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Comparison of the conformational properties of carbasugars and glycosides: the role of the endocyclic oxygen

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ABSTRACT

A series of carbasugars were prepared and their conformational properties studied by means of NMR spectroscopy. The results were compared to those previously found for O-, S-, and C-β-glycoside analogs. While the rotational populations of the hydroxymethyl group in O-, S-, and C-glycosides are known to depend on the structural nature of their aglycon, in carbasugars it proved to be independent of the *pseudo*-aglycon. This result confirms that endocyclic oxygen is necessary for the observed relationship between the structure of the aglycon and the rotational populations of the hydroxymethyl group, and indicates that the stereoelectronic *exo*-anomeric effect is mainly responsible for such conformational dependence.

1. Introduction

Recent studies on the reactivity of glycosides have revealed an extremely interesting relationship between the populations of the hydroxymethyl group, namely of the *gg*, *gt*, and *tg* rotamers, and the reactivity at the anomeric carbon.[1] This observation is coherent with our previous conformational studies, on the rotational dependence of the hydroxymethyl group on the structure of the aglycon in O-,[2] S-,[3] and C-glycosides.[4] The stereoelectronic *exo*- and *endo*-anomeric effects (Fig. 1),[5–7] in O- and S-glycosides, and the *exo*-deoxoanomeric effect,[8] in C-glycosides, may well be involved in these conformational relationships, non-bonded interactions between these groups being excluded.

Carbasugars, carbohydrates in which the ring oxygen is replaced by a methylene group, are attractive carbohydrate mimics because of their chemical stability and biological properties.[9,10] Moreover, in these analogs the *exo*-and *endo*-anomeric effects cannot be present. If these stereoelectronic effects are involved in the above-mentioned conformational dependence in glycosides, and assuming that non-bonded interactions between the hydroxymethyl group and the aglycon do not operate, the rotameric population about the hydroxymethyl group should be independent of the aglycon nature in the case of carbasugars. In other words, the populations of the hydroxymethyl group (torsion angle ω, Fig. 2)[11] in carbasugars will be completely independent of the structure of the *pseudo*-anomeric aglycon.

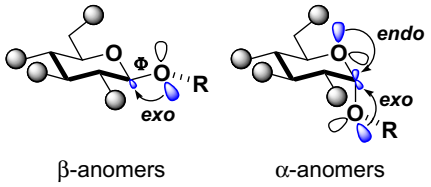

Figure 1. Alkyl β-D- and α-D-glucopyranosides showing the orbitals involved in the *exo*- and *endo*-anomeric effects.

To test our hypothesis and gain further insight into the factors influencing the conformational preferences of the hydroxymethyl group in glycosides, a simple, readily accessible set of conveniently substituted carbocycles were synthesized and conformationally analyzed in solution by NMR spectroscopy. The results were compared to those previously found for O-, S-, and C-β-glycoside analogues.

2. Results and discussion

2.1. Synthesis

There are a plethora of different approaches for the synthesis of carbapyranosides.[12] To obtain a set of them with the appropriate substituent for comparison with the O- and C-glycosides, the synthetic approach shown in Scheme 1 was envisioned. The carbasugar analogs were prepared through Yu's protocol,[13] starting from a non-carbohydrate starting material, the commercially available (±)-3-cyclohexene carboxylic acid.

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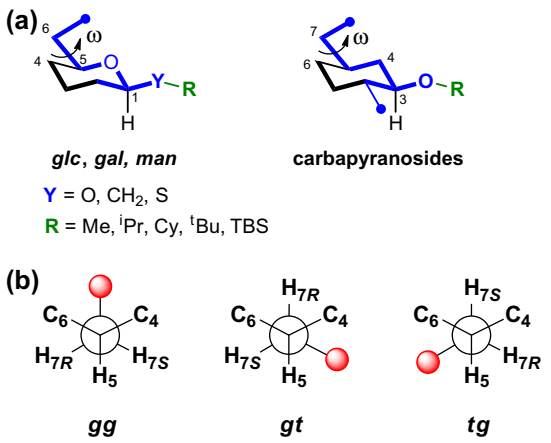


Figure 2. (a) Molecular structure of glycopyranosides (left) and carbapyranosides (right), blue color showing identical structural pattern (upper line). (b) Rotamers around the C5–C7 bond in carbapyranosides: *gauche–gauche* (*gg*), *gauche–trans* (*gt*), and *trans–gauche* (*tg*) (bottom line).

As shown in Scheme 1, this carboxylic acid reacted under standard iodolactonization conditions to give the corresponding *trans*-iodolactone. After elimination of iodine with DBU and treatment with sodium methoxide in methanol, the methyl 5-hydroxy-3-cyclohexene-1-carboxylate **1** was obtained in 96% yield. These methanolysis conditions improved on those previously published,[13a] using $NaHCO_3$ in MeOH and obtaining compound **1** in 81% yield.

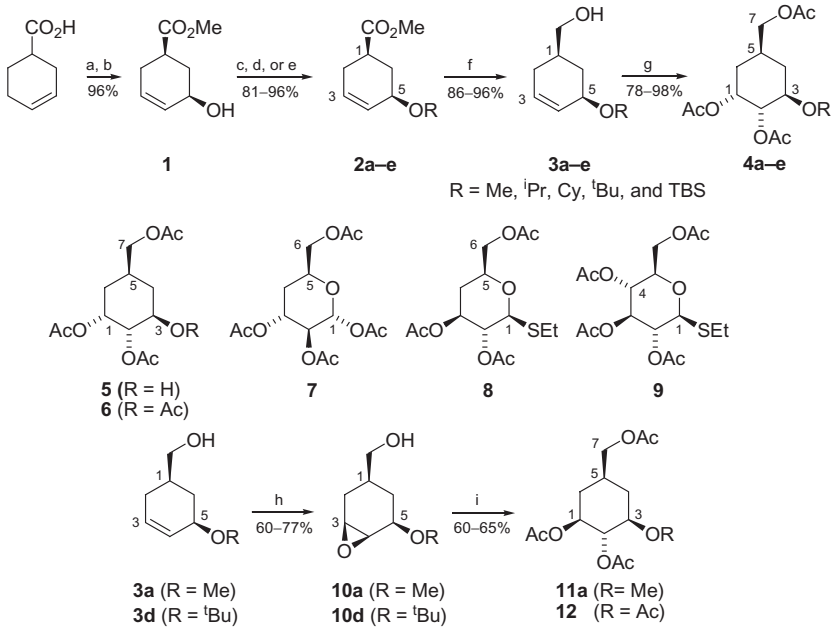
The alkylation of the allylic alcohol with sodium hydride and methyl iodide in DMF provided the methyl ether derivative **2a** (92%).[14] A number of different trials were carried out to prepare ^{i}Pr, Cy, and ^{t}Bu analogs, varying conditions ($AgClO_4$, $AgBF_4$, AgF, $AgNO_3$, Ag_2O, AgO_2CCF_3 and AgOTf) and solvents (CH_2Cl_2, CH_3CN, toluene, and cyclohexane). The best conditions for the introduction of the alkyl group were: the use of Ag_2O, alkyl iodides, and cyclohexane as solvent. Except acetonitrile, the rest of the solvents were also effective. The yield for the ^{i}Pr and ^{t}Bu derivatives **2b** and **2d** was 81% and 91%, respectively; only in the case of cyclohexyl derivative **2c** was it low (31%). In addition, the silyl derivative **2e** was obtained with a 96% yield by the conventional procedure using *tert*-butylsilyl chloride and imidazole.

