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Reactions of enantiopure cyclic diols with sulfonyl chloride

Derek R. Boyd, Narain D. Sharma, Magdalena Kaik, Peter B. A. McIntyre, John F. Malone and Paul J. Stevenson*

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Monocyclic allylic cis-1,2-diols reacted with sulfonyl chloride at 0 °C in a regio- and stereo-selective manner to give 2-chloro-1-sulfochloridates, which were hydrolysed to yield the corresponding trans-1,2-chlorohydrins. At -78 °C, with very slow addition of sulfonyl chloride, cyclic sulfates were formed in good yields, proved to be very reactive with nucleophiles and rapidly decomposed on attempted storage. Reaction of a cyclic sulfate with sodium azide yielded a trans-azido hydrin without evidence of allylic rearrangement occurring. An enantiopure bicyclic cis-1,2-diol reacted with sulfonyl chloride to give, exclusively, a trans-1,2-dichloride enantiomer with retention of configuration at the benzylic centre and inversion at the non-benzylic centre; a mechanism is presented to rationalise the observation.

Introduction

Enantiopure cis-dihydrodiol bacterial metabolites, derived from monosubstituted halobenzenes, are useful intermediates in organic synthesis. Their unsubstituted alkene bonds can be chemoselectively functionalised and the halogen atom of the vinyl halide replaced with a wide range of additional functionality. This versatile chemistry makes these substrates ideal for the synthesis of complex cyclohexane-based natural products.

Since the advent of the Sharpless asymmetric dihydroxylation reaction, resulting in the ready availability of a wide range of chiral 1,2-diols, there has been increased activity in utilizing them as key chiral intermediates in organic synthesis. This has led to a resurgence of interest in cyclic sulfate derivatives of 1,2-diols, as electrophiles for nucleophilic substitution reactions. Cyclic sulfates are generally more reactive towards nucleophilic attack than the corresponding epoxides. We were particularly interested in using the previously unreported cyclic sulfate esters of cis-tetrahydrodiol derivatives of aromatic compounds. The cis-1,2-dihydrodiol precursors are available in multi-gram quantities from our fermentation reactions.

Many reports on the preparation and use of sulfinate esters, derived from cyclic allylic diols, have appeared in the chemical literature. These electrophiles are suitably activated to react, regioselectively, with nucleophiles at the allylic position and this methodology has been used in the synthesis of Tamiflu. To date, only one example of a well characterised cyclic sulfate ester of a cyclic diol, having an allylic hydroxyl group, has been reported. However, this was prepared indirectly by the oxidation of a cyclic sulfinate ester followed by the subsequent introduction of unsaturation through dehydration.

A number of methods are available for preparing cyclic sulfate esters and the subject has been reviewed. The most direct route involves reaction of the vic-diol with sulfonyl chloride or 1,1'-sulfonylbis(1H-imidazole). This procedure works well with: (i) 1,2-diols containing electron withdrawing groups and (ii) cyclic diols and (iii) some acyclic 1,2-diols. Recently, ionic liquids have been employed as solvents for such reactions, with the advantage that sulfonyl chloride is hydrolytically stable in this medium. These direct methods are however not generally applicable and complex mixtures may result from simple alkyl substituted acyclic 1,2-diols. The problem has been attributed to: (a) the intrinsic ring strain of cyclic sulfates slowing down the final cyclisation, and (b) the innate chlorinating power of sulfonyl chloride. A more general approach involves assembling the comparatively less strained cyclic sulfinate esters (cyclic sulfites), derived from thionyl chloride, followed by their oxidation to yield cyclic sulfate esters. The Sharpless modification of this procedure, which demonstrated that the sulfinate esters could be oxidised to the sulfate esters, using sodium periodate and a catalytic quantity of ruthenium salts, led to a major advance in the routine use of cyclic sulfate esters in organic synthesis.

