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Tetrahedron: *Asymmetry* 16 (2005) 1393–1402

Chemoenzymatic synthesis of enantiopure α-substituted cyclohexanones from aromatic compounds

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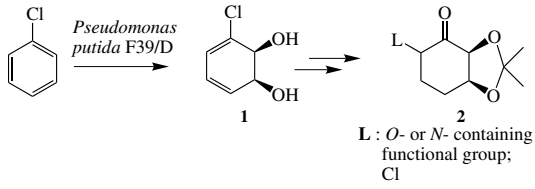
Received 5 January 2005; accepted 7 February 2005

Abstract—A series of chiral α-substituted cyclohexanones have been synthesized from chemoenzymatically produced chlorocyclohexadienediol. These highly functionalized ketones can be used in the total synthesis of diverse natural products, such as bengamides. A study of the reactivity of α-chlorooxiranes, common intermediates in the synthetic scheme, showed that under nucleophilic opening conditions an intermediate chloroketone may or may not form, depending on the nature of the nucleophiles present in the reaction medium. The stereochemical outcome of this reaction is presented.

1. Introduction

α-Heterosubstituted ketones are important synthons for the asymmetric syntheses of natural products, fine chemicals, and medicines.[1] Of them, α-hydroxy- and α-aminoketones are the most used and, consequently, numerous studies have been aimed at their stereoselective synthesis.[2] The α-aminoketones are generally prepared by the reaction of organometallic reagents with α-amino acid derivatives.[3] Other methods, such as the Neber rearrangement, the reaction of α-haloketones with amines, and the Dakin–West reaction are less used because of diminished yields and/or poor control of regio- and/or enantioselectivity.[4] α-Hydroxyketones, on the other hand, can be prepared by both oxidative and non-oxidative methods.[5] Among the latter transformations, representative methods include the enzymatic kinetic resolution of α-hydroxyketones and derivatives.[6]

In connection with our work on the biotransformation of aromatic substrates,[7] we herein report a chemoenzymatic route to a series of chiral α-heterosubstituted cyclic ketones starting from monohalogenated aromatic compounds such as chlorobenzene. These simple aromatics are converted to chiral cyclohexadienediols **1**, through whole-cell oxidation using *Pseudomonas putida* F/39D,[8] and then carried out to the desired ketones of type **2** (Scheme 1). The methodology of the microbial oxidation of aromatics has been extensively used in organic synthesis.[9]



Scheme 1.

2. Results and discussion

2.1. Synthesis of ketones 3 and 4

Halogen-derived diene diols **1** are currently being studied in our laboratory as potential starting materials in the asymmetric synthesis of bengamides and its derivatives. The proposed retrosynthetic pathway shows that both the polyoxygenated side chain and the ε-caprolactam nucleus can be obtained from compounds of type **1** (Scheme 2). [10]

Hydroxyketone **4** was obtained from chlorobenzene, via diol **1**, through a concise sequence (Scheme 3). Regioselective reduction of **1** with a diimide prepared in situ[11] gave diol **5**, which was then protected to give acetonide **6**. After treatment of vinylic chloride **6** with *m*-CPBA, α-chlorooxirane **7** was obtained as a single isomer in 65%

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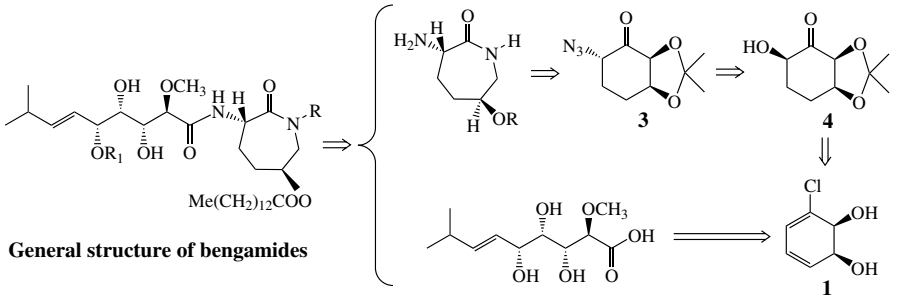
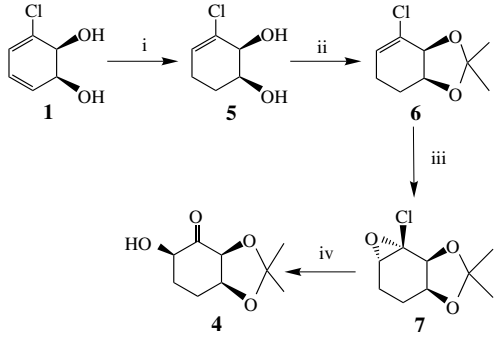
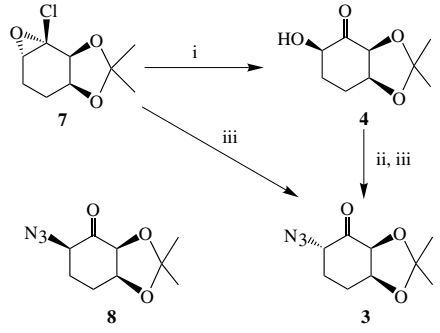
doi:10.1016/j.tetasy.2005.02.012



Scheme 2.



Scheme 3. Reagents and conditions: (i) $KO_2CN{=}NCO_2K$, AcOH, MeOH, rt, 90%; (ii) 2,2-dimethoxypropane, *p*-TsOH (catalytic), acetone, rt, 95%; (iii) *m*-CPBA, CH_2Cl_2, rt, 65%; (iv) $NaHCO_3$, H_2O, 100 °C, 5 min, 85%.



Scheme 4. Reagents and conditions: (i) $NaHCO_3$, H_2O, 100 °C, 5 min, 85%; (ii) MsCl, Et_3N, CH_2Cl_2, 80%; (iii) NaN_3, DMF, rt, 40%.

yield. The choice of the protecting group was determinant in the selectivity of the epoxidation. Thus, whereas the acetonide gave complete diastereoselection, the use of silyl ethers and acylating agents, or even the free diol **5**, resulted in mixtures of isomeric epoxides (vide infra). We were concerned about the behavior of the acetonide group in the subsequent hydrolysis of the halogenoepoxide since its instability under hydrolytic conditions in related systems is known.[12] However, after careful optimization ketone **4** was obtained in 85% yield. The best conditions proved to be refluxing **7** in aqueous bicarbonate for 5 min. Prolonged reaction times resulted in a loss of the acetonide integrity.

