79; H, 10.50%.

3.4. (4*S*)-2,2-Dimethyl-4-[(1*R*,2*R*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-1,3-dihydroxy-3-phenylpropyl]-1,3-dioxolane, 9b

Oil: $[\alpha]_D^{22}$ −26.3 (*c* 3.1, $CHCl_3$). ^1H NMR (400 MHz) δ 7.35–7.25 (5H, *m*), 4.90 (1H, *dd*, $J=7$, 3.3 Hz), 4.36 (1H, *ddd*, $J=7$, 6.5, 5.5 Hz), 4.02 (1H, *dd*, $J=8$, 6.5 Hz), 3.84 (1H, *dd*, $J=3.6$, 3.3 Hz), 3.76 (1H, *dd*, $J=8$, 7 Hz), 3.50 (1H, *ddd*, $J=7$, 5.5, 3.6 Hz), 2.95 (1H, *d*, $J=7$ Hz, OH), 2.53 (1H, *d*, $J=7$ Hz, OH), 1.40 (3H, *s*), 1.37 (3H, *s*), 0.84 (9H, *s*), −0.03 (3H, *s*), −0.36 (3H, *s*). ^{13}C NMR (100 MHz) δ 142.1, 109.3, 18.1 (C), 128.2, 128.1, 127.4, 77.9, 76.0, 72.5, 71.8 (CH), 66.4 (CH_2), 26.6, 25.9, 25.5, −4.6, −5.2 (CH_3). IR ν_{max} 3400 (br), 3020, 1215, 1066, 756 cm^{-1}. HR FAB MS *m*/*z* 405.2065 $(M+Na)^+$. Calcd for $C_{20}H_{34}O_5NaSi$, 405.2073. Anal. calcd for $C_{20}H_{34}O_5Si$: C, 62.79; H, 8.96. Found C, 62.62; H, 9.00%.

3.5. Acetylation of diols 9a–b to diacetates 10a–b

A solution of diol **9** (1 mmol), Et_3N (700 μL, 5 mmol), DMAP (12 mg, 0.1 mmol) and Ac_2O (380 μL, ca. 4 mmol) in dry CH_2Cl_2 (4 mL) was stirred overnight at room temperature. After this time, the reaction mixture was worked-up and washed with aqueous 1 M HCl (extraction with CH_2Cl_2). Column chromatography on silica gel was made with hexanes–EtOAc, 9:1. Chemical yields: **10a**, 87%; **10b**, 83%.

3.6. (1*R*,2*R*,3*S*)-3-Acetoxy-2-(*tert*-butyldimethylsilyloxy)-1-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-methylpentyl acetate, 10a

Oil: $[\alpha]_D^{22}$ −4.8 (*c* 2, $CHCl_3$). ^1H NMR (500 MHz) δ 4.95 (1H, *dd*, $J=6$, 4.2 Hz), 4.85 (1H, *t*, $J=6$ Hz), 4.40 (1H, *ddd*, $J=6.6$, 6, 4.2), 4.03 (1H, *dd*, $J=8.6$, 6.6 Hz), 4.00 (1H, *t*, $J=6$ Hz), 3.80 (1H, *dd*, $J=8.6$, 5.9 Hz), 2.13 (1H, *m*), 2.12 (3H, *s*), 2.08 (3H, *s*), 1.41 (3H, *s*), 1.35 (3H, *s*), 0.96 (3H, *d*, $J=6.5$ Hz), 0.89 (9H, *s*), 0.87 (3H, *d*, $J=6.5$ Hz), 0.13 (3H, *s*), 0.12 (3H, *s*). ^{13}C NMR (125 MHz) δ 170.5, 170.4, 109.3, 18.0 (C), 77.8, 73.9, 73.7, 70.3, 28.4 (CH), 66.0 (CH_2), 26.1, 25.7, 25.6, 21.1, 20.0, 17.8, −4.6, −4.8 (CH_3). IR ν_{max} 2961, 2930, 2859, 1743, 1473, 1372, 1200, 1104, 1069, 916, 839, 778, 735 cm^{-1}. HR EIMS *m*/*z* (% rel. int.) 417.2316 (M^+–Me, 15), 317 (32), 259 (28), 197 (60), 117 (89), 101 (100). Calcd for $C_{21}H_{40}O_7Si$–Me, 417.2308. Anal. calcd for $C_{21}H_{40}O_7Si$: C, 58.30; H, 9.32. Found C, 58.15; H, 9.50%.

3.7. (1*R*,2*R*,3*S*)-3-Acetoxy-2-(*tert*-butyldimethylsilyloxy)-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-1-phenylpropyl acetate, 10b

Oil: $[\alpha]_D^{22}$ −31.5 (*c* 1, $CHCl_3$). ^1H NMR (500 MHz) δ 7.35–7.20 (5H, *m*), 5.95 (1H, *d*, $J=5.8$ Hz), 4.80 (1H, *t*, $J=5$ Hz), 4.40 (1H, *ddd*, $J=6.6$, 6.3, 5 Hz), 4.18 (1H, *t*, $J=5.5$ Hz), 4.03 (1H, *dd*, $J=8.6$, 6.6 Hz), 3.78 (1H, *dd*, $J=8.6$, 6.3 Hz), 2.10 (3H, *s*), 1.83 (3H, *s*), 1.38 (3H, *s*), 1.36 (3H, *s*), 0.89 (9H, *s*), 0.10 (3H, *s*), −0.16 (3H, *s*). ^{13}C NMR (125 MHz) δ 170.3, 169.7, 138.0, 109.4, 18.0 (C), 128.2, 128.0, 127.4, 75.2, 73.7, 73.6, 72.8 (CH), 66.0 (CH_2), 26.2, 25.7, 25.6, 21.2, 20.6, −4.7, −5.3 (CH_3). IR ν_{max} 2950, 2932, 2858, 1744, 1473, 1372, 1210, 1069, 952, 838, 779 cm^{-1}. HR EIMS *m*/*z* (% rel. int.) 451.2146 (M^+–Me, 8), 351 (88), 317 (34), 231 (56), 156 (37), 117 (98), 101 (100). Calcd for $C_{24}H_{38}O_7Si$–Me, 451.2152. Anal. calcd for $C_{24}H_{38}O_7Si$: C, 61.77; H, 8.21. Found C, 61.88; H, 8.40%.

