DOI: 10.1002/ejoc.200801130

Fluorinated Analogues of Amicetose and Rhodinose – Novel Racemic and Asymmetric Routes

Jonathan M. Percy,*[a] Ricard Roig,[b][‡] and Kuldip Singh[b]

Keywords: Synthetic methods / Carbohydrates / Fluorination / Diastereoselectivity / Epoxidation

Trifluoroethanol was converted into difluorinated (racemic) analogues of amicetose and rhodinose by metallated difluoroenol acetal chemistry, protection, release of the latent difluoromethyl ketone, stereoselective reduction and ozonolysis in acidic methanol. A fortuitous separation of diastereoisomers allowed the diastereoisomeric pyranoses to be obtained cleanly. Though reductive defluorination allowed a facile entry to the route, the corresponding monofluoro sugar analogues could not be separated. Instead, Sharpless asymmetric epoxidation followed by epoxide ring-opening with an unusual nucleophilic fluoride source allowed enantiomerically highly enriched and selectively protected fluorodiols to be obtained. Ozonolysis then afforded the methyl pyranosides, which could be transformed in a number of ways.

Introduction

Amicetose (**1**) and rhodinose (**2**) (Figure 1) are highly deoxygenated (2,3,6-trideoxy) sugars which occur in a range of important antibiotic natural products; kigamicins,[1] polyketomycins[2,3] and tetracenomycins[4] contain **1**, whereas lactonamycins,[5] landomycins[6–9] and urdamycins[10] feature **2** in their saccharide motifs.

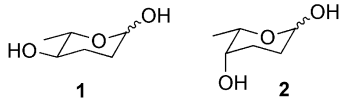


Figure 1. L-Amicetose (**1**) and L-rhodinose (**2**).

There are many chemical syntheses of the free sugars,[11,12] but the 6-fluoro analogues are less well known and may have a role to play in elucidating aspects of the mechanisms of sugar transfer. Our own interest lies in quantifying fluorine atom effects on glycoside hydrolytic reactivity.

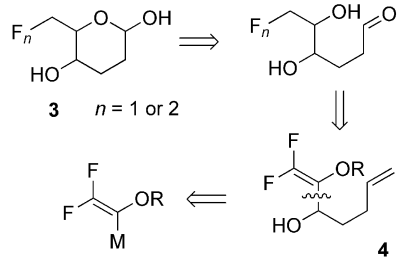
Nucleophilic fluorinating agents have played a valuable role in the synthesis of fluorinated carbohydrates. Deoxyhexoses fluorinated at C-6 have been synthesised by using DAST to transform isolated hydroxy groups, and fluoride ion to open cyclic sulfates derived from carbohydrates.

Lundt and co-workers[13] prepared an amicetoside from D-gluconic acid by an epoxide-opening reaction, but we found few other examples of syntheses of fluorinated analogues of the highly deoxygenated sugars.

Syntheses from carbohydrates are valuable, and allow the preparation of enantiomerically enriched materials from chiral-pool sources. However, it is often the case that an entirely new synthesis is required for each target. One of the goals of our work is the development of divergent methodologies by which families of related sugars can be synthesised in enantiomerically enriched form using asymmetric transformations of achiral precursors,[14–16] or by resolution.[17] Very direct synthetic access, even if it leads to the preparation of racemic modifications in the first instance, is also useful in certain contexts. Our metallated difluoroenol chemistry[18,19] appeared to offer an extremely direct approach to a range of difluorinated amicetose and rhodinose analogues **3**, through the reaction with pentenal, unmasking of the ketone latent in **4** and reduction, followed by alkene ozonolysis (Scheme 1).

The separate evolution of the two diol hydroxy groups affords an opportunity for selective protection, and the ability to form furanoses or pyranoses at will. Also, the relatively high reactivity of difluoroalkenes like **4** towards reductive defluorination potentially extends the strategy to monofluorinated analogues. We decided to explore this very direct route, because even the racemic materials were useful for an ongoing programme which studied structure-reactivity relationships. Furthermore, we could use these racemic routes to develop the key oxidative and other transformations needed to deliver the free sugars.

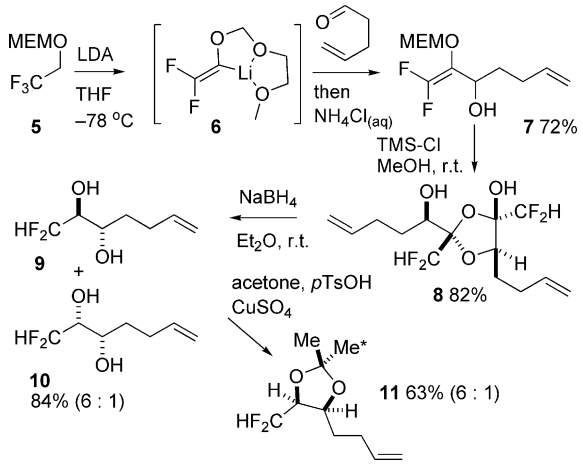
[a] WestCHEM Department of Pure and Applied Chemistry, University of Strathclyde, Thomas Graham Building, 295 Cathedral Street, Glasgow G1 1XL, UK
Fax: +44-141-548-4822
E-mail: jonathan.percy@strath.ac.uk
[b] Department of Chemistry, University of Leicester, University Road, Leicester LE1 7RH, UK
[‡] Current address: International Flavours and Fragrances, Avda. Felipe Klein 2, 12580 Benicarlo (Castellon), Spain
Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.



Scheme 1.

Results and Discussion

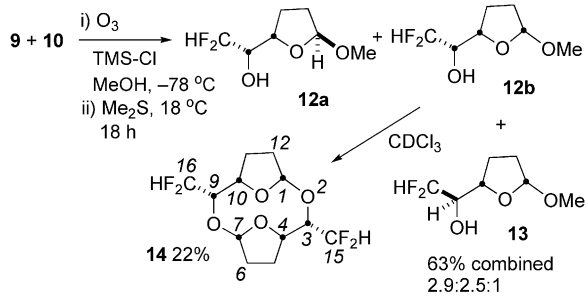
The initial steps were well established and could be scaled easily. Metallated difluoroenol acetal **6**, generated in situ from **5**, reacted smoothly with pentenal to afford **7** in good yield.[20] The protecting group was removed in acidic methanol; we obtained crystalline dioxolane **8**, which underwent relatively rapid reduction with sodium borohydride in diethyl ether delivering *anti*-diol **9** as the major product in good yield, with *syn*-**10** present as a side product. The (Felkin–Anh) sense of stereoselection is normal for the reduction of ketones with α-C–O bonds.[21] The relative configuration was also confirmed by formation of acetonide **11** and NOESY; both ring methine protons show cross peaks to the same methyl group (Me*) of the acetonide (Scheme 2).



Scheme 2.

Ozonolysis is the mildest and most direct way to complete the synthesis, and a mixture of amicetose and rhodinose was prepared by using this approach;[22] Weinreb and co-workers described an extremely effective ozonolysis reaction of alkene polyols absorbed on silica gel;[23] so we explored this methodology. We obtained a complex product mixture, which appeared to contain oligomers and was difficult to deconvolute. However, the ozonolysis in methanol containing chlorotrimethylsilane delivered a much simpler mixture of products following reductive (dimethyl sulfide) workup.

The signals of three anomeric protons were clearly visible in the $\{^{19}F\}^{1}H$ NMR spectrum; J values between 3.6 and 4.2 Hz, and cross peaks in the HMBC spectrum (which established the C-1/4-H and C-4/1-H connections clearly, and was used to deconvolute the complex 1D spectrum) showed that the three major products, assigned tentatively as **12a**, **12b** and **13** (ratio **12a**/**12b**/**13** = 2.9:2.5:1) were furanosides. Upon standing in the NMR solvent ($CDCl_3$), **14** crystallised, and we were able to obtain the molecular structure in the crystal (Scheme 3).[24,25] We were also able to prepare this material by leaving the ozonolysis solution overnight (after dimethyl sulfide treatment) before product isolation. Though the isolated yield of this product was low, the ^{19}F NMR spectrum of the crude ozonolysis product identifies **14** as the major product under these conditions. The conformation of **14** in the solid state resembles the "up-down-up-down" solution conformation described for a related macrocycle by Winkler et al. by NMR elucidation. We therefore believe that macrocycle **14** tells us about the vicinal coupling constants in a furanose with a pseudoaxial C–O bond at C-1 ($J_{1,2a}$ value of 4.2 Hz), as well as confirming the *anti* configuration of major diol **9**. As the initial diol diastereoisomer ratio from **8** is 6:1, it seems most likely that **12b** arises from the major diol, and contains a pseudoaxial C–O bond with **13**, the same anomer of the furanoside from the minor *syn*-diol. We searched the conformers available to **12b** using the molecular mechanics (MMFF94) Monte–Carlo method implemented in Spartan'06,[26] and found no conformers with a pseudoaxial C–O bond at C-1. Single-point energy calculations (B3LYP/6-31G*) were carried out for each of the (30+) conformers generated, the geometries of the six lowest-energy conformers were optimised (without constraints), and frequencies were calculated by using the MP2 method. Conformational searching was carried out again, restricting the geometry around C-1 and C-2 to resemble the arrangement in **14**, and then optimising (without constraints). The global minima for **12a** and **13** were now found; these had a pseudoaxial C–O bond at C-1 and a hydrogen bond from the C-5 hydroxy group across to the exocyclic acetal oxygen atom (the calculated O–H···O distance is 1.9 Å) and were up to 4 kJ mol^{-1} lower in (free) energy than the lowest-energy species from the unconstrained search.



Scheme 3.

Hydroxy groups next to fluorinated centres are very good hydrogen-bond donors because of the strong additional polarisation arising from the electronegative fluorine atoms; so the role of this hydroxy group is unsurprising. Figure 2a overlays macrocycle **14** and monomeric furanoside **12b** and shows quite good agreement between them. Figure 2b shows the overlay of **12b** and **13**. Whereas we realise that packing forces are likely to influence the conformation in the crystal and may produce an arrangement different to that adopted in solution, the similarities between the coupling constants measured for **12b**, **13** and **14** suggests that our calculated low-energy conformers are representative of the species present in chloroform solution.

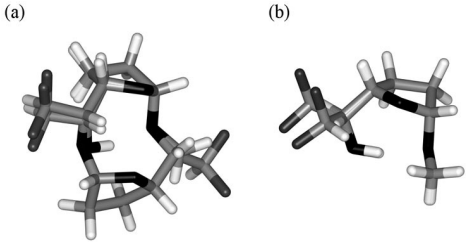
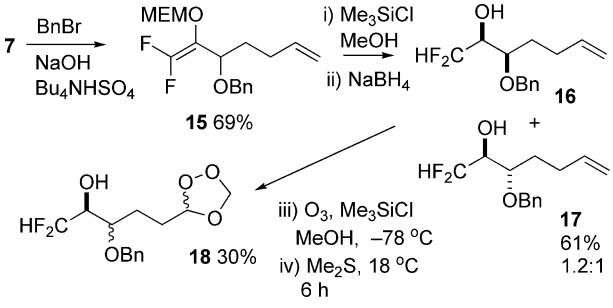


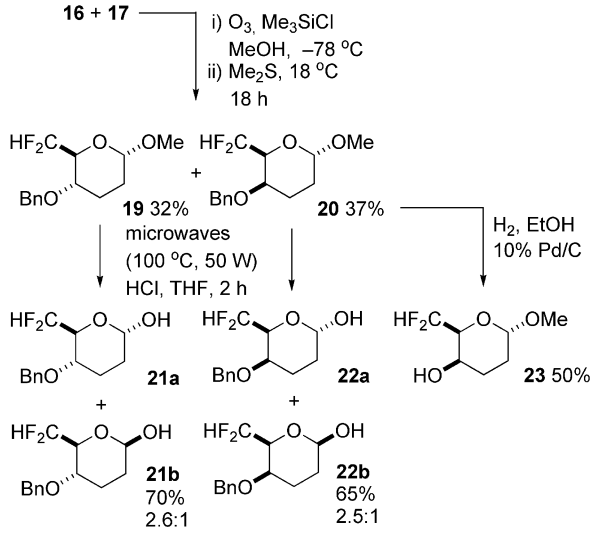
Figure 2. Overlays of (a) X-ray structure of **14** and calculated (MP2/6-31G*) structure of furanoside **12b**; (b) calculated (MP2/6-31G*) structures of furanosides **12b** and **13**, which differ only in the configuration at C-5.

We really wanted to synthesise the pyranosides, so modification of the route was essential. Benzylation of alcohol **7** under phase-transfer-catalysed conditions[27] afforded a moderate yield of **15**, but unfortunately, reduction following enol-acetal methanolysis, was unselective and afforded a 1:1 mixture of *syn*/*anti* diastereoisomers **16** and **17**. Ozonolysis afforded stable ozonide **18** as a complex mixture of diastereoisomers in the first instance (Scheme 4).



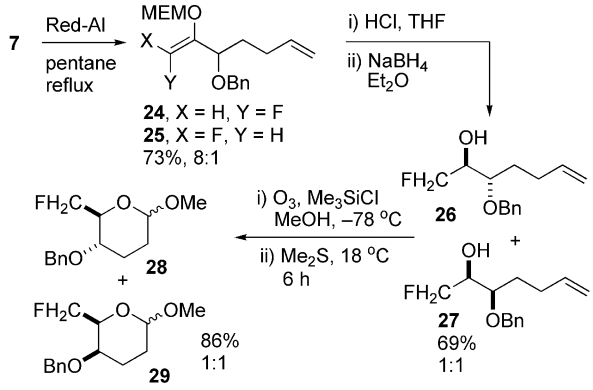
Scheme 4.

However, extended exposure to dimethyl sulfide secured the separable methyl pyranosides **19** and **20**; our illustrations represent the D sugars though of course these are racemic. Both **19** and **20** appear to have axial C–O bonds at the anomeric carbon atom; 1-H appears as a doublet in each case ($J_{1,2a}$ = 3.2 or 3.0 Hz), inconsistent with the presence of diaxial couplings; both pyranosides show NOESY cross peaks between the methoxy group and 5-H, consistent with this assignment. Amicetoside **19** and rhodinoside **20** can be distinguished by $J_{4,5}$ ($J_{4,5}$ = 9.8 Hz for the amicetoside or 1.8 Hz for the rhodinoside). Some oxidation of the benzyl ether methylene group to a benzoyl carbonyl group during ozonolysis was noted; we removed the benzoate by the addition of solid sodium hydroxide to the ozonolysis solution after the reduction was complete. Glycoside hydrolysis was carried out efficiently in THF in with microwaves to afford the hemiacetals **21a** and **21b**, and **22a** and **22b**, as a 2.5:1 mixture in each case (Scheme 5).



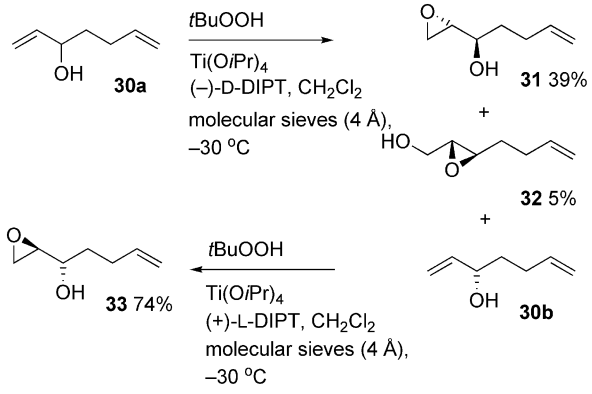
Scheme 5.

Once again, the assignment of the anomeric configuration based on the differences in $J_{1,2a}$ values appears unambiguous (vide supra). The α-anomer of the 4-*O*-benzylamicetose **21a** crystallised sufficiently well for the molecular structure in the crystal to be determined by X-ray methods supporting all the stereochemical assignments strongly. We also removed the benzyl ether from a mixture of **19** and **20** by hydrogenolysis in ethanol to afford (an inseparable mixture of) **23** and **24** in good yield. Monofluoro analogues of both pyranosides could be approached by reductive defluorination[28,29] of **7**, which afforded a mixture of alkene diastereoisomers **24** and **25**. Hydrolysis and reduction afforded a mixture of *anti*- and *syn*-diol monobenzyl ethers **26** and **27** (Scheme 6).



Scheme 6.

Ozonolysis then secured a 1:1 mixture of amicetosides **28** and rhodinosides **29**; the ^{1}H NMR spectra were heavily overlapped, but we could see what appeared to be one major anomer in each case, with small J values ($J_{1,2a}$ = 3.2 or 3.0 Hz) to 1-H in each case, but a full assignment was impossible. A full discussion of the anomer population and the analogy with **19** and **20** lies outside the scope of this paper and will be published elsewhere. Another route was clearly required, and the key goal was the control of the diol configuration; fortunately, methodology is available which addresses both relative and absolute diol configuration, and ensures pyranose formation. Scheme 7 shows the synthesis of enantiomerically enriched epoxy alcohol starting materials.



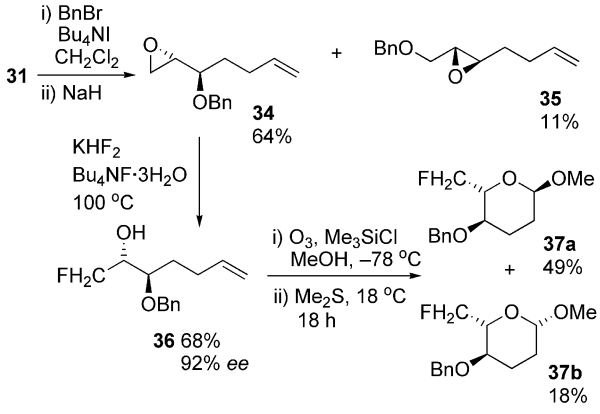
Scheme 7.

Sharpless asymmetric epoxidation[30–33] is rarely performed on terminal secondary allylic alcohols, with the exception of divinyl alcohol.[34] Racemic heptadienol **30a** was prepared from vinyl bromide and pentenal by the Grignard reagent, and Sharpless asymmetric epoxidation to **31** was carried out at –30 °C, requiring 15 d to reach completion (full conversion of one enantiomer).[35] Payne rearrangement could be suppressed if the exposure time of crude product to aqueous hydroxide in the workup is limited to 30 min; significant quantities of Payne product **32** was obtained if the workup was carried out over a longer period.[36] Traces of **30** were present in **31**, even after the most rigorous purification we could achieve.