The stereochemistry of the newly formed hydroxyl in ketone **4** was, in principle, assigned by analogy to that reported for basic openings of α-chlorooxiranes in closely related systems.[12]

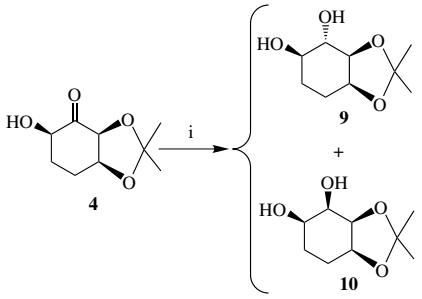
With hydroxyketone **4** in hand, prepared in 50% overall yield from diol **1**, we turned our attention to the synthesis of α-azidoketone **3** (Scheme 4). The free hydroxyl group in **4** was transformed into a mesylate, and then **3** obtained through inversion with sodium azide in DMF at room temperature. In our synthetic scheme for the preparation of derivatives of bengamides, it was convenient to have access to both epimers of the azido group. To this end, chlorooxirane **7** was subjected to opening conditions using sodium azide in DMF to cleave the epoxide and produce the epimeric azide **8**. Unexpectedly, these conditions afforded the previously obtained ketone **3** as the only azide containing product. Even though the crude of reaction showed clean conversion to the azide, the reaction mixture proved to be difficult to handle and azide **3** was obtained in an isolated yield ranging between 30% and 40% (Scheme 4).

The discrepancy in the results of the chlorooxirane openings raised some doubts on the stereochemical outcome of this reaction and thus, the structure of ketone **4** had to be reconsidered. The point to be confirmed was the configuration of the α-carbon bearing the free hydroxyl group in **4**.

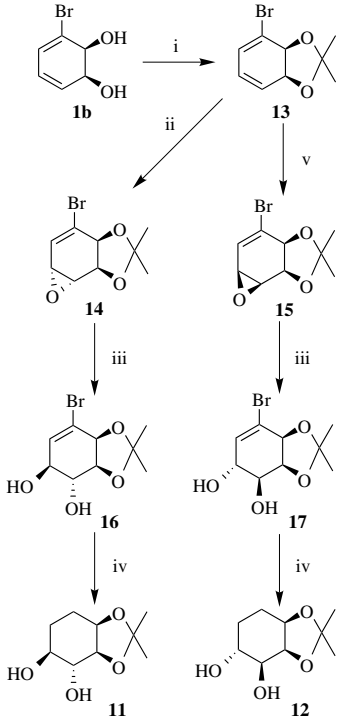
2.2. Absolute configuration determination of ketone 4

The configuration at the α-carbon was determined by converting **4** into a derivative of known configuration prepared by independent methods. Thus, ketone **4** was reduced with $NaBH_4$ in MeOH to give a near 1:1 mixture of diprotected tetraols **9** and **10**, differing only at the configuration of the new chiral stereogenic (epimers at C_3) (Scheme 5).

On the other hand, two diprotected tetraols **11** and **12** (epimers at C_4) were prepared starting from bromobenzene, to be used as standards (Scheme 6). The configuration of **11** and **12** was unequivocally set since both were obtained from known compounds **16** and **17**[13] by olefin reduction with concomitant dehalogenation, via catalytic hydrogenation over Raney nickel. In addition, **11** is a known compound.[14] When the ^1H and ^{13}C NMR spectra of products **9** and **10** were compared against those from standard diprotected tetraols **11** and **12**,



Scheme 5. Reagents and conditions: (i) $NaBH_4$, MeOH, rt, 40% **9** and 45% **10**.

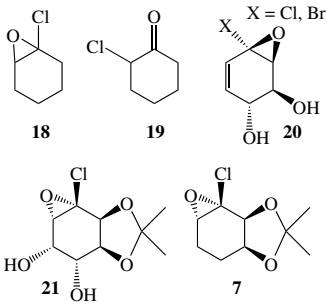


Scheme 6. Reagents and conditions: (i) 2,2-dimethoxypropane, *p*-TsOH (catalytic), acetone, rt, 95%; (ii) *m*-CPBA, CH_2Cl_2, rt, 80%; (iii) 10% KOH, THF, reflux, 60%; (iv) H_2/Raney-Ni, MeOH, rt, 50%; (v) NBS, THF–H_2O, rt; then 5 N NaOH, Et_2O–H_2O, 40 °C, 55%.

the spectra of **9** turned out to be exactly the same as those of **11**, indicating that both compounds possess the same relative configuration.[15] Therefore, the relative configuration at C_4 in **9** was established, which is the same as the configuration of the α-carbon bearing the free hydroxyl group in **4**. In this way, our original assumption about the stereochemistry of ketone **4** was confirmed. The identity of azidoketone **3** was also confirmed, since it was obtained from **4** through a simple and well-documented inversion sequence.[16]

2.3. Nucleophilic opening of α-chlorooxirane 7

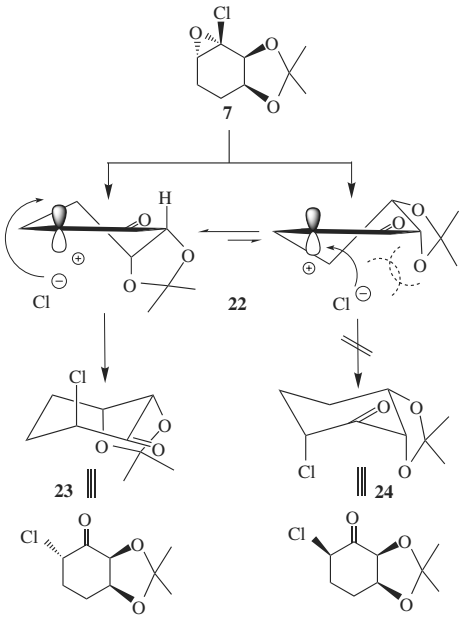
Considering the different stereochemical results of the α-chlorooxirane openings, when using different nucleophiles, to give **3** or **4**, a closer examination of the stereochemical course of this reaction was required.



Scheme 7.

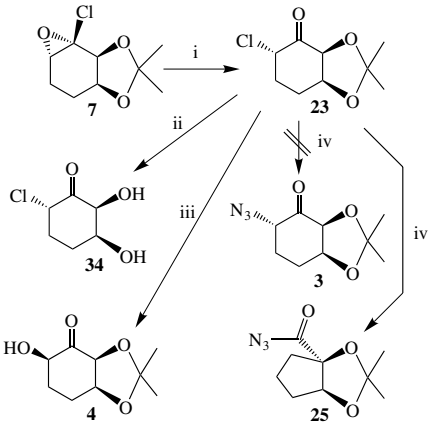
Compound **7** possesses a number of features that deserve attention, namely its stability and capacity to undergo an epoxide–carbonyl rearrangement. Halogeno-substituted oxiranes are generally unstable and rearrange easily unless they are stabilized by suitable substitution.[17] Thus, chloroepoxide **18** reported by Gasteiger rearranges at room temperature to **19**[18] and also the more functionalized haloepoxides **20** are unstable at room temperature (Scheme 7).[19] However, the highly oxygenated chlorooxirane **21** reported by Hudlicky is remarkably stable.[12]

