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Chiral building blocks from D-xylose and their application in synthesis of avocadotriol monoacetate

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ABSTRACT

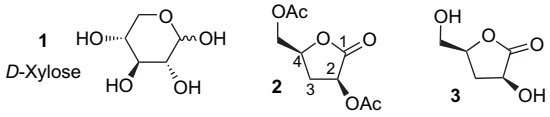
Facile routes to several enantiomerically pure flexible chiral building blocks carrying a hidden *syn* or *anti* 1,3-diol motif were developed with the inexpensive and readily available carbohydrate D-xylose as the starting material. Application of the newly developed chiral building blocks in total synthesis is exemplified through a synthesis of (2*S*,4*S*)- and (2*S*,4*R*)-avocadotriol. Both triols were selectively acetylated on the primary hydroxyl group in high yields with Novozyme 435/vinyl acetate. On the basis of comparison of the ^{1}H NMR, optical rotation, and melting point data, the natural avocadotriol 1-monoacetate was assigned to be of (2*R*,4*R*) configuration.

1. Introduction

D-xylose (**1**) is one of the carbohydrates frequently employed as chiral pools in synthesis. However, like most other carbohydrates, **1** rarely can be utilized directly because of co-existence of several hydroxyl groups. In most cases, differentiation between the hydroxyl groups and deoxygenation at one or more positions are prerequisites for execution of chiron-based synthetic plans. It is hence highly desirable to convert **1**, through practical routes, into generally applicable chiral building blocks that are directly usable in synthesis.

One of the good starting points for such endeavors appears to be the diacetate **2** reported[1] by Okabe, which can be conveniently prepared from **1** through a practical sequence consisting of (1) Br_2 oxidation of **1** into a five-membered lactone, (2) acetylation of all the hydroxyl groups, (3) Et_3N-mediated elimination of the AcO at the C-3, and (4) Ra-Ni catalyzed hydrogenation of the double bond formed by the elimination to reintroduce a stereogenic center at the C-2 in a highly stereoselective way. The two acetyl groups in diacetate **2** can be readily removed by treatment with a base in MeOH, yielding a known[2] diol **3**.

There have been some records in the literature on elaboration of **3** into various chiral building blocks.[3] However, because relatively expensive reagents (e.g., TBDPSCl and BH_3) and inconvenient operations were involved, explorations on more practical routes to flexible chiral building blocks at lower cost are still warranted.



2. Results and discussions

A key issue in making use of diol **3** as a precursor for chiral building blocks is to differentiate the two hydroxyl groups. Because one of them is primary and the other secondary, on the basis of common knowledge of organic chemistry, one usually takes it for granted that the reaction would preferentially occur at the primary OH. However, as will be shown in the following, this is not always the case.

Another hidden problem that deserves to be mentioned is the preparation of **3** from **2** (Scheme 1). According to the literature cleavage of the acetyl groups can be readily achieved with KOH/EtOH–H_2O/rt/12 h followed by *p*-TsOH/THF/rt/24 h,[3a,c] KCN/MeOH,[4] NaOMe/MeOH then Amberlite IR-120 H resin,[5a] or 10% NaOH/MeOH/rt/12 h then acidification with HCl (cleaving a monoacetate).[2] Although none of the literature ever explicitly mentioned any difficulties about **3**, in repeating the documented procedures we noticed that the outcomes of the different protocols did vary considerably. Over hydrolysis led to ring-opening of the lactone,

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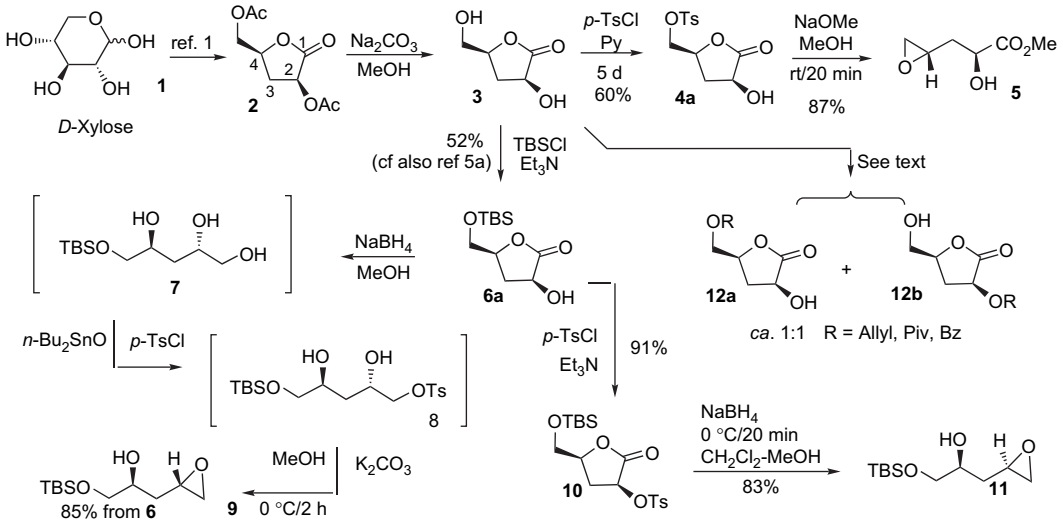


Scheme 1.

which tended to lower the yield. Acidification also made remarkable difference. It appears that the acidic resin conditions of Vargeese and Abushanab[5a] more often afforded higher yields of diol **3**.

It is interesting to note that the IR spectrum of **3** also changed with time. Freshly chromatographed **3** (neat) showed apparently two carbonyl absorptions, with one at 1737 cm^{-1} and the other at 1771 cm^{-1}. However, recording the spectrum after the sample was allowed to stand at ambient temperature for an hour or so essentially only one carbonyl absorption signal at 1771 cm^{-1} could be seen.