3.8. Oxidative cleavage of acetals 10a–b with periodic acid hydrate

Acetal **10** (1 mmol) was dissolved in dry EtOAc (10 mL) and treated with H_5IO_6 (410 mg, 1.8 mmol). The mixture was then stirred at room temperature until consumption of the starting material (ca. 2–3 h, TLC monitoring!). After this, solid sodium thiosulfate pentahydrate (250 mg, ca. 1 mmol) was added to the reaction mixture, which was then stirred for 15 min, filtered through Celite (the Celite pad was additionally washed with 10 mL of EtOAc) and evaporated under reduced pressure. The oily residue was then subjected to column chromatography on silica gel (hexanes–EtOAc, 4:1). Chemical yields: **11a**, 79%; **11b**, 81%.

3.9. (2*S*,3*R*,4*S*)-2,4-Diacetoxy-3-(*tert*-butyldiphenylsilyloxy)-5-methylhexanal, 11a

Oil: $[\alpha]_D^{22}$ +33.9 (*c* 0.85, $CHCl_3$). ^1H NMR (500 MHz) δ 9.71 (1H, *s*), 5.14 (1H, *d*, *J*=5.7 Hz), 4.78 (1H, *dd*, *J*=8.5, 3.5 Hz), 4.26 (1H, *dd*, *J*=5.7, 3.5 Hz), 2.17 (3H, *s*), 2.01 (1H, *m*), 2.00 (3H, *s*), 0.96 (3H, *d*, *J*=6.5 Hz), 0.93 (9H, *s*), 0.89 (3H, *d*, *J*=6.5 Hz), 0.16 (3H, *s*), 0.15 (3H, *s*). ^{13}C NMR (125 MHz) δ 170.1, 169.9, 18.0 (C), 195.9, 77.3, 76.8, 71.5, 28.4 (CH), 25.7, 20.8, 20.5, 19.4, 18.4, −4.4, −4.8 (CH_3). IR ν_{max} 2950, 2932, 2860, 1748 (br), 1473, 1372, 1222, 1095, 1035, 839, 779, 734 cm^{-1}. HR EIMS *m*/*z* (% rel. int.) 361.2050 ($M+H^+$, 2), 301 (14), 259 (37), 201 (36), 183 (47), 127 (63), 117 (100), 75 (57). Calcd for $C_{17}H_{33}O_6Si$, 361.2046. Anal. calcd for $C_{17}H_{32}O_6Si$: C, 56.64; H, 8.95. Found C, 56.49; H, 8.80%.

3.10. (2*S*,3*R*,4*S*)-2,4-Diacetoxy-3-(*tert*-butyldiphenylsilyloxy)-4-phenylbutanal, 11b

Oil: $[\alpha]_D^{22}$ +58.4 (*c* 3.1, $CHCl_3$). ^1H NMR (500 MHz) δ 9.67 (1H, *s*), 7.40–7.25 (5H, *m*, aromatic), 5.85 (1H, *d*, *J*=5 Hz), 4.88 (1H, *d*, *J*=4.4 Hz), 4.40 (1H, *dd*, *J*=5, 4.4 Hz), 2.18 (3H, *s*), 2.06 (3H, *s*), 0.87 (9H, *s*), 0.03 (3H, *s*), −0.24 (3H, *s*). ^{13}C NMR (125 MHz) δ 169.8, 169.4, 136.7, 18.0 (C), 196.3, 77.6, 75.4, 74.2 (CH), 25.7, 20.9, 20.4, −5.1, −5.4 (CH_3). IR ν_{max} 2958, 2932, 2858, 1747 (br), 1473, 1372, 1225, 1142, 1093, 951, 838, 780, 702 cm^{-1}. HR EIMS *m*/*z* (% rel. int.) 335.1671 ($M+H^+$–HOAc, 3), 277 (45), 245 (62), 235 (54), 217 (55), 203 (63), 159 (46), 117 (100), 91 (60), 75 (90). Calcd for $C_{20}H_{31}O_6Si$–HOAc, 335.1678. Anal. calcd for $C_{20}H_{30}O_6Si$: C, 60.89; H, 7.66. Found C, 60.60; H, 7.79%.

3.11. Formation of MOM derivatives of diols 9

A solution of 1,3-diol **9** (2 mmol) and DIPEA (1.75 mL, 10 mmol) in dry CH_2Cl_2 (40 mL) was treated under Ar with MOM chloride (608 μL, 8 mmol) and heated at reflux for 48 h. After cooling, the mixture was worked-up (extraction with CH_2Cl_2). Column chromatography on silica gel (hexanes–EtOAc, 9:1) afforded the protected derivatives. Chemical yields: **12a**, 78%; **12b**, 80%.

3.12. (4*S*)-2,2-Dimethyl-4-[(1*R*,2*R*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-1,3-bis(methoxymethoxy)-4-methylpentyl]-1,3-dioxolane, 12a

White solid: mp 58.5–59°C; $[\alpha]_D^{22}$ −36.6 (*c* 2, $CHCl_3$). ^1H NMR (500 MHz) δ 4.75 (1H, *d*, *J*=6.8 Hz), 4.74 (2H, *s*), 4.58 (1H, *d*, *J*=6.8 Hz), 4.27 (1H, *q*, *J*=6.6 Hz), 4.03 (1H, *dd*, *J*=8.4, 6.6 Hz), 3.95 (1H, *dd*, *J*=8.4, 6.6 Hz), 3.88 (1H, *dd*, *J*=8, 4 Hz), 3.58 (1H, *dd*, *J*=6.6, 4 Hz), 3.42 (3H, *s*), 3.40 (3H, *s*), 3.33 (1H, *dd*, *J*=8, 3.2 Hz), 1.40 (3H, *s*), 1.35 (3H, *s*), 1.00 (3H, *d*, *J*=7 Hz), 0.91 (9H, *s*), 0.90 (3H, *d*, *J*=7 Hz), 0.12 (3H, *s*), 0.10 (3H, *s*). ^{13}C NMR (125 MHz) δ 108.7, 18.0 (C), 83.6, 79.6, 75.6, 73.5, 28.2 (CH), 98.5, 97.1, 66.3 (CH_2), 55.9, 55.8, 26.5, 26.0, 25.8, 20.8, 16.7, −4.6, −4.8 (CH_3). IR ν_{max} 2956, 2931, 2894, 2859, 1471, 1379, 1369, 1254, 1215, 1154, 1100, 1035, 919, 863, 837, 777 cm^{-1}. HR EIMS *m*/*z* (% rel. int.) 421.2635 (M^+–Me, 1), 303 (21), 261 (26), 187 (24), 159 (40), 143 (87), 101 (100). Calcd for $C_{21}H_{44}O_7Si$–Me, 421.2622. Anal. calcd for $C_{21}H_{44}O_7Si$: C, 57.76; H, 10.16. Found C, 57.69; H, 10.40%.