Reduction of the ester derivatives by $LiAlH_4$ afforded the corresponding primary alcohols **3a–e**, in excellent yields (86–96%). Catalytic osmylation of the olefins, using OsO_4[15] and *N*-methylmorpholine *N*-oxide in acetone–water (6:1), resulted in the *cis*-hydroxylation on the opposite face from the neighboring ether group. Then the compounds were acetylated to give the corresponding alkyl β-deoxocarbapyranosides **4a–e** in good yields (78–98%). In addition, the silyl compound **4e** was deprotected by adding Py–HF to give **5** in 84% yield. Treatment of **5** with acetic anhydride and pyridine led to compound **6** in 97% yield. The 4-deoxysugar **7** was prepared as described by Hirota et al.,[16] in order to compare its conformational properties with those of our model carbasugars. Compounds **11a** and **12** were obtained from compounds **3a** and **3d** by treating them first with *m*-CPBA in CH_2Cl_2 at room temperature overnight to give compounds **10a** and **10d**, respectively, and then by opening the epoxides with acetic anhydride and a catalytic amount of H_2SO_4.

2.2. Characterization and spectroscopic analysis

Compounds **2–6**, and **10–12** were characterized on the basis of their one- (^{1}H and ^{13}C) and two-dimensional (COSY, HSQC, and T-ROESY) NMR spectra. The configuration of the stereogenic carbons C1, C2, and C3 of compounds **4a–e**, **5,** and **6** was assigned in each case on the basis of the H–H coupling constants. The substituents on C1 were found to be in axial disposition and those on C2 and C3 equatorial, and the ring adopts a $^{6}C_3$ chair conformation, as shown in Figure 2, equivalent to the $^{4}C_1$ chair conformation of glycosides. This is in agreement with the conclusions of a conformational study carried out with six methyl carbapyranosides,[17] based on NMR comparison of the chemical shifts and coupling constants of these compounds with the corresponding glycosides.

The ^{1}H NMR chemical shifts in $CDCl_3$ and CD_3CN of the prochiral protons at C7 of compounds **4a–c**, **4e** and **5** were in close proximity (Fig. 3). Only the *tert*-butyl derivative **4d** showed isochronic signals



Scheme 1. Reagents and conditions: (a) I_2, KI, $NaHCO_3$, H_2O; (b) (1) DBU, toluene, reflux; (2) MeONa (cat.), MeOH; (c) MeI, NaH, DMF; (d) ^{i}PrI, CyI or ^{t}BuBr, Ag_2O, cyclohexane; (e) TBSCl, imidazole, DMAP, CH_2Cl_2; (f) $LiAlH_4$, 0 °C; (g) (1) OsO_4 (cat.), NMO, acetone–water (6:1); (2) Py–Ac_2O; (h) *m*-CPBA, CH_2Cl_2; (i) Ac_2O, H_2SO_4 (cat.).

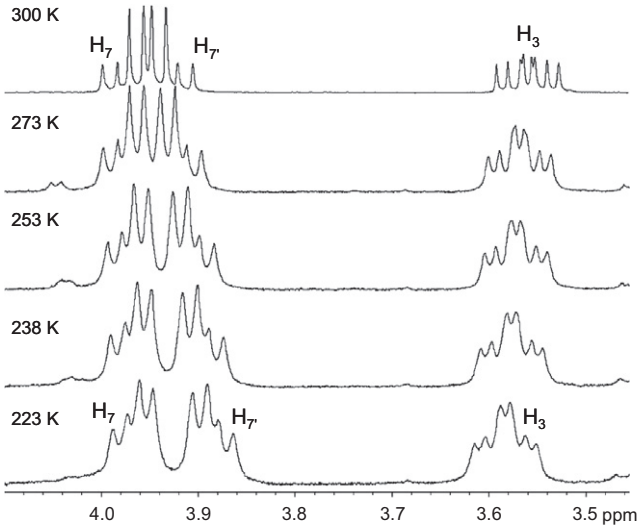


Figure 3. Fragment of the ^{1}H NMR spectrum of compound **4a** at different temperatures in $CDCl_3$ (400 MHz).

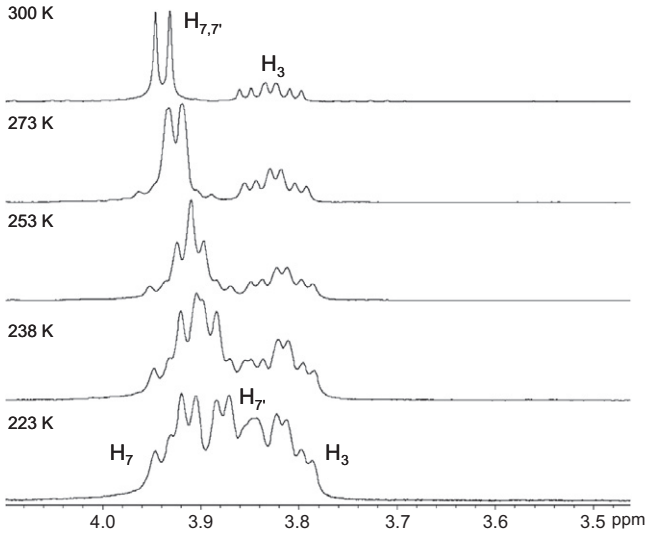


Figure 4. Fragment of the ^{1}H NMR spectrum of compound **4d** at different temperatures in $CDCl_3$ (400 MHz).

Table 1
$^3J_{H5,H7}$ Coupling constants for compounds **4**–**6**, and **11** and **12** in $CDCl_3$ and DMSO-d_6 at 300 K and 500 MHz

Compound	R	$CDCl_3$		DMSO-d_6	
		$^3J_{H5,H7}$	$^3J_{H5,H7'}$	$^3J_{H5,H7}$	$^3J_{H5,H7'}$
4a	Me	6.0	6.1	6.1	6.4
4b	^{i}Pr	6.0	5.9	6.1	6.1
4c	Cy	6.0	5.9	6.0	6.1
4d	^{t}Bu	6.0	6.0	6.3	6.0
4e	TBS	5.8	6.1	6.0	6.0
5	H	5.9	6.0	6.2	6.4
6	Ac	5.6	6.1	5.8	6.6
11a	Me	5.7	6.4	6.1	6.4
12	Ac	6.0	6.0	6.3	6.3

for these protons (Fig. 4). However, changing the solvent to DMSO caused the prochiral protons to display higher chemical shift differences. Experiments recorded in the temperature range of 300–223 K showed a greater separation for the chemical shift of H7 and H7′ as the temperature decreased (Figs. 3 and 4).

The $^3J_{H5,H7}$ coupling constants, in $CDCl_3$ and DMSO-d_6, for compounds **4a**–**e**, **5,** and **6** are shown in Table 1. Analysis of the data revealed that both couplings remained almost constant throughout the series, about 6.0 Hz in $CDCl_3$. When the NMR experiments were recorded at different temperatures (Figs. 3 and 4) the values were the same. According to the Karplus equation,[18] which describes the correlation between the ^3J-coupling constants and dihedral torsion angles in NMR, the local geometry around the C5–C7 bond and populations of the *gg*, *gt*, and *tg* rotamers remained unaltered by changing the *pseudo*-aglycon. Therefore, it can be concluded that the rotational populations of the hydroxymethyl group for these carbapyranosides are independent of the *pseudo*-aglycon (Fig. 5). In addition, this conclusion confirms the absence of non-bonded interactions between the *pseudo*-aglycon and the hydroxymethyl group, and that the conformational variations observed for O-,[2] S-,[3] and C-β-glycopyranosides[4] after changing the structural nature of the aglycon are due to other factors, probably stereoelectronic effects.