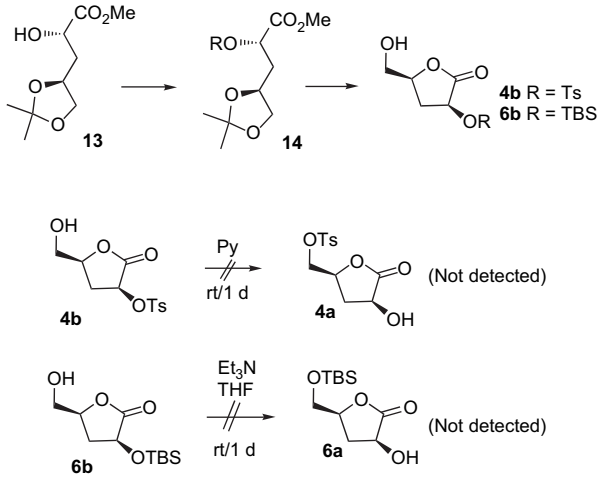
With **3** in hand, we attempted selective tosylation under the literature[3b] conditions (*p*-TsCl/Py/rt/20 h). Somewhat unexpected, after 20-h reaction (Scheme 1) only small amounts of **4a** was formed while most of the starting **3** remained unchanged. However, with extension of the reaction time to 5 days, the desired **4a** could be formed in 60% yield.

In our hands tosylate **4a** was isolated as a white solid with the optical rotation ($[\alpha]_D^{26}$ +21.8 (*c* 1.7, $CHCl_3$)) slightly smaller than that reported[3b] in the literature (an oil, $[\alpha]_D^{20}$ +28.6 (*c* 1.4, $CHCl_3$)). In the beginning we suspected that our sample was partially racemized over the prolonged reaction. However, ^1H and ^{13}C NMR and HPLC[3d] analyses all excluded the possibility of co-existence of the C-2 epimer or any other impurities. Therefore, the **4a** was believed to be pure and used as such in the next step. On treatment with NaOMe in MeOH at ambient temperature for 20 min, tosylate **4a** was smoothly converted into epoxide **5** in 87% isolated yield.

Diol **3** could also be converted to mono-TBS ether **6a** as described by Vargeese and Abushanab,[5a] although in our hands the yield for **6a** (of larger optical rotation than that reported in the literature) was only 52%, with substantial part of starting **3** unreacted. Extension of reaction time or using more reagents led to a significantly increased content of di-TBS protected species in the product mixture. Treatment of **6a** with $NaBH_4$ in MeOH gave an intermediate triol **7**, which was selectively tosylated under the conditions of Martinelli[6] to afford **8**. On treatment with K_2CO_3/MeOH the crude **8** underwent facile cyclization, producing epoxide **9** in 85% overall yield from **6a**.

Tosylation of **6a** gave **10** in 91% yield. Careful treatment of **10** with $NaBH_4$ in CH_2Cl_2/MeOH led to reduction of the lactone carbonyl group followed by cyclization, affording epoxide **11** with an inverted configuration at the C-2.

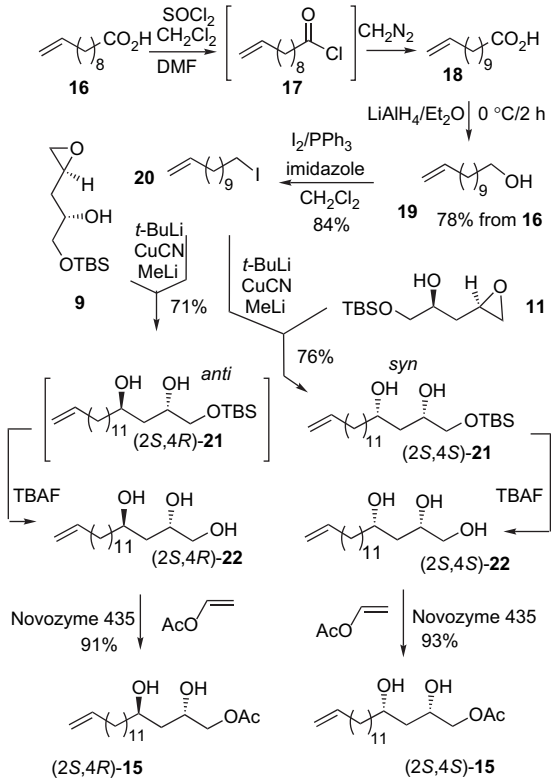
It is noteworthy that although protection of either **4a** or **6a** was relatively facile,[5b] the apparent preference for the primary OH did not seem to exist with other protecting groups. For instance, attempts to use allyl, benzoyl (Bz) or pivalyol (Piv) group as the protecting group always led to an almost 1:1 mixture of two positional isomers, indicating that the secondary OH was just as reactive as the primary one in these cases. The selectivity appears to depend very much on the protecting group involved in the reaction. It is not clear yet why no product with a Ts or TBS on the secondary OH was formed in these cases. However, it can be definitely excluded that under the given conditions any **4b** or **6b** (both prepared from **13**,[1] Scheme 2) might be converted into **4a** or **6a**, respectively, via intramolecular migration of the protecting group from the secondary OH to the primary one (Scheme 2).



Scheme 2.