Enantiomer **33** (of **31**) was prepared by using the complementary tartrate ligand, and the alcohol **30b** resolved during the preparation of **31**. The absolute configuration was assigned on the basis that the expected epoxy alcohol products have optical rotations of the same sign as those reported for the corresponding divinyl alcohol products.

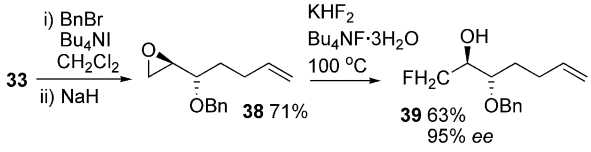
Benzylation of **31** was carried out in dichloromethane by using sodium hydride as the base affording **34** in good (64% yield) with Payne co-product **35** (11%) setting the stage for the crucial fluorination step.

Amine·HF salts are the most widely used reagents for the nucleophilic ring opening of epoxides with fluoride ion, though they can deliver low regioselectivities with terminal epoxides.[37] We therefore examined methods based on TBAF; the salt itself has been used for epoxide ring-opening,[38] but various TBAF·HF salts have proved very effective. We failed to ring-open **34** upon exposure to $Bu_4NH_2F_3$[39] or cat. KHF_2/$Bu_4NH_2F_3$,[40,41] recovering starting material under a range of conditions. With KHF_2 in ethylene glycol,[42] we recovered mostly the product of ring opening by the conjugate base of the solvent, whereas TBAF alone achieved ring opening in low conversion to **36** (Scheme 8).



Scheme 8.

The serendipitous combination of KHF_2 and TBAF at 100 °C (effectively a molten salt mixture) achieved a completely regioselective and high-yielding reaction to deliver **36**. Ozonolysis was carried out as described previously to afford the D-amicetoside anomers **37a** and **37b**. NOESY (5-H/OMe for **37a** and 1-H/5-H for **37b**) cross peaks were used to support the assignment of anomeric configuration in each case. We also progressed **33** through the fluorination reaction to **39** via benzyl ether **38** (Scheme 9).



Scheme 9.

The *ee* values of **36** (92% *ee*) and **39** (95% *ee*) were determined by chiral HPLC (Chiralcel OD-H column, 0.1% *i*PrOH in petroleum ether as eluant); these represent the levels of enantiomeric enrichment after the Sharpless epoxidation, benzylation and fluorination, so it is extremely unlikely that fluorination leads to a significant loss in enantiomeric purity. The *ee* values are only slightly lower than the 96% *ee* reported for the synthesis of **40** by asymmetric epoxidation of the internal secondary allylic alcohol, a reaction which takes only 3 d (Figure 3).[35]

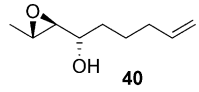
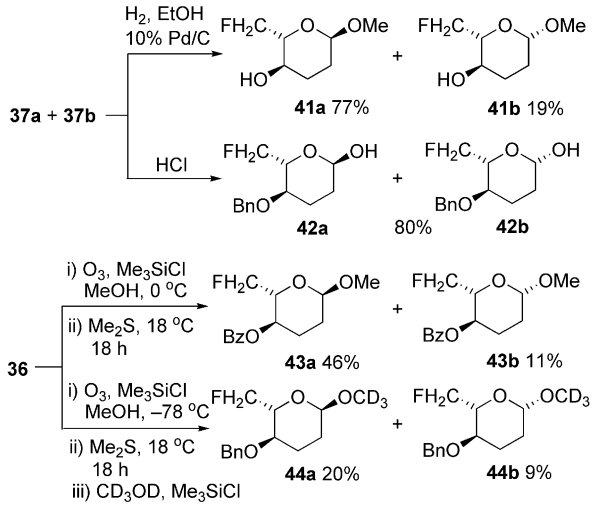


Figure 3. Epoxy alcohol **40** prepared by Page et al.[35]

Subsequent reactions were carried out for **36** only, on the assumption that the same results would be obtained from the reactions of enantiomer **39**.

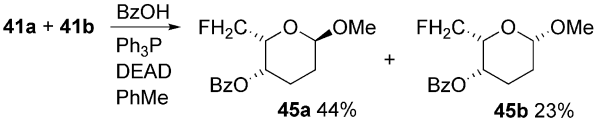
Debenzylation of **37a** and **37b** by hydrogenolysis occurred cleanly to afford **41a** and **41b**, and **37a** and **37b** were hydrolysed cleanly under microwave conditions in acidic THF to afford the free 4*O*-benzylamicetoses **42a** and **42b**.

Ozonolysis at 0 °C delivered good yields of benzoates **43a** and **43b** by in situ oxidation of the benzyl ether.[43] This sequence is potentially useful because it preserves the orthogonality of C-4 and C-1 (hemiacetal) hydroxy group protection but switches the manifold of conditions available for release of the former hydroxy group. Acetal exchange with CD_3OD proved facile and was a useful tactic allowing 4-H and 5-H signals to be seen clearly in **44a** and **44b** without overlap from the methoxy group signal (Scheme 10).



Scheme 10.

The separation was difficult and attenuated the isolated purified yield of two individual anomers (a mixed fraction was also recovered). The L-rhodinoside series could be entered in **45a** and **45b** by Mitsunobu inversion of **41a** and **41b**.[44,45] Crystals of adequate quality for crystallographic analysis were obtained for **45a** showing that the relationship between the stereogenic centres at C-1, C-4 and C-5 was assigned correctly (Scheme 11).



Scheme 11.

Conclusions

The racemic route to the difluoro sugars was direct and effective; though mixtures of amicetosides and rhodinosides were produced, they were separable. While the additional steps related to the protecting-group chemistry result in the formation of a mixture of diastereoiosmers, the location of the protecting group and thus the formation of pyranosides is unambiguous. The ozonolysis procedure in acidic methanol suppressed oligosaccharide formation and assisted with the isolation of monosaccharides.

The asymmetric route to the monofluoro species was successful, delivering the products in high degrees of enantiomeric enrichment. Clearly the epoxide-based route cannot be used to deliver the difluoro sugars, but the evolution of the asymmetric route to address initially a problem of relative configuration has yielded very satisfying results and allowed the identification of an interesting reagent combination for effective and highly regioselective nucleophilic epoxide ring opening with fluoride ion. The investigation of the scope and limitations of this reagent are ongoing; a fuller study of furanose/pyranose equilibria for these and related sugars will be published elsewhere.

Experimental Section

General: General experimental procedures and details of instrumentation are given in the Supporting Information. The preparations of **7** and **8** have been reported fully.[20] Magnesium turnings (127 mmol, 3.1 g) were washed with HCl (15 mL of a 5 M solution), then water (2 × 10 mL), then acetone (2 × 10 mL), then dried in vacuo and cooled under Ar. Powdered molecular sieves (4 Å) (6.3 g) in a 250 mL single-necked round-bottomed flask equipped with a magnetic stirrer bead, were heated under vacuum (below 50 Torr) with a Bunsen burner, and cooled to room temperature under argon. The cooled sieves were then covered with solvent through cannula. PE = petroleum ether.

CCDC-709168 (for **14**), -709169 (for **21a**) and -709170 (for **45a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request.cif.

(2*R,3*R**)-1,1-Difluorohept-6-enediol (9) and (2*S**,3*R**)-1,1-Difluorohept-6-enediol (10):** Sodium borohydride (1.2 mmol, 46 mg) was added in portions to a solution of dioxolane **8** (0.58 mmol, 0.19 g) in diethyl ether (10 mL). After stirring at room temperature overnight, the mixture was diluted with water (5 mL), neutralised with concentrated HCl, and extracted with EtOAc (3 × 15 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to leave a colourless oil, which was purified by Biotage column chromatography (gradient 20% → 50% EtOAc/PE) to afford an inseparable mixture of diols **9** and **10**) (0.16 g, 84%, 99% by GC-MS, 6:1 by NMR) as a clear colourless oil. R_f (20% EtOAc/PE) = 0.20. IR (neat): $\tilde{\nu}_{max}$ = 3366 [br. (OH)], 2923 [w (CH_2)], 1642 [w (C=C)], 1417 (w), 1151 [s (C–O)], 1048 [s (C–O)] cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.90 (ddd, $^2J_{H,F}$ = 56.0, $^2J_{H,F}$ = 55.0, J = 4.0 Hz, 1 H, 1-H), 5.84 (ddt, J = 17.1, J = 10.2, J = 6.8 Hz, 1 H, 6-H), 5.09 (ddd, J = 17.1, ^2J = 3.3, ^4J = 1.7 Hz, 1 H, 7_a-H), 5.02 (ddd, J = 10.2, ^2J = 3.3, ^4J = 1.2 Hz, 1 H, 7_b-H), 3.95–3.66 (m, 2 H, 2-H, 3-H), 3.04 (br. s, 1 H, OH), 2.46 (br. s, 1 H, OH), 2.36–2.06 (m, 2 H, 5-H), 1.79–1.58 (m, 2 H, 4-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.8 (C-6), 137.6, 115.5 (C-7), 115.0 (dd, $^1J_{C,F}$ = 241.9 Hz, $^1J_{C,F}$ = 242.5 Hz, C-1), 77.4 (dd, $^2J_{C,F}$ = 23.3 Hz, $^2J_{C,F}$ = 20.4 Hz, C-2), 70.7 (dd, $^3J_{C,F}$ = 4.4 Hz, $^3J_{C,F}$ = 3.0 Hz, C-3), 31.3 (d, $^4J_{C,F}$ = 2.0 Hz, C-4), 29.8 ppm; the ^1H and ^{13}C NMR spectra are effectively those of major diastereoisomer **9**.

^{19}F NMR (282 MHz, $CDCl_3$): major diastereoisomer **9**: δ = –128.3 (ddd, $^2J_{F,F}$ = 292.1, $^2J_{F,H}$ = 55.0, $^3J_{F,H}$ = 7.1 Hz, 1 F, CHF_aF_b), –132.0 (ddd, $^2J_{F,F}$ = 292.1, $^2J_{F,H}$ = 56.2, $^3J_{F,H}$ = 15.2 Hz, 1 F, CHF_aF_b) ppm; minor diastereoisomer **10**: ^{19}F NMR (282 MHz, $CDCl_3$): δ = –129.2 (dddd, $^2J_{F,F}$ = 292.0, $^2J_{F,H}$ = 55.7, $^3J_{F,H}$ = 9.9, $^4J_{F,H}$ = 1.1 Hz, 1 F, CHF_aF_b), –130.4 (ddd, $^2J_{F,F}$ = 292.0, $^2J_{F,H}$ = 56.6, $^3J_{F,H}$ = 10.6 Hz, 1 F, CHF_aF_b) ppm. HRMS (EI): calcd. for $C_7H_{12}F_2O_2$ [M$^+$] 166.08054; found 166.08044. MS (EI): *m*/*z* (%) = 148 (2) [M$^+$ + NH_4], 130 (4), 111 (5), 97 (19), 85 (30), 67 (100), 57 (42). t_R (GC) = 8.95 min (major diastereoisomer).

(2*R,3*S**)-1,1-Difluoro-*O*-isopropylidenehept-6-ene (11):** *p*-Tolyluenesulfonic acid monohydrate (0.15 mmol, 28 mg) was added to a stirred solution of anhydrous copper sulfate (2.6 mmol, 0.403 g) and diols **9** and **10** (0.76 mmol, 127 mg, 6:1 by NMR) in dry acetone (25 mL). After 5 h at reflux, the mixture was cooled, filtered, and concentrated in vacuo to leave a colourless oil. Kugelrohr distillation afforded acetonide **11** (100 mg, 63%, 99% by GC-MS) as a mixture of isomers (6:1 by NMR) as a clear colourless oil. R_f (20% EtOAc/PE) = 0.67. B.p. 20 °C/0.07 Torr. IR (neat): $\tilde{\nu}_{max}$ = 2988 [w (CH_2)], 2939 [w (CH_2)], 1642 [w (C=C)], 1373 (w), 1220 (s), 1070 (s) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.75 (ddd, *J* = 17.1, *J* = 10.2, *J* = 6.9 Hz, 1 H, 6-H), 5.61 (ddd, $^2J_{H,F}$ = 55.7, $^2J_{H,F}$ = 54.6, *J* = 5.6 Hz, 1 H, 1-H), 5.00 (dddd, *J* = 17.1, ^2J = 1.9, ^4J = 1.6, ^4J = 1.2 Hz, 1 H, 7_a-H), 4.94 (ddt, *J* = 10.2, ^2J = 1.9, ^4J = 1.2 Hz, 1 H, 7_b-H), 4.18 (dddd, *J* = 8.0, *J* = 6.4, *J* = 5.8, $^3J_{H,F}$ = 2.3 Hz, 1 H, 3-H), 4.00 (ddt, $^3J_{H,F}$ = 10.5, $^3J_{H,F}$ = 9.0, *J* = 5.8 Hz, 1 H, 2-H), 2.30–2.17 (m, 1 H, 5_a-H), 2.15–2.03 (m, 1 H, 5_b-H), 1.72–1.62 (m, 1 H, 4-H), 1.41 (CH_3), 1.30 (CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.3 (C-6), 115.5 (C-7), 113.9 (dd, $^1J_{C,F}$ = 244.7, $^1J_{C,F}$ = 242.2 Hz, C-1), 110.6, 76.0 (dd, $^2J_{C,F}$ = 28.2, $^2J_{C,F}$ = 21.5 Hz, C-2), 75.7 (dd, $^3J_{C,F}$ = 4.5, $^3J_{C,F}$ = 0.6 Hz, C-3), 30.7 (d, $^5J_{C,F}$ = 1.3 Hz, C-5), 27.8 (d, $^4J_{C,F}$ = 3.0 Hz, C-4), 27.6, 25.3 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –125.1 (ddd, $^2J_{F,F}$ = 297.2, $^2J_{F,H}$ = 54.6, $^3J_{F,H}$ = 9.0 Hz, 1 F), –127.3 (dddd, $^2J_{F,F}$ = 297.2, $^2J_{F,H}$ = 55.7, $^3J_{F,H}$ = 10.5, $^4J_{F,H}$ = 2.3 Hz, 1 F) ppm; distinct signals can also be observed for the acetonide of the minor diastereoisomer **10**. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.5 (C-6), 115.2 (C-7), 114.8 (dd, $^1J_{C,F}$ = 244.0 Hz, $^1J_{C,F}$ = 243.2 Hz, C-1), 110.6, 79.3 (dd, $^2J_{C,F}$ = 27.0 Hz, $^2J_{C,F}$ = 24.9 Hz, C-2), 77.2 (C-3), 32.8, 29.8, 27.3, 26.4 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –124.0 (ddd, $^2J_{F,F}$ = 296.0 Hz, $^2J_{F,H}$ = 55.4 Hz, $^3J_{F,H}$ = 9.1 Hz, 1 F), –128.8 (ddd, $^2J_{F,F}$ = 296.0 Hz, $^2J_{F,H}$ = 55.5 Hz, $^3J_{F,H}$ = 9.9 Hz, 1 F) ppm. HRMS (EI): calcd. for $C_{10}H_{16}O_2F_2$ [M$^+$] 206.11184; found 206.11187. MS (EI): *m*/*z* (%) = 206 (1) [M$^+$], 191 (100), 164 (11), 151 (16), 131 (25), 111 (66), 91 (29), 85 (26), 67 (25), 59 (40). t_R (GC) = 9.17 min (major).

