Osmylation of chiral *cis*-cyclohexadienediols

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A study on the osmylation of a series of chiral *cis*-cyclohexadienediols is described. Dihydroxylation takes place preferentially on the more electron-rich double bond. For 3-methylcyclohexa-3,5-diene-1,2-diol, **1a**, the presence of protecting groups on the diol functionality is crucial in determining the degree of regio- and stereoselectivity of the reaction. X-ray crystal structure data of the major product of the osmylation of diene **1a**, a protected (2*S*)-2-methylconduritol E, is reported. The regioselectivity of the reaction also depends on the method of osmylation used, the stoichiometric procedure being more selective than the catalytic one.

The use of *cis*-cyclohexadienediols in organic synthesis has experienced increasing interest, as shown by the number of reviews that have appeared recently in the literature, highlighting the synthetic and reactivity aspects of these compounds.[1] Part of this interest is due to the rich functionality content and their highly selective reactivity modes, that enables them to be used as starting materials for the synthesis of a wide variety of biologically active products (alkaloids, carbohydrates, conduritols, inositols, *etc.*).[2] Dihydroxylation of the cyclohexadiene ring is one of the most common reactions used in the preparation of all these classes of compounds.

The regio- and stereochemistry of the *cis*-dihydroxylation of double bonds using osmium tetraoxide has been extensively studied.[3] Whereas the reaction on isolated double bonds is quite reliable, with conjugated dienic systems the oxidation becomes less predictable. For instance, Sharpless and others[4] have reported polyosmylation of acyclic conjugated systems when using one equivalent of *N*-methylmorpholine *N*-oxide and catalytic amounts of osmium tetraoxide. The relationship between each group of *cis*-diols formed is *erythro*, and only traces of products resulting from monoosmylation are present. On the other hand, Carless *et al.*[5a] have reported *cis*-diols as the major products when the same conditions are applied to cyclic dienic systems (in particular, cyclohexadienediols). The products, obtained as a diastereomeric mixture, always resulted from attack on the less substituted olefin (regardless of its electronic density). Also, the osmylation of acyclic dienic systems, conjugated or isolated, using one equivalent of potassium ferricyanide and catalytic amounts of osmium tetraoxide, gives mainly monoosmylated products.[4c] Under these conditions, the osmylation takes place preferentially on the more electron-rich double bond of conjugated dienes and on the *trans*- over the *cis*-substituted olefins. For nonconjugated systems, however, the preference is towards the more substituted olefins. Regarding the stereochemistry of the osmylation reaction, several models have been presented, such as those by Kishi, Vedejs and Houk and their coworkers, which give different relative weight to stereoelectronic and steric effects in the transition state.[6,7] For asymmetric dihydroxylations, a model has been proposed that accounts for the experimental results.[8] Also, the osmylation of aromatic systems under photochemical conditions, leading to polyhydroxylated cyclohexane derivatives, has been recently reported.[9]

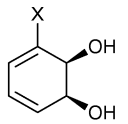
cis-Cyclohexadienediols of the type **1**–**3**, available *via* microbial oxidation of aromatic substrates with enzymes from a mutant strain of *Pseudomonas*, *P. putida* 39D,[10] have been repeatedly used in osmylations.

Interestingly enough, the vast majority of the reported osmylations of these dienediols concerns those that possess a large difference between the reactivity of the two double bonds towards electrophilic reagents. In this way, osmylations of halocyclohexadienediols,[1e,11] as well as cyanocyclohexadienediols,[11b,12] give regiospecifically the dihydroxylated products resulting from attack on the more electron-rich double bond. Reports about osmylations of other cyclohexadienediols are very scarce.[5,13] To gain more insight into the selectivity of this reaction, we decided to test cyclohexadienediols **1-3** possessing different substituents as shown, capable of altering both the electronic density of the double bond system and its steric environment.

Results and discussion

The osmylation reaction was performed under both catalytic and stoichiometric conditions, since each method has its advantages and drawbacks.[14]

For this type of system, the direction of approach by osmium tetraoxide to the double bonds is expected to be governed by Kishi's rules, which for cyclohex-2-enol and its *O*-alkyl and acyl derivatives, favour approach *anti* to the adjacent allylic C—O bonds.[7a,b] However, we were cautious about this because of different results reported by Carless for unprotected cyclohexadienediol systems,[5a] in which the



1a X = CH_3
2a X = Cl
3a X = $CH{=}CH_2$

Structures 1–3

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amount of diols resulting from *syn* attack ranged between one-third to one-half of the total osmylated products. Also, the selectivity of this reaction using different protecting groups was addressed.

Stoichiometric *vs.* catalytic osmylation

The substrate chosen for the osmylation study was the acetate derivative **1b**, in which neither the regio- nor the stereoselectivity is highly predictable, since this diacetate possesses a di- and a trisubstituted conjugated double bond and the directing group (acetate) is not so large as to completely shield one face of the molecule.[15] The stoichiometric osmylation was conducted in a *tert*-butyl alcohol–pyridine mixture, using one equivalent of osmium tetraoxide and gaseous hydrogen sulfide to hydrolyze the metal ester complex at the end of the reaction, as shown in Scheme 1.

Table 1 summarizes the results obtained for this osmylation using different ligands and reaction temperatures. The reaction was slow, in some cases taking several days to reach completion. The regioselectivity found was moderate, with the major product being the diol **4b**, resulting from attack on the more substituted olefin. This selectivity increased with temperature, together with the amount of **7**, a product resulting from overoxidation of the alcohol **4b**. The osmium tetraoxide-mediated oxidation of secondary alcohols is known,[16] and has been reported for allylic cyclohexenol derivatives.[5b,11b] Since a pseudo-axial hydrogen atom is removed during the oxidation, there exists the possibility of C—H orbital overlap with the alkene π-electrons in the transition state.