The chiral building blocks derived from D-xylose such as **5**, **9**, and **11** all contain a hidden 1,3-diol motif of either *syn* or *anti* relationship, which may be utilized as precursors for the corresponding fragments in those target compounds encapsulate 1,3-diol(s) partial structures. Avocadotiol monoacetate (**15**),[7] a potent acetyl-CoA carboxylase inhibitor, is one of such compounds (Scheme 3).

The relative configuration of natural **15** was reported to be 1,3-*syn* on the basis of the relative configuration of the related triol.[7a,c] However, the assignment is not conclusive because no structural determination has ever been performed directly on **15** itself. To demonstrate the utility of the chiral building blocks mentioned



Scheme 3.

above and to gain more direct evidence on the relative as well as absolute configuration of the natural **15**, we conducted the total syntheses described below.

We were aware from the beginning that the optical rotations documented in the literature over the years varied considerably from each other, which implied that a definite conclusion on the relative and absolute configurations might not be reachable through simple comparison of the rotations of a synthetic (2*S*,4*S*)-**15** (1,3-*syn*) with those in the literature. To avoid this situation, we also synthesized (2*S*,4*R*)-**15** (1,3-*anti*) in parallel for comparison. As will be seen below, this *anti* isomer indeed played a critical role in confirming the *syn* configuration for the natural **15** despite the interference of the discrepancy between the literature rotation data.

Both isomers of **15** were derived via catenation of a 12-carbon chain species with either **9** or **11** (Scheme 3). The syntheses started with Arndt–Eistert homologation[8] of the readily available 10-undecenoic acid (**16**). The acid was first converted into acid chloride **17** by treatment with $SOCl_2$ in CH_2Cl_2 in the presence of a catalytic amount of DMF as described by Quinkert.[9] The subsequent chain extension and reduction of the carboxylic group were then performed as reported by Kato and Mori,[10] giving alcohol **19** in 78% overall yield from **16**.

Before combining the long chain moiety with either epoxide **9** or **11**, the hydroxyl group terminal of **19** must be activated into a proper carbanion species. This was most conveniently achieved via an iodide, which might undergo iodine–lithium exchange to afford the desired carbanion. In execution of this plan, the alcohol **19** was converted into iodide **20** as described[11] by Bach and Lemarchand. The exchange of the iodide into the corresponding lithium species was realized by reaction with *t*-BuLi.[12] Further addition of CuCN/MeLi[13] to the organolithium generated a cuprate species, which on reaction with epoxide **9** or **11** afforded diol (2*S*,4*R*)-**21** or (2*S*,4*S*)-**21**, respectively.

The (2*S*,4*R*)-**21** was inseparable from the unreacted **9** on silica gel. Therefore, it was directly desilylated without any purification. Removal of the TBS protecting group in **21** with *n*-Bu_4NF (TBAF) led to known[14] tiols (2*S*,4*R*)-**22** or (2*S*,4*S*)-**22**, respectively.

Selective acetylation of the triols was expected to be a difficult task if using conventional acetylation conditions. Therefore, we opted to try those unconventional protocols developed in recent years. Novozyme 435/vinyl acetate appeared rather mild and highly selective,[15] and was thus tested first.

The experimental outcome using this set of conditions was indeed very pleasing. Treatment of triol with Novozyme 435/vinyl acetate led to clean formation of the corresponding 1-monoacetates within 30 min. The position of acetyl group was secured by an unmistakable downfield shift of the methylene group (–CH_2O–) in addition to the coupling information from COSY and HMQC experiments.

It is interesting to note that the two diastereomers, (2*S*,4*R*)-**22** and (2*S*,4*S*)-**22**, showed remarkable difference in reactivity toward vinyl acetate in the absence of Novozyme 435. Stirring of (2*S*,4*S*)-**22** in vinyl acetate at ambient temperature for 5 days resulted in (2*S*,4*S*)-**15** cleanly. However, (2*S*,4*R*)-**22** was essentially complete inert under the same conditions.

The optical rotation for (2*S*,4*S*)-**15** and (2*S*,4*R*)-**15** synthesized in this work was determined to be +6.7 and −11.4, respectively (Fig. 1). The former appears to be compatible with the values reported by Kashman[7b] and Browse,[7d] respectively, suggesting that the natural **15** should be of (2*R*,4*R*) configuration because of the opposite signs. However, the rotation of (2*S*,4*R*)-**15** is also rather close to that of Kawabata,[7a] which implies a (2*S*,4*R*) configuration. Apparently, comparison of the optical rotations alone in this case cannot lead to any definite conclusion.

^{13}C NMR is often considered as a sensitive tool for differentiation between diastereomers. However, in the present case it turns out to be useless because the spectrum for (2*S*,4*S*)-**15** and (2*S*,4*R*)-**15** is identical to each other (and also identical to that of the natural **15**). The critical differences between the diastereomers were finally found in ^1H NMR, in the region of δ 4.22–4.11 (Table 1). The observed relevant signals for (2*S*,4*S*)-**15** were essentially the same as those for the natural one, with all three protons (two H-1′s and H-2) appearing between δ 4.11–4.03. Two protons of (2*S*,4*R*)-**15**, however, appeared at δ 4.22–4.12, a blank region for natural and (2*S*,4*S*)-**15**, providing a critical piece of evidence for rejecting the (2*S*,4*R*) relative configuration (i.e., the 1,3-*anti* configuration) for the natural **15**. It should also be noted that the melting point for (2*S*,4*S*)-**15** is much closer to that for the natural **15** than the (2*S*,4*R*)-**15** (Fig. 1).

Once the 1,3-*anti* configuration was excluded, the remaining task became much easier. Although the three rotation data for the natural **15** in the literature differ considerably from each other, they all are levorotatory. This means the natural **15** must be an mirror image to (2*S*,4*S*)-**15**, possessing a (2*R*,4*R*) configuration.