Racemic Methyl 6,6-Difluoroamicetosides (12a and 12b), and Racemic Methyl 6,6-Difluororhodinoside (13): Trimethylchlorosilane (0.08 mmol, 10 μL) was added to a stirred solution of diol **9** and **10** (0.44 mmol, 73 mg) in methanol (5 mL). The solution was cooled to –78 °C, and a stream of O_3 (0.2 L/min) was carefully bubbled through the solution until it became blue (30 min). The solution was purged with a stream of O_2 until the blue colour was discharged, then dimethyl sulfide (5.4 mmol, 0.4 mL) was added. The mixture was stirred at room temperature overnight (18 h), then concentrated in vacuo to leave a colourless oil, which was purified by Biotage column chromatography (gradient 35% → 50% EtOAc/PE) to afford an inseparable mixture of methyl furanosides **12a**, **12b** and **13** (50 mg, 63%, 99% by GC-MS, 2.9:2.5:1 by NMR) as a clear oil. R_f (50% EtOAc/PE) = 0.66. IR (neat): $\tilde{\nu}_{max}$ = 3409 [br. (OH)], 2959 [w (CH_2)], 1444 (w), 1207 (w), 1150 (w), 1031 [s (C–O)] cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): the following signals are distinct for **12a**: δ = 5.78 (td, $^2J_{H,F}$ = 55.2 Hz, *J* = 3.6 Hz, 1 H, 6-H), 5.05 (dd, *J* = 3.6 Hz, *J* = 1.4 Hz, 1 H, 1-H), 4.18 (ddd, *J* = 13.1 Hz, *J* = 5.5 Hz, 1.8, 1 H, 4-H), 3.84 (dddd, $^3J_{H,F}$ = 16.2 Hz, $^3J_{H,F}$ = 7.7 Hz, *J* = 5.5 Hz, *J* = 3.6 Hz, 1 H, 5-H), 3.33 (s, 3 H, OCH_3), 2.96 (s, 1 H, OH) ppm; for **12b**: δ = 5.83 (td, $^2J_{H,F}$ = 55.1 Hz, *J* = 3.3 Hz, 1 H, 6-H), 4.99 (dd, *J* = 4.2 Hz, *J* = 0.9 Hz, 1 H, 1-H), 4.38 (td, *J* = 7.0 Hz, *J* = 3.8 Hz, 1 H, 4-H), 3.93 (ddt, $^3J_{H,F}$ = 12.7 Hz, $^3J_{H,F}$ = 11.7 Hz, *J* = 3.8 Hz, 1 H, 5-H), 3.38 (s, 3 H, OCH_3), 2.88 (s, 1 H, OH); for **13**: δ = 5.77 (td, $^2J_{H,F}$ = 56.0 Hz, *J* = 4.8 Hz, 1 H, 6-H), 5.10 (dd, *J* = 4.2 Hz, *J* = 1.4 Hz, 1 H, 1-H), 4.29 (td, *J* = 7.0 Hz, *J* = 2.8 Hz, 1 H, 4-H), 3.66 (tdd, $^3J_{H,F}$ = 9.8 Hz, *J* = 5.4 Hz, *J* = 2.8 Hz, 1 H, 5-H), 3.48 (s, 1 H, OH), 3.34 (s, 3 H, OCH_3) ppm; common to all three furanosides **12a**, **12b** and **13**: δ = 2.19–1.81 (m, 12 H, 2-H, 3-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): the following signals are distinct for **12a** and **12b**: δ = 115.3 (t, $^1J_{C,F}$ = 242.4 Hz, C-6), 115.0 (dd, $^1J_{C,F}$ = 243.2 Hz, $^1J_{C,F}$ = 241.6 Hz, C-6), 105.4 [C-1 (**12b**)], 105.2 [C-1 (**12a**)], 78.8 (t, $^3J_{C,F}$ = 4.0 Hz, C-4), 76.1 (t, $^3J_{C,F}$ = 4.1 Hz, C-4), 72.6 (t, $^2J_{C,F}$ = 22.4 Hz, C-5), 72.1 (t, $^2J_{C,F}$ = 22.0 Hz, C-5), 32.8 [OCH_3 (**12b**)], 31.9 [OCH_3 (**12a**)], 32.8 (C-2), 31.9 (C-2), 24.3 (C-3), 23.0 (C-3) ppm; for **13**: δ = 115.1 (t, $^1J_{C,F}$ = 256.9 Hz, C-6), 105.7 (C-1), 74.8 (t, $^3J_{C,F}$ = 3.8 Hz, C-4), 72.3 (t, $^2J_{C,F}$ = 21.4 Hz, C-5), 32.1 (OCH_3), 32.1 (C-2), 25.5 (C-3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): for **12a**: δ = –129.7 (d, $^2J_{F,F}$ = 290.3 Hz, $^2J_{F,H}$ = 55.2 Hz, $^3J_{F,H}$ = 7.7 Hz, 1 F), –133.0 (d, $^2J_{F,F}$ = 290.3 Hz, $^2J_{F,H}$ = 55.2 Hz, $^3J_{F,H}$ = 16.2 Hz, 1 F); for **12b**: δ = –130.0 (d, $^2J_{F,F}$ = 291.3 Hz, $^2J_{F,H}$ = 55.1 Hz, $^3J_{F,H}$ = 11.7 Hz, 1 F), –130.4 (d, $^2J_{F,F}$ = 291.3 Hz, $^2J_{F,H}$ = 55.1 Hz, $^3J_{F,H}$ = 12.7 Hz, 1 F) ppm; for **13**: δ = –128.60 (d, $^2J_{F,H}$ = 56.0 Hz, 1 F), –128.63 (d, $^2J_{F,H}$ = 56.0 Hz, 1 F). HRMS (EI): calcd. for $C_7H_{11}O_3F_2$ [M$^+$ – H] 181.06763; found 181.06765. MS (EI): *m*/*z* (%) = 182 (1) [M$^+$], 150 (14), 133 (1), 104 (10), 101 (68), 85 (6), 69 (100). t_R (GC) = 8.96 min (**12a**), 9.06 min (**12b**), 9.31 min (**13**) (assigned by integrating the GC curve).

(1*S,3*S**,4*S**,7*S**,9*S**,10*S**)-3,9-Bis(difluoromethyl)-2,8,13,14-tetraoxatricyclo[8.2.1.14,7]tetradecane (14):** Chlorotrimethylsilane (0.08 mmol, 10 μL) was added to a stirred solution of diols **9** and **10** (0.30 mmol, 0.05 g) in methanol (5 mL). The solution was cooled to –78 °C, and a stream of O_3 (0.2 L/min) was carefully bubbled through the solution until it became blue (30 min). The solution was purged with a stream of O_2 until the blue colour was discharged, then dimethyl sulfide (5.4 mmol, 0.4 mL) was added. The mixture was stirred at room temperature overnight (18 h), then concentrated in vacuo to leave a colourless oil, which was taken up in $CDCl_3$ (0.35 mL). After 1 h, the solution was concentrated in vacuo to leave a colourless oil, which was purified by Biotage column chromatography (gradient 20% → 50% EtOAc/PE) to afford tricycle **14** (10 mg, 22%, 99% by GC-MS) as clear colourless needles. M.p. 105–109 °C. R_f (20% EtOAc/PE) = 0.46. $C_{12}H_{16}O_4F_4$ (300.10): calcd. C 48.0, H 5.4; found C 47.9, H 5.2. IR (neat): $\tilde{\nu}_{max}$ = 2967 [w (CH_2)], 2925 [w (CH_2)], 1317 (w), 1196 (w), 1092 [s (C–O)], 1046 [s (C–O)] cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.52 (td, $^2J_{H,F}$ = 55.2, *J* = 4.8 Hz, 2 H, 15-H, 16-H), 5.09 (d, *J* = 4.2 Hz, 2 H, 1-H, 7-H), 4.26 (t, *J* = 7.9 Hz, 2 H, 4-H, 10-H), 4.07–3.96 (m, 2 H, 3-H, 9-H), 2.34–2.16 (m, 2 H, 5_a-H, 11_a-H), 2.11–1.97 (m, 2 H, 6_a-H, 12_a-H), 1.87–1.66 (m, 4 H, 6_b-H, 12_b-H, 5_b-H, 11_b-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 115.1 (t, $^1J_{C,F}$ = 245.3 Hz, C-15, C-16), 103.5 (C-1, C-7), 78.0 (t, $^3J_{C,F}$ = 4.0 Hz, C-4, C-10), 75.1 (d, $^2J_{C,F}$ = 21.3 Hz, C-3, C-9), 33.6 (C-6, C-12), 21.7 (C-5, C-11) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –126.3 (dd, $^2J_{F,H}$ = 55.2 Hz, $^3J_{F,H}$ = 6.6 Hz, 2 F), –126.3 (dd, $^2J_{F,H}$ = 55.2 Hz, $^3J_{F,H}$ = 7.4 Hz, 2 F). HRMS (EI): calcd. for $C_{12}H_{16}O_4F_4$ [M$^+$] 300.09847; found 300.09841. MS (EI): *m*/*z* (%) = 300 (1) [M$^+$], 239 (11), 219 (16), 192 (28), 176 (56), 150 (29), 138 (32), 133 (33), 104 (18), 99 (16), 85 (55), 69 (100). t_R (GC) = 15.87 min. The relative stereo-

chemistry and identity of this product were confirmed by XRD analysis; crystal data: empirical formula $C_{12}H_{16}O_4F_4$, M = 300.25, crystal size 0.25 × 0.17 × 0.15 mm, monoclinic, space group $C2/c$, unit cell dimensions a = 17.5445(16), b = 9.0382(8), c = 8.2241(8) Å, β = 102.802(2)°, V = 1271.7(2) Å^3, Z = 4, $D_{calcd.}$ = 1.568 Mg m^{-3}, $F(000)$ = 624, μ(Mo-K_α) = 0.152 mm^{-1}, T = 150(2) K, 4503 total reflections measured, 1126 independent (R_{int} = 0.0368), which were used in all calculations. Final R indices [for reflections with $I > 2\sigma(I)$] were $R1$ = 0.0505, $\omega R2$ = 0.1428; R indices (all data) were $R1$ = 0.0536, $\omega R2$ = 0.1454.

3-Benzyloxy-1,1-difluoro-2-[(2′-methoxyethoxy)methoxy]hepta-1,6-diene (15): A mixture of alcohol **7** (5.0 mmol, 1.26 g), benzyl bromide (7.3 mmol, 0.88 mL), sodium hydroxide (37 mmol, 2.96 mL of a 50% aqueous solution), and tetrabutylammonium hydrogen sulfate (0.26 mmol, 90 mg) was stirred at 0 °C for 30 min. The mixture was warmed to room temperature and stirred overnight. Saturated aqueous ammonium chloride solution (10 mL) was added, and the mixture was extracted with diethyl ether (3 × 20 mL). The combined organic extracts were washed with water (10 mL), dried ($MgSO_4$) and concentrated in vacuo to give a clear oil, which was purified by Biotage column chromatography (gradient 0% → 20% EtOAc/PE) to afford benzyl ether **15** (1.19 g, 69%, 99% by GC-MS) as a clear colourless oil. R_f (20% EtOAc/PE) = 0.59. IR (neat): $\tilde{\nu}_{max}$ = 2881 [w (CH_2)], 1748 (s), 1641 [w (C=C)], 1454 (w), 1228 (s), 1091 [s (C–O)], 1069 [s (C–O)] cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.24 (m, 5 H, Ph), 5.76 (ddt, J = 16.9, J = 10.2, J = 6.6 Hz, 1 H, 6-H), 5.08 (^2J = 6.1 Hz, 1 H, OCH_aH$_b$O), 4.96 (^2J = 6.1 Hz, 1 H, OCH$_a$$H_b$O), 5.02–4.92 (m, 2 H, 7-H), 4.64 (^2J = 11.7 Hz, 1 H, CH_aH$_b$Ph), 4.33 (^2J = 11.7 Hz, 1 H, CH$_a$$H_b$Ph), 4.06 (dddd, J = 10.0, $^4J_{H,F}$ = 3.7, J = 3.1, $^4J_{H,F}$ = 2.1 Hz, 1 H, 3-H), 3.90 (ddd, ^2J = 10.9, J = 5.3, J = 3.7 Hz, 1 H, CH_aH$_b$OMe), 3.78 (ddd, ^2J = 10.9, J = 5.3, J = 3.7 Hz, 1 H, CH$_a$$H_b$OMe), 3.56–3.52 (m, 2 H, OCH_2CH$_2$OMe), 3.37 (s, 3 H, OCH$_3$), 2.19–2.01 (m, 2 H, 5-H), 1.97–1.67 (m, 2 H, 4-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.1 (dd, $^1J_{C,F}$ = 294.2, $^1J_{C,F}$ = 284.8 Hz, C-1), 137.9, 137.7 (C-6), 128.4, 127.9, 127.7, 115.1 (C-7), 112.4 (dd, $^2J_{C,F}$ = 36.5, $^2J_{C,F}$ = 9.9 Hz, C-2), 97.1 (OCH$_2$O), 73.9 (t, $^3J_{C,F}$ = 3.2 Hz, C-3), 71.6 (OCH$_2$$CH_2$OMe), 70.4 (CH$_2$Ph), 68.3 (O$CH_2CH_2$OMe), 59.0 (OCH$_3$), 31.2 (t, $^4J_{C,F}$ = 2.0 Hz, C-4), 29.6 (C-5) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –97.5 (d, $^2J_{F,F}$ = 63.1, $^4J_{F,H}$ = 2.1 Hz, 1 F), –109.2 (d, $^2J_{F,F}$ = 63.1, $^4J_{F,H}$ = 3.7 Hz, 1 F) ppm. MS (EI): m/z (%) = 112 (2), 105 (3), 91 (85), 59 (100). t_R (GC) = 19.83 min. A satisfactory ion peak for HRMS (CI, EI, ES) could not be obtained for this compound despite repeated attempts with a number of ionisation techniques.

(2*S,3*S**)-Benzyloxy-1,1-difluorohept-6-en-2-ol (16) and (2*S**,3*R**)-Benzyloxy-1,1-difluorohept-6-en-2-ol (17):** Chlorotrimethylsilane (4.73 mmol, 0.6 mL) was added to a solution of **15** (4.7 mmol, 1.60 g) in MeOH (5 mL). The mixture was stirred overnight (18 h), then concentrated in vacuo and the residue taken up in Et_2O (5 mL); sodium borohydride (9.2 mmol, 0.35 g) was added in portions, and the mixture was stirred overnight. The mixture was diluted with water (5 mL), neutralised with concentrated HCl, and extracted with EtOAc (3 × 15 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to leave a colourless oil, which was purified by Biotage column chromatography (gradient 20% → 50% EtOAc/PE) to afford an inseparable mixture of alcohols **16** and **17** (0.732 g, 61%, 99% by GC-MS, 1.2:1 by GC-MS) as a mixture of diastereoisomers as a clear colourless oil. R_f (10% EtOAc/PE) = 0.25. IR (neat): $\tilde{\nu}_{max}$ = 3434 [br. (OH)], 2934 [w (CH_2)], 1641 [w (C=C)], 1455 (w), 1056 [s (C–O)]. ^{1}H NMR (300 MHz, $CDCl_3$): signals for both diastereoisomers, unless specified: δ = 7.42–7.29 (m, 5 H, Ph), 5.90–5.77 (m, 1 H, 6-H), 5.76 (ddd, $^2J_{H,F}$ = 56.5, $^2J_{H,F}$ = 55.8, J = 5.2 Hz, 1 H, 1-H major), 5.11–4.98 (m, 2 H, 7-H), 4.66 (d, ^2J = 11.2 Hz, 1 H, CH_aH$_b$Ph major), 4.52 (d, ^2J = 11.2 Hz, 1 H, CH$_a$$H_b$Ph major), 3.74–3.61 (m, 2 H, 2-H, 3-H), 2.76 (d, J = 8.5 Hz, 1 H, OH major), 2.33–1.67 (m, 4 H, 4-H, 5-H), 5.90 (ddd, $^2J_{H,F}$ = 56.2, $^2J_{H,F}$ = 55.0, J = 3.7 Hz, 1 H, 1-H minor), 5.90–5.77 (m, 1 H, 6-H), 5.11–4.98 (m, 2 H, 7-H), 4.61 (d, ^2J = 11.3 Hz, 1 H, CH_aH$_b$Ph), 4.55 (d, ^2J = 11.3 Hz, 1 H, CH$_a$$H_b$Ph), 3.86 (dddd, $^3J_{H,F}$ = 17.0, $^3J_{H,F}$ = 6.2, J = 6.0, J = 3.7 Hz, 1 H, 2-H), 3.74–3.61 (m, 1 H, 3-H), 2.56 (d, J = 5.2 Hz, 1 H, OH), 2.33–1.67 (m, 4 H, 4-H, 5-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): two distinct series of signals observed, but not assigned: δ = 138.1 (C-6), 137.7, 137.6 (C-6), 128.6, 128.1, 128.1, 128.0, 127.9, 115.5 (t, $^1J_{C,F}$ = 244.1 Hz, C-1), 115.5 (C-7), 115.2 (C-7), 115.1 (dd, $^1J_{C,F}$ = 242.9, $^1J_{C,F}$ = 241.1 Hz, C-1), 77.4 (dd, $^3J_{C,F}$ = 3.9, $^3J_{C,F}$ = 3.6 Hz, C-3), 75.7 (dd, $^3J_{C,F}$ = 4.8, $^3J_{C,F}$ = 2.7 Hz, C-3), 72.5 (CH$_2$Ph), 72.4 (CH$_2$Ph), 72.0 (dd, $^2J_{C,F}$ = 24.9, $^2J_{C,F}$ = 23.2 Hz, C-2), 71.7 (dd, $^2J_{C,F}$ = 23.0, $^2J_{C,F}$ = 20.6 Hz, C-2), 29.6, 29.4, 29.0, 28.9 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): major diastereoisomer: δ = –128.5 (dddd, $^2J_{F,F}$ = 290.0 Hz, $^2J_{F,H}$ = 55.8 Hz, $^3J_{F,H}$ = 9.4 Hz, $^4J_{F,H}$ = 1.5 Hz, 1 F, CHF_aF$_b$), –129.4 (ddd, $^2J_{F,F}$ = 290.0 Hz, $^2J_{F,H}$ = 56.5 Hz, $^3J_{F,H}$ = 10.9 Hz, 1 F, CHF$_a$$F_b$) ppm; minor diastereoisomer: δ = –129.1 (ddd, $^2J_{F,F}$ = 289.8 Hz, $^2J_{F,H}$ = 55.0 Hz, $^3J_{F,H}$ = 6.2 Hz, 1 F, CHF_aF$_b$), –132.7 (ddd, $^2J_{F,F}$ = 289.8 Hz, $^2J_{F,H}$ = 56.2 Hz, $^3J_{F,H}$ = 17.0 Hz, 1 F, CHF$_a$$F_b$) ppm. HRMS (EI): calcd. for $C_{14}H_{18}F_2O_2$ [M$^+$] 256.12749; found 256.12753. MS (EI): m/z (%) = 256 (1) [M$^+$], 175 (12), 157 (8), 107 (8), 91 (100). t_R (GC) = 16.51 min (major), 16.61 min (minor).