We observed that compound **7** shows an intermediate stability ($t_{1/2}$ in toluene at 110 °C is ca. 10 h). Regarding the rearrangement (such as **18** to **19**), the conversion of α-halogenooxiranes to α-halocarbonyl compounds is generally easy, as a consequence of the release of the three-membered ring strain.[17a] Thus, **7** could function as a synthon for the preparation of α-substituted cyclohexanones, thus taking advantage of its high reactivity. However, halogenooxiranes do not only offer higher reactivity than α-halocarbonyl compounds, their reactions may also follow different pathways. For example, **18** reacts with sodium methoxide in methanol to give in quantitative yield, 2-methoxycyclohexanone,[20] whereas 2-chlorocyclohexanone **19** affords products from both Favorski rearrangements and attacks to the carbonyl group.[20] In addition, the reactions of phosphites with α-chlorocarbonyl compounds give variable amounts of Arbuzov- and Perkow-products, whereas 2-chlorooxiranes only give β-ketophosphonic acid esters.[21] Consequently, it seems to be necessary to gain some insight into the mechanism of reaction of **7** to the carbonyl compounds **3** and **4**. In one of the most complete studies about the mechanism of the epoxide–carbonyl rearrangement, McDonald postulated that the thermal rearrangement proceeds by disrotatory C_β–O bond opening to an α-ketocarbonium–chloride ion pair of type **22**.[22] Further kinetic attack of the chloride produces an axial C–Cl bond in the final α-chloroketone (Scheme 8). If necessary, the chloride ion could migrate from one face of the epoxide to the opposite face to yield the product through an axial attack.[22,23] To minimize the 1,3-diaxial interaction between the incoming nucleophile and the protecting group, the proposed mechanism yields chloroketone **23** from **7**, as shown. If strong nucleophiles are present, it would be expected that they would compete with the chloride ion for the carbocation.

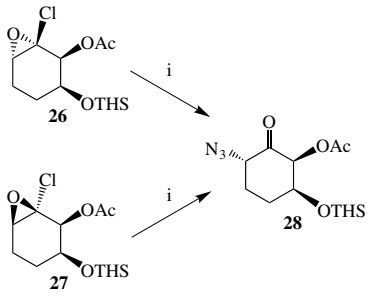


Scheme 8.

Our data are consistent with the proposed mechanism (Scheme 8). In polar media with poor nucleophiles, such as the conditions we used (H_2O–$NaHCO_3$ at 100 °C), chlorooxirane **7** forms the chloroketone, which reacts further to produce α-hydroxyketone **4** via an S_N2 mechanism.[16,24] On the other hand, in the presence of stronger nucleophiles such as the azide ion in DMF, the α-azidoketone **3** is obtained instead. This compound results from the kinetic attack of the azide ion to the carbocation forming an axial C–N bond in an analogous way as for the formation of chloroketone **23**. To test this hypothesis, the corresponding chloroketone **23** was prepared via thermal rearrangement of α-chlorooxirane **7** and subjected to the reaction conditions previously used to obtain hydroxyketone **4** and azidoketone **3** (Scheme 9). Heating **7** at 110 °C in DMF produced chloroketone **23** in moderate yield. Compound **23** can be easily deprotected in acidic conditions to give diol **34**. As expected,



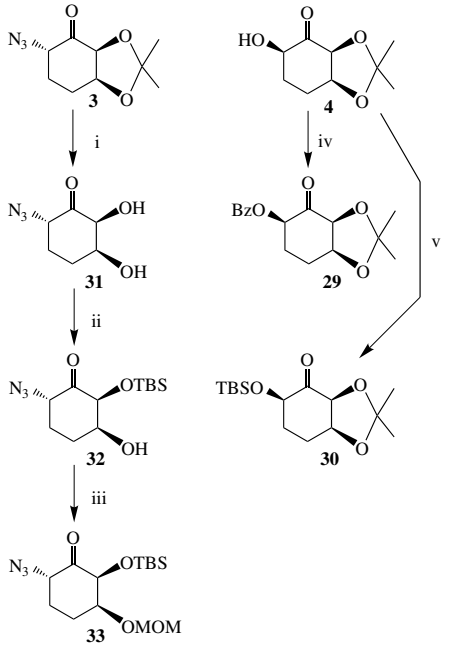
Scheme 9. Reagents and conditions: (i) 110 °C, DMF, 50%; (ii) Dowex 50 WX8-200, MeOH–H_2O, rt, 90%; (iii) $NaHCO_3$, H_2O, 100 °C, 5 min, 75%; (iv) NaN_3, DMF, 90 °C, 50%.



Scheme 10. Reagents and conditions: (i) NaN_3, acetone–H_2O, rt, 85% from **26**, 65% from **27**.

ketone **4** was obtained uneventfully after the treatment of **23** with H_2O–$NaHCO_3$ at 100 °C, whereas the conditions used for azide displacement (NaN_3 in DMF at room temperature) did not afford a noticeable reaction after 24 h. Heating the reaction mixture at 90 °C instead produced 50% of the ring-contracted product **25**, via a formal Favorski rearrangement (Scheme 9).[18]

In consequence, chloroketone **23** is not an intermediate in the formation of azidoketone **3** from chlorooxirane **7**, in agreement with the proposed mechanism. Moreover, the observed formation of the kinetic product resulting from the axial attack of the nucleophile to the α-ketocarbonium–chloride ion pair is reinforced by the reactions of isomeric chlorooxiranes **26** and **27** with sodium azide (Scheme 10).[25] When treated with sodium azide, both compounds afforded the same azidoketone, **28**, as the only product. This outcome is again in agreement with the proposed mechanism.



Scheme 11. Reagents and conditions: (i) Dowex 50 WX8-200, MeOH–H_2O, rt, 90%; (ii) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt, 85%; (iii) chloromethylmethyl ether, DIPEA, CH_2Cl_2, rt, 85%; (iv) BzCl, Et_3N, CH_2Cl_2, rt, 70%; (v) TBSCl, imidazole, DMF, 4 °C, 85%.

2.4. Synthesis of other ketones

Considering the outcome of the reaction using an azide ion, other *N*-containing nucleophiles were tested. Chlorooxirane **7** was thus treated with succinimide, hydrazine hydrate, benzylamine, and methylamine in an attempt to obtain the corresponding ketones. Unfortunately in all cases, the reaction was extremely sluggish and only decomposition products were obtained. Although there is a precedent in the literature about the opening of the halogenooxirane using sulfur containing nucleophiles,[18] Hudlicky had reported that the use of amines as nucleophiles was unsuccessful and the use of aqueous ammonia conducted to condensation to form pirazines.[12] On the other hand, regarding the oxygen-containing series, hydroxyketone **4** is easily acylated or silylated. For example, either benzoylated derivative **29** or silyl ether **30** are made in high yield from **4** (Scheme 11). Ketone **3** can be easily deprotected to give **31**. The diol functionality can also be selectively protected as shown.

3. Conclusions

A series of enantiopure α-substituted cyclohexanones, **3**, **4**, **23**, and **28**–**34**, with potential applications as synthetic intermediates have been successfully prepared through simple reactions. The yields and the conciseness of the sequences allow for the preparation of these synthons in multigram quantities. Their use in the synthesis of the nucleus of bengamides will be reported in due course. All the preparations have a chlorooxirane as a common intermediate, and the conditions for the epoxide opening using both nitrogen- and oxygen-containing nucleophiles were investigated. Our results are consistent with the proposed mechanism of an α-halogenooxirane opening through an epoxide–carbonyl rearrangement. Depending on the presence of strong nucleophiles in the reaction medium, an intermediate haloketone may or may not form, since the nucleophiles compete with the chloride ion to form kinetic products.