3.13. (4*S*)-2,2-Dimethyl-4-[(1*R*,2*R*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-1,3-bis(methoxymethoxy)-3-phenylpropyl]-1,3-dioxolane, 12b

Oil: $[\alpha]_D^{22}$ +19.8 (*c* 4.5, $CHCl_3$). ^1H NMR (500 MHz) δ 7.40–7.20 (5H, *m*), 4.87 (1H, *d*, *J*=3.1 Hz), 4.77 (1H, *d*, *J*=6.7 Hz), 4.71 (1H, *d*, *J*=6.7 Hz), 4.59 (1H, *d*, *J*=6.3 Hz), 4.53 (1H, *d*, *J*=6.3 Hz), 4.53 (1H, *overl. m*), 4.12 (1H, *dd*, *J*=8.3, 6.3 Hz), 4.00 (1H, *dd*, *J*=8.3, 7.2 Hz), 3.88 (1H, *dd*, *J*=4.5, 3.1 Hz), 3.60 (1H, *dd*, *J*=8, 4.5 Hz), 3.42 (3H, *s*), 3.36 (3H, *s*), 1.39 (3H, *s*), 1.38 (3H, *s*), 0.88 (9H, *s*), −0.03 (3H, *s*), −0.49 (3H, *s*). ^{13}C NMR (125 MHz) δ 139.5, 108.2, 18.0 (C), 128.0, 127.8, 127.5, 80.2, 76.7, 76.5 (CH), 97.5, 95.1, 66.3 (CH_2), 56.5, 55.7, 26.7, 26.0, 25.8, −4.6, −6.0 (CH_3). IR ν_{max} 3087, 3064, 3030, 2931, 2857, 2823, 1494, 1472, 1460, 1375, 1369, 1254, 1214, 1150, 1100, 1085, 1030, 964, 937, 811, 776, 703 cm^{-1}. HR EIMS *m*/*z* (% rel. int.) 455.2463 (M^+–Me, 3), 409 (5), 319 (44), 243 (48), 207 (27), 101 (100). Calcd for $C_{24}H_{42}O_7Si$–Me, 455.2465. Anal. calcd for $C_{24}H_{42}O_7Si$: C, 61.24; H, 8.99. Found C, 61.10; H, 8.79%.

3.14. Hydrolytic cleavage of acetonides, 12

A solution of compound **12** (2 mmol) in MeOH (20 mL) containing a catalytic amount of water (0.2 mL) was treated with PPTS (25 mg, 0.1 mmol) and stirred for about 48 h at room temperature (TLC monitoring!). After this, solid $NaHCO_3$ (25 mg) was added to the reaction mixture, which was then stirred for 10 min and filtered through Celite (the Celite pad was additionally washed with EtOAc). Solvent removal under reduced pressure was followed by column chromatography of the residue on silica gel (hexanes–EtOAc, 1:1) to afford 1,2-diols **13**. Chemical yields: **13a**, 83%; **13b**, 85%.

3.15. (2*S*,3*R*,4*R*,5*S*)-4-(*tert*-Butyldimethylsilyloxy)-3,5-bis(methoxymethoxy)-6-methylheptane-1,2-diol, 13a

Oil: $[\alpha]_D^{22}$ +36.3 (*c* 0.85, $CHCl_3$). ^1H NMR (500 MHz) δ 4.84 (1H, *d*, *J*=6.5 Hz), 4.75 (1H, *d*, *J*=6.3 Hz), 4.66 (1H, *d*, *J*=6.5 Hz), 4.62 (1H, *d*, *J*=6.3 Hz), 4.10 (1H, *dd*, *J*=7.7, 4.4 Hz), 4.02 (1H, *m*), 3.70 (3H, *br m*), 3.44 (3H, *s*), 3.41 (3H, *s*), 3.32 (1H, *dd*, *J*=7.2, 4.4 Hz), 3.00 (1H, *d*, *J*=6.5 Hz, OH), 2.90 (1H, *t*, *J*=7 Hz, OH), 1.98 (1H, *octup*, *J*=6.8 Hz), 1.03 (3H, *d*, *J*=6.8 Hz), 0.96 (3H, *d*, *J*=6.8 Hz), 0.91 (9H, *s*), 0.13 (3H, *s*), 0.10 (3H, *s*). ^{13}C NMR (125 MHz) δ 18.0 (C), 85.4, 79.7, 73.9, 70.0, 29.0 (CH), 99.2, 98.2, 63.6 (CH_2), 56.4, 55.9, 26.0, 20.8, 19.4, −4.7 (CH_3). IR ν_{max} 3450 (br), 2958, 2931, 2858, 1472, 1388, 1253, 1152, 1040, 919, 836, 776 cm^{-1}. HR EIMS *m*/*z* (% rel. int.) 365.2372 (M^+–OMe, 1), 333 (8), 275 (16), 231 (59), 187 (100), 147 (380), 73

(63). Calcd for $C_{18}H_{40}O_7Si$–OMe, 365.2359. Anal. calcd for $C_{18}H_{40}O_7Si$: C, 54.51; H, 10.17. Found C, 54.49; H, 10.29%.

3.16. (2*S*,3*R*,4*R*,5*S*)-4-(*tert*-Butyldimethylsilyloxy)-3,5-bis(methoxymethoxy)-5-phenylpentane-1,2-diol, 13b

Oil: $[\alpha]_D^{22}$ +79.4 (*c* 1.25, $CHCl_3$). ^1H NMR (500 MHz) δ 7.40–7.20 (5H, *m*), 4.85 (1H, *d*, *J*=4.2 Hz), 4.64 (1H, *d*, *J*=6.3 Hz), 4.63 (1H, *d*, *J*=6.5 Hz), 4.57 (1H, *d*, *J*=6.3 Hz), 4.56 (1H, *d*, *J*=6.5 Hz), 4.10 (1H, *dd*, *J*=5.8, 4.2 Hz), 4.05 (1H, *m*), 3.66 (2H, *m*), 3.42 (1H, *dd*, *J*=5.8, 3.8 Hz), 3.39 (3H, *s*), 3.34 (3H, *s*), 2.60 (1H, *br s*, OH), 1.70 (1H, *br s*, OH), 0.91 (9H, *s*), 0.04 (3H, *s*), −0.23 (3H, *s*). ^{13}C NMR (125 MHz) δ 138.5, 18.2 (C), 128.2, 127.9, 127.8, 80.8, 78.9, 75.6, 70.3 (CH), 98.7, 95.2, 64.0 (CH_2), 56.3, 56.1, 26.1, −4.6, −5.1 (CH_3). IR ν_{max} 3400 (br), 2927, 2890, 2858, 1457, 1253, 1205, 1144, 1115, 1014, 942, 835, 772 cm^{-1}. HR CIMS *m*/*z* (% rel. int.) 431.2450 (M+H^+, 40), 399 (16), 369 (26), 337 (100), 279 (36), 205 (39), 157 (46), 146 (46). Calcd for $C_{21}H_{39}O_7Si$, 431.2465. Anal. calcd for $C_{21}H_{38}O_7Si$: C, 58.57; H, 8.89. Found C, 58.60; H, 8.79%.