The stereoselectivity was complete, since no evidence for the formation of isomers resulting from attack on the β-face was observed (^{1}H and ^{13}C NMR). The stereochemical assignments were made using NOE experiments [see Fig. 1(A) for NOE enhancements on **5b**], chemical shift reagents [namely Eu(dpm)$_3$] and information from coupling constants. For example, the (C-4) C*H*OH for **5b** had a coupling of 4.0 Hz (axial–equatorial) and 10.0 Hz (axial–axial). These data are consistent with the diol adopting a conformation with the hydroxy and acetoxy groups on C-4 and C-5 equatorial and the hydroxy group on C-3 pseudo-axial. In addition, the structure of diol **4b**, showing the *anti* relationship of the newly introduced diol functionality to the acetates, was confirmed by X-ray crystallography (Fig. 2).[17]

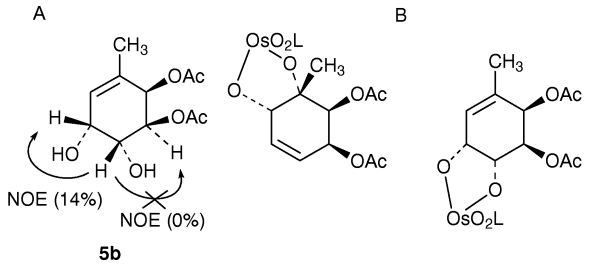
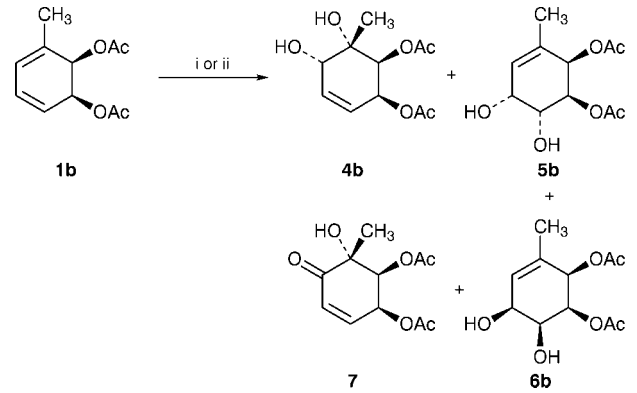


Fig. 1 (A) NOE enhancements on compound **5b**. (B) Regioisomeric osmium complexes of **4b** and **5b**. L: ligand or electron pair

When triethylamine was used as the base, only minor changes in stereoselectivity were observed; diol **6b**, a diastereomer of **5b**, was detected in small amounts. The difference in facial selectivity displayed by different amine–osmium tetraoxide adducts in protic solvents is unusual, and at this stage it is not possible to rationalize these results without further study.

For the catalytic method, the conditions chosen were the most cited in the literature, namely *N*-methylmorpholine *N*-oxide (NMO) as oxidating agent[18] (Scheme 1). In this case the reaction was much faster and hence, lower temperatures could be used. In Table 2, the results for different temperatures are presented. As for the stoichiometric case, diol **4b** was the major product, although with lower selectivity (*ca.*



Scheme 1 Reagents: i, OsO_4, *t*-BuOH-py (or TEA), then H_2S; ii, *N*-methylmorpholine *N*-oxide, acetone–H_2O, OsO_4 (cat.)

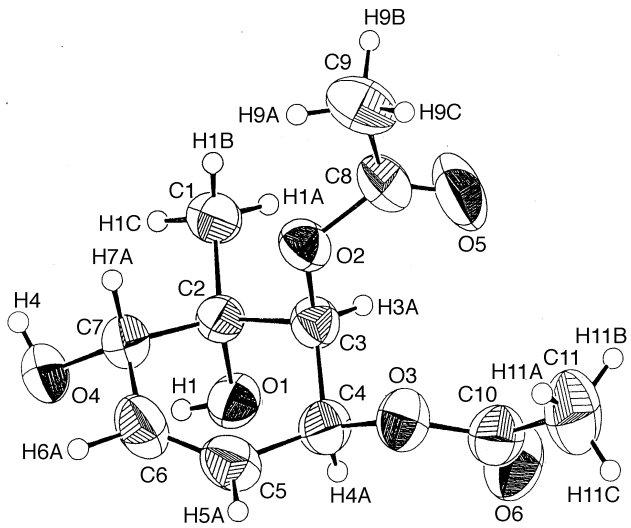


Fig. 2 X-Ray structure of diol **4b**.

Table 1 Stoichiometric osmylation of diol **1b**

Ligand	Conditions (T/°C, t/h)[a]	Ratio[b] **4b** : **5b** : **6b** : **7**	Overall yield/%
Pyridine	50, 48	60 : 20 : 0 : 20	65
Pyridine	80, 24	65 : 15 : 0 : 20	65
Pyridine	100, 24	75 : 0 : 0 : 25	65
Et_3N, 1.5 eq	50, 44	70 : 15 : 0 : 15	70
Et_3N, 2.5 eq	50, 80	55 : 13 : 7 : 25	70

[a] Time to reach final concentrations. [b] Ratio determined by ^{1}H NMR analysis, values given are ±5%.

Table 2 Catalytic osmylation of diol **1b**

Conditions (T/°C, t/h)[a]	Ratio[b] **4b** : **5b**	Overall yield/%
−10, 0.7	70 : 30	65
0, 0.4	65 : 35	65
25, 0.3	65 : 35	65
50, 0.2	65 : 35	65

[a] Time to reach final concentrations. [b] Ratio determined by ^{1}H NMR analysis, values given are ±5%.

2:1). For this method, the selectivity remained virtually unchanged (within experimental error) over the entire range of temperatures used, and no products from overoxidation were detected. The stereoselectivity was again complete; total blocking of the β-face by means of the acetate groups was obtained; diol **6b** was not detected.