Linear correlations between the *gg* and *gt* rotational populations around the C5–C6 bond with the corresponding Taft's steric parameters (E_S)[19] have been recently detected for S-glucopyranosides,[3] C-glycopyranosides,[4] and alkyl α- and β-D-glucopyranosyl-(1→6)-β-D-glucopyranosides[20] by means of NMR and CD. Thus, it was observed that as Taft's steric parameter increased for the alkyl group attached to the anomeric or *pseudo*-anomeric atom, the $^3J_{H5,H6R}$ increased; that is the population of the *gt* rotamer increased at the expense of the *gg* rotamer. The E_S values are composite terms, derived from both potential energy steric effects (steric strains) and entropy effects (steric hindrances to motions). According to Taft,[19] introduction of a straight-chain alkyl group in place of the standard hydrogen substituent raises the activation energy due to steric hindrance. Therefore, the bulkier alkyl groups freeze out the rotation around the O1–C1 bond and therefore the more stable *exo-syn* rotamer increases its population (Fig. 6). This rotamer, also called the *exo*-anomeric rotamer, fulfills the geometric requirements for the *exo*-anomeric effect.

To gain further knowledge of such rotational behavior the coupling constants, $^3J_{H5,H6}$ and $^3J_{H5,H7}$ for glycosides and carbasugars, respectively, were represented against Taft's steric parameters (E_S)[19] (Fig. 7). The representation revealed that for all glycosides there is a linear correlation of the $^3J_{H5,H6R}$ coupling constant with Taft's steric parameters, but for carbapyranosides the $^3J_{H5,H7}$ coupling constants remain invariable, independently of the E_S value of the substituent. Since these constants depend on the rotamer populations,[18] there can be no relationship at all between the structure of the *pseudo*-aglycon (E_S) and the hydroxymethyl rotamer populations for our carbapyranoside models, in contrast to glycopyranosides.

The lack of a substituent at C6, or at the equivalent position C4 in the glycosides (Fig. 2), is a drawback in the interpretation of the data, since the invariable rotamer populations exhibited by our carbasugars could be erroneously assigned to this absence. However, 4-deoxysugars such as **7** ($^3J_{H5,H6}$ = 1.3 and 5.6 Hz)[16] and **8** ($^3J_{H5,H6}$ = 4.3 and 6.0 Hz)[21] showed different $^3J_{H5,H6}$ coupling constants for the two prochiral hydrogens, indicating that the absence of the substituent at C6 in the carbasugars is not the origin of the immobility of their coupling constants. Obviously, the substituent at C4 (glycosides) is the strongest influence on the rotamer population of the hydroxymethyl group. Thus, the thio-glucopyranoside **9**,[3] the equatorially substituted derivative at C4 in **8**, showed different coupling constants ($^3J_{H5,H6}$ = 2.2 and 4.9 Hz) as a consequence of the non-bonded interaction between this substituent and the hydroxymethyl group. Therefore, the above results indicate that the *gg*, *gt* and *tg* populations of the hydroxymethyl group in our carbapyranosides are independent of the structural nature of the R group.

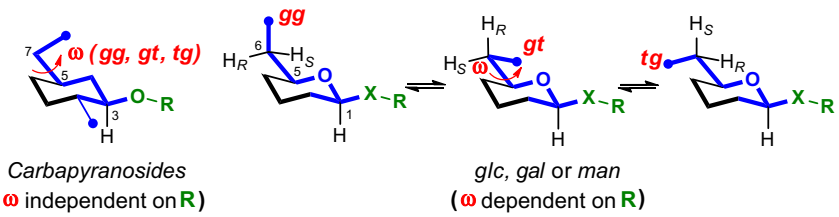


Figure 5. Molecular structure of glycopyranosides in their three main rotamers around the C5–C6 bond (left) and carbapyranosides (right).

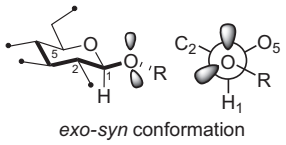


Figure 6. *exo-syn* Rotamer around the O1–C1 bond.

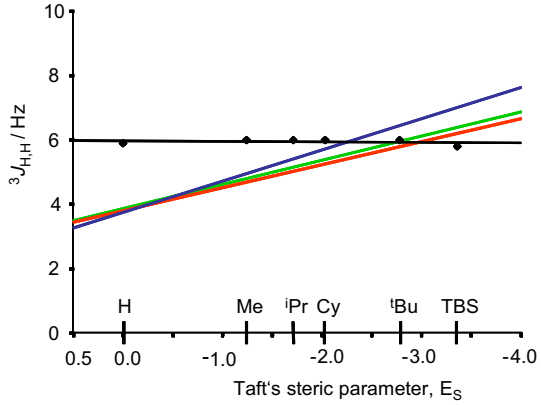


Figure 7. Plot of $J_{H5,H7}$ coupling constant of carbopyranoses **4a–e** and **5**, black line; and $J_{H5,H6R}$ of: O-glycopyranoses,[2] red line; S-glycopyranoses,[3] green line; and C-glycopyranoses,[4] blue line; versus the corresponding E_S value for the aliphatic substituent ($CDCl_3$).

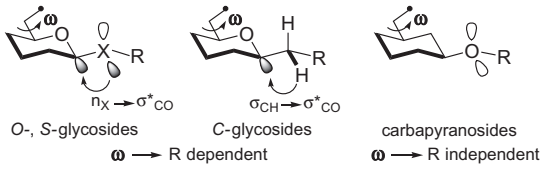


Figure 8. Molecular orbitals involved in the *exo*-anomeric effect for O- and S-glycosides (left), and in the *exo*-deoxoanomeric effect for C-glycosides (middle). Absence of the σ^*_{CO} orbital necessary for involvement in a stereoelectronic effect for carbapyranosides (right).

It is known that the C3 substituent in 4,6-*O*-benzylidene mannopyranosyl triflates is important in the β-mannopyranosylation reaction,[22] and also that the reactivity of glycoside hydrolysis depends on the hydroxymethyl rotamer population.[1] So, to test if steric effects due to the axial configuration at C1 in our carbapyranoside models (C3 position in glycosides) are transmitted around the ring through a series of buttressing interactions, modifying the hydroxymethyl rotamer behavior, compounds **11a** and **12** having an equatorial configuration at C1 were synthetized and their $^3J_{H5,H7}$ coupling constants analyzed. As can be observed in Table 1, their $^3J_{H5,H7}$ values are very similar to those of compounds **4–6** indicating that the configuration at C1 does not alter the rotamer population, and therefore is in agreement with our above data interpretation.

The rotational dependence of the hydroxymethyl group in O-, and S-glycosides on the structural nature of the aglycon has been explained by the different values of the *exo*-anomeric effect (Fig. 8),[2,3] whereas the rotational dependence observed in C-glycosides on the aglycon was explained by the *exo*-deoxoanomeric effect.[4] This assignment is based on the linear relationship between the increased *gt* and decreased *gg* population of the hydroxymethyl group and (i) the pK_a of the alcohol bonded to the anomeric carbon or (ii) Taft's steric parameters (E_S) of the aglycon, and (iii) that no other effect accounts for these rotational changes. It is also clear from this study that non-bonded interactions between the *pseudo*-aglycon and the hydroxymethyl group must be excluded. Furthermore, the parallelism between this dependence and the well-known relationship between the pK_a of the substituent at the anomeric carbon and the lengths of the *endo*- (O5–C1) and *exo*-cyclic (C1–O1) bonds[6] support the stereoelectronic origin of the former.