3-Benzyloxy-1,1-difluoro-5-(1,2,4-trioxolan-3-yl)pentan-2-ol (18): Dry silica gel (1.41 g) was added to a solution of alcohols **16** and **17** (0.60 mmol, 155 mg) in dry dichloromethane (5 mL). The solvent was evaporated in vacuo, and the silica gel mixture was dried under vacuum at room temperature for 1 h. The mixture was cooled to –78 °C, and a stream of dry O_3 was carefully passed upwards through the silica gel supported by a frit in a U-shaped tube. After 1 h, the mixture was purged with O_2 and N_2, eluted from the silica with methanol (50 mL), quenched with dimethyl sulfide (0.5 mL) and stirred for 6 h. After concentration, purification by silica gel column chromatography (gradient 0 → 20% EtOAc/PE) afforded ozonide **18** (56 mg, 30%, 80% by GC-MS) as a complex mixture of diastereoisomers as a colourless oil. R_f (20% EtOAc/PE) = 0.36. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.28 (m, 10 H, Ph), 5.90 (ddd, $^2J_{H,F}$ = 56.0, $^2J_{H,F}$ = 54.9, J = 3.4 Hz, 1 H, 1-H), 5.76 (ddd, $^2J_{H,F}$ = 56.1, $^2J_{H,F}$ = 56.0, J = 4.9 Hz, 1 H, 1-H), 5.20 (s, 1 H, 6-H), 5.19 (s 1 H, 6-H), 5.18 (s, 1 H, OCH$_2$O), 5.17 (s, 1 H, OCH$_2$O), 5.07 (s, 1 H, OCH$_2$O), 5.05 (s, 1 H, OCH$_2$O), 4.68–4.42 (m, 4 H, CH$_2$Ph), 3.91–3.58 (m, 4 H, 2-H, 3-H), 2.55 (br. s, 1 H,OH), 2.22 (br. s, 1 H, OH), 1.98–1.55 (m, 8 H, 4-H, 5-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.4, 137.3, 128.61, 128.59, 128.21, 128.11, 128.08, 127.97, 127.95, 127.80, 115.3 (t, $^1J_{C,F}$ = 244.2 Hz, C-1), 114.9 (dd, $^1J_{C,F}$ = 243.7, $^1J_{C,F}$ = 240.5 Hz, C-1), 103.4, 103.2, 94.14, 94.11, 77.24, 76.96 (t, $^3J_{C,F}$ = 3.8 Hz, C-3), 75.4 (t, $^3J_{C,F}$ = 3.4 Hz, C-3), 72.7 (CH$_2$Ph), 72.3 (CH$_2$Ph), 72.2 (t, $^2J_{C,F}$ = 24.5 Hz, C-2), 71.5 (t, $^2J_{C,F}$ = 22.5 Hz, C-2), 27.0, 26.3, 24.8, 23.5 ppm. Signals of four distinct diastereoisomers are visible in the ^{19}F NMR spectrum: ^{19}F NMR (376 MHz, $CDCl_3$): first diastereoisomer: δ = –128.86 (dd, $^2J_{F,F}$ = 290.52, $^2J_{F,H}$ = 55.8, $^3J_{F,H}$ = 10.1 Hz, 1 F, CHF_aF$_b$), –129.35 (dd, $^2J_{F,F}$ = 290.52, $^2J_{F,H}$ = 56.2, $^3J_{F,H}$ = 14.8 Hz, 1 F, CHF$_a$$F_b$) ppm; second diastereoisomer: δ = –128.88 (dd, $^2J_{F,F}$ = 290.50 Hz, $^2J_{F,H}$ = 55.6 Hz, $^3J_{F,H}$ = 10.8 Hz, 1 F, CHF_aF$_b$), –129.32 (dd, $^2J_{F,F}$ = 290.50 Hz, $^2J_{F,H}$ = 56.1 Hz, $^3J_{F,H}$ = 17.3 Hz, 1 F, CHF$_a$$F_b$) ppm; third diastereoisomer: δ = –129.86 (dd, $^2J_{F,F}$ = 289.46 Hz, $^2J_{F,H}$ = 54.9 Hz, $^3J_{F,H}$ = 4.8 Hz, 1 F, CHF_aF$_b$), –133.12 (dd, $^2J_{F,F}$ = 289.46 Hz, $^2J_{F,H}$ = 56.0 Hz, $^3J_{F,H}$

= 17.5 Hz, 1 F, CHF_aF_b) ppm; fourth diastereoisomer: δ = –129.72 (dd, $^2J_{F,F}$ = 289.45 Hz, $^2J_{F,H}$ = 55.0 Hz, $^3J_{F,H}$ = 5.8 Hz, 1 F, CHF_aF_b), –133.27 (dd, $^2J_{F,F}$ = 289.45 Hz, $^2J_{F,H}$ = 56.1 Hz, $^3J_{F,H}$ = 17.3 Hz, 1 F, CHF_aF_b). HRMS (EI): calcd. for $C_{14}H_{18}F_2O_5$ [M^+] 304.11223; found 304.11226. MS (EI): *m*/*z* (%) = 304 (2) [M^+], 240 (35), 191 (3), 151 (39), 105 (55), 85 (99), 51 (100).

Racemic α-Methyl 5-*O*-Benzyl-6,6-difluoroamicetoside (19) and Racemic α-Methyl 5-*O*-Benzyl-6,6-difluororhodinoside (20): Chlorotrimethylsilane (0.79 mmol, 100 μL) was added to a stirred solution of alcohols **16** and **17** (3.99 mmol, 1.02 g) in methanol (50 mL). The solution was cooled to –78 °C, and a stream of dry O_3 (0.2 L/min) was carefully bubbled through the solution until it became blue (30 min). The solution was purged with a stream of O_2 until it became colourless (5 min), then dimethyl sulfide (68 mmol, 5.0 mL) was added. The mixture was stirred at room temperature (12 h) overnight (18 h), then solid NaOH (0.2 g, 5 mmol) was added. After 1 h, the solution was neutralised with concentrated HCl (0.7 mL), diluted with Et_2O (50 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to leave a colourless oil containing a mixture of diastereoisomers (1:1), which was purified by Biotage column chromatography (gradient 5% → 10% EtOAc/PE) to afford (in order of elution): (i) α-Methyl rhodinoside **20** (396 mg, 37%, 99% by GC-MS) as a clear colourless oil. R_f (20% EtOAc/PE) = 0.59. IR (neat): $\tilde{\nu}_{max}$ = 2939 [w (CH_2)], 2902 [w (CH_2)], 1454 [w (CH_3)], 1337 (w), 1219 [w (C–O–C)], 1131 [s (C–O)], 1076 [s (C–O)] cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.27 (m, 5 H, Ph), 5.93 (ddd, $^2J_{H,F}$ = 58.1, $^2J_{H,F}$ = 55.0, *J* = 6.8 Hz, 1 H, 6-H), 4.80 (d, *J* = 3.2 Hz, 1 H, 1-H), 4.63 (d, ^2J = 11.7 Hz, 1 H, CH_aH_bPh), 4.44 (d, ^2J = 11.7 Hz, 1 H, CH_aH_bPh), 3.85 (dddd, $^3J_{H,F}$ = 11.4, *J* = 6.8, $^3J_{H,F}$ = 4.1, *J* = 1.8 Hz, 1 H, 5-H), 3.71 (br. s, 1 H, 4-H), 3.39 (s, 3 H, OCH_3), 2.01 (ddt, ^2J = 14.0, *J* = 14.0, *J* = 4.6 Hz, 1 H, 2_a-H), 1.98–1.91 (m, 1 H, 3_a-H), 1.84 (ddd, ^2J = 14.0, *J* = 14.0, *J* = 4.2, *J* = 2.5 Hz, 1 H, 3_b-H), 1.60–1.53 (m, 1 H, 2_b-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.9, 128.4, 127.8, 128.8, 114.9 (dd, $^1J_{C,F}$ = 243.3, $^1J_{C,F}$ = 237.9 Hz, C-6), 97.9 (C-1), 71.0 (CH_2Ph), 70.2 (dd, $^2J_{C,F}$ = 30.5, $^2J_{C,F}$ = 22.9 Hz, C-5), 69.8 (dd, $^3J_{C,F}$ = 6.9, $^3J_{C,F}$ = 2.0 Hz, C-4), 54.8 (OCH_3), 23.7 (C-2), 20.0 (C-3) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –130.5 (ddd, $^2J_{F,F}$ = 295.4, $^2J_{F,H}$ = 58.1, $^3J_{F,H}$ = 11.4 Hz, 1 F, CHF_aF_b), –131.4 (dddd, $^2J_{F,F}$ = 295.4, $^2J_{F,H}$ = 55.0, $^3J_{F,H}$ = 4.1, $^4J_{F,H}$ = 1.8 Hz, 1 F, CHF_aF_b) ppm. HRMS (EI): calcd. for $C_{14}H_{18}F_2O_3$ [M^+] 272.12240; found 272.12241. MS (EI): *m*/*z* (%) = 272 (1) [M^+], 240 (4), 191 (3), 160 (3), 134 (4), 125 (4), 107 (17), 101 (24), 91 (100). t_R (GC) = 17.81 min. (ii) α-Methyl amicetoside **19** (352 mg, 32%, 99% by GC-MS) as a clear colourless oil. R_f (20% EtOAc/PE) = 0.53. IR (neat): $\tilde{\nu}_{max}$ = 2939 [w (CH_2)], 1455 [s (CH_3)], 1372 (w), 1224 [s (C–O–C)], 1127 [s (C–O)], 1050 [s (C–O)] cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.26 (m, 5 H, Ph), 6.06 (dd, $^2J_{H,F}$ = 54.6, $^2J_{H,F}$ = 53.8 Hz, 1 H, 6-H), 4.76 (d, *J* = 3.0 Hz, 1 H, 1-H), 4.64 (d, ^2J = 11.5 Hz, 1 H, CH_aH_bPh), 4.46 (d, ^2J = 11.5 Hz, 1 H, CH_aH_bPh), 3.84 (ddd, $^3J_{H,F}$ = 20.7, *J* = 9.8, $^3J_{H,F}$ = 7.3 Hz, 1 H, 5-H), 3.53 (ddd, *J* = 10.1, *J* = 9.8, *J* = 4.5 Hz, 1 H, 4-H), 3.37 (s, 3 H, OCH_3), 2.10–2.03 (m, 1 H, 3_a-H), 1.88–1.64 (m, 3 H, 2-H, 3_b-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.8, 128.5, 127.9, 127.7, 114.0 (dd, $^1J_{C,F}$ = 243.5, $^1J_{C,F}$ = 242.5 Hz, C-6), 102.1 (C-1), 72.0 (dd, $^3J_{C,F}$ = 6.3, $^3J_{C,F}$ = 1.8 Hz, C-4), 70.6 (CH_2Ph), 70.0 (t, $^2J_{C,F}$ = 18.9 Hz, C-5), 54.7 (OCH_3), 28.3 (C-2), 23.7 (C-3) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –133.5 (dddd, $^2J_{F,F}$ = 283.2, $^2J_{F,H}$ = 53.8, $^3J_{F,H}$ = 7.3, $^4J_{F,H}$ = 1.7 Hz, 1 F, CHF_aF_b), –136.1 (ddd, $^2J_{F,F}$ = 283.2, $^2J_{F,H}$ = 54.6, $^3J_{F,H}$ = 20.7 Hz, 1 F, CHF_aF_b) ppm. HRMS (EI): calcd. for $C_{14}H_{18}F_2O_3$ [M^+] 272.12240; found 272.12236. MS (EI): *m*/*z* (%) = 272 (1) [M^+], 240 (4), 191 (3), 160 (5), 134 (4), 125 (3), 107 (16), 101 (17), 91 (100). t_R (GC) = 17.34 min. (iii) Mixed fraction containing a mixture of diastereoisomers (132 mg, 12%).

Racemic α-5-*O*-Benzyl-6,6-difluoroamicetose (21a) and Racemic β-5-*O*-Benzyl-6,6-difluoroamicetose (21b): Concentrated hydrochloric acid (20 μL) was added to a solution of amicetoside **19** (0.11 mmol, 30 mg) in THF (4 mL) containing water (250 μL). The solution was stirred and heated (microwaves, 50 W) to 100 °C for 2 h. The tube was cooled, opened, and the contents were diluted with Et_2O (10 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to leave a colourless oil containing a mixture of anomers, which was purified by Biotage column chromatography (gradient 20% → 50% EtOAc/PE) to afford α- and β-amicetoses **21a** and **21b** (20 mg, 70%, 95% by GC-MS) as an inseparable 2.6:1 mixture (by NMR), from which anomer **21a** crystallized as white needles. M.p. 62–65 °C. R_f (35% EtOAc/PE) = 0.57. $C_{13}H_{16}O_3F_2$ (258.11): calcd. C 60.5, H 6.2; found C 60.3, H 6.3. IR (neat): $\tilde{\nu}_{max}$ = 3410 [br. (OH)], 2954 [w (CH_2)], 2873 [w (CH_2)], 1400 (w), 1353 (w), 1221 (w), 1150 [s (C–O)], 1079 [s (C–O)], 1045 [s (C–O)] cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): α-anomer **21a**: δ = 7.38–7.28 (m, 5 H, Ph), 6.06 (ddd, $^2J_{H,F}$ = 54.5, $^2J_{H,F}$ = 54.0, *J* = 1.1 Hz, 1 H, 6-H), 5.35 (d, *J* = 2.8 Hz, 1 H, 1-H), 4.66 (d, ^2J = 11.4 Hz, 1 H, CH_aH_bPh), 4.48 (d, ^2J = 11.4 Hz, 1 H, CH_aH_bPh), 4.11 (dddd, $^3J_{F,H}$ = 20.5, $^3J_{H,F}$ = 7.4, *J* = 9.9, *J* = 1.8 Hz, 1 H, 5_a-H), 3.75–3.47 (m, 1 H, 4-H), 2.71 (br. s, 1 H, OH), 2.30–1.44 (m, 4 H, 2-H, 3-H) ppm; β-anomer **21b**: ^1H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.28 (m, 5 H, Ph), 6.04 (ddd, $^2J_{H,F}$ = 54.5, $^2J_{H,F}$ = 54.4, *J* = 2.0 Hz, 1 H, 6-H), 4.92 (d, *J* = 7.3 Hz, 1 H, 1-H), 4.62 (d, ^2J = 11.4 Hz, 1 H, CH_aH_bPh), 4.50 (d, ^2J = 11.4 Hz, 1 H, CH_aH_bPh), 3.75–3.47 (m, 2 H, 4-H, 5-H), 3.08 (br. s, 1 H, OH), 2.30–1.44 (env, 4 H, 2-H, 3-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): signals for both anomers, unless stated otherwise: δ = 137.8, 137.6, 128.5, 128.5, 128.0, 127.9, 127.8, 127.7, 114.1 (dd, $^1J_{C,F}$ = 243.8, $^1J_{C,F}$ = 242.5 Hz, C-6), 95.8 [C-1 (**21b**)], 91.0 [C-1 (**21a**)], 72.2 (dd, $^3J_{C,F}$ = 6.1, $^3J_{C,F}$ = 1.93 Hz, C-4), 71.2 [CH_2Ph (**21b**)], 70.7 [CH_2Ph (**21a**)], 70.3 (t, $^2J_{C,F}$ = 18.8 Hz, C-5), 30.0 [C-2 (**21b**)], 28.3 [C-2 (**21a**)], 26.1 [C-3 (**21b**)], 22.9 [C-3 (**21a**)] ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –131.5 [dddd, $^2J_{F,F}$ = 286.3, $^2J_{F,H}$ = 54.5, $^3J_{F,H}$ = 7.7, $^4J_{F,H}$ = 1.5 Hz, 1 F, CHF_aF_b (**21b**)], –133.3 [dddd, $^2J_{F,F}$ = 283.1, $^2J_{F,H}$ = 54.0, $^3J_{F,H}$ = 7.4, $^4J_{F,H}$ = 1.8 Hz, 1 F, CHF_aF_b (**21a**)], –133.7 [ddd, $^2J_{F,F}$ = 286.3, $^2J_{F,H}$ = 54.4, $^3J_{F,H}$ = 17.4 Hz, 1 F, CHF_aF_b (**21b**)], –135.8 [ddd, $^2J_{F,F}$ = 283.1, $^2J_{F,H}$ = 54.5, $^3J_{F,H}$ = 20.5 Hz, 1 F, CHF_aF_b (**21a**)] ppm. HRMS (EI): calcd. for $C_{13}H_{16}F_2O_3$ [M^+] 258.10675; found 258.10671. MS (EI): *m*/*z* (%) = 258 (1) [M^+], 240 (1), 177 (3), 154 (1), 134 (4), 107 (27), 91 (100). t_R (GC) = 18.54 min. The stereochemistry and identity of the crystalline anomer **21a** were confirmed by XRD analysis. Crystal data: empirical formula $C_{13}H_{16}O_3F_2$, *M* = 258.26, crystal size 0.36 × 0.11 × 0.04 mm, monoclinic, space group $P2_1/n$, unit cell dimensions *a* = 20.750(3), *b* = 4.6956(8), *c* = 26.025(4) Å, β = 98.453(3)°, *V* = 2508.1(7) Å^3, *Z* = 8, $D_{calcd.}$ = 1.368 Mg m^{-3}, *F*(000) = 1088, μ(Mo-K_α) = 0.115 mm^{-1}, *T* = 150(2) K, 17038 total reflections measured, 4424 independent (R_{int} = 0.0885), which were used in all calculations. Final *R* indices [for reflections with $I > 2\sigma(I)$] were *R*1 = 0.0471, $\omega R2$ = 0.0880; *R* indices (all data) were *R*1 = 0.0850, $\omega R2$ = 0.0999.