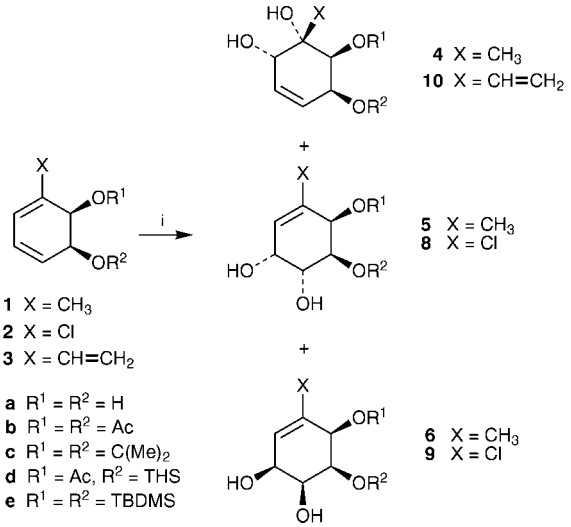
Comparison between stoichiometric and catalytic osmylation of diene **1b** affords interesting conclusions: (*i*) for both methods, the more reactive double bond is the trisubstituted one, (*ii*) the stereoselectivity is complete for both the catalytic and the stoichiometric (when pyridine is used) methods, (*iii*) temperature affects regioselectivity in different manners, depending on the method used, (*iv*) when changing from the stoichiometric to the catalytic method, the regioselectivity drops. Accordingly, whereas the temperature has no effect on the regioselectivity of the catalytic process, an increase of temperature in the stoichiometric method leads to a higher selectivity. At those temperatures though, the presence of overoxidation products such as **7** prevents the reaction from being used for preparative purposes. The stoichiometric process displays a regioselectivity of no less than 4 : 1, much higher than the 2 : 1 exhibited by the catalytic method. This difference in selectivity suggests that different osmium oxidating species are present depending on the method used (*i.e.* an osmium tetraoxide–amine complex in the stoichiometric method and a trioxo osmium(VIII) glycolate ester with catalytic osmium tetraoxide and NMO).[8b,8c] It has been assumed that the product (diastereomer)-determining step involves a competitive and irreversible interaction of the osmium species on the two double bonds of the system, regardless of the operative mechanism of the osmylation ([3 + 2] or [2 + 2] cycloadditions).[8c,19] In an attempt to prove this assumption, the formation of osmium(IV) glycolates corresponding to diols **4b** and **5b**, obtained by stoichiometric osmylation of diene **1b** in deuterated pyridine [Fig. 1(**B**)], was monitored by NMR. Once complexation had taken place at ambient temperature, the reaction mixture was heated up to 80 °C; no change in the ratio of the complexes as determined by NMR was seen. Also, both complexes were stable under chromatographic conditions and, therefore, could be separated by preparative TLC. Each complex was isolated and heated in deuterated pyridine and in deuterated acetone up to 45 °C for 30 min while being monitored by NMR. Again, no evidence of equilibration between the two complexes was observed.

Because the majority of the osmylation reactions reported in recent years deal with the catalytic process, this method was chosen to continue the study of this reaction. In addition, it is much faster and requires less of the expensive and toxic reagent than the stoichiometric method.

Effect of protecting groups

The results in regio- and stereoselectivity prompted us to further study the behaviour of systems of type **1**–**3** when different directing groups and substituents are present (Scheme 2 and Table 3).

In a first trial, the catalytic osmylation of the simple diol **1a** was reexamined, see Table 3, entries 1 and 2. This reaction had been previously reported by Carless *et al.*,[5a] who found a regioselectivity of 70 : 30 favouring the less substituted double bond, after 48 h of reaction at 20 °C. In our hands, this reaction was complete in 1 h at ambient temperature, and the regioselectivity dropped to 55 : 45. We also found some diosmylation product (10%). The products were isolated as acetates, to prevent losses due to the high solubility of the polyols. The stereoselectivity was complete for attack on the more electron-rich double bond. On the other hand, for the disubstituted olefin, the ratio for α : β attack was 4 : 1, showing a significant increase in selectivity with respect to the previously reported values of 2 : 1.[5a] Catalytic osmylation of



Scheme 2 Reagents: i, NMO, acetone–H_2O, OsO_4 (cat.), rt

different alkyl- and silyl-protected methylcyclohexadienediols **1** gave monoosmylated products **4** and **5** in the same 2 : 1 ratio as for the diacetates (Table 3, entries 3 to 5). In both cases, no evidence of diosmylated products was detected (^{1}H NMR). For all cases, the major products obtained, **4a**–**d**, were protected (or unprotected in **4a**) (2*S*)-2-methylconduritol E. In systems such as **1a**, the preference of an electrophilic reagent for the trisubstituted double bond had already been reported for epoxidations.[20]

For the halodienic system **2**, there are three reports dealing with the osmylation of the free diol **2a**[5a] and its acetonide **2c**.[11,15] In all cases the reported regioselectivity is complete, giving the products of attack on the more electron-rich olefin. The stereoselectivity changes from exclusive *anti* attack for the acetonide **2c**, to a 55 : 45 *anti* : *syn* ratio for the diol **2a**. We obtained similar results; moreover, a clear cut in stereoselectivity depending on the presence of free *versus* protected diol became apparent. Thus, regardless of the nature of the protecting group (acetonide, silyl ether, acetate, or a combination of them), osmylation afforded exclusively the *anti* product (Table 3, entries 6 to 9).

A different cyclohexadiene system, **3**, was then studied, in which the electronic density is different than that in **1** and **2**. In this case, there are three double bonds susceptible to electrophilic attack. Catalytic osmylation of triene **3**, protected either as the diacetate **3b** or the disilyl ether **3e**, afforded a 4 : 1 mixture of mono- and diosmylated compounds. These products resulted from the attack on the more substituted double bond to give **10**, and further reaction at the terminal olefin (monitored by TLC) to give diosmylated products (Table 3, entries 10 and 11). Consequently, the order of reactivity for

Table 3 Effect of protecting groups

Entry	Substrate	Product ratio	Overall yield/%
1	**1a**	**4a** : **5a** : **6a** (30 : 47 : 23)[a]	82[a]
2	**1a**	**4a** : **6a** : **6a** (40 : 40 : 10)[b]	72
3	**1b**	**4b** : **5b** (65 : 35)	65
4	**1c**	**4c** : **5c** (67 : 33)	55
5	**1d**	**4d** : **5d** (70 : 30)	70
6	**2a**	**8a** : **9a** (50 : 50)	70
7	**2b**	**8b** (100)	65
8	**2c**	**8c** (100)	70
9	**2d**	**8d** (100)	85
10	**3b**	**10b** (80)[c]	56
11	**3e**	**10e** (80)[c]	70

[a] Ref. 5*a*. [b] Plus 10% of diosmylation. [c] Plus 20% of diosmylation.

the double bonds of this system is as follows: trisubstituted > terminal > disubstituted olefin. The stereoselectivity of the attack on the trisubstituted olefin was complete, giving rise to the α-diol. The configuration of the newly formed stereogenic centre of the side chain was not determined, but it is likely to be only one stereoisomer, by inspection of the ^{13}C NMR spectra.