Results and discussion

We have recently reported that the unsubstituted alkene bond in cis-1,2-dihydrodiols, derived from monosubstituted benzenes, can be chemoselectively reduced to give cis-tetrahydrodiols, Table 1. The enhanced stability of these derivatives, over the corresponding cis-dihydrodiols, they are ideal precursors for enantioselective synthesis. To explore the chemistry further by chemoselective activation of the allylic hydroxyl group, substitution reactions at the allylic position were carried out and synthesis of previously unreported reactive cyclic sulfate esters seemed to be the obvious choice.
Products obtained from selected reactions of cis-tetrahydrodriols 1a-f and 6 with thionyl and sulfuryl chlorides, under various conditions (A-C), are presented in Scheme 1 and Table 1. Reaction of diol 1a with thionyl chloride gave cyclic sulfite 2a as a mixture (5:1) of diastereoisomers in 89% yield. Attempted oxidation of diastereoisomers 2a to give cyclic sulfate ester 3a, using the Sharpless procedure, was unsuccessful. Only 20% of the starting material, containing none of the minor diastereoisomer, was recovered. It is known that alkenes are susceptible to oxidation under these conditions, and thus it is likely that the failure of this reaction was due to the formation of polar products, which were lost on aqueous workup. Problems in carrying out this type of oxidation, in the presence of alkene functionality, have been reported.13,16 Our attention was next focussed on the direct formation of cyclic sulfate esters 3 using sulfuryl chloride.

Table 1 Reactions of cis-tetrahydrodriols 1 and 6 with SOCl2 or SOCl2 to yield products 2-5, 7 and 8.

<table>
<thead>
<tr>
<th>cis-Diol</th>
<th>Substituent</th>
<th>Conditions</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>Yield (%)</th>
<th>Yield (%)</th>
<th>Yield (%)</th>
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<tr>
<td>1a</td>
<td>Cl</td>
<td>X</td>
<td>2a (89)</td>
<td>4a (45)</td>
<td>3a (70)</td>
<td>6.9</td>
<td>4.0</td>
<td>5.6</td>
</tr>
<tr>
<td>1b</td>
<td>Br</td>
<td>na</td>
<td>4b (51)</td>
<td>3b (72)</td>
<td>4.0</td>
<td>5.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1c</td>
<td>I</td>
<td>na</td>
<td>4c (55)</td>
<td>na</td>
<td>4.0</td>
<td>5.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1d</td>
<td>CF3</td>
<td>na</td>
<td>na</td>
<td>3d (61)</td>
<td>4.0</td>
<td>5.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1e</td>
<td>CO2Me</td>
<td>na</td>
<td>na</td>
<td>3e (34), 5e (14)</td>
<td>4.0</td>
<td>5.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1f</td>
<td>Ph</td>
<td>na</td>
<td>na</td>
<td>5f (29)*</td>
<td>4.0</td>
<td>5.6</td>
<td></td>
<td></td>
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<tr>
<td>6</td>
<td>Br, Acetamide</td>
<td>na</td>
<td>7 (46)</td>
<td>8 (73)</td>
<td>4.0</td>
<td>5.6</td>
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**Conditions**

A: SOCl2, CH2Cl2, 0 °C; B: SOCl2, Et2N, CH2Cl2, 0 °C; C: SOCl2, Et2N, DMAP, CH2Cl2, -78 °C.

* A sample of 5f, as a 7:1 mixture of trans: cis diastereoisomers (29%) was isolated but the mixture was not characterised.

**Scheme 1**

Reagents and conditions: (i) C,H,N, SOCl2, CH2Cl2, 0 °C, 30 min; (ii) RuCl3, NaI, CH2N2H2O, 0 °C, 1 h; (iii) SOCl2, Et2N, CH2Cl2, 0 °C → RT, 12 h; (iv) NaI, MeOH, H2O, 3:6:1, 25 °C, 5 min; (v) SOCl2, DMAP, CH2Cl2, -78 °C, 1.5 h; (vi) NaI, DMSO, 60 °C, 4h, 93%; (vii) NaI, (CH3)2CO:H2O (6:1), 0 °C → RT, 68%.

**Fig. 1** X-ray crystal structure of (1S,2R)-3-iodo-2-chlorocyclohex-3-enyl sulfochloridate 4e

**Reaction of cis-diols 1a-c and 6 with excess sulfuryl chloride**

at 0 °C, in the presence of triethylamine, gave 2-chloro-1-sulfochloridates 4a-c, and 7 (Table 1, conditions B). The triethylamine Lewis salt of sulfur trioxide, present in the crude mixture after aqueous workup, was removed by crystallisation from hexane. Surprisingly, significant proportions of 2-chloro-1-sulfochloridates 4a-c and sulfochloridate 7 survived the aqueous workup, though hydrolysis might have been a contributing factor to the modest isolated yields (45-55%).