Racemic α-5-*O*-Benzyl-6,6-difluororhodinose (22a) and Racemic β-5-*O*-Benzyl-6,6-difluororhodinose (22b): Concentrated hydrochloric acid (20 μL) was added to a solution of rhodinoside **20** (0.46 mmol, 126 mg) in THF (4 mL) containing water (250 μL). The solution was stirred and heated (microwaves, 50 W) to 100 °C for 2 h. The tube was cooled, opened, and the contents were diluted with Et_2O (10 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to leave a colourless oil containing a mixture of anomers, which was purified by Biotage column chromatography (gradient 20% → 50%

EtOAc/PE) to afford the rhodinose (78 mg, 65%, 99% by GC-MS) as a 2.5:1 (by NMR) mixture of inseparable α- and β-anomers **22a** and **22b** as a clear colourless oil. R_f (35% EtOAc/PE) = 0.51. IR (neat): $\tilde{\nu}_{max}$ = 3411 [s (OH)], 2954 [w (CH_2)], 2913 [w (CH_2)], 1150 (s), 1077 (s), 1046 (s), 1018 (s) cm^{-1}. α-anomer: ^1H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.28 (m, 5 H, Ph), 5.94 (ddd, $^2J_{H,F}$ = 58.2, $^2J_{H,F}$ = 54.8, J = 6.8 Hz, 1 H, 6-H), 5.37 (s, 1 H, 1-H), 4.63 (d, ^2J = 11.6 Hz, 1 H, CH_aH$_b$Ph), 4.44 (d, ^2J = 11.6 Hz, 1 H, CH$_a$$H_b$Ph), 4.12 (dddd, $^3J_{H,F}$ = 11.2, J = 6.4, $^3J_{H,F}$ = 4.2, J = 1.7 Hz, 1 H, 5-H), 3.81–3.09 (m, 2 H, 4-H, OH), 2.22–1.46 (m, 4 H, 2-H, 3-H) ppm. β-anomer: ^1H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.28 (m, 5 H, Ph), 5.98 (ddd, $^2J_{H,F}$ = 57.5, $^2J_{H,F}$ = 55.0, J = 6.6 Hz, 1 H, 6-H), 4.80 (dd, J = 9.3, J = 2.4 Hz, 1 H, 1-H), 4.61 (d, ^2J = 11.6 Hz, 1 H, CH_aH$_b$Ph), 4.44 (d, ^2J = 11.6 Hz, 1 H, CH$_a$$H_b$Ph), 3.81–3.09 (m, 3 H, 4-H, 5-H, OH), 2.22–1.46 (m, 4 H, 2-H, 3-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): both anomers: δ = 137.8, 137.7, 128.4, 127.9, 127.8, 114.9 (dd, $^1J_{C,F}$ = 243.1, $^1J_{C,F}$ = 238.2 Hz, C-6, α-anomer), 114.2 (dd, $^1J_{C,F}$ = 243.0, $^1J_{C,F}$ = 239.1 Hz, C-6, β-anomer), 96.3 (C-1, β-anomer), 91.4 (C-1, α-anomer), 77.3 (dd, $^2J_{C,F}$ = 28.8, $^2J_{C,F}$ = 24.2 Hz, C-5, β-anomer), 71.0 (CH_2Ph, β-anomer), 70.9 (CH_2Ph, α-anomer), 70.2 (dd, $^2J_{C,F}$ = 30.7, $^2J_{C,F}$ = 22.6 Hz, C-5, α-anomer), 69.7 (dd, $^3J_{C,F}$ = 6.9 Hz, 1.9, C-4, α-anomer), 68.8 (dd, $^3J_{C,F}$ = 6.1, $^3J_{C,F}$ = 2.5 Hz, C-4, β-anomer), 27.0 (C-2, β-anomer), 24.3 (C-3, β-anomer), 23.9 (C-3, α-anomer), 19.2 (C-2, α-anomer) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –130.2 (ddd, $^2J_{F,F}$ = 296.3, $^2J_{F,H}$ = 57.5, $^3J_{F,H}$ = 9.8 Hz, 1 F, CHF_aF$_b$, α-anomer), –130.5 (ddd, $^2J_{F,F}$ = 296.2, $^2J_{F,H}$ = 58.2, $^3J_{F,H}$ = 11.2 Hz, 1 F, CHF_aF$_b$, β-anomer), –130.8 (dddd, $^2J_{F,F}$ = 296.3, $^2J_{F,H}$ = 55.0, $^3J_{F,H}$ = 4.9, $^4J_{F,H}$ = 1.8 Hz, 1 F, CHF$_a$$F_b$, α-anomer), –131.5 (dddd, $^2J_{F,F}$ = 296.2, $^2J_{F,H}$ = 54.8, $^3J_{F,H}$ = 4.2, $^4J_{F,H}$ = 2.0 Hz, CHF$_a$$F_b$, β-anomer) ppm. HRMS (EI): calcd. for $C_{13}H_{16}F_2O_3$ [M^+] 258.10675; found 258.10676. MS (EI): *m/z* (%) = 258 (1) [M^+], 240 (1), 177 (3), 160 (3), 134 (3), 107 (23), 91 (100). t_R (GC) = 18.3 min.

α-Methyl 6,6-Difluororhodinoside (23): A solution of **20** (0.38 mmol, 104 mg) in ethanol containing 10% palladium on carbon (40 mg) was stirred under hydrogen for 48 h. The mixture was filtered through Celite, and the filter bed was washed with EtOH (3 × 2 mL); the combined filtrate and washings were concentrated in vacuo to afford methyl rhodinoside **23** (35 mg, 50%) as a clear colourless oil. R_f (20% EtOAc/PE) = 0.31. IR (neat): $\tilde{\nu}_{max}$ = 3366 (OH), 2953 (CH_2), 1460 (w), 1317 (w), 1117 (w), 1050 (s), 978 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.86 (ddd, $^2J_{H,F}$ = 56.6, $^2J_{H,F}$ = 55.4, J = 6.3 Hz, 1 H, 6-H), 4.81 (s, 1 H, 1-H), 4.00 (s, 1 H, 4-H), 3.91–3.82 (m, 1 H, 5-H), 3.39 (s, 3 H, OCH_3), 2.11–1.53 (m, 5 H, 2-H, 3-H, OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 114.9 (dd, $^1J_{C,F}$ = 241.7, $^1J_{C,F}$ = 240.1 Hz, C-6), 98.0 (C-1), 69.9 (dd, $^2J_{C,F}$ = 27.6, $^2J_{C,F}$ = 24.6 Hz, C-5), 63.1 (dd, $^3J_{C,F}$ = 5.0, $^3J_{C,F}$ = 3.6 Hz, C-4), 54.9 (OCH_3), 25.0 (C-3), 23.3 (C-2) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –130.5 (ddd, $^2J_{F,F}$ = 296.6, $^2J_{F,H}$ = 56.6, $^3J_{F,H}$ = 9.9 Hz, 1 F), –131.0 (ddd, $^2J_{F,F}$ = 296.6, $^2J_{F,H}$ = 55.4, $^3J_{F,H}$ = 7.4 Hz, 1 F) ppm. HRMS (EI): calcd. for $C_7H_{12}F_2O_3$ [M^+] 182.07545; found 182.07542. MS (EI): *m/z* (%) = 182 (2) [M^+], 151 (30), 133 (16), 125 (43), 101 (51), 88 (100).

(1*E*)-3-Benzyloxy-1-fluoro-2-[(2′-methoxyethoxy)methoxy]hepta-1,6-diene (24) and (1*Z*)-3-Benzyloxy-1-fluoro-2-[(2′-methoxyethoxy)-methoxy]hepta-1,6-diene (25): A solution of difluorobenzyl ether **7** (5.85 mmol, 2.0 g) and sodium bis(2-methoxyethoxy)aluminium hydride (Red-Al, 22.7 mmol, 6.5 mL of a 3.5 M solution in toluene) in dry pentane (20 mL) was heated to reflux over 3 h. The reaction mixture was cooled and poured carefully onto ice (5 g). The white suspension was neutralised (to pH paper) with concentrated hydrochloric acid. The mixture was extracted with EtOAc (3 × 20 mL), then the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to leave a colourless oil as a mixture of diastereoisomers (8:1 by NMR), which was purified by Biotage column chromatography (gradient 20% → 50% EtOAc/PE) to afford (*E*)-fluoroallylic alcohol **24** (1.38 g, 73%, 99% by GC-MS) as a clear colourless oil. R_f (35% EtOAc/PE) = 0.78. IR (neat): $\tilde{\nu}_{max}$ = 2931 [w (CH_2)], 2879 (CH_2), 1641 [w (C=C)], 1454 (w), 1097 [s (C–O)], 1069 [s (C–O)] cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.24 (m, 5 H, Ph), 7.10 (d, $^2J_{H,F}$ = 80.8 Hz, 1 H, 1-H), 5.79 (ddt, J = 16.9, J = 10.2, J = 6.6 Hz, 1 H, 6-H), 4.99 (ddd, J = 16.9, J = 3.4, J = 1.6 Hz, 1 H, 7$_a$-H), 4.97–4.92 (m, 3 H, OCH_2O, 7$_b$-H), 4.58 (d, ^2J = 11.8 Hz, 1 H, CH_aH$_b$Ph), 4.41 (td, J = 7.4, $^4J_{H,F}$ = 3.5 Hz, 1 H, 3-H), 4.38 (d, ^2J = 11.8 Hz, 1 H, CH$_a$$H_b$Ph), 3.76 (dt, ^2J = 11.0, J = 4.7 Hz, 1 H, OCH_aH$_b$CH$_2$OMe), 3.72 (dt, ^2J = 11.0, J = 4.7 Hz, 1 H, OCH$_a$$H_bCH_2$OMe), 3.55 (t, J = 4.7 Hz, 2 H, CH_2OMe), 3.39 (s, 3 H, OMe), 2.21–2.01 (m, 2 H, 5-H), 1.95–1.86 (m, 1 H, 4$_a$-H), 1.71 (ddt, ^2J = 13.3, J = 9.1, J = 6.5 Hz, 1 H, 4$_b$-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.7 (d, $^2J_{C,F}$ = 25.1 Hz, C-2), 139.6 (d, $^1J_{C,F}$ = 20.6 Hz, C-1), 138.3, 137.9 (C-6), 128.3, 128.0, 127.6, 115.0 (C-7), 94.8 (OCH_2O), 71.8 (d, $^3J_{C,F}$ = 1.3 Hz, C-3), 71.5 (OCH_2CH_2OMe), 70.6 (CH_2Ph), 67.5 (OCH_2-CH_2OMe), 59.0 (OCH_3), 31.1 (d, $^4J_{C,F}$ = 2.4 Hz, C-4), 29.7 (C-5) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –171.2 (dd, $^2J_{F,H}$ = 80.8, $^4J_{F,H}$ = 3.5 Hz) ppm. MS (EI): *m/z* (%) = 175 (1), 166 (1), 157 (2), 129 (1), 122 (3), 112 (11), 91 (100), 59 (98). t_R (GC) = 20.8 min. Satisfactory HRMS (CI, EI, ES) could not be obtained for this compound. (*Z*)-fluoroallylic alcohol **25** could not be separated fully from **24**. R_f (35% EtOAc/PE) = 0.81. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –155.8 (d, $^2J_{F,H}$ = 77.5 Hz, 1 F) ppm. MS (EI): *m/z* (%) = 175 (1), 166 (1), 157 (2), 129 (1), 122 (3), 112 (11), 91 (100), 59 (98); t_R (GC) 20.9 min. The (*E*)/(*Z*) configuration was assigned on the basis of a NOESY cross peak between signals at δ = 7.10 (=CHF) and 4.97–4.92 (OCH_2O) ppm for **24**. A mixture of **24** and **25** can be used satsifactorily in the next step; the sample of **24** was purified for characterisation purposes.

(2*S,3*S**)-3-Benzyloxy-1-fluorohept-6-en-2-ol (26) and (2*S**,3*R**)-Benzyloxy-1-fluorohept-6-en-2-ol (27):** Hydrochloric acid (0.5 mL of a 3 M aqueous solution) was added to a solution of **24** (3.78 mmol, 1.23 g) in THF (10 mL). The mixture was stirred for 12 h, then diluted with Et_2O (10 mL), then sodium borohydride (5.93 mmol, 0.229 g) was added in several portions. The mixture was stirred overnight, then diluted with water (5 mL), neutralised (to pH paper) with concentrated HCl, and extracted with EtOAc (3 × 15 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to leave a colourless oil, which was purified by Biotage column chromatography (gradient 20% → 50% EtOAc/PE) to afford alcohols **26** and **27** (0.625 g, 69%, 99% by GC-MS) as an inseparable (1:1 by NMR) mixture as a clear colourless oil. R_f (20% EtOAc/PE) = 0.46. IR (neat): $\tilde{\nu}_{max}$ = 3431 [br. (OH)], 2921 [w (CH_2)], 1641 [w (C=C)], 1454 (w), 1073 [s (C–O] cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.41–7.27 (m, 5 H, Ph), 5.91–5.75 (m, 1 H, 6-H), 5.11–4.94 (m, 2 H, 7-H), 4.83–4.36 (m, 4 H, 6-H, CH_2Ph), 4.02–3.72 (m, 1 H, 2-H), 3.62–3.52 (m, 1 H, 3-H), 2.37–1.62 (m, 5 H, 4-H, 5-H, OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.2 (C-6), 138.1, 137.9 (C-6), 128.6, 128.5, 128.0, 127.9, 127.9, 115.2 (C-7), 115.1 (C-7), 84.5 (d, $^1J_{C,F}$ = 166.8 Hz, C-1), 83.9 (d, $^1J_{C,F}$ = 170.0 Hz, C-1), 78.3 (d, $^3J_{C,F}$ = 6.5 Hz, C-3), 77.6 (d, $^3J_{C,F}$ = 5.3 Hz, C-3), 72.7 (CH_2Ph), 72.5 (CH_2Ph), 71.7 (d, $^2J_{C,F}$ = 18.8 Hz, C-2), 71.2 (d, $^2J_{C,F}$ = 19.8 Hz, C-2), 29.7, 29.5, 29.4, 29.2 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –230.0 (td, $^2J_{F,H}$ = 47.3, $^3J_{F,H}$ = 16.9 Hz, CH_2F), –232.9 (td, $^2J_{F,H}$ = 47.5, $^3J_{F,H}$ = 19.7 Hz, CH_2F) ppm. HRMS (EI): calcd. for $C_{14}H_{19}FO_2$ [M^+]

238.13691; found 238.13690. MS (EI): *m*/*z* (%) = 238 (1) [M$^+$], 175 (9), 157 (8), 131 (2), 107 (7), 91 (100). t_R (GC) = 16.47 min (both diastereoisomers).

Racemic Methyl 5-*O*-Benzyl-6-fluoroamicetoside (28) and Racemic Methyl 5-*O*-Benzyl-6-fluororhodinoside (29): Chlorotrimethylsilane (0.16 mmol, 20 μL) was added to a stirred solution of alcohols **26** and **27** (0.39 mmol, 93 mg) in methanol (5 mL). The solution was cooled to –78 °C, and a stream of dry ozone (0.2 L/min) was carefully bubbled through the solution until a blue colour persisted (ca. 30 min). The solution was purged with a stream of dry oxygen until colourless (5 min), then dimethyl sulfide (5.4 mmol, 0.4 mL) was added. The mixture was stirred at room temperature overnight (18 h), then solid sodium hydroxide (0.1 g, 2.5 mmol) was added. After 1 h, the solution was neutralised with concentrated HCl (0.7 mL), diluted with Et_2O (50 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to leave a colourless oil, which was purified by Biotage column chromatography (gradient 1% → 2% EtOAc/PE) to afford an inseparable mixture of methyl pyranosides **28** and **29** (85 mg, 86%, 99% by GC-MS) as a clear colourless oil. R_f (20% EtOAc/PE) = 0.68. IR (neat): $\tilde{\nu}_{max}$ = 2938 [w (CH_2)], 2896 [w (CH_2)], 1454 [s (CH_3)], 1217 [s (C–O–C)], 1128 (s), 1071 [s (C–O)]. Amicetoside **28** (one major anomer): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.25 (m, 5 H, Ph), 4.88–4.34 (m, 5 H, 1-H, 6-H, CH_2Ph), 4.09–3.99 (m, 1 H, 5-H), 3.83–3.44 (m, 1 H, 4-H), 3.35 (s, 3 H, OCH_3), 2.22–1.21 (m, 4 H, 2-H, 3-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.3, 128.4, 127.8, 127.7, 97.6 (C-1), 82.7 (d, $^1J_{C,F}$ = 171.1 Hz, C-6), 71.8 (d, $^3J_{C,F}$ = 6.8 Hz, C-4), 70.9 (d, $^2J_{C,F}$ = 18.0 Hz, C-5), 70.7 (CH_2Ph), 54.5 (OCH_3), 28.8 (C-2), 23.9 (C-3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = 234.8 (td, $^2J_{F,H}$ = 47.7, $^3J_{F,H}$ = 28.4 Hz) ppm. Rhodinoside **29** (one major anomer): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.25 (m, 5 H, Ph), 4.88–4.34 (m, 5 H, 1-H, 6-H, CH_2Ph), 4.09–3.99 (m, 1 H, 5-H), 3.83–3.44 (m, 1 H, 4-H), 3.38 (s, 3 H, OCH_3), 2.22–1.21 (env., 4 H, 2-H, 3-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.2, 128.4, 127.8, 127.7, 97.9 (C-1), 83.7 (d, $^1J_{C,F}$ = 166.8 Hz, C-6), 70.4 (d, $^3J_{C,F}$ = 7.0 Hz, C-4), 69.2 (d, $^2J_{C,F}$ = 21.9 Hz, C-5), 70.8 (CH_2Ph), 54.7 (OCH_3), 24.1 (C-2), 20.5 (C-3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –230.3 to –230.7 (m) ppm. HRMS (EI): calcd. for $C_{14}H_{19}FO_3$ [M$^+$] 254.13182; found 254.13189. MS (EI): *m*/*z* (%) = 254 (1) [M$^+$], 222 (1), 191 (3), 147 (1), 107 (17), 101 (14), 91 (100). t_R (GC) = 17.94 and 18.15 min (not assignable).