4. Experimental

4.1. General

All non-hydrolytic reactions were carried out in a nitrogen atmosphere with standard techniques for the exclusion of air. All solvents were distilled prior to use. Melting points were determined on a Gallenkamp capillary melting point apparatus and are uncorrected. Mass spectra were recorded on a Shimadzu GC–MS QP 1100 EX instrument using the electron impact mode (70 or 20 eV) or chemical ionization (if indicated). Infrared spectra were recorded either on neat samples (KBr disks) or in solution on Perkin–Elmer 1310 or Bomem, Hartmann & Braun FTIR spectrometers. NMR spectra were obtained in $CDCl_3$ on a Bruker Avance DPX-400 instrument. Proton chemical shifts (δ) are reported in ppm downfield from TMS as an internal reference, and carbon chemical shifts are reported in ppm relative to the center line of the $CDCl_3$ triplet (77.0 ppm). Elemental analyses were performed by Atlantic Microlab Inc., Norcross, GA, USA. Optical rotations were measured on a Zuzi 412 polarimeter using a 1 dm cell. $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}.

Diols **1** and **1b** were obtained by fermentation of the corresponding arenes.[7] Analytical TLC was performed on silica gel 60F-254 plates and visualized with UV light (254 nm) and/or *p*-anisaldehyde in acidic ethanolic solution. Flash column chromatography was performed using silica gel (Kieselgel 60, EM reagent, 230–400 mesh).

4.2. (1*S*,2*S*)-3-Chlorocyclohex-3-ene-1,2-diol, 5

To a solution of diol **1** (1.0 g, 6.8 mmol) in MeOH (50 mL) at room temperature was added PAD (5.0 g, 27 mmol) and AcOH (5 mL) in portions. After 4 h of stirring, the solvent was evaporated and the residue was taken in Et_2O. The ethereal solution was neutralized with saturated aqueous $NaHCO_3$, washed with brine (2×), and dried over $MgSO_4$. After filtration of the solids, the solvent was evaporated to give a residue, which was chromatographed (silica, EtOAc/hexanes 1:1) to yield **5** (0.9 g, 90%). This compound was fully characterized as the acetonide **6**.

4.3. (1*S*,2*S*)-3-Chloro-1,2-*O*-isopropylidenecyclohex-3-ene-1,2-diol, 6

To a solution of diol **5** (0.5 g, 3.4 mmol) in acetone (10 mL) at rt was added 2,2-dimethoxypropane (0.4 g, 4.0 mmol) and a catalytic amount of *p*-TsOH. After stirring for 1 h at rt, Amberlist A-21 (0.1 g) was added and the mixture was stirred for an additional 15 min period. The resin was filtered off and the resulting solution was concentrated under reduced pressure to afford a light yellow oil. Column chromatography (SiO_2; hexanes/EtOAc, 90:10) gave pure **6** as a colorless oil (0.6 g, 95%). $R_f = 0.4$ (hexanes/EtOAc, 90:10); $[\alpha]_D^{25} = +64.6$ (*c* 1.1, acetone); IR (KBr) 2986, 2934, 1651, 1381, 1369, 1242, 1221 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.41 (s, 3H), 1.44 (s, 3H), 1.76 (m, 1H), 2.00 (m, 3H), 2.29 (m, 1H), 4.40 (m, 2H), 5.98 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 21.5 (CH_2), 24.8 (CH_2), 26.6 (CH_3), 27.8 (CH_3), 74.3 (CH), 75.6 (CH), 109.6 (C), 128.1 (CH), 131.3 (C); MS (CI, CH_4) *m*/*z* (relative intensity): 188 (3), 175 (53), 173 (100), 149 (51), 113 (65); EA calculated for $C_9H_{13}O_2Cl$: C, 57.30%, H, 6.95%. Found: C, 57.21%, H, 7.11%.

4.4. (1*S*,2*S*,3*R*,4*S*)-3-Chloro-3,4-oxy-1,2-*O*-isopropylidenecyclohexane-1,2-diol, 7

To a solution of **6** (0.1 g, 0.53 mmol) in $CHCl_3/CH_2Cl_2$ (1:2, 20 mL) heated to reflux, was added *m*-CPBA (0.4 g, 2.2 mmol). After 5 h at reflux, the mixture was diluted with CH_2Cl_2 (50 mL), and successively washed with 10% $NaHSO_3$ (2 × 50 mL), 50% $NaHCO_3$ (2 × 50 mL), and brine (1 × 20 mL). The organic layer was dried and concentrated in vacuo to give an oil, which was purified by column chromatography (SiO_2; hexanes/EtOAc, 90:10) to afford **7** as a white solid (70 mg,

65%). $R_f = 0.5$ (hexanes/EtOAc, 90:10); mp = 71.0–73.3 °C; $[\alpha]_D^{25} = +50.5$ (*c* 0.62, acetone); IR (KBr) 2993, 2936, 2899, 1246, 1228, 1159, 1082, 903 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41 (s, 3H), 1.52 (s, 3H), 1.66 (m, 1H), 1.70 (m, 1H), 1.95 (m, 1H), 2.21 (m, 1H), 3.58 (d, $J = 3$ Hz, 1H), 4.32 (m, 1H), 4.38 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 18.3 (CH_2), 18.6 (CH_2), 25.8 (CH_3), 27.4 (CH_3), 62.1 (CH), 72.2 (CH), 74.5 (CH), 78.0 (C), 109.8 (C); MS (CI, CH_4) *m/z* (relative intensity): 205 (8), 203 (39), 156 (36), 139 (100), 129 (26), 111 (33); EA calculated for $C_9H_{13}O_3Cl$: C, 52.82%; H, 6.40%. Found: C, 51.55%; H, 5.50%.

4.5. (2*S*,3*S*,6*R*)-6-Hydroxy-2,3-isopropylidenedioxycyclohexanone, 4

To an aqueous solution of $NaHCO_3$ (18 mg, 0.21 mmol in 5 mL) was added **7** (42 mg, 0.21 mmol) and the resulting solution was heated to reflux for 5 min. After cooling down to rt, the solution was extracted with EtOAc (3×10 mL), dried and concentrated under reduced pressure to obtain a crude solid which was purified by column chromatography (SiO_2; hexanes/EtOAc, 1:1) to furnish **4** as a white solid (33 mg, 85%). $R_f = 0.3$ (hexanes/EtOAc, 1:1); mp = 112.3–114.9 °C; IR (KBr) 3200 (broad), 2978, 2955, 2936, 1745, 1167, 1142, 1024 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (s, 3H), 1.43 (s, 3H), 1.85 (m, 1H), 2.02 (m, 1H), 2.23 (m, 2H), 3.61 (s, broad, OH, 1H), 4.18 (dd, $J = 12$, 6 Hz, 1H), 4.45 (d, $J = 5$ Hz, 1H), 4.60 (broad, 1H); ^{13}C NMR ($CDCl_3$) δ 22.6 (CH_2), 26.1 (CH_3), 27.1 (CH_3), 29.8 (CH_2), 74.4 (CH), 77.5 (CH), 79.1 (CH), 110.3 (C), 208.9 (C); MS (EI, 20 eV) *m/z* (relative intensity): 186 (5), 171 (34), 143 (80), 128 (29), 111 (17), 43 (100). Further characterization was done on the silylated derivative **30**.