A relationship has been observed between the bond lengths around the ring oxygen and anomeric carbon and the spatial disposition of the hydroxymethyl group in the X-ray structural analysis of the 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl chloride,[23] where both *gg* and *gt* rotamers occur simultaneously in the crystal. The structure of the *gt* rotamer displayed an unusually long C5–O5 distance and that of the *gg* only short distances for the C1–Ol and the C1–O5 bonds, confirming the relationship between the ring atomic distances and the orientation of the 6-substituent. In addition, recent crystallographic studies of tetrafluorinated methyl galactoside anomers[7] revealed that the values for the C1–O1 and C1–O5 bond lengths and the O5–C1–O1–CH3 dihedral angles are in line with what could be expected from the anomeric and *exo*-anomeric effects.

All these results point to the stereoelectronic n_X—σ^*_{CO} (X = O or S) in glycosides, or σ_{CH}—σ^*_{CO} in C-glycosides, being involved in the rotational behavior of the hydroxymethyl group. Carbapyranosides, lacking the necessary endocyclic oxygen for the stereoelectronic effect, cannot display this rotational dependence. As expected, no relationship between the *pseudo*-aglycon and the hydroxymethyl group was observed confirming the role of the endocyclic oxygen (Fig. 8).

3. Conclusions

A set of carbapyranoside derivatives were synthesized by means of Yu's protocol,[13] and some chemical improvements were made. The model set was then characterized and their conformational properties analyzed by ^{1}H NMR in different solvents and temperatures. Their $^3J_{H5,H7}$ coupling constants, either in $CDCl_3$ or DMSO, were independent of the structure of the *pseudo*-aglycon. Therefore, in contrast to O-, S- and C-β-glycosides,[2–4] the rotational populations of the hydroxymethyl group in carbapyranosides seem not to depend on the structure of their *pseudo*-aglycon. The absence of the endocyclic oxygen, and consequently of the

stereoelectronic *exo*-and *endo*-anomeric effects, has a crucial role in such rotational behavior.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded at 500 MHz, and ^{13}C NMR at 100 MHz, VTU 300.0 K. Chemical shifts are reported in parts per million. The residual solvent peak ($CDCl_3$) was used as an internal reference, 7.26 for protons and 77.0 ppm for the central peak of carbon. ^{1}H NMR experiments at different temperatures were recorded in a 400 MHz instrument. For analytical thin-layer chromatography, silica gel ready-foils were used, developed with 254 nm UV light and/or spraying $AcOH/H_2O/H_2SO_4$ (80:16:4) and heating at 150 °C. Flash column chromatography was performed using silica gel (60 Å). All reagents were obtained from commercial sources and used without further purification. Solvents were dried and distilled before use. All reactions were performed under a dry nitrogen atmosphere.

4.2. General procedure for the reduction of methyl esters

To a solution of the methyl ester in dry THF (2 mL/mmol) at 0 °C, 2 equiv of $LiAlH_4$ (1.0 M in Et_2O) were added. After 2 h, 1 equiv of NaOH (4% in water) was added; the ice bath retired and the reaction stirred for 1.5 h. Then, the mixture was diluted with water and extracted twice with CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The product was purified by column chromatography.

4.3. General procedure for the dihydroxylation and acetylation

To a solution of the starting material in 2 mL/mmol of the acetone–H_2O mixture (6:1), 1.1 equiv of $NMO{\cdot}H_2O$ and OsO_4 as catalyst were added and the reaction stirred overnight. The reaction was quenched with a few drops of saturated $Na_2S_2O_3$ solution and left stirred for 15 min. Then, the reaction was concentrated and the crude dissolved in 10 mL/mmol of Py–Ac_2O (1:1). When it was completed, the solvent was removed under reduced pressure and the residue re-dissolved in EtOAc, washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and the solvent evaporated in vacuum. The product was purified by column chromatography.

4.4. General procedure for the epoxidation

To a stirred solution of the alkene in CH_2Cl_2 (10 mL/mmol) *m*-CPBA 60% (2 equiv) was added and the reaction mixture was stirred overnight. The solids were filtrated and the filtrate was washed with saturated $NaHCO_3$ and water. The combined organic layers were dried over Na_2SO_4, filtered, concentrated, and purified by column chromatography on silica gel, previously neutralized by adding 1% triethylamine to the eluting system.

4.5. General procedure for the epoxide opening

Epoxides were treated with a catalytic amount of sulfuric acid in acetic anhydride (2.5 mL/mmol). The reaction mixture was stirred for 3 h at room temperature, then was cooled to 0 °C and water (25 mL/mmol) was added followed by stirring for 1 h. The aqueous layer was extracted with ethyl ether, and the combined organic extracts washed with $NaHCO_3$ and water. The organic phase was dried over Na_2SO_4 and concentrated to give a crude product which was purified by chromatography on silica gel.

4.6. Methyl (±)-(1*R*,5*R*)-5-hydroxy-3-cyclohexene-1-carboxylate 1

(±)-3-Cyclohexene carboxylic acid (500 mg, 3.96 mmol) was dissolved in a solution of $NaHCO_3$ (1.00 g in 10 mL, 3 equiv) in water. Then a solution of I_2 (1.06 g, 1.05 equiv) and KI (3.94 g, 6 equiv) in 10 mL of water was added and the flask protected from light. After 24 h, it was extracted with CH_2Cl_2, washed successively with $Na_2S_2O_3$ and $NaHCO_3$ water solutions, dried over anhydrous Na_2SO_4, and the solvent was evaporated. The crude was re-dissolved in 24 mL of dry toluene under nitrogen atmosphere, and 1.8 mL (1.5 equiv) of DBU was added. The reaction was heated at reflux for 6 h. Then it was filtered on Celite and concentrated. The crude was re-dissolved in 5 mL of dry MeOH and NaOMe added. After 30 min, this was neutralized with Amberlite IR-120, filtered, concentrated, and purified by column chromatography on silica gel (*n*-hexane/EtOAc 5:5) to yield compound **1** (1.20 g, 96%). Spectroscopic data of this compound were identical to those reported in Ref. 13c.

4.7. Methyl (±)-(1*R*,5*R*)-5-methoxy-3-cyclohexene-1-carboxylate 2a

100 mg (0.64 mmol) of the alcohol **1** was dissolved in 1.3 mL of dry DMF (2 mL/mmol). Then 400 μL (10 equiv) of iodomethane and 32 mg (2 equiv) of sodium hydride were added, and the reaction was stirred for 1 h. Next, it was diluted with CH_2Cl_2, neutralized with a saturated aqueous solution of NH_4Cl, and washed with water. The aqueous fraction was re-extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by column chromatography on silica gel (*n*-hexane/EtOAc 8:2) to yield compound **2a** (100 mg, 92%). Spectroscopic data of this compound were identical to those reported in Ref. 14.