Determination of the molecular formulae of compounds 4a-c, initially, proved difficult as these compounds did not provide meaningful mass spectroscopic data. However, the 13C-NMR spectrum of compound 4a clearly showed a signal at δ 55.6 ppm that was entirely consistent with the replacement of a hydroxyl group with a chlorine atom at the C-2 position. The huge increase in chemical shift of the homoallylic H-1 proton signal from δ 4.0 to δ 5.37 strongly suggested that the other hydroxyl group had been converted to an ester. A single crystal X-ray structure of compound 4e (Fig. 1) established the gross structure as a 3-iodo-2-chloro-1-sulfochloridate and confirmed that the chlorine atom was introduced at the C-2 position with clean inversion of configuration. In the solid state, the molecule adopted a conformation in which the chlorine atom and chlorosulfonyl ester group were trans-diastereoisomers. This same conformation was also prevalent in CDCl3 solution, since proton H-2 appeared as a doublet, J 2.3 Hz, in the 1H-NMR spectrum, indicating a predominant conformer with a diequatorial arrangement of the two adjacent hydrogen atoms. The allylic chloro substituent adopted a pseudoaxial position, presumably to minimise allylic 1,2-strain with the iodine atom and increase hyperconjugation of the polar bond with the alkene.

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ester 3 is slow, then a second chlorosulfonyl ester may form through reaction with the allylic hydroxyl group at C-2. The pseudomolecular allylic chlorosulfonate ester is sufficiently activated to facilitate rapid nucleophilic attack of chloride ion and conversion into the allylic chloride, with inversion of configuration, giving rise to trans products, 4a-c and 7. When stored at room temperature for over a month, compounds 4a-c and 7 were found to partially decompose at room temperature after 24 h.

trans-2-Chloro-1-chlorosulfonate esters 4a and 4b were converted to trans-chlorohydrins 5a and 5b in 81% and 82% yields, respectively, using a standard procedure involving sodium iodide in aqueous methanol. This two-step procedure provides a cheap alternative to the Mattock reagent, for regio- and stereoselectively converting cyclic allylic cis-diols 1a and 1b to trans-chlorohydrins 5a and 5b respectively.

Reaction of cis-diols 1a,b,d,e and 6, at low temperature and high dilution, with very slow addition of sulfuryl chloride in the presence of DMAP (Table 1 Conditions C, conditions used by Myers), gave the desired cyclic sulfates 3a,3b,3d,3e and 8 in moderate to good yields (34-73%). These conditions were essential to achieve the desired chemoselectivity and to favour intramolecular ring closure of the intermediate mono chlorosulfate ester and formation of the cyclic sulfate ester over other processes. Low temperature single crystal X-ray crystallography established the structure of cyclic sulfate 3a. In the case of cis-diol 1e the modified conditions gave a 2:5:1 ratio of cyclic sulfate 3e to chlorohydrin 5e and similarly diol 1f gave a modest yield (29%) of impure chlorohydrin 5f but no cyclic sulfite 3f indicating that these reactions were very substrate dependant. The cyclic allylic sulfate esters 3a,3b,3d,3e and 8 were found to partially decompose at room temperature after 24 h.

We have recently reported the synthesis of (1S,2S)-trans-1,2-azidohydrin 9a as the predominant product from a ring opening reaction of the corresponding epoxide, and have demonstrated that this equilibrates with the isomeric azidohydrin 10a, via an allyl azide [3,3] sigmatropic rearrangement on gentle heating, to give a 4:1 mixture of isomers 9a:10a. Cyclic sulfate 3a reacted with sodium azide, at room temperature, to give, exclusively, azidohydrin 9a without evidence of azidohydrin isomer 10a. The corresponding less reactive cyclic sulfite 2a did not react with sodium azide under these conditions. However, on heating, with sodium azide in DMSO, cyclic sulfite 2a formed azidohydrin 9a together with the rearranged isomer 10a. It is, therefore, advantageous, in some cases, to use the more reactive cyclic sulfite 3 rather than cyclic sulfite 2.