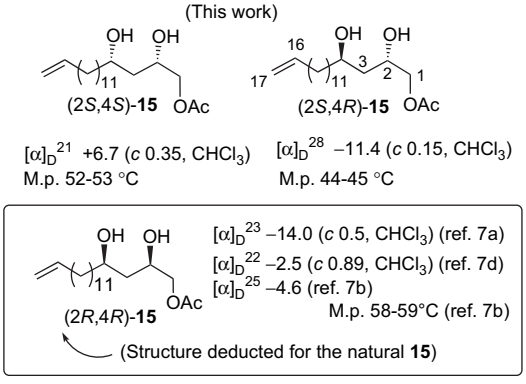


Figure 1. The absolute configurations and physical data for synthetic (2*S*,4*S*)- and (2*S*,4*R*)-**15** as well as the natural **15**.

Table 1
Comparison of ^{1}H NMR data of the synthetic and natural **15**, with the unmistakable differences in the δ 4.22–4.03 region italicized[a]

Natural **15** (Ref. 7a)	Natural **15** (Ref. 7d)	(2*S*,4*S*)-**15** (this work)	(2*S*,4*R*)-**15** (this work)
5.79 (ddt, *J*=17.1, 10.2, 6.7 Hz, 1H, H-16)	5.82 (ddt, *J*=17, 10.5, 6.7 Hz)	5.81 (ddt, *J*=17.0, 10.2, 6.6 Hz, 1H)	5.81 (ddt, *J*=18.0, 10.4, 6.8 Hz, 1H)
4.97 (d, *J*=17.1 Hz, 1H, one of H-17)	4.99 (ddt, *J*=17, 1.6, 1.2 Hz)	4.99 (dd, *J*=17.0, 1.6 Hz, 1H)	4.99 (dd, *J*=17.2, 1.6 Hz, 1H)
4.91 (d, *J*=10.2 Hz, 1H, one of H-17)	4.93 (ddt, *J*=10.5, 2.1, 1.2 Hz)	4.93 (d, *J*=10.4 Hz, 1H)	4.92 (dd, *J*=10.4, 1.2 Hz, 1H)
4.11–4.07 (2H, m, one of H-1 and H-2)	*4.11 (m)*	*4.15–4.06 (m, 2H)*	*4.22–4.12 (m, 2H)*
3.98 (dd, J=11.9, 4.5 Hz, 1H, one of H-1)	*3.89 (m)*	*4.04–3.96 (m, 1H),*	*4.03 (dd, J=11.2, 7.6 Hz, 1H)*
3.90–3.85 (m, 1H, H-4)		3.93–3.84 (m, 1H)	3.97–3.89 (m, 1H)
2.09 (s, Ac)	2.09 (s)	2.10 (s, 3H)	2.10 (s, 3H)
2.04–2.00 (m, 2H H-15)	2.04 (br q, *J*=7 Hz)	2.03 (q, *J*=6.8 Hz, 2H)	2.03 (q, *J*=7.2 Hz, 2H)
1.58–1.50 (m, 2H, H-3), 1.438–1.43 (m, 2H, H-5), 1.24 (m, 18H)	1.47–1.32 (m)	1.65–1.18 (m, 22H)	1.72–1.22 (m, 22H)

[a] The data from Ref. 7b are not included here because they were oversimplified (all designated as 'm' without giving the ranges of the multiplets) and hence not informative enough for comparison. For clarity, the signals for OH groups are not shown here.

3. Conclusions

Facile access to several flexible chiral building blocks has been developed with inexpensive and readily available D-xylose as the starting material. The newly synthesized chiral building blocks all possess a hidden 1,3-diol motif and may find applications in synthesis of various target molecules containing 1,3-diol partial structures.[16] Such a potential is illustrated through a synthesis of (2*S*,4*S*)-**15** and (2*S*,4*R*)-**15**, which served as reference samples in direct data comparison in an effort to assign the absolute configuration of natural avocadotriol monoacetate (natural **15**). On the basis of careful comparison of the ^{1}H NMR spectra, the relative configuration of natural **15** was secured to be 1,3-*syn*. The absolute configuration of the natural **15** was then deducted to be (2*R*,4*R*) because its rotation is of opposite sign to that of (2*S*,4*S*)-**15**. The rapid, mild, and highly selective acetylation of the 1,2,4-triols using Novozyme 435/vinyl acetate at ambient temperature may be also of preparative significance in synthesis.

4. Experimental

4.1. General

Unless otherwise stated, the ^{1}H NMR and ^{13}C NMR spectra were recorded in deuterochloroform at ambient temperature using a Varian Mercury 300 or a Bruker Avance 300 instrument (operating at 300 MHz for proton). The FTIR spectra were scanned with a Nicolet Avatar 360 FTIR spectrometer. The ESIMS and ESIHRMS were recorded with a PE Mariner API-TOF and an APEX III (7.0 Tesla) FTMS mass spectrometer, respectively. The melting points were uncorrected. Optical rotations were recorded on a Jasco P-1030 polarimeter. Dry THF and Et_2O were distilled from Na/Ph_2CO under N_2 prior to use. Dry DMF, CH_2Cl_2, and pyridine were distilled over CaH_2 under N_2 prior to use. PE (chromatography eluent) stands for petroleum ether (bp 60–90 °C). DMF stands for *N*,*N*′-dimethylformamide. Molecular sieves (4 Å) were activated by heating 3×1 min (with the moisture briefly ventilated between the heating sessions by opening the oven door) in a 700 W household microwave oven using ca. 75% of the full power. Novozyme 435 (immobilized on macroporous acrylic resin) was purchased from Sigma–Aldrich and used as received.