4.8. Methyl (±)-(1*R*,5*R*)-5-*iso*-propoxy-3-cyclohexene-1-carboxylate 2b

Alcohol **1** (215 mg, 1.38 mmol) was dissolved in 2.7 mL of dry cyclohexane (2 mL/mmol), and 645 mg (2 equiv) of silver oxide and 430 μL (3 equiv) of *iso*-propyl iodide were added. The reaction was stirred during 24 h. Then, it was diluted with CH_2Cl_2, filtered on Celite, concentrated, and purified by column chromatography on silica gel (*n*-hexane/EtOAc 8.5:1.5) to yield the compound **2b** (215 mg, 81%): TLC R_f = 0.5 (*n*-hexane/EtOAc 7:3); ^{1}H NMR ($CDCl_3$): δ 5.68 (m, H-3), 5.61 (m, H-4), 4.01 (m, H-5), 3.67 (quint, J = 6.1 Hz), 3.62 (s, 3H), 2.57 (m, H-1), 2.25 (m, H-6), 2.19 (m, H-2 and H-2′), 1.54 (ddd, J = 9.5, 9.5 and 12.4 Hz, H-6′), 1.09 (d, J = 6.1 Hz, 3H), 1.08 (d, J = 6.1 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 175.0 (s), 129.7 (d, C-4), 127.0 (d, C-3), 71.3 (d, C-5), 69.2 (d), 51.6 (q), 38.3 (d, C-1), 32.1 (t, C-6), 27.4 (t, C-2), 22.9 (q), 22.4 (q); Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.66; H, 9.32.

4.9. Methyl (±)-(1*R*,5*R*)-5-cyclohexyloxy-3-cyclohexene-1-carboxylate 2c

100 mg (0.64 mmol) of the alcohol **1** were dissolved in 1.3 mL of dry cyclohexane (2 mL/mmol), and 750 mg (5 equiv) of silver oxide and 840 μL (10 equiv) of cyclohexyl iodide were added. The reaction was stirred for 5 days. Then, it was diluted on CH_2Cl_2, filtered on celite, concentrated, and purified by column chromatography on silica gel (*n*-hexane/EtOAc 8.5:1.5) to yield compound **3c** (25 mg) and recovered 47 mg of the starting material **1**: TLC R_f = 0.7 (*n*-hexane/EtOAc 7:3); ^{1}H NMR ($CDCl_3$): δ 5.72 (m, H-3), 5.67 (m, H-4), 4.10 (m, H-5), 3.68 (s, 3H), 3.38 (m, 1H), 2.61 (m,

H-1), 2.31 (m, H-6), 2.25 (m, H-2 and H-2′), 1.85 (m, 2H), 1.63 (m, 2H), 1.59 (ddd, J = 9.5, 9.5 and 12.4 Hz, H-6′), 1.51 (m, 1H), 1.30–1.20 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 175.1 (s), 130.0 (d, C-4), 127.0 (d, C-3), 75.5 (d), 71.3 (d, C-5), 51.7 (q), 38.5 (d, C-1), 33.3 (t), 32.8 (t), 32.3 (t, C-6), 27.5 (t, C-2), 25.7 (t), 24.3 (t), 24.2 (t); Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.61; H, 9.45.

4.10. Methyl (±)-(1*R*,5*R*)-5-*tert*-butoxy-3-cyclohexene-1-carboxylate 2d

Alcohol **1** (118 mg, 0.76 mmol) was dissolved in 1.5 mL of dry cyclohexane (2 mL/mmol). Next 354 mg (2 equiv) of silver oxide and 260 μL (3 equiv) of *tert*-butyl bromide were added, and the reaction was stirred for 12 h. Then, it was diluted on CH_2Cl_2, filtered on Celite, concentrated, and purified by column chromatography on silica gel (*n*-hexane/EtOAc 8.5:1.5) to yield compound **2d** (147 mg, 91%): TLC R_f = 0.7 (*n*-hexane/EtOAc 7:3); ^{1}H NMR ($CDCl_3$): δ 5.71 (m, H-3), 5.57 (m, H-4), 4.16 (m, H-5), 3.69 (s, 3H), 2.66 (m, H-1), 2.24–2.17 (m, H-2, H-2′ and H-6), 1.63 (ddd, J = 9.5, 9.5 and 12.7 Hz, H-6′), 1.21 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 175.1 (s), 131.7 (d, C-4), 126.7 (d, C-3), 73.9 (s), 66.5 (d, C-5), 51.7 (q), 39.0 (d, C-1), 34.1 (t, C-6), 28.3 (q × 3), 27.3 (t, C-2); Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.90; H, 9.58.

4.11. Methyl (±)-(1*R*,5*R*)-5-*tert*-butyl-dimethyl-silyloxy-3-cyclohexene-1-carboxylate 2e

110 mg (0.70 mmol) of alcohol **1** were dissolved in 3.5 mL of dry CH_2Cl_2 (5 mL/mmol). Then 194 mg (4 equiv) of imidazole and 217 mg (2 equiv) of *tert*-butyl dimethyl silyl chloride were added, and the reaction stirred during 1 h. Next, it was diluted with CH_2Cl_2, washed with $NaHCO_3$ water solution, dried over anhydrous Na_2SO_4, concentrated, and purified by column chromatography on silica gel (*n*-hexane/EtOAc 9.5:0.5) to yield the compound **2e** (182 mg, 96%). Spectroscopic data of this compound were identical to those reported in Ref. 24.

4.12. (±)-(1*R*,5*R*)-5-Methoxy-3-cyclohexen-1-yl-methanol 3a

Following the general procedure for the reduction of methyl esters, 88.0 mg of compound **2a** yielded 64.1 mg (87%) of **3a**, after column chromatography (*n*-hexane/EtOAc 4:6): TLC R_f = 0.5 (*n*-hexane/EtOAc 3:7); ^{1}H NMR ($CDCl_3$): δ 5.77 (m, H-3 and H-4), 3.88 (m, H-5), 3.56 (m, 2H), 3.38 (s, 3H), 2.14–2.10 (m, H-2 and H-6), 1.90 (m, H-1), 1.84–1.75 (m, H-2′ and OH), 1.31 (ddd, J = 9.5, 9.5 and 12.4 Hz, H-6′); ^{13}C NMR ($CDCl_3$): δ 128.8 (d, C-4), 128.1 (d, C-3), 75.2 (d, C-5), 67.2 (t), 55.7 (q), 34.8 (d, C-1), 31.1 (t, C-6), 28.2 (t, C-2); Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.59; H, 10.07.

4.13. (±)-(1*R*,5*R*)-5-*iso*-Propoxy-3-cyclohexen-1-yl-methanol 3b

Following the general procedure for the reduction of methyl esters, 100 mg of compound **2b** yielded 74 mg (86%) of **3b**, after column chromatography (*n*-hexane/EtOAc 4:6): TLC R_f = 0.5 (*n*-hexane/EtOAc 4:6); ^{1}H NMR ($CDCl_3$): δ 5.77 (m, H-3), 5.70 (m, H-4), 4.02 (m, H-5), 3.77 (quint, J = 6.1 Hz, 1H), 3.55 (m, 2H), 2.13–2.03 (m, H-2 and H-6), 1.93–1.75 (m, H-1, H-2′ and OH), 1.39 (ddd, J = 9.5, 9.5 and 12.4 Hz, H-6′), 1.17 (d, J = 6.1 Hz, 3H), 1.15 (d, J = 6.1 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 129.1 (d, C-4), 128.4 (d, C-3), 71.0 (d, C-5), 69.2 (d), 67.0 (t), 34.5 (d, C-1), 32.4 (t, C-6), 28.1 (t, C-2), 22.8 (q), 22.7 (q); Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.55; H, 10.68.

4.14. (±)-(1*R*,5*R*)-5-Cyclohexyloxy-3-cyclohexen-1-yl-methanol 3c

Following the general procedure for the reduction of methyl esters, 160 mg of compound **2c** yielded 129 mg (91%) of **3c**, after column chromatography (*n*-hexane/EtOAc 4:6): TLC R_f = 0.5 (*n*-hexane/EtOAc 1:1); ^{1}H NMR ($CDCl_3$): δ 5.78 (m, H-3), 5.71 (m, H-4), 4.06 (m, H-5), 3.55 (m, 2H), 3.40 (m, 1H), 2.13–2.03 (m, H-2 and H-6), 1.97–1.72 (m, 7H), 1.52 (m, 1H), 1.39 (ddd, J = 9.5, 9.5 and 12.4 Hz, H-6′), 1.28–1.17 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 129.3 (d, C-4), 128.3 (d, C-3), 70.8 (d, C-5), 75.3 (d), 66.9 (t), 34.7 (d, C-1), 33.1 (t), 32.9 (t), 32.5 (t, C-6), 28.1 (t, C-2), 25.6 (t), 24.2 (t), 24.2 (t); Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.24; H, 10.65.