3.17. Conversion of 1,2-diols 13 into epoxides 14

Diol **13** (1 mmol) was dissolved under Ar in dry CH_2Cl_2 (10 mL) and treated with *n*-Bu_2SnO (5 mg, 0.02 mmol), *p*-TsCl (210 mg, 1.1 mmol) and Et_3N (170 μL, ca. 1.2 mmol).[19] The mixture was stirred overnight at room temperature, then filtered through Celite (the Celite pad was additionally washed with EtOAc) and evaporated under reduced pressure. The crude tosylate was then dissolved in MeOH (8 mL) and treated with K_2CO_3 (140 mg, ca. 1 mmol). The reaction mixture was then stirred at room temperature for 1 h (TLC monitoring!), filtered through Celite (the Celite pad was additionally washed with EtOAc) and evaporated under reduced pressure. Column chromatography on silica gel (hexanes–EtOAc, 9:1) gave epoxides **14**. Overall chemical yields: **14a**, 65%; **14b**, 66%.

3.18. (2*S*)-2-[(1*R*,2*R*,3*S*)-2-(*tert*-Butyldimethylsilyloxy)-1,3-bis(methoxymethoxy)-4-methylbutyl]oxirane, 14a

Oil: $[\alpha]_D^{22}$ −47.1 (*c* 2, $CHCl_3$). ^1H NMR (500 MHz) δ 4.80 (1H, *d*, *J*=6.6 Hz), 4.78 (1H, *d*, *J*=6.8 Hz), 4.70 (1H, *d*, *J*=6.6 Hz), 4.61 (1H, *d*, *J*=6.8 Hz), 3.87 (1H, *dd*, *J*=7.4, 4 Hz), 3.47 (1H, *dd*, *J*=7.4, 3.8 Hz), 3.41 (3H, *s*), 3.40 (3H, *s*), 3.36 (1H, *dd*, *J*=6.2, 4 Hz), 3.15 (1H, *m*), 2.80 (1H, *t*, *J*=4.8 Hz), 2.70 (1H, *dd*, *J*=4.8, 3 Hz), 2.00 (1H, *m*), 1.03 (3H, *d*, *J*=6.8 Hz), 0.92 (3H, *d*, *J*=6.8 Hz), 0.91 (9H, *s*), 0.11 (3H, *s*), 0.09 (3H, *s*). ^{13}C NMR (125 MHz) δ 18.0 (C), 83.6, 79.3, 74.6, 52.2, 28.8 (CH), 98.5, 96.2, 43.9 (CH_2), 55.9, 26.0, 20.8, 17.0, −4.4, −4.8 (CH_3). IR ν_{max} 2957, 2934, 2860, 1472, 1254, 1154, 1100, 1032, 836, 776 cm^{-1}. HR EIMS *m*/*z* (% rel. int.) 347.2217 (M^+–OMe, 9), 231 (26), 159 (57), 89 (45), 75 (100). Calcd for $C_{18}H_{38}O_6Si$–OMe, 347.2254. Anal. calcd for $C_{18}H_{38}O_6Si$: C, 57.11; H, 10.12. Found C, 57.30; H, 10.00%.

3.19. (2*S*)-2-[(1*R*,2*R*,3*S*)-2-(*tert*-Butyldimethylsilyloxy)-1,3-bis(methoxymethoxy)3-phenylpropyl]oxirane, 14b

Oil: $[\alpha]_D^{22}$ +57.8 (*c* 2, $CHCl_3$). ^1H NMR (500 MHz) δ 7.40–7.25 (5H, *m*), 4.87 (1H, *d*, *J*=5.3 Hz), 4.78 (1H, *d*, *J*=6.6 Hz), 4.63 (1H, *d*, *J*=6.6 Hz), 4.62 (1H, *d*, *J*=6.6 Hz), 4.56 (1H, *d*, *J*=6.6 Hz), 3.94 (1H, *dd*, *J*=5.3, 4.2 Hz), 3.41 (3H, *s*), 3.40 (1H, *m*), 3.28 (3H, *s*), 2.97 (1H, *dd*, *J*=7.2, 4.2 Hz), 2.80 (1H, *t*, *J*=4.7 Hz), 2.50 (1H, *dd*, *J*=4.7, 2.8 Hz), 0.91 (9H, *s*), 0.01 (3H, *s*), −0.22 (3H, *s*). ^{13}C NMR (125 MHz) δ 139.2, 18.3 (C), 128.2, 128.0, 127.8, 80.5, 78.5, 77.1, 53.1 (CH), 96.5, 95.3, 44.6 (CH_2), 56.2, 55.9, 26.1, −4.7, −5.0 (CH_3). IR ν_{max} 3071, 3032, 2930, 2891, 2857, 1494, 1472, 1403, 1361, 1254, 1214, 1151, 1103, 1036, 939, 920, 867, 811, 777, 703 cm^{-1}. HR EIMS *m*/*z* (% rel. int.) 381.2101 (M^+–OMe, 1), 221 (35), 193 (33), 177 (36), 143 (52), 119 (42), 89 (100), 73 (66). Calcd for $C_{21}H_{36}O_6Si$–OMe, 381.2097. Anal. calcd for $C_{21}H_{36}O_6Si$: C, 61.13; H, 8.79. Found C, 61.28; H, 8.79%.