Conclusions

In summary, despite the higher selectivity obtained using the stoichiometric methodology, the catalytic process is usually preferred in terms of cost and overall efficiency.

Monoosmylation of cyclohexadiene systems of the type **1**–**3** is dependent on the protecting group of the diol functionality for both regio- and stereoselectivity. Regarding the stereoselectivity, the preference for *anti* products is complete in all cases except for free diol systems, in which *syn* products are formed in minor amounts in protic solvents, and only on the disubstituted olefin.[21] It is worth noting that for diol **1a** the ratio for *anti* : *syn* products was 4 : 1, improving the previously reported value of 2 : 1.[5a] The regiochemistry of the osmylation favours the reaction on the more electron-rich double bond (the trisubstituted double bond of **1** and **3**, and the non-halogenated double bond of **2**). For **1a**, the ratio of this preference depends on the presence of any protecting group of the diol functionality, changing from 70 : 30 when the diol is protected to 45 : 55 when the diol is free. The inversion of regioselectivity when passing from free diol to protected diol is interesting, but however, could not be rationalized. This approach to the osmylation of trisubstituted double bonds in cyclohexadienediols holds promise for the preparation of naturally occurring polyoxygenated compounds, such as forskolin and related diterpenes, and is currently under investigation.

Experimental

General

All nonhydrolytic reactions were carried out in a nitrogen atmosphere with standard techniques for the exclusion of air. All solvents were distilled prior to use. Pyridine was dried over NaOH pellets at reflux and distilled over 4 Å molecular sieves.

Melting points were determined on a Gallenkamp capillary melting point apparatus and are uncorrected. Mass spectra were recorded on a Shimadzu GS-MS QP 1100 EX instrument using the electron impact mode (70 eV) or chemical ionization (if indicated). Infrared spectra were recorded either on neat samples (KBr disks) or in solution (with solvent subtraction) on Perkin–Elmer 1310, or Bomem, Hartmann & Braun FTIR spectrometers. Proton NMR spectra were obtained on Bruker Avance DPX-400, Bruker AC-200, or Varian XL-100 instruments. Carbon NMR were obtained on a Bruker Avance DPX-400 at 100 MHz. Proton chemical shifts (δ) are reported in ppm downfield from tetramethylsilane as an internal reference (0.0 ppm), and carbon chemical shifts are reported in ppm relative to the center line of the $CDCl_3$ triplet (77.0 ppm). *J* values are given in Hz. Ultraviolet spectra of samples dissolved in ethanol were recorded on a Shimadzu Digital spectrophotometer. Combustion analyses were performed in a Fisons EA 1108 CHNS-O analyser. X-ray studies were done on a AFC75-Rigaku single crystal diffractometer, over recrystallized samples. Optical rotations were measured on a Perkin Elmer 241 polarimeter using a 2 mL cell. $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}.

Diols **1a**, **2a** and **3a** were obtained by fermentation of the corresponding arenes.[20] Analytical TLC was performed on silica gel 60F-254 plates and visualized with UV light (254 nm) and/or *p*-anisaldehyde in glacial acetic acid. Flash column chromatography was performed using silica gel (Kieselgel 60, EM Reagents, 230–400 mesh).

General procedure for acetylation of diols

To a cold solution of the diol (2 mmol) in acetic anhydride (30 mmol), was added triethylamine (0.61 g, 6 mmol) while stirring. After 2 h of stirring at 4 °C, the solution was diluted with ether (50 mL) and poured onto cold saturated aqueous Na_2CO_3. The aqueous alkaline layer was extracted with ether, and the combined organic layer was washed with water (1 × 15 mL), saturated aqueous $CuSO_4$ (1 × 15 mL), brine (2 × 10 mL), and then dried over $MgSO_4$, filtered, and the solvent was evaporated to obtain the crude acetate as an oil, which was purified by column chromatography.

General procedure for dihydroxylation

Method A: stoichiometric osmylation using pyridine. To a stirred solution of protected diol (0.5 mmol) in pyridine (1.0 g, 12.5 mmol), was added a solution of osmium tetraoxide in *tert*-butyl alchol (2.5% in weight, 5.08 g). The reaction mixture was allowed to react at different temperatures and times. At the end of the chosen period, hydrogen sulfide (prepared by addition of concentrated hydrochloric acid over solid sodium sulfide) was bubbled into the reaction until a fine black precipitate was obtained. The mixture was filtered through Celite and the resulting solution was extracted with ether (2 ×). The combined organic layer was washed with saturated aqueous $CuSO_4$ (3 × 10 mL), brine (2 × 10 mL) and then dried over $MgSO_4$, filtered, and the solvent was evaporated to give a residue which was chromatographed (silica gel, petroleum ether–AcOEt, 60 : 40) to obtain pure diols.

Method B: stoichiometric osmylation using triethylamine. To a stirred solution of protected diol (0.5 mmol) in *tert*-butyl alcohol (3 mL), was added triethylamine (76 mg for the reaction with 1.5 eq of amines and 126 mg for the reaction with 2.5 eq of amine) and a solution of osmium tetraoxide in *tert*-butyl alcohol (2.5% in weight, 5.08 g). The reaction was then continued as above.