4.15. (±)-(1*R*,5*R*)-5-*tert*-Butoxy-3-cyclohexen-1-yl-methanol 3d

Following the general procedure for the reduction of methyl esters, 120 mg of compound **2d** yielded 100 mg (96%) of **3d**, after column chromatography (*n*-hexane/EtOAc 4:6): TLC R_f = 0.5 (*n*-hexane/EtOAc 1:1); ^{1}H NMR ($CDCl_3$): δ 5.74 (m, H-3), 5.61 (m, H-4), 4.10 (m, H-5), 3.54 (m, 2H), 2.09 (m, H-2), 1.95–1.90 (m, H-1, H-6 and OH), 1.76 (m, H-2′), 1.42 (ddd, J = 8.4, 8.4 and 10.8 Hz, H-6′), 1.22 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 130.9 (d, C-4), 127.9 (d, C-3), 73.9 (s), 67.0 (t), 65.6 (d, C-5), 34.8 (d, C-1), 34.1 (t, C-6), 28.3 (q × 3), 27.7 (t, C-2); Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.71; H, 11.10.

4.16. (±)-(1*R*,5*R*)-5-*tert*-Butyl-dimethyl-silyloxy-3-cyclohexen-1-yl-methanol 3e

Following the general procedure for the reduction of methyl esters, 74.4 mg of compound **2e** yielded 60.9 mg (91%) of **3e**, after column chromatography (*n*-hexane/EtOAc 5:5): TLC R_f = 0.5 (*n*-hexane/EtOAc 1:1); ^{1}H NMR ($CDCl_3$): δ 5.71 (m, H-3), 5.59 (m, H-4), 4.28 (m, H-5), 3.51 (m, H-7 and H-7′), 2.42 (s, OH), 2.07 (m, H-2), 1.96 (m, H-6), 1.87 (m, H-1), 1.76 (m, H-2′), 1.37 (m, H-6′), 0.88 (s, 9H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 131.1 (d, C-4), 127.8 (d, C-3), 67.2 (t, C-7), 67.0 (d, C-5), 35.0 (t, C-6), 34.7 (d, C-1), 27.8 (t, C-2), 25.9 (q × 3), 18.2 (s), −4.6 (q × 2); Anal. Calcd for $C_{13}H_{26}O_2Si$: C, 64.41; H, 10.81. Found: C, 64.44; H, 10.80.

4.17. (±)-(1*R*,2*S*,3*R*,5*S*)-2-Acetoxy-5-acetoxymethyl-3-methoxy-cyclohexyl acetate 4a

Following the general procedure for dihydroxylation and acetylation, 154 mg of compound **3a** yielded 316 mg (96%) of **4a**, after column chromatography (*n*-hexane/EtOAc 6:4): TLC R_f = 0.4 (*n*-hexane/EtOAc 1:1); ^{1}H NMR ($CDCl_3$): δ 5.41 (ddd, J = 2.4, 3.1 and 3.7 Hz, H-1), 4.77 (dd, J = 3.1 and 9.8 Hz, H-2), 3.98 (dd, J = 6.0 and 11.0 Hz, H-7), 3.93 (dd, J = 6.1 and 11.0 Hz, H-7′), 3.56 (ddd, J = 4.7, 9.8 and 11.1 Hz, H-3), 3.40 (s, 3H), 2.23–2.10 (m, H-4_{eq} and H-5), 2.10 (s, 3H), 2.07 (s, 3H), 2.05 (s, 3H), 1.88 (ddd, J = 3.7, 6.4 and 14.5 Hz, H-6_{eq}), 1.40 (ddd, J = 2.4, 12.5 and 14.5 Hz, H-6_{ax}), 1.15 (ddd, J = 11.5, 11.5 and 11.5 Hz, H-4_{ax}); ^{13}C NMR ($CDCl_3$): δ 170.9 (s), 170.3 (s), 170.0 (s), 76.1 (d, C-3), 75.0 (d, C-2), 69.3 (d, C-1), 67.6 (t, C-7), 57.4 (q), 32.4 (d, C-4), 31.5 (d, C-6), 30.0 (d, C-5), 21.0 (q), 20.9 (q), 20.8 (q); Anal. Calcd for $C_{14}H_{22}O_7$: C, 55.62; H, 7.33. Found: C, 55.65; H, 7.53.

4.18. (±)-(1*R*,2*S*,3*R*,5*S*)-2-Acetoxy-5-acetoxymethyl-3-*iso*-propoxy-cyclohexyl acetate 4b

Following the general procedure for dihydroxylation and acetylation, 74.0 mg of compound **3b** yielded 127 mg (88%) of **4b**, after

column chromatography (*n*-hexane/EtOAc 6:4): TLC R_f = 0.6 (*n*-hexane/EtOAc 1:1); ^{1}H NMR ($CDCl_3$): δ 5.40 (ddd, *J* = 2.4, 3.1 and 3.7 Hz, H-1), 4.73 (dd, *J* = 3.1 and 9.7 Hz, H-2), 3.97 (dd, *J* = 6.0 and 10.9 Hz, H-7), 3.92 (dd, *J* = 5.9 and 10.9 Hz, H-7′), 3.70 (quint, *J* = 6.1 Hz, 1H), 3.66 (ddd, *J* = 4.7, 9.7 and 11.1 Hz, H-3), 2.15–2.05 (m, H-4_{eq} and H-5), 2.10 (s, 3H), 2.06 (s, 3H), 2.03 (s, 3H), 1.88 (ddd, *J* = 3.7, 6.5 and 14.4 Hz, H-6_{eq}), 1.39 (ddd, *J* = 2.4, 12.4 and 14.4 Hz, H-6_{ax}), 1.21 (ddd, *J* = 11.5, 11.5 and 11.5 Hz, H-4_{ax}), 1.14 (d, *J* = 6.1 Hz), 1.10 (d, *J* = 6.1 Hz); ^{13}C NMR ($CDCl_3$): δ 171.0 (s), 170.2 (s), 170.0 (s), 75.3 (d, C-2), 72.8 (d, C-3), 71.7 (d), 69.6 (d, C-1), 67.6 (t, C-7), 34.5 (d, C-4), 31.5 (d, C-6), 30.2 (d, C-5), 23.0 (q), 22.5 (q), 21.0 (q), 20.8 (q), 20.8 (q); Anal. Calcd for $C_{16}H_{26}O_7$: C, 58.17; H, 7.93. Found: C, 58.20; H, 8.15.