4.2. Deacetylation of 2 leading to crude diol 3

Finely powdered Na_2CO_3 (220 mg, 2.1 mmol) was added to a solution of diacetate **2** (6.500 g, 30.0 mmol) in anhydrous MeOH (60 mL) stirred at ambient temperature. The mixture was stirred for 1 h, when TLC showed full disappearance of the starting **2**. The white solids were filtered off through Celite. Amberlite IR-120 H resin was carefully added to the filtrate with stirring until the mixture became neutral (pH testing paper). The resin in the mixture was filtered off through Celite. The filtrate was concentrated to dryness on a rotary evaporator to afford the known diol **3**[2] (crude) as a yellowish oil (4.450 g, 30.2 mmol), which was used as such in the subsequent step.

4.3. Tosylation of diol 3 leading to 4a

A solution of diol **3** (528 mg, 4.0 mmol) and *p*-TsCl (839 mg, 4.401 mmol) in anhydrous pyridine (15 mL) was stirred at ambient temperature for 5 days. Aq satd $CuSO_4$ (20 mL) was added. The mixture was extracted with EtOAc (2×50 mL). The combined EtOAc phases were washed with aq satd $CuSO_4$ until no more blue precipitates formed. The EtOAc phase was then washed in turn with water (5.0 mL) and brine (5.0 mL), and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (1:1 EtOAc/PE) on silica gel gave the known monotosylate **4a**[3b] as a white solid (687 mg, 2.399 mmol, 60%). Mp 101–102 °C;[3e] $[\alpha]_D^{26}$ +21.8 (*c* 1.7, $CHCl_3$) (lit.[3b] $[\alpha]_D^{20}$ +28.6 (*c* 1.47, $CHCl_3$)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, *J*=8.3 Hz, 2H), 7.35 (d, *J*=8.2 Hz, 2H), 4.65–4.51 (m, 2H), 4.23 (dd, *J*=11.4, 2.9 Hz, 1H), 4.11 (dd, *J*=11.6, 5.5 Hz, 1H), 3.69 (d, *J*=4.0 Hz, –OH), 2.63 (ddd, *J*=13.1, 8.5, 6.1 Hz, 1H), 2.44 (s, 3H), 2.12–1.92 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.0, 145.5, 132.0, 130.1, 128.0, 73.5, 69.1, 67.8, 32.3, 21.7.

4.4. Conversion of 4a into epoxide 5

A freshly prepared solution of NaOMe in anhydrous MeOH (2.0 N, 0.35 mL, 0.70 mmol) was added to a solution of **4a** (100 mg, 0.346 mmol) in anhydrous MeOH (2.0 mL) stirred at ambient temperature. The stirring was continued for 20 min, when TLC showed completion of the reaction. The mixture was neutralized with diluted HOAc. Solvent was removed by rotary evaporation. The residue was diluted with EtOAc (20 mL), washed with water (5 mL) and brine (5 mL), and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (2:3 EtOAc/PE) on silica gel gave epoxide **5** as a yellowish sticky oil (44 mg, 0.301 mmol, 87%). $[\alpha]_D^{23}$ −8.0 (*c* 0.65, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.37 (dd, *J*=7.3, 5.1 Hz, 1H), 3.80 (s, 3H), 3.17–3.12 (m, 1H), 2.82 (t, *J*=4.5 Hz, 1H), 2.54 (dd, *J*=5.0, 2.7 Hz, 1H), 1.97–1.92 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 68.4, 52.7, 49.1, 47.2, 37.3; FTIR (film) 3367, 2924, 2854, 1742, 1461, 1261, 1100, 801 cm^{-1}; ESIMS *m*/*z* 169.1 ([M+Na]$^+$). ESIHRMS calcd for $C_6H_{10}O_4Na$ ([M+Na]$^+$): 169.0471; found: 169.0463.

4.5. TBS protection of diol 3 leading to 6a

A solution of diol **3** (0.821 g, 6.215 mmol), dry Et_3N (1.0 mL, 7.125 mmol), and TBSCl (1.032 g, 6.857 mmol) in anhydrous THF (30 mL) was stirred at ambient temperature for 3 days. Water (10 mL) was added. The mixture was concentrated on a rotary evaporator. The residue was dissolved in CH_2Cl_2 (100 mL), washed

in turn with 0.3 N HCl (2×20 mL), water (20 mL), and brine (20 mL), and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (1:2 EtOAc/PE) on silica gel afforded the known[5a] **6a** as a colorless sticky oil (796 mg, 3.231 mmol, 52%). $[\alpha]_D^{25}$ +11.1 (*c* 1.15, EtOH) (lit.[5a] $[\alpha]_D^{25}$ +8.57 (*c* 1.16, EtOH)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.58–4.40 (m, 2H), 3.94 (dd, *J*=11.6, 3.2 Hz, 1H), 3.74 (dd, *J*=11.7, 3.8 Hz, 1H), 3.65 (br s, OH), 2.61 (ddd, *J*=15.1, 8.2, 6.3 Hz, 1H), 2.15 (dt, *J*=12.7, 8.7 Hz, 1H). 0.92 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.3, 77.3, 68.0, 63.9, 32.3, 25.7, 18.2, −3.7, −5.5.