Method C: catalytic osmylation. A stirred solution of protected diol (1.5 mmol) in a mixture of acetone (6 mL) and water (6 mL) was treated with *N*-methylmorpholine *N*-oxide (2.25 mmol, 263 mg) and a catalytic amount of osmium tetraoxide (2 drops of a 2.5% solution in *tert*-butyl alcohol). The reaction mixture was stirred at different temperatures and times. At the end of the chosen period the acetone was evaporated and the residue was taken up into ethyl acetate (20 mL). The resulting solution was washed with saturated aqueous $NaHSO_3$ (2 × 5 mL), saturated aqueous $CuSO_4$ (2 × 5 mL), brine (2 × 5 mL), and then dried over $MgSO_4$, filtered, and the solvent was evaporated to give the crude mixture, which was chromatographed (silica gel, petroleum ether–AcOEt, 60 : 40) to obtain pure diols.

Syntheses

(1*S*, 2*R*)-3-Vinylcyclohexa-3,5-diene-1,2-diyl diacetate, 3b. This compound was obtained by acetylation of diol **3a** according to the general procedure. Clear oil; δ_H (400 MHz, $CDCl_3$): 6.37 (1H, dd, *J* 17.6 and 10.9), 6.12–6.18 (2H, m), 5.93 (1H, d, *J* 5.9), 5.81–5.73 (2H, m), 5.38 (1H, d, *J* 17.6), 5.17 (1H, d, *J* 11), 2.09 (3H, s), 2.06 (3H, s); δ_C (100 MHz, $CDCl_3$): 171.0 (C), 170.5 (C), 135.4 (CH), 133.9 (C), 128.1 (CH), 127.4 (CH), 125.1 (CH), 115.2 (CH_2), 71.2 (CH), 63.5 (CH), 21.20 (CH_3), 21.16 (CH_3); ν_{max} (neat)/cm^{-1}: 3030, 1735, 1600, 1370, 1240;

m/z: 222 (3%), 163 (2), 162 (6), 120 (100); $[\alpha]_D$: −121.0 (*c* 0.31, CH_2Cl_2)

(1*S*, 2*R*)-1,2-Bis(*tert*-butyldimethylsilyl)oxy-3-vinylcyclohexa-3,5-diene, 3e. To a stirred solution of diol **3a** (0.450 g, 3.3 mmol) in DMF (5 mL), was added imidazole (0.700 g, 11 mmol) and *tert*-butyldimethylsilyl chloride (1.600 g, 11 mmol) in one portion at 0 °C. After 3.5 h the reaction was quenched by addition of brine and extracted with ether (3 × 20 mL). The combined organic layer was washed with saturated aqueous $CuSO_4$ (1 × 20 mL), water, brine (3 × 5 mL), and then dried over $MgSO_4$, filtered, and the solvent was evaporated to obtain crude silyl ether **3e**, which was purified by column chromatography (silica gel, petroleum ether). Clear oil; δ_H (100 MHz, $CDCl_3$): 6.40 (1H, dd, *J* 17.5 and 10.8), 5.98–5.83 (3H, m), 5.39 (1H, d, *J* 15.7), 5.17 (1H, d, *J* 10.8), 4.42 (1H, d, *J* 2.5), 4.25 (1H, d, *J* 4.5), 1.05 (9H, s), 0.84 (9H, s), 0.15–0.02 (12H, m); δ_C (100 MHz, $CDCl_3$): 137.1 (C), 135.2 (CH), 126.3 (CH), 125.1 (CH), 123.6 (CH), 113.4 (CH_2), 74.4 (CH), 68.1 (CH), 26.5 (CH_3), 26.4 (CH_3), 18.8 (C), 18.7 (C), −3.8 (CH_3), −4.0 (CH_3), −4.2 (CH_3), −4.3 (CH_3); ν_{max} (neat)/cm^{-1}: 3050, 2960, 2860, 1460, 1250, 1170, 1120; *m/z*: 366 (12%), 309 (2), 251 (3), 235 (8), 221 (23), 104 (11), 57 (7); $[\alpha]_D$: +30.8 (*c* 0.32, CH_2Cl_2).

(1*S*, 2*S*, 3*S*, 4*S*)-2-Hydroxy-2-methylcyclohex-5-ene-1,3,4-triyl triacetate (4a triacetate).[5a] Clear oil; δ_H (100 MHz, $CDCl_3$): 5.82 (1H, m), 5.74 (2H, br s), 5.38 (2H, m), 2.66 (1H, br s), 2.14 (3H, s), 2.09 (3H, s), 2.02 (3H, s), 1.24 (3H, s).

(1*S*, 2*S*, 3*S*, 4*S*)-3,4-Dihydroxy-3-methylcyclohex-5-ene-1,2-diyl diacetate, 4b. This compound was obtained by osmylation of protected diol **1b**,[20] under the conditions stated in Tables 1 and 2. Colourless solid; mp 95.0–95.2 °C; δ_H (200 MHz, $CDCl_3$): 5.84 (1H, m), 5.75 (1H, m), 5.61 (1H, m), 5.36 (1H, dd, *J* 4.0 and 1.0), 4.10 (1H, s), 3.10 (1H, br s), 2.88 (1H, br s), 2.10 (3H, s), 2.03 (3H, s), 1.34 (3H, s); δ_C (50 MHz, $CDCl_3$): 170.5 (C), 170.4 (C), 131.4 (CH), 125.5 (CH), 73.6 (CH), 72.7 (C), 70.0 (CH), 67.9 (CH), 22.5 (CH_3), 20.9 (CH_3), 20.8 (CH_3); ν_{max} (KBr)/cm^{-1}: 3400, 3043, 2971, 1740, 1368, 1242; *m/z*: 184 (1%), 141 (15), 124 (9), 99 (26), 86 (26), 74 (12), 43 (100); $[\alpha]_D$ +155.0 (*c* 0.13, AcOEt); Anal. found: C, 53.94; H, 6.84. $C_{11}H_{16}O_6$ requires C, 54.09; H, 6.60%.