(±)-Hepta-1,6-dien-3-ol (30a): Vinylmagnesium bromide was prepared by slow addition of cold (0 °C) vinyl bromide (125 mmol, 9 mL) to freshly activated magnesium turnings (127 mmol, 3.1 g) in dry THF (50 mL) at 0 °C beneath a dry ice condenser (containing acetone/solid CO_2). The mixture was warmed gently to initiate the reaction. After the reaction was complete (most of the magnesium was consumed), the Grignard reagent solution was diluted with dry THF (50 mL). 5-Pentenal (90 mmol, 8 g) was added dropwise to the mixture at 0 °C, which was stirred for 30 min, then quenched at 0 °C with NH_4Cl (25 mL of a saturated aqueous solution), diluted with water (50 mL) and extracted with Et_2O (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated carefully in vacuo to leave a colourless oil, which was distilled (Kugelrohr, b.p. 20–25 °C/0.2 Torr) to afford alcohol **30a** (8.2 g, 81%, 95% by GC-MS) as a colourless oil. R_f (20% EtOAc/PE) = 0.76. IR (neat): $\tilde{\nu}_{max}$ = 3350 [br. (OH)], 2934 [w (CH_2)], 1641 [w (C=C)], 1425 (w), 991 (s). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.88–5.73 (m, 2 H, 1-H, 6-H), 5.19 (ddd, *J* = 17.2, ^2J = 1.6, ^4J = 1.4 Hz, 1 H, 1_a-H), 5.07 (ddd, *J* = 10.4, ^2J = 1.6, ^4J = 1.4 Hz, 1 H, 1_b-H), 5.01 (ddd, *J* = 17.1, ^2J = 3.5, ^4J = 1.6 Hz, 1 H, 7_a-H), 4.94 (ddd, *J* = 10.2, ^2J = 3.5, ^4J = 1.6 Hz, 1 H, 7_b-H), 4.08 (ddd, *J* = 6.4, *J* = 6.3, *J* = 1.2 Hz, 1 H, 3-H), 2.31 (s, 1 H, OH), 2.16–2.06 (m, 2 H, 5-H), 1.68–1.50 (m, 2 H, 4-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.0 (C-2), 138.3 (C-6), 114.8, 114.7 (C-1, C-7), 72.5 (C-3), 36.0 (C-4), 29.6 (C-5) ppm. HRMS (EI): calcd. for $C_7H_{12}O$ [M$^+$] 112.08882; found 112.08879. MS (EI): *m*/*z* (%) = 112 (1) [M$^+$], 111 (2) [M$^+$ – 1], 97 (11), 83 (23), 79 (100), 70 (45), 57 (79). The spectroscopic data are in agreement with those reported by Salomon et al.[46]

(–)-(2*S*,3*R*)-1,2-Epoxyhept-6-en-3-ol (31) and (+)-(2*R*,3*R*)-2,3-Epoxyhept-6-en-1-ol (32): Titanium tetraisopropoxide (4.79 mmol, 1.50 mL), (–)-diisopropyl D-tartrate (5.36 mmol, 1.15 mL), dienol **30a** (50 mmol, 5.6 g) and *tert*-butyl hydroperoxide (49.5 mmol, 15 mL of a 3.3 M solution in toluene) were added successively to a stirred suspension of powdered molecular sieves (4 Å) in cold (below –20 °C) dry CH_2Cl_2 (100 mL). The mixture was stirred in the freezer below –20 °C for 15 d, then the mixture was filtered through filter paper into a cold (0 °C) solution of ferrous sulfate (72 mmol, 20 g) and tartaric acid (40 mmol, 6 g) in water (60 mL). The two-phase mixture was stirred for 15 min, then the phases were separated, and the aqueous phase was extracted with Et_2O (3 × 30 mL). The combined organic phase and extracts were treated with cold (0 °C) NaOH (10 mL of a 30% w/v solution in brine) at 0 °C, and the phases were stirred vigorously at 0 °C for 30 min. The phases were separated, and the organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo to leave a colourless oil, from which the resolved (3*S*)-hepta-1,6-dien-3-ol (**30b**) distilled at reduced pressure (Kugelrohr, 25 °C/0.01 Torr) to afford a mixture: (i) Epoxy alcohol **31** (2.5 g, 39%, 80% by GC-MS) as a colourless oil. R_f (35% EtOAc/PE) = 0.42. IR (neat): $\tilde{\nu}_{max}$ = 3401 (OH), 2925 [w (CH_2)], 1641 [s (C=C)], 1453 (w), 1258 (w), 1018 (s), 911 (s). $[\alpha]_D^{19}$ = –16.1 (*c* = 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.84 (ddd, *J* = 17.3, *J* = 10.5, *J* = 6.7 Hz, 1 H, 6-H), 5.06 (ddd, *J* = 17.3, ^2J = 3.2, ^4J = 1.5 Hz, 1 H, 7_a-H), 4.99 (ddd, *J* = 10.5, ^2J = 3.2, ^4J = 1.2 Hz, 1 H, 7_b-H), 3.88–3.81 (m, 1 H, 3-H), 3.01 (ddd, *J* = 4.0, *J* = 3.0, *J* = 2.8 Hz, 1 H, 2-H), 2.81 (dd, ^2J = 5.0, *J* = 2.8 Hz, 1 H, 1_a-H), 2.73 (dd, ^2J = 5.0, *J* = 4.0 Hz, 1 H, 1_b-H), 2.35–2.10 (m, 2 H, 5-H), 1.96 (br. s, 1 H, OH), 1.78–1.52 (m, 2 H, 4-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.0 (C-6), 115.1 (C-7), 67.9 (C-3), 54.5 (C-2), 43.5 (C-1), 32.5 (C-4), 29.5 (C-5) ppm. HRMS (EI): calcd. for $C_7H_{12}O_2$ [M$^+$] 128.08373; found 128.08372. MS (EI): *m*/*z* (%) = 128 (1) [M$^+$], 108 (18), 97 (18), 95 (19), 79 (96), 67 (100). t_R (GC) = 8.05 min. (ii) Epoxy alcohol **32** (Payne product) (0.32 g, 5%, 95% by GC-MS) as a colourless oil. R_f (35% EtOAc/PE) = 0.27. IR (neat): $\tilde{\nu}_{max}$ = 3395 [br. (OH)], 2927 [w (CH_2)], 1641 [s (C=C)], 1448 (w), 1084 (w), 912 (s). $[\alpha]_D^{23}$ = +30.5 (*c* = 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.83 (ddt, *J* = 17.0, *J* = 10.2, *J* = 6.7 Hz, 1 H, 6-H), 5.06 (ddd, *J* = 17.0, ^2J = 3.2, ^4J = 1.4 Hz, 1 H, 7_a-H), 5.00 (ddd, *J* = 10.2, ^2J = 3.2, ^4J = 1.7 Hz, 1 H, 7_b-H), 3.89 (ddd, ^2J = 12.6, *J* = 6.1, *J* = 2.6 Hz, 1 H, 1_a-H), 3.58 (ddd, ^2J = 12.6, *J* = 6.7, *J* = 4.7 Hz, 1 H, 1_b-H), 3.00–2.92 (m, 2 H, 2-H, 3-H), 2.74 (dd, *J* = 6.7, *J* = 6.1 Hz, 1 H, OH), 2.31–2.11 (m, 2 H, 5-H), 1.69 (t, *J* = 7.6 Hz, 1 H, 4_a-H), 1.69 (t, *J* = 7.3 Hz, 1 H, 4_b-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.4 (C-6), 115.3 (C-7), 61.8 (C-1), 58.8 (C-2), 55.5 (C-3), 30.8 (C-4), 30.0 (C-5) ppm. HRMS (EI): calcd. for $C_7H_{12}O_2$ [M$^+$] 128.08373; found 128.08372. MS (EI): *m*/*z* (%) = 128 (1) [M$^+$], 110 (5), 97 (37), 91 (13), 83 (27), 79 (48), 67 (100). t_R (GC) = 8.68 min.

(+)-(2*R*,3*S*)-1,2-Epoxyhept-6-en-3-ol (33): As for **31**, from powdered molecular sieves (4 Å) (3.2 g), titanium tetraiisopropyloxide (2.39 mmol, 0.75 mL), diisopropyl L-tartrate (2.83 mmol, 0.6 mL), resolved alcohol **30b** (from the previous procedure) (22.3 mmol, 2.5 g) and *tert*-butyl hydroperoxide (22.2 mmol, 6 mL of a 3.7 M solution in toluene) in dry CH_2Cl_2 (25 mL) at –20 °C over 15 d. The workup was performed with ferrous sulfate (36 mmol, 10 g)

and tartaric acid (20 mmol, 3 g) in water (30 mL). The rest of the workup and isolation were performed as for **31** to afford alcohol **33** (2.1 g, 74%, 99% by GC-MS) as a colourless oil. $[\alpha]_D^{19}$ = +27.6 (c = 1.00, $CHCl_3$). The rest of the data are identical to those reported for **32**. The product of Payne rearrangement has spectral properties identical to those of **32** and was not characterised further.

(+)-(2*S*,3*R*)-3-Benzyloxy-1,2-epoxyhept-6-ene (34) and (–)-(2*R*,3*R*)-1-Benzyloxy-2,3-epoxyhept-6-ene (35): Sodium hydride (1.28 mmol, 51 mg of a 60% dispersion in mineral oil, from which the oil had been washed with dry PE), was added in portions to a stirred solution of epoxy alcohol **31** (1.00 mmol, 0.130 g), benzyl bromide (1.07 mmol, 0.130 mL) and tetrabutylammonium iodide (1.00 mmol, 0.379 g) in dry dichloromethane (2 mL) at room temperature. After 2 h, the white suspension was filtered through filter paper (*CAUTION*: The filter residue contains unreacted sodium hydride!), concentrated in vacuo, and the filtrate was diluted with diethyl ether (10 mL), filtered through cotton wool and concentrated in vacuo to leave a colourless oil, which was purified by Biotage column chromatography (gradient 3% → 10% EtOAc/PE) to afford: (i) Ether **34** (140 mg, 64%, 99% by GC-MS) as a colourless oil. R_f (20% EtOAc/PE) = 0.80. IR (neat): $\tilde{\nu}_{max}$ = 2921 [w (CH_2)], 1640 [s (C=C)], 1454 (s), 1070 [s (C–O)] cm^{-1}. $[\alpha]_D^{23}$ = +14.5 (c = 1.00, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.24 (m, 5 H, Ph), 5.80 (ddt, J = 17.0, J = 10.2, J = 6.6 Hz, 1 H, 6-H), 5.02 (ddd, J = 17.0, ^2J = 3.4, ^4J = 1.7 Hz, 1 H, 7_a-H), 4.96 (ddd, J = 10.2, ^2J = 3.4, ^4J = 1.7 Hz, 1 H, 7_b-H), 4.66 (d, ^2J = 11.6 Hz, 1 H, CH_aH$_b$Ph), 4.49 (d, ^2J = 11.6 Hz, 1 H, CH$_a$$H_b$Ph), 3.28 (dt, J = 6.7, J = 5.4 Hz, 1 H, 3-H), 2.93 (ddd, J = 5.4, J = 3.9, J = 2.6 Hz, 1 H, 2-H), 2.77 (dd, ^2J = 5.3, J = 3.9 Hz, 1 H, 1_a-H), 2.71 (dd, ^2J = 5.3, J = 2.6 Hz, 1 H, 1_b-H), 2.36–2.09 (m, 2 H, 5-H), 1.77–1.62 (m, 2 H, 3-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.5, 138.2 (C-6), 128.4, 127.8, 127.7, 115.0 (C-7), 77.5 (C-3), 72.4 (CH_2Ph), 53.5 (C-2), 45.7 (C-1), 32.1 (C-5), 29.4 (C-4) ppm. HRMS (EI): calcd. for $C_{14}H_{19}FO_3$ [M^+] 218.13068; found 218.13064. MS (EI): m/z (%) = 218 (1) [M^+], 175 (1), 157 (1), 107 (38), 91 (100). t_R (GC) = 16.30 min. (ii) Payne product **35** (24 mg, 11%, 98% by GC-MS) as a colourless oil. R_f (20% EtOAc/PE) = 0.74. IR (neat): $\tilde{\nu}_{max}$ = 3330 [br. (OH)], 2926 [w (CH_2)], 1721 (w), 1641 (w), 1452 (w), 1272 (s), 1096 [s (C–O)], 1070 (s) cm^{-1}. $[\alpha]_D^{22}$ = –7.3 (c = 0.80, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.25 (m, 5 H, Ph), 5.83 (ddt, J = 16.9, J = 10.2, J = 6.6 Hz, 1 H, 6-H), 5.06 (ddd, J = 16.9, ^2J = 3.3, ^4J = 1.6 Hz, 1 H, 7_a-H), 5.00 (ddd, J = 10.2, ^2J = 3.0, ^4J = 1.2 Hz, 1 H, 7_b-H), 4.59 (d, ^2J = 11.9 Hz, 1 H, CH_aH$_b$Ph), 4.55 (d, ^2J = 11.9 Hz, 1 H, CH$_a$$H_b$Ph), 3.71 (dd, ^2J = 11.4, J = 3.3 Hz, 1 H, 1_a-H), 3.47 (dd, ^2J = 11.4, J = 5.6 Hz, 1 H, 1_b-H), 2.96 (ddd, J = 5.6, J = 3.3 Hz, 2.3, 1 H, 2-H), 2.85 (ddd, J = 5.8, J = 5.6, J = 2.3 Hz, 1 H, 3-H), 2.31–2.11 (m, 2 H, 5-H), 1.78–1.55 (m, 2 H, 4-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.0, 137.5 (C-6), 128.4, 127.7, 127.7, 115.3 (C-7), 73.3 (CH_2Ph), 70.4 (C-1), 57.1 (C-2), 55.6 (C-3), 31.0 (C-4), 30.1 (C-5) ppm. HRMS (EI): calcd. for $C_{14}H_{19}FO_3$ [M^+] 218.13068; found 218.13075. MS (EI): m/z (%) = 218 (1) [M^+], 201 (1), 175 (15), 107 (47), 91 (100). t_R (GC) = 17.0 min. (iii) Mixed fraction containing both regioisomers (41 mg, 19%).

(–)-(2*R*,3*R*)-3-Benzyloxy-1-fluorohept-6-en-2-ol (36): Epoxy ether **34** (1.00 mmol, 0.218 g) was added to a stirred mixture of tetrabutylammonium fluoride trihydrate (1.10 mmol, 0.356 g) and potassium hydrogen difluoride (3.88 mmol, 0.302 g) at 110 °C. After 2 h, the mixture was cooled to room temperature, diluted with EtOAc (10 mL) and water (10 mL), then carefully neutralised with $NaHCO_3$ (0.25 g). The organic phase was separated, and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phase and extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to leave a dark red oil, which was purified by Biotage column chromatography (gradient 10% → 20% EtOAc/PE) to afford alcohol **36** (162 mg, 68%, 99% by GC-MS, 92% *ee* by HPLC) as a colourless oil. R_f (20% EtOAc/PE) = 0.51. IR (neat): $\tilde{\nu}_{max}$ = 3424 [br. (OH)], 2920 [w (CH_2)], 1641 [w (C=C)], 1455 (w), 1090 [s (C–O)] cm^{-1}. $[\alpha]_D^{23}$ = –4.6 (c = 1.00, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.23 (m, 5 H, Ph), 5.80 (ddt, J = 17.0, J = 10.2, J = 6.6 Hz, 1 H, 6-H), 5.01 (ddd, J = 17.0, ^2J = 3.4, ^2J = 1.6 Hz, 1 H, 7_a-H), 4.99 (ddd, J = 10.2, ^2J = 3.4, ^4J = 1.1 Hz, 1 H, 7_b-H), 4.54 (s, 2 H, CH_2Ph), 4.50 (ddd, $^2J_{H,F}$ = 47.5, ^2J = 9.6, J = 3.8 Hz, 1 H, CH_aH$_b$F), 4.49 (ddd, $^2J_{H,F}$ = 47.5, ^2J = 9.6, J = 5.6 Hz, 1 H, CH$_a$$H_b$F), 3.87 (dtd, $^3J_{H,F}$ = 20.1, J = 5.6, J = 3.8 Hz, 1 H, 2-H), 3.49 (ddd, J = 7.3, J = 5.6, J = 4.4 Hz, 1 H, 3-H), 2.72 (s, 1 H, OH), 2.29–2.04 (m, 2 H, 5-H), 1.79–1.58 (m, 2 H, 4-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.4 (C-6), 138.2, 128.5, 128.0, 127.9, 115.1 (C-7), 84.6 (d, $^1J_{C,F}$ = 166.9 Hz, C-1), 78.4 (d, $^3J_{C,F}$ = 6.5 Hz, C-3), 72.5 (CH_2Ph), 71.7 (d, $^2J_{C,F}$ = 18.7 Hz, C-2), 29.5 (C-4), 29.3 (C-5) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –232.3 (td, $^2J_{F,H}$ = 47.5, $^3J_{F,H}$ = 20.1 Hz) ppm. HRMS (EI): calcd. for $C_{14}H_{19}FO_2$ [M^+] 238.13691; found 238.13692. MS (EI): m/z (%) = 254 (1) [M^+], 200 (1), 157 (8), 91 (100). t_R (GC) = 16.71 min. HPLC: Chiralcel OD-H, PE/*i*PrOH (99:1), 1 mL/min, 254 nm, t_R = 17.5 min (**36**, major), t_R = 15.9 min (**39**, minor).

(–)-L-α-Methyl 4-*O*-Benzyl-6-fluoroamicetoside (37a) and (–)-L-β-Methyl 4-*O*-Benzyl-6-fluoroamicetoside (37b): Prepared as for **28** and **29** from alcohol **36** (0.78 mmol, 0.187 g) and chlorotrimethylsilane (0.39 mmol, 50 μL), in methanol (5 mL) at –78 °C. The reaction, workup and isolation were carried out as for **28** and **29** to afford a colourless oil containing a 4:1 mixture of α/β anomers (by GC-MS), which was purified by Biotage column chromatography (gradient 1% → 2% EtOAc/PE) to afford: (i) α-Methyl amicetoside **37a** (98 mg, 49%, 99% by GC-MS) as a clear colourless oil. R_f (20% EtOAc/PE) = 0.63. IR (neat): $\tilde{\nu}_{max}$ = 2950 [w (CH_2)], 2897 [w (CH_2)], 1455 [s (CH_3)], 1223 [s (C–O–C)], 1053 [s (C–O)] cm^{-1}. $[\alpha]_D^{23}$ = –144.0 (c = 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.29 (m, 5 H, Ph), 4.70 (d, J = 3.1 Hz, 1 H, 1-H), 4.67 (ddd, $^2J_{H,F}$ = 47.7, J = 10.0, J = 3.7 Hz, 1 H, CH_aH$_b$F), 4.63 (d, ^2J = 11.6 Hz, 1 H, CH_aH$_b$Ph), 4.57 (ddd, $^2J_{H,F}$ = 47.7, J = 10.0, J = 1.6 Hz, 1 H, CH$_a$$H_b$F), 4.48 (d, ^2J = 11.6 Hz, 1 H, CH$_a$$H_b$Ph), 3.75 (dddd, $^3J_{H,F}$ = 28.4, J = 9.7, J = 3.7, J = 1.6 Hz, 1 H, 5-H), 3.48 (ddd, J = 10.1, J = 9.7, J = 4.7 Hz, 1 H, 4-H), 3.34 (s, 3 H, OCH_3), 2.13–2.06 (m, 1 H, 3_a-H), 1.91–1.68 (m, 3 H, 2-H, 3_b-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.3, 128.4, 127.8, 127.7, 97.6 (C-1), 82.7 (d, $^1J_{C,F}$ = 171.1 Hz, C-6), 71.8 (d, $^3J_{C,F}$ = 6.7 Hz, C-4), 70.9 (d, $^2J_{C,F}$ = 18.0 Hz, C-5), 70.8 (CH_2Ph), 54.5 (OCH_3), 28.8 (C-2), 23.9 (C-3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –234.51 (td, $^2J_{F,H}$ = 47.7, $^3J_{F,H}$ = 28.4 Hz) ppm. HRMS (EI): calcd. for $C_{14}H_{19}FO_3$ [M^+] 254.13182; found 254.13184. MS (EI): m/z (%) = 254 (1) [M^+], 222 (2), 191 (5), 107 (16), 101 (37), 91 (100). t_R (GC) = 17.71 min. (ii) Minor β-methyl amicetoside **37b** (35 mg, 18%, 82% by GC-MS). R_f (20% EtOAc/PE) = 0.54. IR (neat): $\tilde{\nu}_{max}$ = 2954 [w (CH_2)], 2869 [w (CH_2)], 1455 [s (CH_3)], 1221 [s (C–O–C)], 1063 [s (C–O)] cm^{-1}. $[\alpha]_D^{18}$ = –7.4 (c = 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.26 (m, 5 H, Ph), 4.63 (dd, $^2J_{H,F}$ = 47.6, J = 3.3 Hz, 2 H, 6-H), 4.61 (d, ^2J = 11.4 Hz, 1 H, CH_aH$_b$Ph), 4.47 (d, ^2J = 11.4 Hz, 1 H, CH$_a$$H_b$Ph), 4.41 (dd, J = 8.7, J = 2.2 Hz, 1 H, 1-H), 3.54 (ddt, $^3J_{H,F}$ = 24.7, J = 9.2, J = 3.2 Hz, 1 H, 5-H), 3.49 (s, 3 H, OCH_3), 3.48 (ddd, J = 9.4, J = 9.2, J = 4.8 Hz, 1 H, 4-H), 2.26 (ddd, J = 4.6, J = 3.9, J = 3.0 Hz, 1 H, 3_a-H), 1.91 (ddd, J = 7.8, J = 3.0, J = 2.2 Hz, 1 H, 2_a-H), 1.60–1.46 (m, 2 H, 2_b-H, 3_b-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.0, 128.5, 127.9, 127.8, 102.7 (C-1), 82.6 (d, $^1J_{C,F}$ = 171.8 Hz, C-6), 77.3 (d, $^2J_{C,F}$ =

18.0 Hz, C-5), 71.8 (d, $^3J_{C,F}$ = 6.8 Hz, C-4), 71.3 (CH_2Ph), 56.4 (OCH_3), 29.7 (C-2), 27.1 (C-3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –232.72 (td, $^2J_{F,H}$ = 47.6, $^3J_{F,H}$ = 24.7 Hz) ppm. HRMS (EI): calcd. for $C_{14}H_{19}FO_3$ [M^+] 254.13182; found 254.13175. MS (EI): *m*/*z* (%) = 254 (1) [M^+], 222 (1) [M^+ – MeOH], 191 (3), 107 (16), 101 (22), 91 (100). t_R (GC) = 17.84 min. (iii) Mixed fraction containing both anomers (28 mg, 14%).