A brief study of benzo-fused cyclic cis-diols 11a-c, in which one of the hydroxyl groups was benzylic (Scheme 2), available as single enantiomer metabolites from earlier biotransformation studies, was undertaken. Reaction of 2,3-dihydro-1H-indene-1,2-diol 11a, and 6,7-dihydro-5H-benzof[7]amulene 11c, with sulfuryl chloride at 0 °C, gave complex mixtures of products whose separation was not attempted. In marked contrast, reaction of (1R,2S)-naphthalene cis-1,2,3,4-tetrahydridiol 11b, under the same reaction conditions, proceeded smoothly and cleanly, to give dichloride 12b in excellent yield. Analysis of the 1H-NMR spectrum gave the coupling constant between H-1 and H-2, (J 2 Hz). This indicated that there was a strong preference, in solution, for a conformer in which these two hydrogens were trans-diequatorial, confirming the structure of diastereoisomer 12b as the trans-1,2-dichloride. Coupling constants of similar magnitude have been reported for the trans-1,2-diazides in the tetrahydronaphthalene series. Surprisingly, one of the chlorine atoms was introduced with retention, whilst the other with inversion of configuration.

trans-Dichloride 12b was found to be optically active but the magnitude of optical rotation ([α]D+12.3), in comparison with the literature values, suggested that the compound was of relatively low enantiopurity (ca. 20% ee). Chiral stationary phase HPLC analysis (Chiralcel OD), however, showed a baseline separation of the enantiomers of racemic trans-dichloride 12b and an early eluting single peak for (+)-trans-dichloride 12b, derived from (1R,2S)-dial 11b, establishing that it was a single enantiomer. 1H-NMR spectroscopy proved that one chiral centre had inverted whilst the other had retained its stereochemistry on chlorination, but could not link these stereochemical events to a discrete chiral centre. X-ray crystallographic analysis, on a single crystal of (+)-dichloride 12b, determined both its relative and absolute configurations (Fig. 3). It confirmed: (i) the trans diastereomer of the racemic dichloride 12b, as determined by HPLC, to be the trans-1,2-dichloride and (ii) that chlorination at the benzylic position proceeded with retention of configuration and at the non-benzylic position with inversion of configuration to give the (1R,2R) enantiomer.
Since many reactions which proceed with retention of configuration involve a double inversion, the cyclic chloronium ion 16b has been presented as a likely intermediate (Scheme 2). Cyclic chloronium ions have previously been postulated, to explain counterintuitive stereoselectivity in ring opening reactions of ω-chloroepoxides. Chlorination with inversion of configuration at the more reactive benzylic position would complete the double inversion and postulate the intermediate 15b as a precursor of the cyclic chloronium ion 16b. Ring opening of intermediate 16b with chloride ion at the reactive benzylic position would complete the double inversion and account for the experimentally observed stereochemistry. Nicolaou has demonstrated catalytic asymmetric addition of chloride to allylic alcohols, where regioselectivity of chloronium ion ring opening is a prerequisite for good ee values and Denmark has recently demonstrated that chiral chloronium ions, containing alkyl groups, are configurationally stable. The generality of this novel dichlorination reaction remains to be fully evaluated, but it is significant that it failed with two (11a and 11c) out of three cyclic substrates.

Fig. 3 X-ray crystal structure of (1R,2R)-1,2-dichloro-1,2,3,4-tetrahydronaphthalene 12b

Reaction of cis-tetrahydrodiol 11b, under Myers’ conditions, failed to give any of the corresponding cyclic sulfate and only the trans-chlorohydrin 13b was isolated (71% yield). In this example, it was likely that the cyclic sulfate was slow to form and both the hydroxyl groups became chlorosulfonated to yield intermediate 14b which eventually led to the formation of chlorohydrin 13b, on warming the reaction mixture to room temperature followed by its aqueous workup.

The relative stereochemistry of chlorohydrin 13b, a known literature compound, was determined as trans, by comparison of the NMR spectroscopic data. It is noteworthy that the coupling constant in trans-chlorohydrin 13b was much larger (J1,2 6.9 Hz) than the corresponding coupling constant in trans-dichloride 10 (J1,2 2.2 Hz). This is consistent with the conformational heterogeneity in chlorohydrin 13b, with two dominant conformers contributing to the observed coupling constant. It may be the result of an intramolecular hydrogen bond, helping to stabilise the conformer in which the hydroxyl and chloro groups are disequatorial. The absolute configuration of compound (-)-13b was assumed to be (1S,2S) on the basis of its formation from intermediate 15b and is in accord with the literature assignment.