(1*S*, 2*S*, 3*S*, 4*S*)-3,4-*O*-Isopropylidene-2-methylcyclohex-5-ene-1,2,3,4-tetraol, 4c. This compound was obtained by osmylation of protected diol **1c**,[20] according to method C, during 1 h at room temperature. Colourless solid; mp 73.0–74.0 °C; δ_H (400 MHz, $CDCl_3$): 5.75 (1H, m), 5.67 (1H, d, *J* 10.3), 4.64 (1H, br s), 4.17 (1H, d, *J* 5.1), 4.11 (1H, br s), 2.95 (1H, br s), 2.71 (1H, br s), 1.43 (3H, s), 1.36 (6H, s); δ_C (100 MHz, $CDCl_3$): 130.1 (CH), 127.9 (CH), 109.9 (C), 80.2 (C), 73.7 (CH), 72.9 (CH), 69.7 (CH), 28.1 (CH_3), 26.9 (CH_3), 24.2 (CH_3); ν_{max} (KBr)/cm^{-1}: 3380 (br), 2975, 2880, 1360, 1240, 1095, 1045, 1007; *m/z*: 185 (20%, $M^+ - CH_3$), 141 (10), 125 (22), 101 (100), 95 (18), 71 (23), 43 (60); $[\alpha]_D$: +84.4 (*c* 0.48, $CHCl_3$); Anal. found: C, 60.40; H, 7.80. $C_{10}H_{16}O_4$ requires C, 59.99; H, 8.05%.

(1*S*, 2*S*, 3*S*, 4*S*)-1-(Dimethylthexylsilyl)oxy-3,4-dihydroxy-3-methylcyclohex-5-en-2-yl acetate, 4d. This compound was obtained by osmylation of protected diol **1d** (prepared by acetylation of the known monosilylated methylcyclohexadienediol),[22] according to method C, during 1 h at room temperature. Clear oil; δ_H (100 MHz, $CDCl_3$): 5.71 (m, 2H), 5.25 (1H, d, *J* 5.0), 4.62 (1H, m), 4.07 (1H, br s), 2.84 (2H, br s), 2.12 (3H, s), 1.60 (1H, m), 1.32 (3H, s), 0.90 (6H, d, *J* 7.0), 0.84 (6H, s), 0.16 (3H, s), 0.12 (3H, s).

(1*R*, 2*R*, 3*R*, 4*R*)-5-Methylcyclohex-5-ene-1,2,3,4-tetrayl tetraacetate (5a tetraacetate).[5a] Clear oil; δ_H (100 MHz, $CDCl_3$): 5.66 (3H, m), 5.44 (2H, m), 2.12 (3H, s), 2.08 (3H, s), 2.02 (3H, s), 2.00 (3H, s), 1.76 (3H, s).

(1*R*, 2*R*, 3*R*, 4*R*)-3,4-Dihydroxy-6-methylcyclohex-5-ene-1,2-diyl diacetate, 5b. This compound was obtained by osmylation of protected diol **1b**,[20] under the conditions stated in Tables 1 and 2. Colourless solid; mp 113.4–113.5 °C; δ_H (200 MHz, $CDCl_3$): 5.78 (1H, m), 5.57 (1H, d, *J* 4.0), 5.24 (1H, dd, *J* 10.0 and 4.0), 4.31 (1H, dd, *J* 4.0 and 3.5), 4.03 (1H, dd, *J* 10.0 and 4.0), 3.20 (2H, br s), 2.10 (3H, s), 2.06 (3H, s), 1.74 (3H, br s); δ_C (50 MHz, $CDCl_3$): 171.1 (C), 170.7 (C), 134.5 (C), 127.0 (CH), 69.9 (CH), 69.8 (CH), 66.8 (CH), 66.3 (CH), 20.8 (CH_3), 20.7 (CH_3), 20.2 (CH_3); ν_{max} (KBr)/cm^{-1}: 3270, 2941, 1743, 1376, 1252; *m/z*: 184 (2%), 142 (8), 124 (26), 113(2), 100(41), 95(18), 43(100); $[\alpha]_D$: −186.8 (*c* 0.12, AcOEt); Anal. found: C, 54.28; H, 6.85. $C_{11}H_{16}O_6$ requires C, 54.09; H, 6.60%.

(1*R*, 2*R*, 3*R*, 4*R*)-3,4-*O*-isopropylidene-5-methylcyclohex-5-ene-1,2,3,4-tetraol, 5c. This compound was obtained by osmylation of protected diol **1c**,[20] according to method C, during 1 h at room temperature. Colourless solid; mp 74.0–75.0 °C; δ_H (400 MHz, $CDCl_3$): 5.61 (1H, br d, *J* 4.2), 4.48 (1H, d, *J* 6.5), 4.35 (1H, t, *J* 6.5), 4.24 (1H, br s), 3.89 (1H, dd, *J* 6.5 and 3.3), 3.33 (1H, br s), 3.07 (1H, br s), 1.86 (3H, s), 1.43 (3H, s), 1.40 (3H, s); δ_C (100 MHz, $CDCl_3$): 136.1 (C), 124.8 (CH), 109.8 (C), 76.3 (CH), 75.8 (CH), 71.5 (CH), 66.8 (CH), 28.3 (CH_3), 26.3 (CH_3), 20.7 (CH_3); ν_{max} (KBr)/cm^{-1}: 3480, 3200 (br), 2980, 2840, 1430, 1360, 1230, 1215, 1070, 1000, 860, 850; *m/z*: 185 (32%, $M^+ - CH_3$), 141 (11), 140 (9), 125 (24), 101 (100), 55 (48), 43 (57); $[\alpha]_D$: −97.5 (*c* 3.78, $CHCl_3$); Anal. found: C, 60.39; H, 7.82. $C_{10}H_{16}O_4$ requires C, 59.99; H, 8.05%.

(1*R*, 2*R*, 3*R*, 4*R*)-2-(Dimethylthexylsilyl)oxy-3,4-dihydroxy-6-methylcyclohex-5-en-1-yl acetate, 5d. This compound was obtained by osmylation of protected diol **1d**, according to method C, during 1 h at room temperature. Clear oil; δ_H (100 MHz, $CDCl_3$): 5.70 (1H, m), 5.50 (1H, d, *J* 4.0), 4.37 (1H, m), 4.14 (1H, dd, *J* 9.0 and 4.0), 3.94 (1H, m), 2.86 (1H, br s), 2.64 (1H, br s), 2.10 (3H, s), 1.74 (3H, br s), 1.60 (1H, m), 0.90 (6H, d, *J* 7.0), 0.85 (6H, s), 0.16 (6H, s).