(–)-(2*R*,3*S*)-3-Benzyloxy-1,2-epoxyhept-6-ene (38): Prepared as for **34** from sodium hydride (2.45 mmol, 98 mg of a 60% dispersion in mineral oil), epoxy alcohol **33** (2.00 mmol, 0.254 g), benzyl bromide (2.06 mmol, 0.250 mL) and tetrabutylammonium iodide (1.13 mmol, 0.425 g) in dichloromethane (4 mL). The same workup and isolation afforded a colourless oil, which was purified by Biotage column chromatography (gradient 3% → 10% EtOAc/PE) to afford ether **38** (307 mg, 71%, 99% by GC-MS) as a colourless oil. R_f (20% EtOAc/PE) = 0.80. $[\alpha]_D^{18}$ = –18.8 (*c* = 1.00, $CHCl_3$). The rest of the spectroscopic data are identical to those reported for **34**. The Payne product was neither isolated nor characterised.

(+)-(2*S*,3*S*)-3-Benzyloxy-1-fluorohept-6-en-2-ol (39): Prepared as for **36** from **34** (1.17 mmol, 0.256 g), tetrabutylammonium fluoride trihydrate (1.23 mmol, 0.399 g) and potassium hydrogen difluoride (5.11 mmol, 0.395 g) at 100 °C. After 1 h, the mixture was cooled to room temperature. The same workup and isolation as for **36** afforded a colourless oil, which was purified by Biotage column chromatography (gradient 10% → 20% EtOAc/PE) to afford alcohol **39** (175 mg, 63%, 99% by GC-MS, 95% *ee* by HPLC) as a colourless oil. R_f (20% EtOAc/PE) = 0.51. $[\alpha]_D^{18}$ = +5.3 (*c* = 1.00, $CHCl_3$). HRMS (EI): calcd. for $C_{14}H_{19}FO_2$ [M^+] 238.13691; found 238.13698. HPLC: Chiralcel OD-H, PE/*i*PrOH (99:1), 1 mL/min, 254 nm, t_R = 15.5 min (**39**, major), t_R = 17.5 min (**36**, minor). The rest of the spectroscopic data are identical to those reported for **36**.

L-α-Methyl 6-Fluoroamicetoside (41a) and L-β-Methyl 6-Fluoroamicetoside (41b): A solution of **37a** and **37b** (0.39 mmol, 98 mg, 4:1 mixture of anomers) in ethanol (6 mL) containing 10% palladium on carbon (30 mg) was stirred under hydrogen at room temperature and atmospheric pressure for 48 h. The mixture was filtered through Celite; the filter bed was washed with EtOH (3 × 2 mL), and the combined filtrates were concentrated in vacuo to leave a dark oil, which was purified by Biotage column chromatography (gradient 30% → 50% EtOAc/PE) to afford: (i) **41a** (49 mg, 77%, 99% by GC-MS) as a clear colourless oil. R_f (35% EtOAc/PE) = 0.28. IR (neat): $\tilde{\nu}_{max}$ = 3408 [br. (OH)], 2943 [w (CH_2)], 1370 (w), 1129 [s (C–O)], 1048 [s (C–O)] cm^{-1}. $[\alpha]_D^{20}$ = –135.6 (*c* = 0.70, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 4.71 (d, *J* = 2.6 Hz, 1 H, 1-H), 4.68 (ddd, $^2J_{H,F}$ = 47.6, ^2J = 10.0, *J* = 3.6 Hz, 1 H, 6_a-H), 4.60 (ddd, $^2J_{H,F}$ = 47.6, ^2J = 10.0, *J* = 1.8 Hz, 1 H, 6_b-H), 3.71–3.58 (m, 2 H, 4-H, 5-H), 3.47 (s, 3 H, OCH_3), 2.20 (br. s, 1 H, OH), 1.93–1.73 (m, 4 H, 2-H, 3-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 97.5 (C-1), 82.8 (d, $^1J_{C,F}$ = 170.4 Hz, C-6), 72.2 (d, $^2J_{C,F}$ = 17.5 Hz, C-5), 65.2 (d, $^3J_{C,F}$ = 7.1 Hz, C-4), 54.6 (OCH_3), 29.0 (C-3), 27.4 (C-2) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –234.7 (td, $^2J_{F,H}$ = 47.6, $^3J_{F,H}$ = 26.8 Hz) ppm. HRMS (EI): calcd. for $C_7H_{12}FO_3$ [M^+ – 1] 163.07705; found 163.07703. MS (EI): *m*/*z* (%) = 164 (1) [M^+], 133 (15), 115 (6), 102 (17), 76 (15), 69 (37), 58 (100). t_R (GC) = 9.90 min. (ii) **41b** (12 mg, 19%). ^1H NMR (400 MHz, $CDCl_3$): δ = 4.68–4.64 (m, 1 H, 6_a-H), 4.54–4.51 (m, 1 H, 6_b-H), 4.38–4.34 (m, 1 H, 1-H), 3.68–3.23 {m [incl. 3.43 (s, 3 H, OCH_3)], 6 H, OH, 4-H, 5-H, OCH_3}, 2.10–1.42 (m, 4 H, 2-H, 3-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 102.7 (C-1), 83.0 (d, $^1J_{C,F}$ = 168.8 Hz, C-6), 78.1 (d, $^2J_{C,F}$ = 18 Hz, C-5), 65.4 (d, $^3J_{C,F}$ = 6.8 Hz, C-4), 56.5 (OCH_3), 30.7 (C-3), 29.9 (C-2) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –233.1 (td, $^2J_{F,H}$ = 45.1, $^3J_{F,H}$ = 22.6 Hz) ppm. The minor product could not be purified rigorously and was characterised more fully after the next step.

L-α-5-*O*-Benzyl-6-fluoroamicetose (42a) and L-β-5-*O*-Benzyl-6-fluoroamicetose (42b): Concentrated hydrochloric acid (20 μL) was added to a solution of **37a** and **37b** (0.40 mmol, 101 mg) in THF (4 mL) and H_2O (150 mg). The solution was stirred and heated (microwaves, 50 W) at 120 °C for 1 h. The mixture was diluted with Et_2O (5 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to leave a colourless oil, which was purified by Biotage column chromatography (gradient 20% → 50% EtOAc/PE) to afford an inseparable (1.7:1 by NMR) mixture of **42a** and **42b** (76 mg, 80%, 99% by GC-MS) as a clear colourless oil. R_f (35% EtOAc/PE) = 0.43. IR (neat): $\tilde{\nu}_{max}$ = 3414 [br. (OH)], 2951 [w (CH_2)], 2874 [w (CH_2)], 1455 (w), 1220 (w), 1068 [s (C–O)], 978 (s) cm^{-1}. α-Anomer (**42a**, major): ^1H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.25 (m, 5 H, Ph), 5.29 (d, *J* = 3.1 Hz, 1 H, 1-H), 4.77–4.44 (m, 4 H, 6-H, CH_2Ph), 4.03 (dddd, $^3J_{H,F}$ = 27.5, *J* = 9.6, *J* = 3.8, *J* = 1.4 Hz, 1 H, 5-H), 3.73–3.35 (m, 1 H, 4-H), 2.32–1.42 (m, 5 H, 2-H, 3-H, OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.2, 128.5, 127.9, 127.7, 91.0 (C-1), 82.9 (d, $^1J_{C,F}$ = 170.9 Hz, C-6), 72.1 (d, $^3J_{C,F}$ = 6.9 Hz, C-4), 71.0 (d, $^2J_{C,F}$ = 17.4 Hz, C-5), 70.8 (CH_2Ph), 28.9 (C-3), 23.1 (C-2) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –234.5 (td, $^2J_{F,H}$ = 47.7, $^3J_{F,H}$ = 27.6 Hz) ppm. β-Anomer (**42b**, minor): ^1H NMR (300 MHz, $CDCl_3$): δ = 4.84 (dd, *J* = 8.6, *J* = 1.8 Hz, 1 H, 1-H), 4.77–4.44 (m, 4 H, 6-H, CH_2Ph), 3.73–3.35 (m, 2 H, 4-H, 5-H), 2.32–1.42 (m, 5 H, 2-H, 3-H, OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.9, 128.5, 127.9, 127.8, 96.1 (C-1), 82.6 (d, $^1J_{C,F}$ = 171.5 Hz, C-6), 77.4 (d, $^2J_{C,F}$ = 17.7 Hz, C-5), 71.5 (d, $^3J_{C,F}$ = 6.8 Hz, C-4), 71.3 (CH_2Ph), 31.3 (C-2), 27.3 (C-3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –233.2 (td, $^2J_{F,H}$ = 47.6, $^3J_{F,H}$ = 24.9 Hz) ppm. HRMS (EI): calcd. for $C_{13}H_{17}FO_3$ [M^+] 240.11617; found 240.11611. MS (EI): *m*/*z* (%) = 240 (1) [M^+], 176 (1), 147 (3), 136 (23), 107 (2), 91 (100). t_R (GC) = 19.37 min (**42b**), 19.43 min (**42a**). The anomers were assigned on the basis of the 1-H coupling constant and a deconvolution of the connectivity from the dqfCOSY spectrum.

(–)-L-α-Methyl 5-*O*-Benzoyl-6-fluoroamicetoside (43a) and (–)-L-β-Methyl 5-*O*-Benzoyl-6-fluoroamicetoside (43b): Prepared as for **28** and **29** from alcohol **36** (2.15 mmol, 0.513 g) and chlorotrimethylsilane (0.39 mmol, 50 μL) in methanol (10 mL), though at the higher temperature of 0 °C over 5 h. The workup and isolation were carried out as for **28** and **29** to afford a yellow oil, which was purified by Biotage column chromatography (gradient 1% → 2% EtOAc/PE) to afford amicetosides **43a** and **43b** as clear colourless oils. (i) Major α-amicetoside **43a** (247 mg, 46%, 99% by GC-MS). R_f (35% EtOAc/PE) = 0.70. IR (neat): $\tilde{\nu}_{max}$ = 2954 [w (CH_2)], 1718 [s (C=O)], 1451 [w (CH_3)], 1276 (s), 1051 [s (C–O)] cm^{-1}. $[\alpha]_D^{23}$ = –155.5 (*c* = 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.02 (dd, *J* = 7.5, ^4J = 1.3 Hz, 2 H, Ph), 7.56 (tt, *J* = 7.5, ^4J = 1.3 Hz, 1 H, Ph), 7.43 (t, *J* = 7.5 Hz, 2 H, Ph), 5.03 (ddd, *J* = 10.3, *J* = 10.2, *J* = 5.0 Hz, 1 H, 4-H), 4.77 (t, *J* = 2.2 Hz, 1 H, 1-H), 4.54 (dd, $^2J_{H,F}$ = 47.5, *J* = 3.9 Hz, 1 H, CH_aH_bF), 4.54 (d, $^2J_{H,F}$ = 47.5, *J* = 2.5 Hz, 1 H, CH_aH_bF), 4.07 (dddd, $^3J_{H,F}$ = 24.6, *J* = 10.2, *J* = 3.9, *J* = 2.5 Hz, 1 H, 5-H), 3.41 (s, 3 H, OCH_3), 2.18–2.12 (m, 1 H, 3_a-H), 2.06–1.82 (m, 3 H, 2-H, 3_b-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.3 (C=O), 133.2, 129.9, 129.6, 128.4, 97.5 (C-1), 82.4 (d, $^1J_{C,F}$ = 172.8 Hz, C-6), 69.5 (d, $^2J_{C,F}$ = 18.3 Hz, C-5), 67.6 (d, $^3J_{C,F}$ = 7.3 Hz, C-4), 54.7 (OCH_3), 28.6 (C-3), 24.0 (C-2) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –232.9 (td, $^2J_{F,H}$ = 47.5, $^3J_{F,H}$ = 24.6 Hz) ppm. HRMS (EI): calcd. for $C_{14}H_{16}FO_4$ [M^+ – 1]

267.10326; found 267.10323. MS (EI): *m*/*z* (%) = 268 (1) [M$^+$], 237 (5), 206 (1), 145 (15), 114 (11), 105 (100). t_R (GC) = 18.61 min. (ii) Minor β-methyl amicetoside **43b** (59 mg, 11%, 94% by GC-MS) as a clear colourless oil. R_f (35% EtOAc/PE) = 0.56. IR (neat): $\tilde{\nu}_{max}$ = 2959 [w (CH_2)], 1718 [s (C=O)], 1451 [w (CH_3)], 1267 (s), 1059 [s (C–O)] cm^{-1}. $[\alpha]_D^{21}$ = –18.0 (*c* = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (dd, *J* = 7.5, ^4J = 1.3 Hz, 2 H, Ph), 7.58 (tt, *J* = 7.5, ^4J = 1.3 Hz, 1 H, Ph), 7.45 (t, *J* = 7.5 Hz, 2 H, Ph), 4.97 (ddd, *J* = 9.2, *J* = 9.0, *J* = 4.9 Hz, 1 H, 4-H), 4.58 (d, $^2J_{H,F}$ = 47.5, *J* = 3.5 Hz, 1 H, CH_aH$_b$F), 4.57 (d, $^2J_{H,F}$ = 47.2, *J* = 4.7 Hz, 1 H, CH$_a$$H_b$F), 4.54 (d, *J* = 2.5 Hz, 1 H, 1-H), 3.89 (dddd, $^3J_{H,F}$ = 21.0, *J* = 9.0, *J* = 4.7, *J* = 3.5 Hz, 1 H, 5-H), 3.52 (s, 3 H, OCH_3), 2.42–2.32 (m, 1 H, 3$_a$-H), 2.04–1.66 (m, 3 H, 2-H, 3$_b$-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.5 (C=O), 133.3, 129.8, 129.6, 128.5, 102.3 (C-1), 82.4 (d, $^1J_{C,F}$ = 173.1 Hz, C-6), 75.8 (d, $^2J_{C,F}$ = 19.2 Hz, C-5), 67.5 (d, $^3J_{C,F}$ = 6.9 Hz, C-4), 56.4 (OCH_3), 29.2 (C-2), 26.6 (C-3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –230.7 (td, $^2J_{F,H}$ = 47.2, $^3J_{F,H}$ = 21.0 Hz) ppm. HRMS (EI): calcd. for $C_{14}H_{16}FO_4$ [M$^+$ – 1] 267.10326; found 267.10320. MS (EI): *m*/*z* (%) = 268 (1) [M$^+$], 237 (3), 146 (10), 126 (4), 114 (6), 105 (100). t_R (GC) = 18.90 min. (iii) Mixed fraction containing both anomers (30 mg, 6%).