3.20. Conversion of 1,2-diols 13 into epoxides 15

Diol **13** (1 mmol) was dissolved under Ar in dry CH_2Cl_2 (10 mL) and treated with PivCl (136 μL, 1.1 mmol), Et_3N (170 μL, ca. 1.2 mmol) and DMAP (6 mg, 0.05 mmol). The mixture was stirred at room temperature for 2 h, then worked-up (extraction with CH_2Cl_2). Removal of volatiles under reduced pressure gave an oily crude monopivalate. The crude compound was then dissolved under Ar in dry CH_2Cl_2 (5 mL) and treated with MsCl (78 μL, 1 mmol), Et_3N (170 μL, ca. 1.2 mmol) and DMAP (6 mg, 0.05 mmol). The mixture was stirred at room temperature for 1 h, then worked-up (extraction with CH_2Cl_2). Removal of volatiles under reduced pressure gave a crude product which was dissolved in MeOH (8 mL) and treated with K_2CO_3 (140 mg, ca. 1 mmol). The reaction mixture was then stirred overnight at room temperature and filtered through Celite (the Celite pad was additionally washed with EtOAc). Removal of volatiles under reduced pressure and column chromatography on silica gel (hexanes–EtOAc, 9:1) gave epoxides **15**. Overall chemical yields: **15a**, 60%; **15b**, 61%.

3.21. (2*R*)-2-[(1*R*,2*R*,3*S*)-2-(*tert*-Butyldimethylsilyloxy)-1,3-bis(methoxymethoxy)-4-methylbutyl]oxirane, 15a

Oil: $[\alpha]_D^{22}$ −34 (*c* 0.5, $CHCl_3$). ^1H NMR (500 MHz) δ 4.78 (1H, *d*, *J*=6.7 Hz), 4.66 (1H, *d*, *J*=6.7 Hz), 4.61 (1H, *d*, *J*=6.7 Hz), 4.60 (1H, *d*, *J*=6.7 Hz), 3.91 (1H, *dd*, *J*=6.7, 4 Hz), 3.60 (1H, *t*, *J*=4 Hz), 3.40 (1H, *dd*, *J*=6.8, 4.4 Hz), 3.39 (3H, *s*), 3.37 (3H, *s*), 3.20 (1H, *dt*, *J*=4, 3.5 Hz), 2.80 (2H, *m*), 1.96 (1H, *m*), 1.02 (3H, *d*, *J*=7 Hz), 0.93 (3H, *d*, *J*=7 Hz), 0.93 (9H, *s*), 0.14 (3H, *s*), 0.13 (3H, *s*). ^{13}C NMR (125 MHz) δ 18.1 (C), 83.5, 76.7, 74.2, 50.7, 29.2 (CH), 98.5, 96.9, 45.5 (CH_2), 55.9, 55.7, 26.0, 20.8, 17.4, −4.3, −4.9 (CH_3). IR ν_{max} 2957, 2930, 2860, 1463, 1033, 836, 776 cm^{-1}. HR FABMS *m*/*z* 379.2508 (M+H^+). Calcd for $C_{18}H_{39}O_6Si$, 379.2516. Anal. calcd for $C_{18}H_{38}O_6Si$: C, 57.11; H, 10.12. Found C, 57.33; H, 10.30%.

3.22. (2*R*)-2-[(1*R*,2*R*,3*S*)-2-(*tert*-Butyldimethylsilyloxy)-1,3-bis(methoxymethoxy)3-phenylpropyl]oxirane, 15b

Oil: $[\alpha]_D^{22}$ +56.8 (*c* 1.6, $CHCl_3$). ^1H NMR (500 MHz) δ 7.35–7.25 (5H, *m*), 4.73 (1H, *d*, *J*=6.6 Hz), 4.62 (2H, *d*, *J*=6.6 Hz), 4.55 (1H, *d*, *J*=6.3 Hz), 4.37 (1H, *d*, *J*=6.6 Hz), 4.07 (1H, *dd*, *J*=6.5, 3.3 Hz), 3.35 (3H, *s*), 3.28 (1H, *m*), 3.22 (3H, *s*), 2.97 (1H, *dd*, *J*=5.5, 3.3 Hz), 2.80 (1H, *dd*, *J*=5.3, 4.2 Hz), 2.62 (1H, *dd*, *J*=5.3, 2.6 Hz), 0.94 (9H, *s*), 0.12 (3H, *s*), 0.00 (3H, *s*). ^{13}C NMR (125 MHz) δ 139.4, 18.4 (C), 128.3, 128.0, 127.9, 79.6, 78.8, 76.5, 51.0 (CH), 97.4, 95.6, 47.1 (CH_2), 55.9, 55.6, 26.2, −4.3, −5.0 (CH_3). IR ν_{max} 3019, 2933, 2857, 1472, 1215, 1035, 759 cm^{-1}. HR EIMS *m*/*z* (% rel. int.) 381.2087 (M^+–OMe, 1), 261 (35), 231 (39), 219 (42), 193 (43), 177 (44), 161 (43), 143 (34), 119 (52), 89 (83), 73 (100). Calcd for $C_{21}H_{36}O_6Si$–OMe, 381.2097. Anal. calcd for $C_{21}H_{36}O_6Si$: C, 61.13; H, 8.79. Found C, 61.06; H, 8.98%.

3.23. Conversion of 1,2-diol 19 into epoxide 18

Compound **19** was prepared in 83% yield from ketone **6** as described in the general aldolization–reduction procedure. It was subsequently transformed into epoxide **18** according to the same procedures described above for the sequence **9**→**15**. Chemical yields of the intermediate products: **20** (82%); **21** (81%); **18** (60%).

3.24. (4*S*)-2,2-Dimethyl-4-[(1*R*,2*R*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-1,3-dihydroxyheptyl]-1,3-dioxolane, 19

Oil: $[\alpha]_D^{22}$ −2.1 (*c* 1.5, $CHCl_3$). ^1H NMR (400 MHz) δ 4.30 (1H, *ddd*, *J*=6.7, 6.4, 5.5 Hz), 4.01 (1H, *dd*, *J*=8.2, 6.4 Hz), 3.84 (1H, *dd*, *J*=8.2, 6.7 Hz), 3.67 (1H, *m*), 3.60 (1H, *dd*, *J*=4.4, 2.2 Hz), 3.57 (1H, *m*), 2.50 (1H, *br s*, OH), 2.15 (1H, *br s*, OH), 1.88 (1H, *m*), 1.70 (1H, *m*), 1.60–1.20 (4H, *br m*), 1.42 (3H, *s*), 1.35 (3H, *s*), 0.91 (9H, *br s*), 0.90 (3H, *t*, *J*=7 Hz), 0.12 (3H, *s*), 0.10 (3H, *s*). ^{13}C NMR (100 MHz) δ 109.2, 18.3 (C), 76.2, 75.5, 72.7, 70.3 (CH), 66.4, 34.5, 28.2, 22.7 (CH_2), 26.7, 26.0, 25.4, 14.1, −4.1, −4.5 (CH_3). IR ν_{max} 3480 (br), 1463, 1380, 1339, 1255, 1217, 1067, 838. 1615 cm^{-1}. HR EIMS *m*/*z* (% rel. int.) 347.2243 (M^+–Me, 23), 247 (60), 215 (98), 187 (62), 173 (65), 161 (83), 143 (100), 101 (77), 75 (88). Calcd for $C_{18}H_{38}O_5Si$–Me, 347.2253. Anal. calcd for $C_{18}H_{38}O_5Si$: C, 59.63; H, 10.56. Found C, 59.41; H, 10.73%.