Conclusion

It was demonstrated that the products, from reactions of chiral allyl- and benzyl-activated cyclic cis-diols with sulfuryl chloride, were dependent on both substrate structure and conditions. Up to four types of enantiopure pure products were identified from this reaction i.e. trans-chlorohydrin, trans-chloro-chlorosulfate ester, cis-cyclic sulfate ester and a trans-dichloride. With monocyclic allylic diols, conditions were found that favoured either formation of the cyclic sulfate esters or chloro-chlorosulfate esters as precursors to trans-chlorohydrins. Cyclic sulfate esters and trans-chlorohydrins demonstrate stereo-complementarity, because the absolute configurations at the electrophilic allylic sites are opposite for each class of compound. It is noteworthy that reaction with sulfuryl chloride can yield either type of product, simply by modifying the reaction conditions. This is likely to enhance the importance of these species as intermediates in enantioselective synthesis.

Experimental

1H and 13C-NMR spectra were recorded on Bruker Avance 400, DPX-300 and DRX-500 instruments. Chemical shifts (δ) are reported in ppm relative to SiMe4 and coupling constants (J) are given in Hz. Mass spectra were run at 70 eV, on a VG Autospec mass spectrometer, using a heated inlet system. IR spectra were recorded on a Perkin-Elmer Model 983G instrument coupled to a Perkin-Elmer 3700 data station using potassium bromide (KBr) disks unless otherwise stated. Accurate molecular weights were determined by the peak matching method, with perfluorokerosene as the standard. Flash column chromatography and preparative layer chromatography (PLC) were performed on Merck Kieselgel type 60 (250-400 mesh) and PF254 plates respectively. Merck Kieselgel type 60F254 analytical plates were employed for TLC.

Dioxathiol-2-oxide 2a

Thionyl chloride (3.24 g 27.2 mmol) was added dropwise to a stirred solution of diol 1a (2.7 g, 18.2 mmol) and pyridine (2.6 g, 32.7 mmol) in DCM (100 mL) at -30 °C. The reaction mixture was allowed to warm to room temperature, water (100 mL) was added, the organic phase separated, washed with water (100 mL), dried (MgSO4) and concentrated. The resulting crude yellow oil was purified by passing it through a pad of alumina and eluting with ethyl acetate/petroleum ether (1: 1), to afford cyclic sulphide 2a (3.15 g, 89%). Product 2a was obtained as an oil consisting of an inseparable mixture (4:1) of two diastereoisomers, resulting from the newly generated chiral sulphur centre. HRMS (LCTOFMS) (Found: [M+1]+ 194.9877. C9H8ClO2S requires 194.9877); Major isomer: 1H-NMR (300 MHz, CDCl3) δH 6.18 (1 H, dd, J 4.9, 3.7, H-6), 5.21 (2 H, 2xm, H-7a and H-3a), 2.32 (1 H, m, H-5), 2.18 (1 H, m, H-5''), 2.07-2.13 (2 H, 2xm, H-4' and H-4''), 4.97 (1 H, bd, J 5.9 H-3a), 4.89 (1 H, dt, J 5.9, 3.0, H-7a), 2.51 (1 H m, H-5), 2.03-2.40 (3 H, 3xm, H-5', H-3 and H-3''); Minor isomer: 13C-NMR (CDCl3, 75 MHz) δC 131.45 (2C), 79.16, 77.96, 24.18, 21.84 and 21.80. Minor isomer: 131.14, 127.25, 82.23, 80.05, 25.68, 21.80. This journal is © The Royal Society of Chemistry [year]
**General procedure A for chloro sulfonofluoridation formation**

Triethyamine (0.16 mL, 1.14 mmol) and sulfuryl chloride (0.09 mL, 1.14 mmol) were added to a solution of cis-diol 1 (0.57 mmol) in DCM (8 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred overnight. The solution was diluted with DCM (5 mL), cooled to 0 °C and water (8 mL) was added. The DCM layer was separated and the remaining aqueous layer extracted with fresh DCM (2 x 5 mL). The combined organic extract was dried (MgSO₄) and the solvent removed to give a yellow oil. The oil was extracted with hexane (3 x 10 mL) and the extract evaporated at 40 °C, to give a concentrated solution, which was left for crystallisation to yield the title compound.