(1*S*, 2*S*, 3*R*, 4*R*)-5-Methylcyclohex-5-ene-1,2,3,4-tetrayl tetraacetate (6a tetraacetate).[5a] Clear oil; δ_H (100 MHz, $CDCl_3$): 5.59 (3H, m), 5.38 (2H, m), 2.10 (3H, s), 2.09 (3H, s), 2.08 (3H, s), 2.06 (3H, s), 1.76 (3H, s).

(1*R*, 2*R*, 3*S*, 4*S*)-3,4-Dihydroxy-6-methylcyclohex-5-ene-1,2-diyl diacetate, 6b. This compound was obtained by osmylation of protected diol **1b**,[20] under the conditions stated in Table 1, and was isolated mainly as its peracetate: **6a** tetracetate. Clear oil; δ_H (100 MHz, $CDCl_3$): 5.70 (1H, m), 5.65 (1H, m), 5.50 (1H, m), 4.36 (1H, m), 4.10 (1H, m), 3.20 (2H, br s), 2.15 (3H, s), 2.09 (3H, s), 1.74 (3H, s).

(2*R*, 3*S*, 4*S*)-3,4-Diacetoxy-2-hydroxy-2-methylcyclohex-5-en-1-one, 7. This compound was obtained by osmylation of protected diol **1b**,[20] under the conditions stated in Table 1. Clear oil; δ_H (100 MHz, $CDCl_3$): 6.82 (1H, dd, *J* 10.0 and 4.0), 6.26 (1H, dd, *J* 10.0 and 1.0), 6.00 (1H, ddd, *J* 4.0, 4.0 and 1.0), 5.42 (1H, d, *J* 4.0), 4.78 (1H, s), 2.12 (3H, s), 2.10 (3H, s) 1.46

(3H, s); δ_C (100 MHz, $CDCl_3$): 198.6 (C), 170.2 (C), 143.4 (CH), 129.4 (CH), 75.1 (C), 73.5 (CH), 66.4 (CH), 21.9 (CH_3), 21.1 (CH_3), 21.0 (CH_3); ν_{max} (neat)/cm^{-1}: 3447(br), 2924, 1750, 1696, 1372, 1283; *m/z*: 139 (11%), 97 (36), 84 (21), 74 (17), 43(100); UV: λ_{max}(EtOH)/nm 235; $[\alpha]_D$: +123.7 (*c* 0.19, $CHCl_3$); Anal. found: C, 54.24; H, 5.85. $C_{11}H_{14}O_6$ requires C, 54.54; H, 5.83%.

(1*R*, 2*R*, 3*S*, 4*S*)-5-Chlorocyclohex-5-ene-1,2,3,4-tetrayl tetraacetate (8a tetraacetate). This compound was obtained by osmylation of diol **2a**, according to method C, during 5 h at 40 °C, and further acetylated. Clear oil; δ_H (400 MHz, $CDCl_3$): 6.08 (1H, d, *J* 5.4), 5.80 (1H, d, *J* 4.3), 5.68 (1H, dd, *J* 5.4 and 4.3), 5.51 (1H, dd, *J* 10.6 and 4.3), 5.39 (1H, dd, *J* 10.6 and 4.3), 2.50 (3H, s), 2.09 (3H, s), 2.04 (3H, s), 2.03 (3H, s); δ_C (100 MHz, $CDCl_3$): 170.3 (C), 170.2 (C), 170.1 (C), 169.9 (C), 134.4 (C), 126.1 (CH), 69.9 (CH), 66.8 (CH), 66.12 (CH), 65.8 (CH), 21.4 (CH_3), 21.0 (CH_3), 20.9 (CH_3), 20.8 (CH_3); ν_{max} (neat)/cm^{-1}: 2975, 1752, 1371, 1225, 1076, 1053, 1016; *m/z*: (CI, CH_4): 291 (29%), 289 (84), 231 (6), 189 (33), 187 (100), 145 (46); $[\alpha]_D$: −129.8 (*c* 0.54, $CHCl_3$); Anal. found: C, 48.24; H, 5.05. $C_{14}H_{17}O_8Cl$ requires C, 48.22; H, 4.92%.

(1*S*, 2*S*, 3*R*, 4*R*)-6-Chloro-3,4-dihydroxycyclohex-5-ene-1,2-diyl diacetate, 8b. This compound was prepared by osmylation of protected diol **2b**, according to method C, during 5 h at 40 °C and further acetylated to obtain **8a** tetraacetate.

(1*R*, 2*R*, 3*S*, 4*S*)-5-Chloro-3,4-*O*-isopropylidenecyclohex-5-ene-1,2,3,4-tetraol, 8c. This compound was obtained by osmylation of protected diol **2c**,[23] according to method C, during 4 h at room temperature. Clear oil; δ_H (400 MHz, $CDCl_3$): 5.95 (1H, m), 4.62 (1H, d, *J* 4.0), 4.43 (1H, t, *J* 4.0), 4.28 (1H, br s), 4.10 (1H, br s), 3.4 (1H, br s), 3.3 (1H, br s), 1.47 (3H, s), 1.45 (3H, s); δ_C (100 MHz, $CDCl_3$): 132.8 (C), 126.9 (CH), 110.4 (C), 76.2 (CH), 75.1 (CH), 69.7 (CH), 66.7 (CH), 27.7 (CH_3), 26.1 (CH_3); ν_{max} (neat)/cm^{-1}: 3407 (br), 2988, 2935, 1652, 1234, 1077, 1052; *m/z*: 207 (10%), 205 (29), 147 (4), 145 (11), 129 (6), 127 (15), 101 (100); $[\alpha]_D$: −27.8 (*c* 0.56, $CHCl_3$).