4.19. (±)-(1*R*,2*S*,3*R*,5*S*)-2-Acetoxy-5-acetoxymethyl-3-cyclohexyloxy-cyclohexyl acetate 4c

Following the general procedure for dihydroxylation and acetylation, 65.0 mg of compound **3c** yielded 89.0 mg (78%) of **4c**, after column chromatography (*n*-hexane/EtOAc 6:4): TLC R_f = 0.6 (*n*-hexane/EtOAc 1:1); ^{1}H NMR ($CDCl_3$): δ 5.40 (ddd, *J* = 2.4, 3.1 and 3.7 Hz, H-1), 4.74 (dd, *J* = 3.1 and 9.7 Hz, H-2), 3.96 (dd, *J* = 6.0 and 10.9 Hz, H-7), 3.92 (dd, *J* = 5.9 and 10.9 Hz, H-7′), 3.71 (ddd, *J* = 4.7, 9.7 and 11.1 Hz, H-3), 3.35 (m, 1H), 2.10–2.00 (m, H-4_{eq} and H-5), 2.10 (s, 3H), 2.06 (s, 3H), 2.02 (s, 3H), 1.87 (ddd, *J* = 3.7, 6.5 and 14.4 Hz, H-6_{eq}), 1.72 (m, 2H), 1.63 (m, 2H), 1.50 (m, 1H), 1.39 (ddd, *J* = 2.4, 12.4 and 14.4 Hz, H-6_{ax}), 1.30–1.20 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 171.0 (s), 170.3 (s), 170.1 (s), 77.7 (d), 75.2 (d, C-2), 72.8 (d, C-3), 69.7 (d, C-1), 67.7 (t, C-7), 34.6 (d, C-4), 33.4 (t), 32.6 (t), 31.6 (d, C-6), 30.3 (d, C-5), 25.6 (t), 24.1 (t), 24.1 (t), 21.2 (q), 20.9 (q), 20.9 (q); Anal. Calcd for $C_{19}H_{30}O_7$: C, 61.60; H, 8.16. Found: C, 61.64; H, 8.34.

4.20. (±)-(1*R*,2*S*,3*R*,5*S*)-2-Acetoxy-5-acetoxymethyl-3-*tert*-butoxy-cyclohexyl acetate 4d

Following the general procedure for dihydroxylation and acetylation, 114 mg of compound **3d** yielded 210 mg (98%) of **4d**, after column chromatography (*n*-hexane/EtOAc 6:4): TLC R_f = 0.6 (*n*-hexano/AcOEt 1:1); ^{1}H NMR ($CDCl_3$): δ 5.41 (ddd, *J* = 2.5, 3.1 and 3.9 Hz, H-1), 4.67 (dd, *J* = 3.1 and 9.6 Hz, H-2), 3.94 (d, *J* = 6.0 Hz, H-7 and H-7′), 3.83 (ddd, *J* = 4.7, 9.6 and 11.1 Hz, H-3), 2.11 (m, H-5), 2.10 (s, 3H), 2.05 (s, 3H), 2.01 (s, 3H), 1.96 (m, H-4_{eq}), 1.87 (ddd, *J* = 3.9, 6.5 and 14.4 Hz, H-6_{eq}), 1.40 (ddd, *J* = 2.5, 12.2 and 14.4 Hz, H-6_{ax}), 1.26 (ddd, *J* = 11.5, 11.5 and 11.5 Hz, H-4_{ax}), 1.17 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 171.0 (s), 170.2 (s), 170.1 (s), 74.7 (d, C-2), 74.1 (s), 69.8 (d, C-1), 67.7 (t, C-7), 67.2 (d, C-3), 36.4 (d, C-4), 31.5 (d, C-6), 30.5 (d, C-5), 28.6 (q × 3), 21.1 (q), 21.0 (q), 20.8 (q); Anal. Calcd for $C_{17}H_{28}O_7$: C, 59.29; H, 8.19. Found: C, 59.32; H, 8.36.

4.21. (±)-(1*R*,2*S*,3*R*,5*S*)-2-Acetoxy-5-acetoxymethyl-3-*tert*-butyl-dimethyl-silyloxy-cyclohexyl acetate 4e

Following the general procedure for dihydroxylation and acetylation, 60.9 mg of compound **3e** yielded 84.5 mg (84%) of **4e**, after column chromatography (*n*-hexane/EtOAc 6:4): TLC R_f = 0.7 (*n*-hexane/EtOAc 1:1); ^{1}H NMR ($CDCl_3$): δ 5.41 (ddd, *J* = 2.5, 3.1 and 3.8 Hz, H-1), 4.68 (dd, *J* = 3.1 and 9.4 Hz, H-2), 3.97 (ddd, *J* = 4.9, 9.4 and 10.9 Hz, H-3), 3.96 (dd, *J* = 5.8 and 10.9 Hz, H-7), 3.93 (dd, *J* = 6.1 and 10.9 Hz, H-7′), 2.13 (m, H-5), 2.08 (s, 3H), 2.06 (s, 3H), 2.01 (s, 3H), 1.95 (m, H-4_{eq}), 1.87 (ddd, *J* = 3.8, 6.4 and 14.4 Hz, H-6_{eq}), 1.41 (ddd, *J* = 2.5, 12.4 and 14.4 Hz, H-6_{ax}), 1.27 (ddd, *J* = 11.5, 11.5 and 11.5 Hz, H-4_{ax}), 0.86 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 170.9 (s), 170.3 (s), 170.0 (s), 76.4 (d, C-2), 69.4 (d, C-1), 67.9 (d, C-3), 67.7 (t, C-7), 36.7 (d, C-4), 31.6 (d, C-6), 30.2 (d, C-5), 25.5 (q × 3), 21.0 (q), 20.9 (q), 20.8 (q), 17.9 (s), −4.6 (q), −4.9 (q); Anal. Calcd for $C_{19}H_{34}O_7Si$: C, 56.69; H, 8.51. Found: C, 56.71; H, 8.66.

4.22. (±)-(1*R*,2*S*,3*R*,5*S*)-2-Acetoxy-5-acetoxymethyl-3-hydroxy-cyclohexyl acetate 5

Compound **4e** (110 mg, 0.27 mmol) was dissolved in 2.7 mL of dry acetonitrile (10 mL/mmol) in a Teflon flask. Under nitrogen atmosphere and at 0 °C 100 μL of the complex Py·HF (7:3) were slowly added. Then, the ice bath was removed and the reaction stirred overnight. It was quenched with saturated $NaHCO_3$ solution, extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, filtered, and the solvent evaporated. The crude was purified by column chromatography on silica gel (*n*-hexane/EtOAc 1:1) to yield compound **5** (65.5 mg, 84%): TLC R_f = 0.2 (*n*-hexane/EtOAc 1:1); ^{1}H NMR ($CDCl_3$): δ 5.44 (ddd, *J* = 2.4, 3.0 and 3.6 Hz, H-1), 4.63 (dd, *J* = 3.0 and 9.8 Hz, H-2), 4.01 (ddd, *J* = 4.7, 9.8 and 11.5 Hz, H-3), 3.98 (dd, *J* = 5.9 and 11.0 Hz, H-7), 3.93 (dd, *J* = 6.0 and 11.0 Hz, H-7′), 2.20–2.14 (m, H-4_{eq}, H-5 and OH), 2.08 (s, 3H), 2.06 (s, 6H), 1.90 (ddd, *J* = 3.6, 6.4 and 14.5 Hz, H-6_{eq}), 1.41 (ddd, *J* = 2.4, 12.6 and 14.5 Hz, H-6_{ax}), 1.24 (ddd, *J* = 11.5, 11.5 and 11.5 Hz, H-4_{ax}); ^{13}C NMR ($CDCl_3$): δ 171.0 (s), 170.9 (s), 170.1 (s), 77.2 (d, C-2), 69.1 (d, C-1), 67.6 (d, C-3), 67.4 (t, C-7), 35.5 (d, C-4), 31.8 (d, C-6), 30.2 (d, C-5), 21.0 (q), 20.9 (q), 20.8 (q); Anal. Calcd for $C_{13}H_{20}O_7$: C, 54.16; H, 6.99. Found: C, 54.15; H, 7.12.