3.25. (4*S*)-2,2-Dimethyl-4-[(1*R*,2*R*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-1,3-bis(methoxymethoxy)heptyl]-1,3-dioxolane, 20

Oil: $[\alpha]_D^{22}$ −10.2 (*c* 1.7, $CHCl_3$). ^1H NMR (500 MHz) δ 4.72 (3H, *m*), 4.60 (1H, *d*, *J*=6.6 Hz), 4.32 (1H, *q*, *J*=6.3 Hz), 3.98 (2H, *m*), 3.85 (1H, *t*, *J*=5.3 Hz), 3.55 (2H, *m*), 3.40 (3H, *s*), 3.38 (3H, *s*), 1.75 (1H, *m*), 1.50–1.30 (5H, *br m*), 1.40 (3H, *s*), 1.33 (3H, *s*), 0.90 (12H, *br s*), 0.11 (3H, *s*), 0.10 (3H, *s*). ^{13}C NMR (125 MHz) δ 108.6, 18.0 (C), 79.3, 78.7, 76.1, 73.5 (CH), 97.7, 96.8, 66.1, 30.2, 28.2, 22.7 (CH_2), 55.9, 55.8, 26.6, 25.9, 25.7, 14.1, −4.6, −4.8 (CH_3). IR ν_{max} 2960, 2934, 2860, 1471, 1378, 1369, 1254, 1214, 1154, 1098, 1028, 918, 901, 837, 777 cm^{-1}. HR EIMS *m*/*z* (% rel. int.) 435.2792 (M^+–Me, 4), 317 (26), 259 (26), 231 (32), 187 (36), 173 (46), 143 (74), 101 (100), 89 (47), 73 (56). Calcd for $C_{22}H_{46}O_7Si$–Me, 435.2778. Anal. calcd for $C_{22}H_{46}O_7Si$: C, 58.63; H, 10.29. Found C, 58.49; H, 10.20%.

3.26. (2*S*,3*R*,4*R*,5*S*)-4-(*tert*-Butyldimethylsilyloxy)-3,5-bis(methoxymethoxy)nonane-1,2-diol, 21

Oil: $[\alpha]_D^{22}$ +17.6 (*c* 0.7, $CHCl_3$). ^1H NMR (500 MHz) δ 4.82 (1H, *d*, *J*=6.6 Hz), 4.74 (1H, *d*, *J*=6.3 Hz), 4.65 (1H, *d*, *J*=6.6 Hz), 4.61 (1H, *d*, *J*=6.3 Hz), 4.02 (2H, *m*), 3.70 (2H, *m*), 3.62 (1H, *dd*, *J*=8, 2 Hz), 3.55 (1H, *m*), 3.44 (3H, *s*), 3.39 (3H, *s*), 1.75 (1H, *m*), 1.50–1.25 (5H, *br m*), 0.91 (3H, *d*, *J*=7 Hz), 0.90 (9H, *br s*), 0.11 (3H, *s*), 0.10 (3H, *s*). ^{13}C NMR (125 MHz) δ 17.9 (C), 81.2, 80.0, 73.6, 70.1 (CH), 99.4, 97.4, 63.2, 29.0, 28.9, 22.6 (CH_2), 56.3, 55.6, 25.8, 14.0, −4.6, −5.0 (CH_3). IR ν_{max} 3400 (br), 2934, 2862, 1473, 1367, 1215, 1179, 1028, 929, 873, 838, 758 cm^{-1}. HR EIMS *m*/*z* (% rel. int.) 347.2247 (M^+–OMe–MeOH, 7), 289 (35), 259 (30), 231 (63), 187 (100), 147 (48), 73 (52). Calcd for $C_{19}H_{42}O_7Si$–OMe–MeOH, 347.2253. Anal. calcd for $C_{19}H_{42}O_7Si$: C, 55.58; H, 10.31. Found C, 55.59; H, 10.41%.

3.27. (2*R*)-2-[(1*R*,2*R*,3*S*)-2-(*tert*-Butyldimethylsilyloxy)-1,3-bis(methoxymethoxy)heptyl]oxirane, 18

Oil: $[\alpha]_D^{22}$ +3.2 (*c* 2.2, $CHCl_3$). ^1H NMR (500 MHz) δ 4.71 (1H, *d*, *J*=6.7 Hz), 4.66 (1H, *d*, *J*=6.5 Hz), 4.61 (1H, *d*, *J*=6.5 Hz), 4.60 (1H, *d*, *J*=6.7 Hz), 3.89 (1H, *dd*, *J*=5, 4.7 Hz), 3.59 (1H, *m*), 3.53 (1H, *t*, *J*=4.7 Hz), 3.37 (3H, *s*), 3.36 (3H, *s*), 3.20 (1H, *dt*, *J*=4.7, 3.5 Hz), 2.80 (2H, *m*), 1.76 (1H, *m*), 1.60–1.30 (5H, *br m*), 0.91 (9H, *s*), 0.90 (3H, *d*, *J*=7 Hz), 0.11 (3H, *s*), 0.10 (3H, *s*). ^{13}C NMR (125 MHz) δ 18.1 (C), 80.0, 77.1, 74.1, 50.7 (CH), 97.5, 96.9, 45.9, 30.2, 28.4, 22.8 (CH_2), 55.6, 55.5, 25.9, 14.1, −4.6, −4.8 (CH_3). IR ν_{max} 2956, 2931, 2893, 2859, 1472, 1379, 1361, 1253, 1215, 152, 1102, 1042, 918, 838, 776, 759 cm^{-1}. HR EIMS *m*/*z* (% rel. int.) 361.2405 (M^+–OMe, 1), 275 (16), 243 (18), 229 (45), 199 (46), 173 (100), 143 (77), 131 (36), 89 (58), 75 (70). Calcd for $C_{19}H_{40}O_6Si$–OMe, 361.2410. Anal. calcd for $C_{19}H_{40}O_6Si$: C, 58.13; H, 10.27. Found C, 58.33; H, 10.30%.