4.6. (2*S*,3*S*,6*S*)-6-Azido-2,3-isopropylidenedioxycyclohexanone, 3

From epoxide **7**: To a solution of **7** (30 mg, 0.15 mmol) in THF–EtOH–H_2O (1:1:1, 20 mL) was added NaN_3 (15 mg, 0.22 mmol) in one portion. After stirring at rt for 6 h the mixture was diluted with H_2O, extracted with EtOAc (3×20 mL), dried, and concentrated under reduced pressure. The residue was purified by chromatography (SiO_2; hexanes/EtOAc, 70:30) to give **3** as a white solid (13 mg, 40%). From alcohol **4**: To a stirred solution of **4** (22 mg, 0.12 mmol) in CH_2Cl_2 (5 mL) at 0 °C, was added MsCl (67 mg, 0.59 mmol in 5 mL of CH_2Cl_2), and Et_3N (60 mg, 0.59 mmol in 3 mL of CH_2Cl_2). The mixture was left to warm up to rt and after 30 min at this temperature the reaction mixture was quenched with water. The mixture was extracted with CH_2Cl_2 (3×15 mL), dried, and concentrated under reduced pressure to give an oil, which was further purified by chromatography (SiO_2; hexanes/EtOAc, 1:1) to afford the corresponding mesylate as a colorless oil (22 mg, 80%). $R_f = 0.5$ (hexanes/EtOAc, 1:1); ^1H NMR ($CDCl_3$) δ 1.41 (s, 3H), 1.45 (s, 3H), 2.11 (m, 1H), 2.23 (m, 1H), 2.30 (m, 1H), 2.40 (m, 1H), 3.25 (s, 3H), 4.46 (d, $J = 5$ Hz, 1H), 4.58 (m, broad, 1H), 5.12 (dd, $J = 12$, 6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 23.1 (CH_2), 26.1 (CH_3), 27.1 (CH_3), 27.7 (CH_2), 39.8 (CH_3), 76.6 (CH), 80.0 (CH), 81.0 (CH), 110.6 (C), 201.9 (C). To a solution of the mesyl derivative (69 mg, 0.26 mmol) in DMF (15 mL) was added NaN_3 (19 mg, 0.78 mmol). After 3 h of stirring at rt, the reaction mixture was quenched with water, and the mixture was extracted with Et_2O (3×20 mL), dried, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2; hexanes/EtOAc, 70:30) to give **3** as a white solid (21 mg, 40%). $R_f = 0.6$ (hexanes/EtOAc, 1:1); mp = 66.5–70.0 °C; $[\alpha]_D^{25} = +94.4$ (*c* 0.30, acetone); IR (KBr) 2995, 2986, 2878, 2106, 1726, 1381, 1226, 1022 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41 (s, 3H), 1.45 (s, 3H), 2.08 (m, 2H), 2.15 (m, 1H), 2.34 (m, 1H), 3.91 (m, 1H), 4.41 (d, $J = 5$ Hz, 1H), 4.59 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 24.1 (CH_2), 26.1 (CH_3), 27.1 (CH_2), 27.2 (CH_3), 65.0 (CH), 76.8 (CH), 79.7 (CH), 110.4 (C), 202.9 (C); MS (EI, 20 eV) *m/z* (relative intensity): 211 (20), 196 (21), 183 (3), 97 (49), 59 (100). Due to the instability of the azido group, it was not possible to obtain an analytically pure sample suitable for combustion analysis.

4.7. (2*S*,3*S*,6*S*)-6-Chloro-2,3-isopropylidenedioxycyclohexanone, 23

A stirred solution of epoxide **7** (71 mg, 0.35 mmol) in DMF (3 mL) was heated to 110 °C. After 30 min, the reaction mixture was quenched with water, and the mixture was extracted with Et_2O (3×20 mL), dried, and concentrated under reduced pressure. Purification of the residue by column chromatography (SiO_2; hexanes/EtOAc, 70:30) gave **23** as a white solid (35 mg, 50%). $R_f = 0.6$ (hexanes/EtOAc, 1:1); mp = 80–82 °C; IR (KBr) 2950, 2938, 1743, 1157, 1136, 1010 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41 (s, 3H), 1.45 (s, 3H), 2.12 (m, 1H), 2.28 (m, 3H), 4.45 (m, 2H), 4.61 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 25.3 (CH_2), 26.2 (CH_3), 27.1 (CH_3), 32.1 (CH_2), 62.3 (CH), 76.8 (CH), 80.2 (CH), 110.5 (C), 199.8 (C); MS (EI, 70 eV) *m/z* (relative intensity): 204 (2), 189 (28), 161 (36), 83 (19), 59 (34), 43 (100). Further characterization was done on the deprotected derivative **34**.

4.8. (2*S*,3*S*,6*S*)-6-Chloro-2,3-dihydroxycyclohexanone, 34

To a solution of **23** (90 mg, 0.44 mmol) in MeOH–H_2O (2:1, 30 mL) was added a spatula tip of acidic resin (Dowex 50W8-200, previously washed with the same solvent system, 3×10 mL). After 4 h of stirring, the resin was filtered off and washed with EtOAc. The combined organic layers were concentrated under reduced pressure and the residue was purified by chromatography (SiO_2; hexanes/EtOAc, 1:1) to furnish **34** as a white solid (70 mg, 95%). $R_f = 0.2$ (hexanes/EtOAc, 1:1); $[\alpha]_D^{25} = +81.6$ (*c* 0.50, acetone); mp = 144.2–145.5 °C; IR (KBr) 3390 (broad), 2934, 1741, 1130, 1099, 1028, 779 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.80 (m, 1H), 1.90 (m, 1H), 2.09 (m, 1H), 2.22 (m, 1H), 4.14 (s, broad, 1H), 4.27 (m, 1H), 4.91 (ddd, $J = 7$, 6, <1, Hz, 1H), 4.96 (d, $J = 2$ Hz, OH, 1H), 5.01 (d, $J = 7$ Hz, OH, 1H); ^{13}C NMR (DMSO-d_6) δ 29.0 (CH_2), 32.6 (CH_2), 63.0 (CH), 73.1 (CH), 78.1 (CH), 202.2 (C); MS (EI,

20 eV) *m/z* (relative intensity): 164 (1), 128 (51), 120 (100), 82 (55), 57 (78); EA calculated for $C_6H_9O_3Cl$: C, 43.79%; H, 5.51%. Found: C, 43.92%; H, 5.84%.