4.23. (±)-(1*R*,2*R*,3*R*,5*R*)-5-(Acetoxymethyl)cyclohexane-1,2,3-triyl triacetate 6

Following the general procedure for acetylation, 110 mg of compound **5** (0.38 mmol) yielded 122 mg (97%) of **6**, after column chromatography (*n*-hexane/EtOAc 6:4): TLC R_f = 0.5 (*n*-hexane/EtOAc 1:1); ^{1}H NMR ($CDCl_3$): δ 5.43 (ddd, *J* = 3.0, 3.2 and 3.2 Hz, H-1), 5.16 (ddd, *J* = 5.0, 10.4 and 11.5, Hz, H-3), 4.85 (dd, *J* = 3.2 and 10.3 Hz, H-2), 3.95 (dd, *J* = 5.6 and 11.0 Hz, H-7), 3.89 (dd, *J* = 6.1 and 11.0 Hz, H-7′), 2.24–2.18 (m, H-4_{eq}, and H-5), 2.10 (s, 3H), 2.06 (s, 3H), 2.03 (s, 3H), 2.00 (s, 3H), 1.90 (ddd, *J* = 3.2, 6.4 and 14.8 Hz, H-6_{eq}), 1.41 (ddd, *J* = 2.4, 12.7 and 14.8 Hz, H-6_{ax}), 1.24 (ddd, *J* = 11.5, 11.5 and 12.6 Hz, H-4_{ax}); ^{13}C NMR ($CDCl_3$): δ 170.8 (s), 170.3 (s), 170.2 (s), 170.0 (s), 73.0 (d, C-2), 69.2 (d, C-1), 68.8 (d, C-3), 67.1 (t, C-7), 32.8 (d, C-4), 31.3 (d, C-6), 29.8 (d, C-5), 20.8 (2 × q), 20.6 (q), 20.6 (q); Anal. Calcd for $C_{15}H_{22}O_8$: C, 54.54; H, 6.71. Found: C, 54.50; H, 6.82.

4.24. Compound 10a

Following the general procedure for epoxidation, 30 mg of compound **3a** (0.21 mmol) yielded 20 mg (60%) of **10a**, after column chromatography (*n*-hexane/EtOAc 4:6): TLC R_f = 0.4 (*n*-hexane/EtOAc 3:7); ^{1}H NMR ($CDCl_3$): δ 3.56–3.50 (m, H-5 and H-7), 3.47 (s, 3H), 3.47 (m, H-7′), 3.29 (br s, H-3), 3.14 (br d, *J* = 3.6 Hz, H-4), 2.16 (m, H-2), 2.02 (m, H-6), 1.60 (m, H-1), 1.50 (m, H-2′), 0.98 (m, H-6′); ^{13}C NMR ($CDCl_3$): δ 75.1 (q), 67.2 (t, C-7), 57.0 (d, C-5), 54.4 (d, C-4), 53.4 (d, C-3), 30.6 (t, C-6), 29.6 (d, C-1), 27.7 (t, C-2); HRMS (EI) Calcd for $C_8H_{14}O_3$: 158.0943. Found: 158.0947.

4.25. Compound 10d

Following the general procedure for epoxidation, 68 mg of compound **3d** (0.37 mmol) yielded 57 mg (77%) of **10d**, after column chromatography (*n*-hexane/EtOAc 4:6): TLC R_f = 0.4 (*n*-hexane/EtOAc 1:1); ^{1}H NMR ($CDCl_3$): δ 3.80 (dd, *J* = 6.2 and 8.9 Hz, H-5), 3.49 (dd, *J* = 5.2, 10.7 Hz, H-7), 3.41 (dd, *J* = 6.4 and 10.7 Hz, H-7′), 3.24 (br s, H-3), 3.03 (d, *J* = 3.6 Hz, H-4), 2.09 (m, H-2), 1.80 (m, H-6), 1.62 (m, H-1), 1.50 (m, H-2′), 1.24 (s, 9H), 1.05 (m, H-6′);

^{13}C NMR ($CDCl_3$): δ 74.7 (s), 67.2 (t, C-7), 65.6 (d, C-5), 56.8 (d, C-4), 53.6 (d, C-3), 32.9 (t, C-6), 29.8 (d, C-1), 28.1 (3 × q), 27.2 (t, C-2); HRMS (EI) Calcd for $C_{11}H_{20}O_3$: 200.1412. Found: 200.1417.

4.26. (±)-(1*R*,2*R*,3*S*,5*R*)-2-Acetoxy-5-acetoxymethyl-3-methoxycyclohexyl acetate 11a

Following the general procedure for epoxide opening, 15 mg of **10a** (0.09 mmol) yielded 17 mg (60%) of compound **11a**, after column chromatography (*n*-hexane/EtOAc 6:4): TLC R_f = 0.4 (*n*-hexane/EtOAc 1:1); ^{1}H NMR ($CDCl_3$): δ 4.94 (dd, J = 9.7 and 9.7 Hz, H-2), 4.82 (ddd, J = 4.8, 9.8 and 11.5 Hz, H-1), 3.98 (dd, J = 5.7 and 10.9 Hz, H-7), 3.92 (dd, J = 6.4 and 10.9 Hz, H-7′), 3.34 (s, 3H), 3.23 (ddd, J = 4.7, 9.5 and 11.5 Hz, H-3), 2.14 (m, H-4$_{eq}$), 2.02 (m, H-6$_{eq}$), 1.78 (m, H-5), 1.24 (m, H-4$_{ax}$), 1.13 (m, H-6$_{ax}$), 2.05 (s, 3H), 2.04 (s, 3H), 1.99 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 171.0 (s), 170.9 (s), 170.4 (s), 79.1 (d, C-3), 76.1 (d, C-2), 71.5 (d, C-1), 67.3 (t, C-7), 57.4 (q), 32.8 (d, C-6), 31.9 (d, C-4), 31.3 (d, C-5), 20.9 (q), 20.8 (q), 20.7 (q); HRMS (EI) Calcd for [$C_{14}H_{22}O_7$+1]: 303.1444. Found: 303.1433.

4.27. (1*R*,2*s*,3*S*,5*s*)-5-(Acetoxymethyl)cyclohexane-1,2,3-triyl triacetate 12

Following the general procedure for epoxide opening, 25 mg of **10d** (0.12 mmol) yielded 26 mg (65%) of compound **12**, after column chromatography (*n*-hexane/EtOAc 6:4): TLC R_f = 0.5 (*n*-hexane/EtOAc 1:1); ^{1}H NMR ($CDCl_3$): δ 5.07 (dd, J = 9.8 and 9.8 Hz, H-2), 4.87 (ddd, J = 5.0, 10.4 and 11.5 Hz, H-1 and H-3), 3.96 (d, J = 6.0 Hz, 2H-7), 2.14–2.09 (m, H-4$_{eq}$ and H-6$_{eq}$), 2.05 (s, 3H), 2.03 (s, 3H), 2.02 (s, 6H), 1.92 (m, H-5), 1.29–1.24 (m, H-4$_{ax}$ and H6$_{ax}$); ^{13}C NMR ($CDCl_3$): δ 170.8 (s), 170.2 (s), 170.1 (2 × s), 74.5 (d, C-2), 71.5 (d, C-1 and C-3), 68.9 (t, C-7), 32.6 (d, C-4 and C-6), 31.3 (d, C-5), 20.9 (2 × q), 20.8 (q), 20.7 (q); HRMS (EI) Calcd for [$C_{15}H_{22}O_8$+1]: 331.1393. Found: 331.1394.

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