3.28. Conversion of epoxide 18 into acrylate 17

CuI (67 mg, 0.35 mmol) was gently heated in vacuo until the solid turned light yellow. The flask was then filled with Ar and cooled to −30°C, followed by addition of dry THF (5 mL). A 1 M solution of vinylmagnesium bromide in THF (3.5 mL, 3.5 mmol) was then added dropwise via syringe. The mixture was then stirred for 15 min at −30°C. Epoxide **18** (295 mg, 0.75 mmol) was dissolved in dry THF (5 mL) and added dropwise to the solution of the organocopper reagent. The reaction mixture was then stirred for 3 h at the same temperature. The reaction was then quenched

with satd. aq. ammonium chloride (15 mL) and worked-up (extraction with CH_2Cl_2). Column chromatography on silica gel (hexanes–EtOAc, 9:1) afforded alcohol **22** (280 mg, 89%).

Alcohol **22** (252 mg, 0.6 mmol) was dissolved under Ar in dry CH_2Cl_2 (10 mL), cooled to 0°C and treated at this temperature with Et_3N (155 μL, 1.1 mmol), acryloyl chloride (81 μL, 1 mmol) and DMAP (6 mg, ca. 0.05 mmol). The mixture was then stirred overnight at room temperature, poured onto satd. aq NH_4Cl and worked-up (extraction with CH_2Cl_2). Column chromatography on silica gel (hexanes–EtOAc, 19:1) furnished acrylate **17** (239 mg, 84%).

3.29. (4*R*,5*R*,6*R*,7*S*)-6-(*tert*-Butyldimethylsilyloxy)-5,7-bis(methoxymethoxy)undec-1-en-4-ol, 22

Oil: $[\alpha]_D^{22}$ +26.3 (*c* 0.9, $CHCl_3$). ^1H NMR (500 MHz) δ 5.95 (1H, *m*), 5.10–5.05 (2H, *m*), 4.68 (2H, *d*, *J*= 6.5 Hz), 4.64 (1H, *d*, *J*=6.5 Hz), 4.60 (1H, *d*, *J*=6.5 Hz), 3.90 (1H, *m*), 3.77 (1H, *dd*, *J*=7.2, 3.8 Hz), 3.60 (1H, *dt*, *J*=8.5, 3.8 Hz), 3.53 (1H, *dd*, *J*=7.2, 4.5 Hz), 3.42 (3H, *s*), 3.38 (3H, *s*), 2.30 (1H, *br dd*, *J*= 14, 6 Hz), 2.20 (1H, *m*), 1.75 (1H, *m*), 1.55–1.25 (5H, *br m*), 0.91 (3H, *d*, *J*=7 Hz), 0.89 (9H, *s*), 0.09 (6H, *s*). ^{13}C NMR (125 MHz) δ 18.0 (C), 136.1, 85.8, 79.3, 73.6, 70.1 (CH), 116.3, 99.0, 96.5, 37.4, 29.4, 28.6, 22.7 (CH_2), 55.9, 25.8, 14.0, −4.4, −4.9 (CH_3). IR ν_{max} 3450 (br), 3030, 2956, 2932, 2859, 1642, 1464, 1255, 1102, 1035, 918, 873, 837, 777 cm^{-1}. HR EIMS *m*/*z* (% rel. int.) 389.2700 (M^+–OMe, 1), 357 (1), 317 (32), 231 (80), 187 (100), 173 (57), 89 45), 73 (80). Calcd for $C_{21}H_{44}O_6Si$–OMe, 389.2723. Anal. calcd for $C_{21}H_{44}O_6Si$: C, 59.96; H, 10.54. Found C, 60.03; H, 10.59%.

3.30. (4*R*,5*R*,6*R*,7*S*)-6-(*tert*-Butyldimethylsilyloxy)-5,7-bis(methoxymethoxy)undec-1-en-4-yl acrylate, 17

White solid: mp 50–51°C; $[\alpha]_D^{22}$ +43.4 (*c* 1, $CHCl_3$). ^1H NMR (500 MHz) δ 6.40 (1H, *d*, *J*=17.2 Hz), 6.12 (1H, *dd*, *J*=17.2, 10.3 Hz), 5.80 (2H, *m*), 5.32 (1H, *br d*, *J*=10.2 Hz), 5.06 (1H, *br d*, *J*=17.2 Hz), 5.00 (1H, *br d*, *J*=10.2 Hz), 4.75 (1H, *d*, *J*=6.6 Hz), 4.68 (1H, *d*, *J*=6.6 Hz), 4.58 (1H, *d*, *J*=6.6 Hz), 4.56 (1H, *d*, *J*=6.6 Hz), 3.81 (1H, *br d*, *J*=8.6 Hz), 3.76 (1H, *br dd*, *J*=8.6, 3.3 Hz), 3.53 (1H, *dt*, *J*=9.2, 3.3 Hz), 3.38 (6H, *s*), 2.58 (1H, *m*), 2.33 (1H, *dd*, *J*=15, 6 Hz), 1.77 (2H, *m*), 1.55–1.25 (4H, *br m*), 0.90 (3H, *d*, *J*=7 Hz), 0.88 (9H, *s*), 0.10 (3H, *s*), 0.08 (3H, *s*). ^{13}C NMR (125 MHz) δ 165.8, 18.0 (C), 134.9, 128.8, 80.1, 79.7, 73.9, 73.5 (CH), 130.2, 116.8, 98.3, 96.4, 33.0, 29.1, 28.3, 22.7 (CH_2), 55.9, 55.8, 25.9, 14.1, −4.5, −4.9 (CH_3). IR ν_{max} 2958, 2929, 2862, 1722, 1641, 1463, 1405, 1256, 1197, 1090, 1028, 976, 873, 835, 810, 776 cm^{-1}. HR EIMS *m*/*z* (% rel. int.) 443.2837 (M^+–OMe, 1), 341 (18), 271 (34), 239 (100), 173 (36), 129 (60). Calcd for $C_{24}H_{46}O_7Si$–OMe, 443.2829. Anal. calcd for $C_{24}H_{46}O_7Si$: C, 60.72; H, 9.77. Found C, 60.89; H, 9.62%.