4.6. Conversion of 6a into epoxide 9

$NaBH_4$ (454 mg, 12 mmol) was added in portions to a solution of **6a** (2.464 g, 10 mmol) in MeOH (50 mL) stirred in an ice-water bath. After completion of the addition, the mixture was stirred at ambient temperature until TLC showed complete disappearance of the starting **6**. Amberlite IR-120 H resin was added with stirring until pH=6 (testing paper). The resin was filtered off. The filtrate was concentrated on a rotary evaporator to give the intermediate triol as a yellowish sticky oil. To this oily residue were added in turn dry THF (50 mL), *n*-Bu_2SnO (72 mg, 0.3 mmol), activated 4 Å molecular sieves (1.5 g), dry Et_3N (1.54 mL, 11 mmol), and *p*-TsCl (1.904 g, 10 mmol). The mixture was stirred at ambient temperature for 1 h, when TLC showed complete disappearance of the triol. The mixture was filtered through Celite. The filtrate was concentrated on a rotary evaporator to dryness. The residue (crude tosylate) was dissolved in MeOH (40 mL). The solution was then stirred in an ice-water bath. Finely powdered anhydrous K_2CO_3 (495 mg, 5.0 mmol) was introduced. After completion of the addition, the mixture was stirred at ambient temperature for ca. 1 h (when TLC showed completion of the reaction). Water (10 mL) was added. The mixture was concentrated on a rotary evaporator to remove MeOH. The residue was extracted with EtOAc (3×50 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (1:2 EtOAc/PE) on silica gel gave epoxide **9** as a colorless oil (1.975 g, 8.5 mmol, 85% from **6a**). $[\alpha]_D^{23}$ −13.8 (*c* 1.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.93–3.83 (m, 1H), 3.66 (dd, *J*=10.0, 3.8 Hz, 1H), 3.44 (dd, *J*=11.0, 7.1 Hz, 1H), 3.15–3.08 (m, 1H), 2.81 (t, *J*=4.5 Hz, 1H), 2.61 (d, *J*=3.7 Hz, 1H), 2.53 (dd, *J*=4.9, 2.7 Hz, 1H), 1.81 (ddd, *J*=14.2, 8.5, 4.1 Hz, 1H), 1.46 (ddd, *J*=14.3, 7.1, 4.3 Hz, 1H), 0.88 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 69.8, 67.1, 49.8, 47.2, 36.0, 25.9, 18.3, −5.4 (2C's); FTIR (film) 3469, 2929, 2958, 1472, 1255, 1090, 837, 778, 669 cm^{-1}; ESIMS *m*/*z* 255.2 ($[M+Na]^+$). ESIHRMS calcd for $C_{11}H_{24}O_3SiNa$ ($[M+Na]^+$): 255.1387; found: 255.1388.

4.7. Tosylation of 6a leading to 10

A solution of **6a** (246 mg, 1.0 mmol), dry Et_3N (0.28 mL, 2.0 mmol), and *p*-TsCl (286 mg, 1.50 mmol) in dry CH_2Cl_2 (5.0 mL) was stirred at ambient temperature overnight. The mixture was diluted with CH_2Cl_2 (50 mL), washed with water (5 mL) and brine (5 mL), and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (1:6 EtOAc/PE) on silica gel afforded **10** as a colorless sticky oil (365 mg, 0.911 mmol, 91%). $[\alpha]_D^{23}$ +19.4 (*c* 1.45, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, *J*=8.6 Hz, 2H), 7.38 (d, *J*=8.9 Hz, 2H), 5.35 (dd, *J*=10.1. 9.0 Hz, 1H), 4.50–4.41 (m, 1H), 3.87 (dd, *J*=11.6, 3.3 Hz, 1H), 3.68 (dd, *J*=11.7, 3.9 Hz, 1H), 2.66 (ddd, *J*=15.2, 9.1, 6.0 Hz, 1H), 2.50–2.35 (m, 4H); ESIMS *m*/*z* 423.1 ($[M+Na]^+$). ESIHRMS calcd for $C_{18}H_{28}O_6SSiNa$ ($[M+Na]^+$): 423.1268; found: 423.1280.

4.8. Conversion of 10 into 11

$NaBH_4$ (20 mg, 0.512 mmol) was added in portions to a solution of **10** (205 mg, 0.512 mmol) in CH_2Cl_2/MeOH (1:1 v/v, 3.0 mL) stirred in an ice-water bath. After completion of the addition, the mixture was stirred at ambient temperature until TLC showed complete disappearance of the starting **10** (ca. 20 min). Water (3 mL) was added. The mixture was concentrated on a rotary evaporator to remove MeOH and CH_2Cl_2. The residue was extracted with EtOAc (2×25 mL). The combined organic layers were washed brine (5 mL) and dried over anhydrous Na_2SO_4. Solvent was removed by rotary evaporation. The residue was dissolved in MeOH (2.5 mL). With cooling (ice-water bath) and stirring, finely powdered anhydrous K_2CO_3 (46 mg, 0.623 mmol) was introduced. After completion of the addition, the mixture was stirred at ambient temperature for ca. 1 h (when TLC showed completion of the reaction). Water (5 mL) was added. The mixture was concentrated on a rotary evaporator to remove MeOH. The residue was extracted with EtOAc (2×20 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (1:7 EtOAc/PE) on silica gel gave **11** as a colorless oil (97 mg, 0.425 mmol, 83% from **10**). $[\alpha]_D^{23}$ +6.9 (*c* 1.15, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80–3.87 (m, 1H), 3.62 (dd, *J*=10.0, 3.9 Hz, 1H), 3.54 (dd, *J*=10.0, 7.0 Hz, 1H), 3.12–3.05 (m, 1H), 2.77 (dd, *J*=4.6, 4.4 Hz, 1H), 2.55 (d, *J*=3.6 Hz, 1H), 2.52 (dd, *J*=5.0, 2.7 Hz, 1H), 1.75 (dt, *J*=14.4, 4.7 Hz, 1H), 1.70–1.62 (m, 1H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 69.9, 66.8, 49.7, 46.7, 35.7, 25.9, 18.3, −5.4 (2C's); FTIR (film) 3462, 2929, 2858, 1472, 1254, 1107, 837, 778, 670 cm^{-1}; ESIMS *m*/*z* 255.1 ($[M+Na]^+$). ESIHRMS calcd for $C_{11}H_{24}O_3SiNa$ ($[M+Na]^+$): 255.1387; found: 255.1388.