(1*S*, 2*S*, 3*R*, 4*R*)-2-(Dimethylthexylsilyl)oxy-6-chloro-3,4-dihydroxycyclohex-5-en-1-yl acetate, 8d. This compound was obtained by osmylation of protected diol **2d** (prepared by acetylation of the known monosilylated chlorocyclohexadienediol),[24] according to method C, during 5 h at 40 °C. Clear oil; δ_H (400 MHz, $CDCl_3$): 6.13 (1H, d, *J* 5.0), 5.72 (1H, d, *J* 4.0), 4.50 (1H, t, *J* 4.0), 4.26 (1H, dd, *J* 8.5 and 4.0), 3.98 (1H, dd, *J* 8.5 and 4.0), 2.12 (3H, s), 1.65 (1H, m), 0.92 (6H, d, *J* 7.0), 0.83 (6H, s), 0.14 (6H, s).

(1*S*, 2*S*, 3*S*, 4*S*)-5-Chlorocyclohex-5-ene-1,2,3,4-tetrayl tetraacetate (9a tetraacetate). This compound was obtained by osmylation of diol **2a**, according to method C, during 5 h at 40 °C, and further acetylated. Clear oil; δ_H (400 MHz, $CDCl_3$): 6.02 (1H, dt, *J* 3.4 and 0.8), 5.71 (1H, dt, *J* 4.9 and 0.7), 5.59 (1H, m), 5.45 (1H, dd, *J* 4.4 and 2.1), 5.34 (1H, dd, *J* 4.9 and 2.1), 2.12 (3H, s), 2.10 (3H, s), 2.07 (3H, s), 2.06 (3H, s); δ_C (100 MHz, $CDCl_3$): 170.3 (C), 170.1 (C), 170.0 (C), 169.9 (C), 132.6 (C), 126.2 (CH), 67.7 (CH), 67.2 (CH), 66.9 (CH), 66.6 (CH), 21.0 (CH_3), 21.0 (CH_3), 20.9 (CH_3), 20.8 (CH_3); ν_{max} (neat)/cm^{-1}: 2942, 1752, 1372, 1225, 1045, 941, 916; *m/z*: (CI, CH_4) 291 (15%), 289 (46), 189 (33), 187 (100), 145 (25); $[\alpha]_D$: +22.2 (*c* 2.0, $CHCl_3$); Anal. found: C, 48.26; H, 5.01. $C_{14}H_{17}O_8Cl$ requires C, 48.22; H, 4.92%.

(1*S*, 2*S*, 3*S*, 4*S*)-3,4-Dihydroxy-3-vinylcyclohex-5-ene-1,2-diyl diacetate, 10b. This compound was obtained by osmylation of protected diol **3b**, according to method C, during 8 h at reflux. Clear oil; δ_H (400 MHz, $CDCl_3$): 5.99 (1H, dd, *J* 17.3 and 10.8), 5.83 (2H, m), 5.65 (1H, ddd, *J* 10.2, 3.8 and 2.0), 5.52 (1H, dd, *J* 17.3 and 1.0), 5.42 (1H, dd, *J* 3.8 and 1.7), 5.35 (1H, dd, *J* 10.8 and 1.0), 4.37 (1H, br s), 2.96 (1H, s), 2.39 (1H, s), 2.09 (3H, s), 2.03 (3H, s); δ_C (100 MHz), 170.6 (C), 170.5 (C), 138.2 (CH), 130.6 (CH), 126.3 (CH), 117.5 (CH_2), 75.0 (C), 73.1 (CH), 68.7 (CH), 68.2 (CH), 21.3 (CH_3), 21.2 (CH_3); ν_{max} (neat)/cm^{-1}: 3450, 1740, 1370, 1240, 1030; *m/z*: 239 (4%, $M^+ - OH$), 221 (4), 196 (27), 153 (19), 60 (75), 43 (100); $[\alpha]_D$: +125.4 (*c* 0.23, CH_2Cl_2).

(1*S*, 2*S*, 3*S*, 4*S*)-3,4-Bis(*tert*-butyldimethylsilyl)oxy-2-vinylcyclohex-5-ene-1,2-diol, 10e. This compound was obtained by osmylation of protected diol **3e**, according to method C, during 8 h at reflux. Clear oil; δ_H (400 MHz, $CDCl_3$): 6.29 (1H, dd, *J* 17.4 and 10.8), 5.65–5.56 (m, 2H), 5.48 (1H, dd, *J* 17.4 and 1.4), 5.31 (1H, dd, *J* 10.8 and 1.4), 4.75 (1H, m), 4.34 (1H, m), 3.92 (1H, m), 2.58 (1H, s), 1.92 (1H, s), 0.98–0.85 (18H, m), 0.17–0.09 (12H, m); δ_C (100 MHz): 141.4 (CH), 132.0 (CH), 126.9 (CH), 115.5 (CH_2), 78.4 (C), 77.1 (CH), 69.7 (CH), 69.2 (CH), 26.7 (CH_3), 26.4 (CH_3), 19.0 (C), 18.8 (C), −3.8 (CH_3), −3.9 (CH_3), −4.1 (CH_3), −4.3 (CH_3); ν_{max} (neat)/cm^{-1}: 3400, 3030, 2940, 2880, 2850, 1460, 1250; *m/z*: 382 (1%, $M^+ - H_2O$), 343 (1), 367 (1), 267 (1), 325 (7); $[\alpha]_D$: +74.1 (*c* 0.27, CH_2Cl_2).

Crystal data for 4b

$C_{11}H_{16}O_6$, $M = 244.24$, monoclinic, space group $P2_1$, colourless crystal, $a = 7.935(7)$, $b = 8.656(3)$, $c = 9.389(3)$ Å, $\beta = 97.87(4)$ Å, $U = 638.9(6)$ Å^3, $Z = 2$, $D_c = 1.270$ g cm^{-3}, $F(000) = 260$, $\mu = 0.104$ mm^{-1}. Rigaku AFC7S diffractometer, graphite monochromated Mo-Kα radiation ($\lambda = 0.71069$ Å), 1592 reflections measured, maximum θ value of 27.47°. Final *R* factor = 0.0469 for 1178 observed reflections ($I > 2\sigma I$).

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