**Gradual procedure A**

General procedure A gave titled compound, yield: 45%; m. p. 49-50 °C (from hexane); Rf 0.9 (Et₂O/hexane, 1:1); [α]D +153.3 (c 0.6, CHCl₃). (Found: C 27.6; H 2.7; S 11.7. C₇H₆Cl₂O₂S requires C 27.1; H 2.7; S 12.1%)

-H-NMR (500 MHz, CDCl₃) δₓ 2.50-2.22 (4 H, m, H₅-5, H₆-6), 4.58 (1 H, bm, H-2), 5.37 (1 H, dt, J 4.5, 2.4, H-1), 6.15 (1 H, dd, J 5.0, 2.9, H-4); ¹³C-NMR (125 MHz, CDCl₃) δₓ 20.29, 21.27, 55.64, 85.91, 127.16, 129.76; v₁max/cm⁻¹ (KBr) 3061.9, 2932.1, 1649.7, 1404.2, 1215.6, 1191.9, 934.9, 919.7.

**Gradual procedure A**

General procedure A gave titled compound, yield: 51%; m. p. 68-70 °C (from hexane); Rf 0.82 (Et₂O/hexane, 1:1); [α]D +119 (c 1.07, CHCl₃). (Found: C 23.9; H 2.3; S 10.1. C₆H₆Br₂Cl₂O₄S requires C 23.3; H 2.3; S 10.3%)

-H-NMR (500 MHz, CDCl₃) δₓ 2.48-2.24 (4 H, m, H₅-5, H₆-6), 4.65 (1 H, bm, H-2), 5.37 (1 H, dt, J 4.4, 2.3, H-1), 6.37 (1 H, dd, J 5.2, 2.7, H-4); ¹³C-NMR (125 MHz, CDCl₃) δₓ 20.31, 22.77, 57.47, 85.99, 116.72, 134.24. LRMS (ED) 310 (M⁺, 1%).

**Gradual procedure A**

General procedure A gave titled compound yield: 55%; m. p. 84-86 °C (from hexane); [α]D +82.2 (c 1.07, CHCl₃). (Found: C 20.8; H 2.2; S 8.5. C₁₀H₇Cl₂O₃S requires C 20.2; H 2.0; S 9.0%)

-H-NMR (300 MHz, CDCl₃) δₓ 6.63 (1 H, dd, J 4.9, 2.8, H-4), 5.35 (1 H, dt, J 4.9, 2.8, H-1), 4.66 (1 H, bs, H-1), 2.52-2.28 (4 H, m, H₅-5, H₆-6); ¹³C-NMR (75 MHz, CDCl₃) δₓ 142.20, 90.11, 85.25, 60.48, 24.12, 19.83; v₁max/cm⁻¹ (KBr) 3261.0, 1724.6, 1624.8, 1400.1, 1187.9, 1211.0, 915.8, 727.4, 591.0.

**Crystal data for 4c**

C₄H₇Cl₂O₃S, M = 357.0, orthorhombic, a = 5.936(1), b = 8.960(3), c = 20.683(6). Å, U = 1100.0(5) Å³.

**General procedure B for cyclic sulfate formation**

4-(Dimethylamino)pyridine (25 mg, 0.21 mmol) was added to a stirred solution of dio 1 (0.52 mmol) in DCM (10 mL) and the resulting solution cooled to -78 °C. Triethylamine (0.29 mL, 2.06 mmol) was added to the cooled solution and the stirring continued for 10 min. A solution of sulfuryl chloride (0.08 mL, 0.98 mmol) in DCM (10 mL) was then slowly added to the cold
reaction mixture via a glass syringe over a period of 1 h. After stirring at -78 °C for 30 min, the solution was diluted with DCM (10 mL) and a saturated solution (10 mL) of sodium bicarbonate was added to the reaction mixture. The organic layer was separated, washed, successively, with brine (10 mL) and water (10 mL), dried (Na₂SO₄) and concentrated. The crude product obtained was purified either by crystallisation or chromatography.