4.9. Synthesis of (2*S*,4*S*)-21

MeLi (3.0 M, in Et_2O, 0.5 mL, 1.5 mmol) was added (via a syringe) dropwsie to a mixture of CuCN (134 mg, 1.496 mmol) in dry Et_2O (6.0 mL) stirred at −78 °C under argon (balloon). After completion of the addition, the mixture was stirred at the same temperature for 30 min (the pale yellow suspension gradually became a solution). The lithium species of **20**, prepared by dropwise addition (via a syringe) of *t*-BuLi (1.5 M, in pentane, 2.5 mL, 3.75 mmol) to a solution of iodide **20**[11] (450 mg, 1.529 mmol) in dry Et_2O (7.0 mL) stirred at −78 °C under argon (balloon) followed by stirring at the same temperature for 30 min, was then introduced via a cannula to the aforementioned MeLi/CuCN solution stirred at −78 °C under argon (balloon). After completion of the addition, the mixture was stirred at the same temperature for 30 min. A solution of epoxide **11** (105 mg, 0.452 mmol) in dry Et_2O (2.0 mL) was added via a syringe. The mixture was stirred at −78 °C for another 3 h, when TLC showed completion of the reaction. Aq satd NH_4Cl/aq NH_3 (9:1 v/v, 10 mL) was added. The mixture was stirred at ambient temperature until a clear biphasic solution was formed before being extracted with Et_2O (3×20 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (1:2 EtOAc/PE) on silica gel gave epoxide (2*S*,4*S*)-**21** as a colorless oil (466 mg, 1.163 mmol, 76%). $[\alpha]_D^{25}$ +3.3 (*c* 0.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83 (ddt, *J*=17.1, 10.3, 6.5 Hz, 1H), 5.00 (d, *J*=17.5 Hz, 1H), 4.92 (d, *J*=10.4 Hz, 1H), 4.01–3.80 (m, 2H), 3.60 (dd, *J*=9.7, 3.7 Hz, 1H), 3.45 (dd, *J*=9.6, 7.2 Hz, 1H), 3.34 (br s, OH), 2.95 (br s, OH), 2.04 (q, *J*=6.8 Hz, 2H), 1.80–1.15 (m, 22H), 0.91 (s, 9H), 0.09 (s, 6H); FTIR (film) 3364, 3077, 2926, 2854, 1641, 1463, 1259, 1093, 909, 837, 778 cm^{-1}; ESIMS *m*/*z* 423.2 ($[M+Na]^+$). ESIHRMS calcd for $C_{23}H_{48}O_3SiNa$ ($[M+Na]^+$): 423.3265; found: 432.3271.

4.10. Synthesis of (2*S*,4*S*)-22

A solution of (2*S*,4*S*)-**21** (137 mg, 0.342 mmol) and *n*-Bu_4NF (1.0 M solution in THF, 2.0 mL, 2.0 mmol) in THF (5.0 mL) was stirred at ambient temperature until TLC showed completion of the reaction. Aq satd NH_4Cl (5.0 mL) was added. The mixture was extracted with EtOAc (3×20 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (2:1 EtOAc/PE) on silica gel gave the known[14] triol (2*S*,4*S*)-**22** as a white solid (93 mg, 0.325 mmol, 95%). Mp 66–67 °C (lit.[14] mp 65.5–66 °C); $[\alpha]_D^{22}$ +6.4 (*c* 1.2, $CHCl_3$) (lit.[14] $[\alpha]_D^{20}$ +6.0 (*c* 1.0, $CHCl_3$)); ^1H NMR (400 MHz, $CDCl_3$) δ 5.81 (ddt, *J*=17.0, 10.3, 6.7 Hz, 1H), 4.99 (dd, *J*=17.1, 1.8 Hz, 1H), 4.92 (dd, *J*=10.1, 0.9 Hz, 1H), 4.00–3.85 (m, 3H), 3.62 (dd, *J*=11.1, 2.5 Hz, 1H), 3.45 (dd, *J*=11.0, 6.5 Hz, 1H), 3.15 (br s, OH), 2.90 (br s, OH), 2.03 (q, *J*=7.0 Hz, 2H), 1.60–1.20 (m, 22H).