4.9. (1*R*,2*S*)-1,2-Isopropylidenedioxycyclopentanecarbonylazide, 25

To a solution of chloroketone **23** (20 mg, 0.10 mmol) in DMF (5 mL) was added NaN_3 (20 mg, 0.30 mmol) in one portion at rt and then the mixture heated to 90 °C. After 1 h of heating, the reaction mixture was quenched with water, and the mixture extracted with Et_2O (3 × 20 mL), dried, and concentrated under reduced pressure. Purification of the residue by column chromatography (SiO_2; hexanes/EtOAc, 90:10) gave 25 as a colorless oil (11 mg, 50%). $R_f = 0.4$ (hexanes/EtOAc, 90:10); IR (KBr) 2941, 2116, 1732, 1458, 1385 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.54 (s, 3H), 1.57 (s, 3H), 1.84 (m, 2H), 1.95 (m, 1H), 2.06 (m, 1H), 2.49 (m, 1H), 2.63 (m, 1H), 4.31 (t, 1H); ^{13}C NMR ($CDCl_3$) δ 17.9 (CH_2), 25.9 (CH_3), 27.2 (CH_2), 27.1 (CH_3), 37.2 (CH_2), 81.8 (CH), 92.6 (C), 112.3 (C), 202.2 (C); MS (EI, 20 eV) *m/z* (relative intensity): 183 (0.5, M^+-N_2), 169 (7, $M^+-N_2-CH_2$), 149 (7), 125 (8), 113 (21), 95 (30). Due to the instability of the azido group, it was not possible to obtain an analytically pure sample suitable for combustion analysis.

4.10. (1*S*,2*R*,3*S*,6*S*)-2-Chloro-6-(dimethylthexylsilyloxy)-2,3-oxycyclohexyl acetate, 26 and (1*S*,2*S*,3*R*,6*S*)-2-chloro-6-(dimethylthexylsilyloxy)-2,3-oxycyclohexyl acetate, 27

To a stirred solution of **5** (0.100 g, 0.68 mmol) in DMF (10 mL) cooled to 0 °C, was added imidazole (100 mg, 1.46 mmol) and THSCl (1.33 g, 0.75 mmol) in portions. The reaction mixture was kept at 4 °C during 24 h and then was diluted with Et_2O (50 mL) and quenched with water (40 mL). The organic layer was successively washed with aqueous 10% $CuSO_4$ (2 × 50 mL) and brine, dried, and concentrated under reduced pressure to give the monoprotected diol as an oily residue (170 mg, 85%), which was pure enough for the next step. The crude was dissolved in Ac_2O (5 mL) and Et_3N (90 mg, 0.88 mmol) and a catalytic amount of DMAP (5 mg) was added in portions. After 24 h of stirring at rt, the reaction mixture was diluted with Et_2O (50 mL) and quenched by the addition of ice–H_2O (30 mL). The pH of the aqueous layer was made slightly basic (litmus paper) by the addition of solid $NaHCO_3$. The aqueous layer was extracted with Et_2O (3 × 20 mL) and the combined organic layer was successively washed with aqueous 10% $CuSO_4$ (3 × 50 mL) and brine (2 × 30 mL), dried, and concentrated under reduced pressure. The oily residue was purified by column chromatography (SiO_2; hexanes/EtOAc, 90:10) to give the diprotected diol in 90% yield. To a stirred solution of the diprotected diol (175 mg, 0.53 mmol) in CH_2Cl_2 (50 mL) was added *m*-CPBA (110 mg, 0.63 mmol) in portions. After 48 h at rt, the mixture was diluted with CH_2Cl_2 (50 mL), and successively washed with 10% $NaHSO_3$ (2 × 50 mL), 50% $NaHCO_3$ (2 × 50 mL), and brine (1 × 20 mL). The organic layer was dried and concentrated in vacuo to give an oil, which was purified by column chromatography (SiO_2; hexanes/EtOAc, 98:2) to afford the isomeric epoxides **26** and **27**. Compound **26** (colorless oil, 112 mg, 60%), $R_f = 0.5$ (hexanes/EtOAc, 90:10); $[\alpha]_D^{25} = +57.8$ (*c* 0.30, acetone); IR (KBr) 2996, 2980, 2945, 1730, 1370, 1262, 1228, 1120, 1088, 890 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.08 (s, 3H), 0.12 (s, 3H), 0.83 (s, 6 H), 0.87 (s, 3H), 0.89 (s, 3H), 1.44 (m, 1H), 1.58 (m, 2H), 1.60 (m, 1H), 1.95 (m, 1H), 2.14 (s, 3H), 2.20 (m, 1H), 3.51 (m, 1H), 3.90 (m, 1H), 5.50 (d, $J = 3$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ −2.62 (CH_3), −2.59 (CH_3), 18.8 (CH_3), 18.9 (CH_3), 20.6 (2 × CH_3), 21.2 (CH_3), 21.6 (CH_2), 24.0 (CH_2), 25.3 (C), 34.6 (CH), 61.7 (CH), 67.2 (CH), 72.1 (CH), 78.4 (C), 169.9 (C); MS (CI, CH_4) *m/z* (relative intensity): 348 (16), 306 (16), 207 (12), 148 (20), 132 (100), 114 (28); EA calculated for $C_{16}H_{29}SiO_4Cl$: C, 55.07%; H, 8.38%. Found: C, 54.93%; H, 8.29%. Compound **27** (white solid, 56 mg, 30%), $R_f = 0.4$ (hexanes/EtOAc, 90:10); mp = 63–65 °C; $[\alpha]_D^{25} = +32.3$ (*c* 0.30, acetone); IR (KBr) 2992, 2978, 2947, 1726, 1356, 1270, 1230, 1140, 1100, 860 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.07 (s, 3H), 0.08 (s, 3H), 0.82 (s, 6 H), 0.87 (s, 3H), 0.88 (s, 3H), 1.43 (m, 1H), 1.59 (m, 1H), 1.66 (m, 1H), 1.96 (m, 1H), 2.13 (m, 1H), 2.19 (s, 3H), 3.50 (m, 1H), 3.87 (m, 1H), 5.52 (d, $J = 3$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ −2.74 (CH_3), −2.66 (CH_3), 18.8 (CH_3), 18.9 (CH_3), 20.5 (2 × CH_3), 21.2 (CH_3), 22.2 (CH_2), 24.3 (CH_2), 25.3 (C), 34.5 (CH), 61.9 (CH), 68.2 (CH), 75.3 (CH), 75.7 (C), 170.5 (C); MS (CI, CH_4) *m/z* (relative intensity): 348 (5), 306 (17), 207 (10), 148 (22), 132 (100), 114 (37); EA calculated for $C_{16}H_{29}SiO_4Cl$: C, 55.07%; H, 8.38%. Found: C, 54.01%; H, 8.25%.