L-α-([D$_3$]Methyl) 5-*O*-Benzyl-6-fluoroamicetoside (44a) and L-β-([D$_3$]Methyl) 5-*O*-Benzyl-6-fluoroamicetoside (44b): Prepared as for **28** and **29** from alcohol **36** (2.65 mmol, 0.633 g) and chlorotrimethylsilane (0.39 mmol, 50 μL) in methanol (10 mL) at –78 °C over 30 min. The solution was purged with a stream of O_2 until it became colourless (5 min), then dimethyl sulfide (13.6 mmol, 1.0 mL) was added. The mixture was stirred overnight (18 h) at room temperature, concentrated in vacuo, taken up in a mixture of [D$_4$]methanol (1 mL) and chlorotrimethylsilane (10 μL) and stirred for 1 h. Solid NaOH (0.2 g, 5 mmol) was added, and after 1 h the solution was neutralised with concentrated HCl (0.7 mL), concentrated in vacuo to leave a colourless oil containing a mixture of anomers, which was purified by Biotage column chromatography (gradient 1% → 2% EtOAc/PE) to afford: (i) **44a** (134 mg, 20%, 99% by GC-MS) as a clear colourless oil. R_f (20% EtOAc/PE) = 0.63. IR (neat): $\tilde{\nu}_{max}$ = 2952 [w (CH_2)], 2895 [w (CH_2)], 1456 [s (CH_3)], 1371 (w), 1224 [s (C–O–C)], 1046 [s (C–O)] cm^{-1}. $[\alpha]_D^{20}$ = –141.1 (*c* = 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.22 (m, 5 H, Ph), 4.68 (d, *J* = 3.0 Hz, 1 H, 1-H), 4.66 (ddd, $^2J_{H,F}$ = 47.7, ^2J = 9.9, *J* = 3.8 Hz, 1 H, CH_aH$_b$F), 4.63 (d, ^2J = 11.6 Hz, 1 H, CH_aH$_b$Ph), 4.56 (ddd, $^2J_{H,F}$ = 47.7, ^2J = 9.9, *J* = 1.7 Hz, 1 H, CH$_a$$H_b$F), 4.46 (d, ^2J = 11.6 Hz, 1 H, CH$_a$$H_b$Ph), 3.74 (dddd, $^3J_{H,F}$ = 28.3, *J* = 9.7, *J* = 3.8, *J* = 1.7 Hz, 1 H, 5-H), 3.47 (ddd, *J* = 9.9, *J* = 9.7, *J* = 4.7 Hz, 1 H, 4-H), 2.09–1.99 (m, 1 H, 3$_a$-H), 1.86–1.61 (m, 3 H, 2-H, 3$_b$-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.3, 128.4, 128.2, 127.7, 97.5 (C-1), 82.7 (d, $^1J_{C,F}$ = 171.2 Hz, C-6), 71.9 (d, $^3J_{C,F}$ = 6.8 Hz, C-4), 70.9 (d, $^2J_{C,F}$ = 17.6 Hz, C-5), 70.8 (CH_2Ph), 28.8 (C-2), 23.9 (C-3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –234.40 (td, $^2J_{F,H}$ = 47.7, $^3J_{F,H}$ = 28.3 Hz) ppm. HRMS (EI): calcd. for $C_{14}H_{19}D_3FO_3$ [M$^+$] 257.15035; found 257.15072. MS (EI): *m*/*z* (%) = 257 (1) [M$^+$], 222 (2), 194 (4), 107 (10), 104 (25), 91 (100). t_R (GC) = 17.73 min. (ii) **44b** (60 mg, 9%, 99% by GC-MS) as a clear colourless oil. R_f (20% EtOAc/PE) = 0.54. IR (neat): $\tilde{\nu}_{max}$ = 2953 [w (CH_2)], 2865 [w (CH_2)], 1455 [s (CH_3)], 1397 (w), 1169 [s (C–O–C)], 1074 [s (C–O)] cm^{-1}. $[\alpha]_D^{20}$ = –3.8 (*c* = 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.24 (m, 5 H, Ph), 4.63 (dd, $^2J_{H,F}$ = 47.7, *J* = 3.2 Hz, 2 H, 6-H), 4.62 (d, ^2J = 11.5 Hz, 1 H, CH_aH$_b$Ph), 4.47 (d, ^2J = 11.5 Hz, 1 H, CH$_a$$H_b$Ph), 4.41 (dd, *J* = 8.8, *J* = 2.2 Hz, 1 H, 1-H), 3.54 (ddt, $^3J_{H,F}$ = 24.8, *J* = 9.1, *J* = 3.2 Hz, 1 H, 5-H), 3.50–3.39 (m, 1 H, 4-H), 2.28–2.20 (m, 1 H, 3$_a$-H), 1.95–1.85 (m, 1 H, 2$_a$-H), 1.67–1.44 (m, 2 H, 2$_b$-H, 3$_b$-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.0, 128.5, 127.9, 127.8, 102.6 (C-1), 82.6 (d, $^1J_{C,F}$ = 171.8 Hz, C-6), 77.3 (d, $^2J_{C,F}$ = 18.1 Hz, C-5), 71.8 (d, $^3J_{C,F}$ = 6.8 Hz, C-4), 71.3 (CH_2Ph), 29.7 (C-2), 27.1 (C-3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –232.72 (td, $^2J_{F,H}$ = 47.7, $^3J_{F,H}$ = 24.8 Hz) ppm. HRMS (EI): calcd. for $C_{14}H_{19}D_3FO_3$ [M$^+$] 257.15035; found 257.15071. MS (EI): *m*/*z* (%) = 257 (1) [M$^+$], 222 (1), 194 (2), 107 (5), 104 (9), 91 (100). t_R (GC) = 17.83 min. (iii) Mixed fraction containing both anomers (238 mg, 35%).

(+)-L-α-Methyl 4-*O*-Benzoyl-6-fluororhodinoside (45a) and (–)-L-β-Methyl 4-*O*-Benzoyl-6-fluororhodinoside (45b): Diethyl azodicarboxylate (4.76 mmol, 0.75 mL) was added to a stirred solution of a mixture of methyl pyranosides **41a** and **41b** (0.81 mmol, 0.133 g, 2.5:1) and triphenylphosphane (4.95 mmol, 1.312 g) in dry toluene (10 mL) at room temperature, followed immediately by benzoic acid (4.95 mmol, 0.610 g). After 3 h, the mixture was concentrated in vacuo to leave a yellow liquid, which was purified by Biotage column chromatography (gradient 10% → 20% EtOAc/PE) to afford: (i) **45a** (95 mg, 44%, 98% by GC-MS), as a clear colourless oil, which crystallized very slowly as white needles. M.p. 51–54 °C. R_f (35% EtOAc/PE) = 0.71. IR (neat): $\tilde{\nu}_{max}$ = 2941 [w (CH_2)], 2900 [w (CH_2)], 1716 [s (C=O)], 1451 (w), 1268 (s) , 1111(s), 1022 [s (C–O)]. $[\alpha]_D^{20}$ = +59.6 (*c* = 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.13–8.06 (m, 2 H, Ph), 7.63–7.54 (m, 1 H, Ph), 7.50–7.41 (m, 2 H, Ph), 5.21 (s, 1 H, 4-H), 4.88 (d, *J* = 2.4 Hz, 1 H, 1-H), 4.51 (dd, $^2J_{H,F}$ = 46.9, *J* = 5.8 Hz, 1 H, 6$_a$-H), 4.49 (dd, $^2J_{H,F}$ = 46.9, *J* = 5.8 Hz, 1 H, 6$_b$-H), 4.27 (dtd, $^3J_{H,F}$ = 15.2, *J* = 5.8, *J* = 1.0 Hz, 1 H, 5-H), 3.44 (s, 3 H, OCH_3), 2.25–1.74 (m, 2$_a$-H, 3-H), 1.70–1.61 (m, 1 H, 2$_b$-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.8 (C=O), 133.6, 130.0, 129.7, 128.5, 97.9 (C-1), 83.0 (d, $^1J_{C,F}$ = 169.7 Hz, C-6), 68.1 (d, $^2J_{C,F}$ = 21.6 Hz, C-5), 67.1 (d, $^3J_{C,F}$ = 7.2 Hz, C-4), 54.9 (OCH_3), 24.3 (C-2), 22.6 (C-3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –230.8 (td, $^2J_{F,H}$ = 46.9, $^3J_{F,H}$ = 15.2 Hz) ppm. HRMS (EI): calcd. for $C_{14}H_{17}FO_4$ [M$^+$] 268.11109; found 268.11107. MS (EI): *m*/*z* (%) = 268 (1) [M$^+$], 237 (6), 206 (4), 146 (5), 126 (3), 114 (6), 105 (100). t_R (GC) = 18.43 min. The stereochemistry and identity of the crystalline anomer were confirmed by XRD analysis; crystal data: empirical formula $C_{14}H_{17}O_4F$, *M* = 268.28, crystal size 0.13 × 0.10 × 0.08 mm, orthorhombic, space group *P*2(1)2(1)2, unit cell dimensions *a* = 13.508(3), *b* = 7.6277(15), *c* = 13.127(3) Å, *V* = 1352.6(4) Å^3, *Z* = 4, $D_{calcd.}$ = 1.317 Mg m^{-3}, *F*(000) = 568, μ(Mo-K_α) = 0.104 mm^{-1}, *T* = 150(2) K, 1401 total reflections measured, 1401 independent, (R_{int} = 0.0000), which were used in all calculations. Final *R* indices [for reflections with $I > 2\sigma(I)$] were *R*1 = 0.0512, $\omega R2$ = 0.0701; *R* indices (all data) were *R*1 = 0.0763, $\omega R2$ = 0.0757. (ii) **45b** (51 mg, 23%, 99% by GC-MS) as a clear colourless oil. R_f (35% EtOAc/PE) = 0.51. IR (neat): $\tilde{\nu}_{max}$ = 2961 [w (CH_2)], 2842 [w (CH_2)], 1716 [s (C=O)], 1452 (w), 1268 (s) , 1110 (s), 1078 [s (C–O]. $[\alpha]_D^{19}$ = –32.7 (*c* = 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.13–8.05 (m, 2 H, Ph), 7.62–7.55 (m, 1 H, Ph), 7.50–7.41 (m, 2 H, Ph), 5.19–5.16 (m, 1 H, 4-H), 4.57 (dd, $^2J_{H,F}$ = 46.8, *J* = 6.4 Hz, 1 H, 6$_a$-H), 4.56 (dd, $^2J_{H,F}$ = 46.8, *J* = 5.2 Hz, 1 H, 6$_b$-H), 4.52 (dd, *J* = 8.5, *J* = 2.7 Hz, 1 H, 1-H), 4.03 (dddd, $^3J_{H,F}$ = 13.2, *J* = 6.3, *J* = 5.6, *J* = 1.6 Hz, 1 H, 5-H), 3.58 (s, 3 H, OCH_3), 2.29–2.15 (m, 1 H, 2$_a$-H), 1.96–1.71 (env., 3 H, 2$_b$-H, 3-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.8 (C=O), 133.3, 130.2, 129.8, 128.5, 103.0 (C-1), 82.2 (d, $^1J_{C,F}$ = 169.7 Hz, C-6), 75.2 (d, $^2J_{C,F}$ = 22.3 Hz, C-5), 66.0 (d, $^3J_{C,F}$ = 6.4 Hz, C-4), 56.5 (OCH_3), 26.8 (C-2), 26.2 (C-3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –230.6 (td, $^2J_{F,H}$ = 46.8, $^3J_{F,H}$ = 13.2 Hz) ppm. HRMS (EI): calcd. for $C_{14}H_{17}FO_4$ [M$^+$] 268.11109; found 268.11120. MS (EI): *m*/*z* (%) = 268 (1) [M$^+$], 237 (2), 206 (3), 146 (4), 126 (4), 105 (100). t_R (GC) = 18.60 min.

Supporting Information (see footnote on the first page of this article): General experimental, HPLC chromatograms for **36** and **39**, characterisation spectra for **19**, **20**, **21a** and **21b**, **22a** and **22b**, **37a**, **37b**, **41a**, **42a** and **42b**, details of computational procedures.

Acknowledgments

We thank the University of Leicester for funding (studentship to R. R.) and EPSRC's National Mass Spectrometry Service Centre, University of Wales, Swansea for mass spectrometric measurements.

[1] T. Someno, S. Kunimoto, H. Nakamura, H. Naganawa, D. Ikeda, *J. Antibiot.* **2005**, *58*, 56–60.
[2] K. Herold, F. A. Gollmick, I. Groth, M. Roth, K. D. Menzel, U. Mollmann, U. Grafe, C. Hertweck, *Chem. Eur. J.* **2005**, *11*, 5523–5530.
[3] D. S. Micalizzi, J. P. Dougherty, L. A. Noecker, G. R. Smith, R. M. Giuliano, *Tetrahedron: Asymmetry* **2003**, *14*, 3183–3188.
[4] M. Perez, F. Lombo, L. L. Zhu, M. Gibson, A. F. Brana, R. Rohr, J. A. Salas, C. Mendez, *Chem. Commun.* **2005**, 1604–1606.
[5] X. Zhang, L. B. Alernany, H. P. Fiedler, M. Goodfellow, R. J. Parry, *Antimicrobial. Agents Chemother.* **2008**, *52*, 574–585.
[6] B. Ostash, U. Rix, L. L. R. Rix, T. Liu, F. Lombo, A. Luzhetskyy, O. Gromyko, C. C. Wang, A. F. Brana, C. Mendez, J. A. Salas, V. Fedorenko, J. Rohr, *Chem. Biol.* **2004**, *11*, 547–555.
[7] W. R. Roush, R. J. Neitz, *J. Org. Chem.* **2004**, *69*, 4906–4912.
[8] M. Q. Zhou, G. A. O'Doherty, *Org. Lett.* **2008**, *10*, 2283–2286.
[9] L. L. Zhu, A. Luzhetskyy, M. Luzhetska, C. Mattingly, V. Adams, A. Bechthold, J. Rohr, *Chembiochem* **2007**, *8*, 83–88.
[10] D. Hoffmeister, G. Drager, K. Ichinose, J. Rohr, A. Bechthold, *J. Am. Chem. Soc.* **2003**, *125*, 4678–4679.
[11] R. M. De Lederkremer, C. Marino, *Adv. Carbohydr. Chem. Biochem.* **2008**, *61*, 143–216.
[12] A. Kirschning, M. Jesberger, K. U. Schoning, *Synthesis* **2001**, 507–540.
[13] J. Junnemann, I. Lundt, J. Thiem, *Acta Chem. Scand.* **1994**, *48*, 265–268.
[14] A. Caravano, R. A. Field, J. M. Percy, G. Rinaudo, R. Roig, K. Singh, *Org. Biomol. Chem.*, DOI: 10.1039/B815342F.
[15] L. R. Cox, G. A. DeBoos, J. J. Fullbrook, J. M. Percy, N. S. Spencer, M. Tolley, *Org. Lett.* **2003**, *5*, 337–339.
[16] L. R. Cox, G. A. DeBoos, J. J. Fullbrook, J. M. Percy, N. Spencer, *Tetrahedron: Asymmetry* **2005**, *16*, 347–359.
[17] C. Audouard, I. Barsukov, J. Fawcett, G. A. Griffith, J. M. Percy, S. Pintat, C. A. Smith, *Chem. Commun.* **2004**, 1526–1527.
[18] S. T. Patel, J. M. Percy, R. D. Wilkes, *Tetrahedron* **1995**, *51*, 9201–9216.
[19] J. A. L. Miles, L. Mitchell, J. M. Percy, K. Singh, E. Uneyama, *J. Org. Chem.* **2007**, *72*, 1575–1587.
[20] G. A. Griffith, I. H. Hillier, J. M. Percy, R. Roig, M. A. Vincent, *J. Org. Chem.* **2006**, *71*, 8250–8255.
[21] A. P. Davis in *Stereoselective Synthesis* (Eds.: G. Helmchen, R. W. Hoffmann, J. Mulzer), Georg Thieme Verlag, Stuttgart, **1996**, vol. E21, 7, pp. 3994–3999.
[22] T. Itoh, A. Yoshinaka, T. Sato, T. Fujisawa, *Chem. Lett.* **1985**, 1679–1680.
[23] S. W. Remiszewski, T. R. Stouch, S. M. Weinreb, *Tetrahedron* **1985**, *41*, 1173–1178.
[24] J. F. Stoddart, W. A. Szarek, *Can. J. Chem.* **1968**, *46*, 9.
[25] T. Winkler, B. Ernst, *Helv. Chim. Acta* **1988**, *71*, 120–123.
[26] *Spartan'06*, Wavefunction, Irvine, CA, **2006**. The full citation is given in the Supporting Information.
[27] S. T. Patel, J. M. Percy, R. D. Wilkes, *J. Org. Chem.* **1996**, *61*, 166–173.
[28] S. Hayashi, T. Nakai, N. Ishikawa, D. J. Burton, D. G. Naae, H. S. Kesling, *Chem. Lett.* **1979**, 983–986.
[29] J. M. Percy, R. D. Wilkes, *Tetrahedron* **1997**, *53*, 14749–14762.
[30] T. Katsuki, A. W. M. Lee, P. Ma, V. S. Martin, S. Masamune, K. B. Sharpless, D. Tuddenham, F. J. Walker, *J. Org. Chem.* **1982**, *47*, 1373–1378.
[31] S. Y. Ko, A. W. M. Lee, S. Masamune, L. A. Reed, K. B. Sharpless, F. J. Walker, *Science* **1983**, *220*, 949–951.
[32] A. W. M. Lee, V. S. Martin, S. Masamune, K. B. Sharpless, F. J. Walker, *J. Am. Chem. Soc.* **1982**, *104*, 3515–3516.
[33] P. Ma, V. S. Martin, S. Masamune, K. B. Sharpless, S. M. Viti, *J. Org. Chem.* **1982**, *47*, 1378–1380.
[34] V. Jager, D. Schroter, B. Koppenhoefer, *Tetrahedron* **1991**, *47*, 2195–2210.
[35] P. C. B. Page, C. M. Rayner, I. O. Sutherland, *J. Chem. Soc., Perkin Trans. 1* **1990**, 2403–2408.
[36] Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune, K. B. Sharpless, *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780.
[37] G. Haufe, *Sci. Synth.* **2006**, *34*, 345–378.
[38] P. A. Grieco, E. Williams, T. Sugahara, *J. Org. Chem.* **1979**, *44*, 2194–2199.
[39] P. Barbier, P. Mohr, M. Muller, R. Masciadri, *J. Org. Chem.* **1998**, *63*, 6984–6989.
[40] D. Landini, D. Albanese, M. Penso, *Tetrahedron* **1992**, *48*, 4163–4170.
[41] D. Landini, M. Penso, *Tetrahedron Lett.* **1990**, *31*, 7209–7212.
[42] P. A. Grieco, T. Sugahara, Y. Yokoyama, E. Williams, *J. Org. Chem.* **1979**, *44*, 2189–2193.
[43] P. Angibeaud, J. Defaye, A. Gadelle, J. P. Utille, *Synthesis* **1985**, 1123–1125.
[44] For a review of the Mitsonobu reaction, see: R. Dembinski, *Eur. J. Org. Chem.* **2004**, 2763–2772.
[45] G. J. Wang, J. R. Ella-Menye, M. S. Martin, H. Yang, K. Williams, *Org. Lett.* **2008**, *10*, 4203–4206.
[46] R. G. Salomon, D. J. Coughlin, S. Ghosh, M. G. Zagorski, *J. Am. Chem. Soc.* **1982**, *104*, 998–1007.

Received: November 14, 2008
Published Online: January 13, 2009