4.11. Synthesis of (2*S*,4*S*)-15

A solution of (2*S*,4*S*)-**21** (20 mg, 0.0698 mmol) and Novozyme 435 (2 mg) in CH_2=CHOAc (2.0 mL) was stirred at ambient temperature for ca. 20 min, when TLC showed completion of the reaction. The solids were filtered off. The filtrate was concentrated on a rotary evaporator. The residue was chromatographed (1:2 EtOAc/PE) on silica gel to give (2*S*,4*S*)-**15** as a white solid (21 mg, 0.0649 mmol, 93%). Mp 52–53 °C; $[\alpha]_D^{21}$ +6.7 (*c* 0.35, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.81 (ddt, *J*=17.0, 10.2, 6.6 Hz, 1H), 4.99 (dd, *J*=17.0, 1.6 Hz, 1H), 4.93 (d, *J*=10.4 Hz, 1H), 4.15–4.06 (m, 2H), 4.04–3.96 (m, 1H), 3.93–3.84 (m, 1H), 3.38 (br s, OH), 2.65 (br s, OH), 2.10 (s, 3H), 2.03 (q, *J*=6.8 Hz, 2H), 1.65–1.18 (m, 22H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 139.3, 114.1, 72.5, 70.8, 68.6, 39.1, 38.2, 33.8, 29.6, 29.5, 29.1, 28.9, 25.3, 20.9; FTIR (KBr) 3439, 3075, 2919, 2851, 1710, 1641, 1468, 1262, 1139, 1093, 1043, 909, 800 cm^{-1}; ESIMS *m*/*z* 351.3 ($[M+Na]^+$). ESIHRMS calcd for $C_{19}H_{36}O_4Na$ ($[M+Na]^+$): 351.2506; found: 351.2499.

4.12. Synthesis of (2*S*,4*R*)-22

MeLi (3.0 M, in Et_2O, 0.34 mL, 0.990 mmol) was added (via a syringe) dropwsie to a mixture of CuCN (89 mg, 0.994 mmol) in dry Et_2O (4.0 mL) stirred at −78 °C under argon (balloon). After completion of the addition, the mixture was stirred at the same temperature for 30 min (the pale yellow suspension gradually became a solution). The lithium species of **20**, prepared by dropwise addition (via a syringe) of *t*-BuLi (1.5 M, in pentane, 1.7 mL, 2.55 mmol) to a solution of iodide **20** (300 mg, 1.020 mmol) in dry Et_2O (7.0 mL) stirred at −78 °C under argon (balloon) followed by stirring at the same temperature for 30 min, was then introduced via a cannula to the aforementioned MeLi/CuCN solution stirred at −78 °C under argon (balloon). After completion of the addition, the mixture was stirred at the same temperature for 30 min. A solution of epoxide **9** (70 mg, 0.301 mmol) in dry Et_2O (2.0 mL) was added via a syringe. The mixture was stirred at −78 °C for another 3 h, when TLC showed completion of the reaction. Aq satd NH_4Cl/aq NH_3 (9:1 v/v, 10 mL) was added. The mixture was stirred at ambient temperature until a clear biphasic solution was formed before being extracted with Et_2O (3×20 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), and dried over anhydrous Na_2SO_4. The solvent was removed by rotary evaporation. The residue was dissolved in THF (5.0 mL). *n*-Bu_4NF (1.0 M solution in THF, 1.3 mL, 1.3 mmol) was added. The mixture was stirred at ambient temperature until TLC showed completion of the reaction. Aq satd NH_4Cl (5.0 mL) was added. The mixture was extracted with EtOAc (3×20 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (2:1 EtOAc/PE) on silica gel gave the known[14] triol (2*S*,4*R*)-**22** as a white solid (86 mg, 0.215 mmol, 71% from **9**). Mp 83–84 °C (lit.[14] mp 82.5 °C); $[\alpha]_D^{27}$ −6.7 (*c* 1.1, $CHCl_3$) (lit.[14] $[\alpha]_D^{20}$ −7.3 (*c* 1.0, $CHCl_3$)); ^1H NMR (300 MHz, $CDCl_3$) δ 5.81 (ddt, *J*=16.9, 10.1, 7.0 Hz, 1H), 4.99 (d, *J*=17.5 Hz, 1H), 4.92 (d, *J*=10.6 Hz, 1H), 4.10–3.85 (m, 2H), 3.65 (dd, *J*=11.4, 3.4 Hz, 1H), 3.51 (dd, *J*=11.0, 7.2 Hz, 1H), 2.95 (br s, OH), 2.17 (br s, OH), 2.02 (q, *J*=7.0 Hz, 2H), 1.80–1.20 (m, 22H).

4.13. Synthesis of (2*S*,4*R*)-15

A solution of (2*S*,4*R*)-**22** (16 mg, 0.0558 mmol) and Novozyme 435 (2 mg) in CH_2=CHOAc (2.0 mL) was stirred at ambient temperature for ca. 20 min, when TLC showed completion of the reaction. The solids were filtered off. The filtrate was concentrated on a rotary evaporator. The residue was chromatographed (1:2 EtOAc/PE) on silica gel to give (2*S*,4*R*)-**15** as a white solid (17 mg, 0.0508 mmol, 91%). Mp 44–45 °C; $[\alpha]_D^{28}$ −11.4 (*c* 0.15, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.81 (ddt, *J*=18.0, 10.4, 6.8 Hz, 1H), 4.99 (dd, *J*=17.2, 1.6 Hz, 1H), 4.92 (dd, *J*=10.4, 1.2 Hz, 1H), 4.22–4.12 (m, 2H), 4.03 (dd, *J*=11.2, 7.6 Hz, 1H), 3.97–3.89 (m, 1H), 2.77 (br s, OH), 2.10 (s, 3H), 2.03 (q, *J*=7.2 Hz, 2H), 1.72–1.22 (m, 22H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 139.3, 114.1, 72.5, 70.8, 68.6, 39.1, 38.2, 33.8, 29.6, 29.5, 29.2, 28.9, 25.3, 20.9; FTIR (KBr) 3389, 3077, 2921, 2850, 1741, 1641, 1464, 1370, 1260, 1089, 1035, 909, 799 cm^{-1}. ESIMS *m*/*z* 351.1 ($[M+Na]^+$). ESIHRMS calcd for $C_{19}H_{36}O_4Na$ ($[M+Na]^+$): 351.2506; found: 351.2505.

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