4.11. (2*S*,3*S*,6*S*)-2-Acetoxy-6-azido-3-(dimethylthexylsilyloxy)cyclohexanone, 28

From chlorooxirane **26**: To a solution of **26** (30 mg, 0.09 mmol) in acetone–H_2O (1:1, 10 mL) was added NaN_3 (15 mg, 0.22 mmol) in one portion. After 1 h of stirring at rt the reaction mixture was quenched with water, and the mixture extracted with Et_2O (3 × 10 mL), dried, and concentrated under reduced pressure. Purification of the residue by column chromatography (SiO_2; hexanes/EtOAc, 90:10) gave **28** as a colorless oil (26 mg, 85%). From chlorooxirane **27**: To a solution of **27** (30 mg, 0.09 mmol) in acetone–H_2O (1:1, 10 mL) was added NaN_3 (15 mg, 0.22 mmol) in one portion. After 2 days of stirring at rt, the reaction mixture was quenched with water, and the mixture was extracted with Et_2O (3 × 10 mL), dried, and concentrated under reduced pressure. Purification of the residue by column chromatography (SiO_2; hexanes/EtOAc, 90:10) gave **28** as a colorless oil (20 mg, 65%). $R_f = 0.5$ (hexanes/EtOAc, 70:30); $[\alpha]_D^{25} = +89.7$ (*c* 0.60, acetone); IR (KBr) 2993, 2985, 2950, 1748, 1732, 1388, 1250, 1115, 880 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.10 (s, 3H), 0.15 (s, 3H), 0.83 (s, 6 H), 0.86 (d, 3H), 0.87 (d, 3H), 1.59 (m, 1H), 1.96 (m, 2H), 2.18 (m, 5 H), 3.92 (t, $J = 10$ Hz, 1H), 4.45 (m, 1H), 5.12 (m, 1H); ^{13}C NMR ($CDCl_3$) δ −2.58 (CH_3), −2.45 (CH_3), 18.8 (CH_3), 19.0 (CH_3), 20.3 (CH_3), 20.6 (CH_3), 20.9 (CH_3), 25.4 (C), 25.4 (CH_2), 27.6 (CH_2), 34.5 (CH), 65.1 (CH), 72.5 (CH), 78.8 (CH), 170.1 (C),

197.5 (C). Due to the instability of the azido group, it was not possible to obtain an analytically pure sample suitable for combustion analysis.

4.12. (2*S*,3*S*,6*R*)-6-Benzoyloxy-2,3-isopropylidenedioxycyclohexanone, 29

To a stirred solution of **4** (40 mg, 0.22 mmol) in CH_2Cl_2 was added Et_3N (44 mg, 0.44 mmol), followed by benzoyl chloride (45 mg, 0.33 mmol). After 2 h of stirring at rt the reaction mixture was diluted with CH_2Cl_2, washed successively with 5% HCl (2 × 10 mL), water (2 × 10 mL), and brine (1 × 10 mL), dried and concentrated under reduced pressure. The residue was purified by chromatography (SiO_2; hexanes/EtOAc, 70:30) to give **29** as a colorless oil (44 mg, 70%). $R_f = 0.7$ (hexanes/EtOAc, 1:1); $[\alpha]_D^{25} = +61.8$ (*c* 0.40, acetone); IR (KBr) 2986, 2937, 1751, 1720, 1290, 1124 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42 (s, 3H), 1.46 (s, 3H), 2.17 (m, 1H), 2.27 (m, 2H), 2.42 (m, 1H), 4.54 (d, $J = 4$ Hz, 1H), 4.62 (m, 1H), 5.40 (m, 1H), 7.46 (m, 2H), 7.59 (m, 1H), 8.09 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 23.6 (CH_2), 26.4 (CH_3), 26.7 (CH_2), 27.4 (CH_3), 75.9 (CH), 77.2 (CH), 80.2 (CH), 110.6 (C), 128.8 (CH), 129.8 (CH), 130.3 (CH), 133.7 (CH), 165.8 (C), 201.7 (C); MS (EI, 20 eV) *m*/*z* (relative intensity): 290 (3), 247 (10), 105 (100), 99 (11), 77 (20). Due to its instability, it was not possible to obtain an analytically pure sample of this compound.

4.13. (2*S*,3*S*,6*R*)-6-(*tert*-Butyldimethylsilyloxy)-2,3-isopropylidenedioxycyclohexanone, 30

To a stirred solution of **4** (40 mg, 0.22 mmol) in DMF (0.5 mL) cooled to 0 °C, was added imidazole (50 mg, 0.73 mmol) and TBSCl (95 mg, 0.66 mmol) in portions. The reaction mixture was kept at 4 °C for 24 h and then diluted with Et_2O (10 mL) and quenched with water (20 mL). The aqueous layer was extracted with Et_2O (2 × 10 mL) and the combined organic layer was successively washed with aqueous 10% $CuSO_4$ (2 × 10 mL) and brine, then dried and concentrated under reduced pressure. The oily residue was purified by column chromatography (SiO_2; hexanes/EtOAc, 90:10) to give **30** as a white solid (56 mg, 85%). $R_f = 0.3$ (hexanes/EtOAc, 90:10); mp 96.0–100.1 °C; $[\alpha]_D^{25} = +64.2$ (*c* 0.30, acetone); IR (KBr) 2986, 2945, 2926, 2899, 2855, 1736, 1253, 794 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.04 (s, 3H), 0.13 (s, 3H), 0.92 (s, 9H), 1.38 (s, 3H), 1.44 (s, 3H), 2.02 (m, 3H), 2.25 (m, 2H), 4.21 (m, 1H), 4.34 (d, $J = 4$ Hz, 1H), 4.54 (m, 1H); ^{13}C NMR ($CDCl_3$) δ −4.9 (CH_3), −4.1 (CH_3), 18.9 (C), 23.7 (CH_2), 26.2 (3 × CH_3), 26.4 (CH_3), 27.4 (CH_3), 30.9 (CH_2), 76.5 (CH), 77.3 (CH), 80.2 (CH), 110.3 (C), 206.5 (C). MS (EI, 70 eV) *m*/*z* (relative intensity): 285 (10), 245 (8), 244 (19), 243 (100), 185 (50), 167 (18), 157 (38), 129 (51); EA calculated for $C_{15}H_{28}O_4Si$: C, 59.96%; H, 9.39%. Found: C, 59.21%; H, 9.35%.

4.14. (2*S*,3*S*,6*S*)-6-Azido-2,3-dihydroxycyclohexanone, 31

To a solution of **3** (90 mg, 0.43 mmol) in MeOH/H_2O (2:1, 30 mL), was added a spatula tip of acidic resin (Dowex 50W8-200, previously washed with the same solvent system, 3 × 10 mL). After 4 h of stirring, the resin was filtered off and washed with EtOAc. The combined organic layers were concentrated under reduced pressure and the residue was purified by chromatography (SiO_2; hexanes/EtOAc, 1:1) to afford **34** as a white solid (73 mg, 90%). $R_f = 0.2$ (hexanes/EtOAc, 1:1); mp = 121–123 °C; IR (KBr) 3370 (broad), 2990, 2982, 2880, 1738, 1395, 1240 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.90 (m, 1H), 2.20 (m, 3H), 2.74 (s, OH, 1H), 3.87 (s, OH, 1H), 4.00 (m, 1H), 4.21 (m, 1H), 4.40 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 26.5 (CH_2), 27.7 (CH_2), 64.7 (CH), 72.5 (CH), 77.4 (CH), 205.1 (C). Due to the instability of the azido group, it was not possible to obtain an analytically pure sample suitable for combustion analysis.