3.31. Ring-closing metathesis of acrylate, 17

A solution of acrylate **17** (237 mg, 0.5 mmol) and Grubbs catalyst $PhCH{=}RuCl_2(PCy_3)_2$ (41 mg, 0.05 mmol) in dry, degassed CH_2Cl_2 (50 mL) was heated under Ar at reflux for 2 h. After removal of all volatiles in vacuo, the crude residue was chromatographed on silica gel (hexanes–EtOAc, 4:1) to furnish lactone **23** (185 mg, 83%).

3.32. (5*R*)-6-[(1*R*,2*R*,3*S*)-2-(*tert*-Butyldimethylsilyloxy)-1,3-bis(methoxymethoxy)heptyl]-5,6-dihydropyran-2-one, 23

White solid: mp 72–73°C; $[\alpha]_D^{22}$ +43.8 (*c* 1.25, $CHCl_3$). ^1H NMR (500 MHz) δ 6.88 (1H, *dt*, *J*=9.7, Hz), 5.98 (1H, *dd*, *J*=9.7, 2.5 Hz), 4.80 (2H, *m*), 4.69 (1H, *d*, *J*=6.2 Hz), 4.65 (1H, *d*, *J*=6.5 Hz), 4.51 (1H, *d*, *J*=6.2 Hz), 3.90 (1H, *br dd*, *J*=7.9, 2.5 Hz), 3.76 (1H, *br dd*, *J*=7.9, 4 Hz), 3.50 (1H, *dt*, *J*=9.5, 3.3 Hz), 3.38 (3H, *s*), 3.35 (3H, *s*), 2.73 (1H, *ddt*, *J*=18, 12, 2.5 Hz), 2.30 (1H, *br dt*, *J*=18, 5 Hz), 1.77 (1H, *m*), 1.50–1.25 (5H, *br m*), 0.90 (3H, *d*, *J*=7 Hz), 0.88 (9H, *s*), 0.09 (3H, *s*), 0.08 (3H, *s*). ^{13}C NMR (125 MHz) δ 164.0, 18.0 (C), 145.5, 121.0, 80.6, 78.4, 77.1, 72.9 (CH), 98.3, 97.1, 29.1, 28.9, 24.0, 22.7 (CH_2), 56.1, 55.8, 25.9, 14.1, −4.5, −4.9 (CH_3). IR ν_{max} 2955, 2934, 2858, 1712, 1469, 1385, 1252, 1149, 1123, 1102, 1042, 1018, 923, 838, 779 cm^{-1}. HR EIMS *m*/*z* (% rel. int.) 415.2509 (M^+–OMe, 3), 313 (26), 283 (100), 231 (16), 197 (11), 173 (10), 129 (12), 97 (16), 73 (20). Calcd for $C_{22}H_{42}O_7Si$–OMe, 415.2516. Anal. calcd for $C_{22}H_{42}O_7Si$: C, 59.16; H, 9.48. Found C, 59.29; H, 9.50%.

3.33. Conversion of lactone 23 into boronolide 16

A solution of lactone **23** (90 mg, 0.2 mmol) in dry SMe_2 (2 mL) was cooled under Ar to −10°C and treated with freshly distilled $BF_3{\cdot}Et_2O$ (500 μL, ca. 4 mmol). The resulting solution was stirred for 30 min at the same temperature, then poured into satd. aq $NaHCO_3$ and worked-up (extraction with CH_2Cl_2). After removal of all volatiles in vacuo, the crude residue was used directly in the next step.

The crude product from above was dissolved in acetonitrile (3 mL) and treated with 48% aq HF (50 μL, 1.2 mmol). The resulting solution was stirred for 3 h at room temperature, then neutralized with solid $NaHCO_3$, filtered and evaporated to dryness under reduced pressure. The oily residue was dissolved under Ar in dry CH_2Cl_2 (5 mL) and treated with Et_3N (170 μL, 1.2 mmol), acetic anhydride (96 μL, 1 mmol) and DMAP (12 mg, ca. 0.1 mmol). The mixture was then stirred for 3 h at room temperature, poured onto satd. aq NH_4Cl and worked-up (extraction with CH_2Cl_2). Column chromatography on silica gel (hexanes–EtOAc, 1:1) furnished **16** (34 mg, 46% overall), which showed physical and spectral properties identical to those published:[15a,c] colourless crystals, mp 88–90°C, lit.[1] mp 90°C; $[\alpha]_D^{22}$ +25.1 (*c* 0.1, EtOH), lit.[1] $[\alpha]_D^{22}$ +25 (*c* 0.2, EtOH). ^1H NMR (500

MHz) δ 6.86 (1H, *ddd*, $J=9.7$, 6.2, 2.5 Hz), 6.02 (1H, *dd*, 9.7, 2.5 Hz), 5.33 (2H, *m*), 5.00 (1H, *q*, $J=6$ Hz), 4.52 (1H, *dt*, $J=12$, 4.5 Hz), 2.52 (1H, *ddt*, $J=18$, 11.8, 2.5 Hz), 2.30 (1H, *m*), 2.12 (3H, *s*), 2.08 (3H, *s*), 2.06 (3H, *s*), 1.55 (2H, *m*), 1.25 (4H, *m*), 0.87 (3H, *t*, $J=6.5$ Hz). ^{13}C NMR (125 MHz) δ 170.5, 169.9, 169.7, 162.5, 144.1, 121.5, 75.2, 71.7, 70.8, 70.7, 30.3, 27.1, 25.2, 22.4, 21.0, 20.7, 20.6, 13.9. IR ν_{max} 1736 (br), 1374, 1220, 1030, 816 cm^{-1}. HR EIMS *m*/*z* (% rel. int.) 371.1699 (M+H$^+$, 1), 273 (16), 242 (86), 182 (69), 140 (100), 97 (37). Calcd for $C_{18}H_{27}O_8$, 371.1706.

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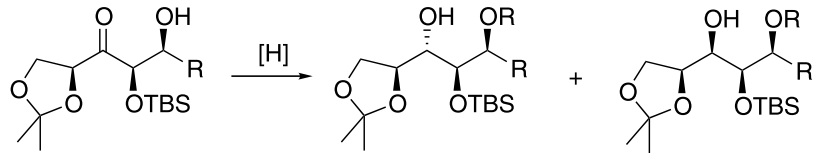

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R = H normal reduction
R = Ac Tishchenko reduction

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