4.15. (2*S*,3*S*,6*S*)-6-Azido-2-(*tert*-butyldimethylsilyloxy)-3-hydroxycyclohexanone, 32

To a stirred solution of **31** (30 mg, 0.16 mmol) in CH_2Cl_2 (3 mL) was added 2,6-lutidine (90 mg, 0.85 mmol) and TBSOTf (90 mg, 0.34 mmol) in portions at 0 °C. The reaction was then left to stand at rt for 4 h, after which time was diluted with Et_2O (10 mL) and quenched with 10% HCl (20 mL). The aqueous layer was extracted with Et_2O (2 × 10 mL) and the combined organic layer washed with brine (2 × 10 mL), dried, and concentrated under reduced pressure. The solid residue was purified by column chromatography (SiO_2; hexanes/EtOAc, 90:10) to give **32** as a white solid (41 mg, 85%). $R_f = 0.8$ (hexanes/EtOAc, 1:1); mp = 110–112 °C; IR (KBr) 3290 (broad), 2980, 2965, 2949, 2860, 1740, 1390, 1210, 890 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.06 (s, 3H), 0.20 (s, 3H), 0.93 (s, 9H), 1.84 (m, 1H), 2.16 (m, 3H), 2.71 (s, OH, 1H), 3.81 (m, 1H), 4.24 (m, 2H); ^{13}C NMR ($CDCl_3$) δ −5.2 (CH_3), −4.2 (CH_3), 18.7 (C), 26.1 (3 × CH_3), 26.9 (CH_2), 27.5 (CH_2), 65.3 (CH), 74.3 (CH), 78.8 (CH), 202.5 (C). Due to the instability of the azido group, it was not possible to obtain an analytically pure sample suitable for combustion analysis.

4.16. (2*S*,3*S*,6*S*)-6-Azido-2-(*tert*-butyldimethylsilyloxy)-3-(methoxymethyloxy)cyclohexanone, 33

To a stirred solution of **32** (25 mg, 0.09 mmol) in CH_2Cl_2 (5 mL) was added diisopropylethylamine (13 mg, 0.1 mmol) and MOMCl (8 mg, 0.1 mmol) in portions. After 12 h of stirring at rt, the solution was concentrated under reduced pressure and the residue was taken in Et_2O (10 mL). The solution was extracted with 10% HCl 10% (20 mL) and the aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic layer was successively washed with 5% $NaHCO_3$ (2 × 10 mL) and brine (2 × 10 mL), dried, and concentrated under reduced pressure. The oily residue was purified by column chromatography (SiO_2; hexanes/EtOAc, 90:10) to afford **33** as a colorless oil (25 mg, 85%). $R_f = 0.3$ (hexanes/EtOAc, 90:10); IR (KBr) 2995, 2970, 2935, 2820, 1742, 1385, 1263, 1140, 1085, 795 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.04 (s, 3H), 0.17 (s, 3H), 0.94 (s, 9H), 1.84 (m, 1H), 2.16 (m, 3H), 3.37 (s, 3H), 3.80 (m, 1H), 4.25 (m, 2H), 4.67 (d, $J = 4$ Hz,

1H), 4.82 (d, $J = 4$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ −5.1 (CH_3), −4.2 (CH_3), 18.8 (C), 26.1 ($3 \times CH_3$), 27.2 (CH_2), 27.8 (CH_2), 55.9 (CH_3), 65.2 (CH), 79.1 (CH), 79.4 (CH), 97.0 (CH_2), 202.1 (C). Due to the instability of the azido group, it was not possible to obtain an analytically pure sample suitable for combustion analysis.

4.17. (1*S*,2*S*,3*S*,4*R*)-1,2-*O*-Isopropylidenecyclohexane-1,2,3,4-tetraol, 9 and (1*S*,2*S*,3*R*,4*R*)-1,2-*O*-isopropylidenecyclohexane-1,2,3,4-tetraol, 10

To a solution of ketone **4** (0.4 g, 2.2 mmol) in MeOH (30 mL) was added $NaBH_4$ (90 mg, 2.4 mmol) in portions at rt. After 15 min of stirring, the mixture was concentrated under reduced pressure and the residue was taken in Et_2O (50 mL). The organic layer was successively washed with 10% $NaHCO_3$ (2×25 mL) and brine (2×10 mL), dried, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2; EtOAc) to afford **9** and **10** as white solids. Compound **9** (0.26 g, 40%), $R_f = 0.2$ (EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.37 (s, 3H), 1.54 (s, 3H), 1.72 (m, 2H), 1.80 (m, 1H), 2.16 (m, 1H), 3.28 (s, OH, 2H), 3.42 (m, 1H), 3.52 (m, 1H), 3.90 (m, 1H), 4.26 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 24.1 (CH_2), 26.6 (CH_3), 26.9 (CH_2), 28.7 (CH_3), 71.8 (CH), 74.4 (CH), 78.7 (CH), 81.2 (CH), 109.5 (C); Compound **10** (0.29 g, 45%), $R_f = 0.3$ (EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.36 (s, 3H), 1.57 (s, 3H), 1.67 (m, 2H), 1.81 (m, 1H), 1.90 (m, 1H), 2.75 (s, OH, 1H), 3.05 (s, OH, 1H), 3.75 (m, 1H), 3.88 (m, 1H), 4.24 (m, 1H), 4.33 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 23.0 (CH_2), 25.7 (CH_3), 26.1 (CH_2), 28.0 (CH_3), 69.1 (CH), 69.3 (CH), 73.7 (CH), 77.0 (CH), 109.4 (C).

4.18. (1*R*,2*R*,3*S*,4*R*)-1,2-*O*-Isopropylidenecyclohexane-1,2,3,4-tetraol, 12

To a solution of vinylic bromide **17**[13] (95 mg, 0.26 mmol) in MeOH (50 mL) was added Raney-Ni (under aqueous NaOH, 100 mg). Hydrogen was bubbled through the mixture for 1 min to evacuate the air and then the mixture was stirred in a hydrogen atmosphere. After 30 min, the catalyst was filtered off and the solution was concentrated under reduced pressure. The residue was taken in EtOAc (40 mL), washed with brine (2×20 mL), dried, and concentrated under reduced pressure to give a crude which was purified by chromatography (SiO_2; EtOAc) to furnish **12** as a white solid (40 mg, 50%). $R_f = 0.2$ (EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.28 (m, 1H), 1.34 (s, 3H), 1.49 (s, 3H), 1.62 (m, 1H), 1.83 (m, 1H), 1.96 (m, 1H), 3.20 (s, OH, 2H), 3.54 (m, 1H), 3.82 (m, 1H), 4.21 (m, 1H), 4.42 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 26.1 (CH_2), 26.5 (CH_3), 27.5 (CH_2), 28.0 (CH_3), 70.2 (CH), 74.6 (CH), 75.1 (CH), 78.1 (CH), 109.7 (C).

Acknowledgements

Support of this work from the Universidad de la República-CSIC (Uruguay) and PEDECIBA (Project URU/97/016) is gratefully acknowledged. The authors thank Prof. T. Hudlicky for providing the cultures of *P. putida* F39/D.

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25. Oxiranes **26** and **27** were prepared in a similar way as **7** by epoxidation of a differentially protected vinylic chloride. The replacement of the acetonide by other protecting groups allows for the preparation of isomeric chlorooxiranes due to the diminished facial selectivity of the system.