(1S,2S)-3-Chlorocyclohex-3-ene-1,2-cyclic sulfate 3a.

Using general procedure B, diol 1a gave a crude product, which was purified by PLC and then crystallised from Et₂O/hexane to give cyclic sulfate 3a as colourless needles. Yield: 70%; m. p. 71-72 °C; Rf 0.4 (Et₂O/hexane, 1:1); [α]D +106.0 (c 0.73, CHCl₃); (Found: C, 34.4; H, 2.8. C₂H₆Cl₆SO₄ requires C, 34.2; H, 3.3%).

HRMS (LC-TOFMS) (Found: [M+NH₄]^+ 228.0087; C₂H₁₂Cl₆SO₄ requires 228.0092); δ-H (400 MHz, CDCl₃) 3.07 (3 H, s, OH) 2.20 (1 H, m, HS1), 2.40 (1 H, dd, J 4.4, HS2), 4.06 (1 H, dtd, J 4.4, 13, 6, HS3), 5.04 (1 H, d, J 5.3, HS4), 5.29 (1 H, d, J 5.3, HS5), 5.43 (1 H, ddd, J 4.4, 13, 18, HS6), 5.54 (1 H, d, J 5.3, HS5'), 5.96 (1 H, d, J 5.3, HS6').

Crystal data for 3a: C₁₂₃H₁₂Cl₆O₆S₄, M = 210.6, orthorhombic, a = 6.6774(1), b = 10.9657(2), c = 11.0172(2) Å, U = 806.73(2) Å³, T = 100(2) K, space group P2₁2₁2₁ (no. 19).

Following the general procedure B, the title compound was isolated as a byproduct in the above reactions as a pale yellow oil. Yield: 20 mg, 14%; Rf 0.52 (Et₂O/hexane, 1:1); [α]D +89.0 (c 0.9, CHCl₃); HRMS (LC-TOFMS) (Found: M+ 190.0401. C₆H₁₂Cl₂O₄ requires 190.0391); δ-H (400 MHz, CDCl₃) 3.81 (3 H, s, OH) 2.25 (1 H, m, HS1), 2.43 (1 H, m, HS2), 3.94 (2 H, m, HS3), 4.14 (1 H, dd, J 4.4, 13, 6, HS4), 5.25 (1 H, d, J 5.3, HS5), 5.42 (1 H, d, J 5.3, HS6), 5.72 (1 H, d, J 5.3, HS4), 6.43 (1 H, m, HS5), 7.19 (1 H, m, HS6), 7.79 (1 H, m, HS6').

5e. Following the general procedure B, the title compound was isolated as a byproduct in the above reactions as a pale yellow oil. Yield: 20 mg, 14%; Rf 0.52 (Et₂O/hexane, 1:1); [α]D +89.0 (c 0.9, CHCl₃); HRMS (LC-TOFMS) (Found: M+ 190.0401. C₆H₁₂Cl₂O₄ requires 190.0391); δ-H (400 MHz, CDCl₃) 3.81 (3 H, s, OH) 2.25 (1 H, m, HS1), 2.43 (1 H, m, HS2), 3.94 (2 H, m, HS3), 4.14 (1 H, dd, J 4.4, 13, 6, HS4), 5.25 (1 H, d, J 5.3, HS5), 5.42 (1 H, d, J 5.3, HS6), 5.72 (1 H, d, J 5.3, HS4), 6.43 (1 H, m, HS5), 7.19 (1 H, m, HS6), 7.79 (1 H, m, HS6').

(1S,2S)-2-Chloro-3-phenylcyclohex-3-ene-1-carboxylic acid 5f and (1S,2R)-2-Chloro-3-phenylcyclohex-3-ene-1-carboxylic acid 5f

Following the general procedure B, diol 1e (280 mg, 1.47 mmol) gave a crude product, which on purification by PLC (Et₂O/hexane, 1:1) gave cyclic sulfate 5f as colourless oil. Yield: 20 mg, 14%; Rf 0.52 (Et₂O/hexane, 1:1); [α]D +89.0 (c 0.9, CHCl₃); HRMS (LC-TOFMS) (Found: M+ 190.0401. C₆H₁₂Cl₂O₄ requires 190.0391); δ-H (400 MHz, CDCl₃) 3.81 (3 H, s, OH) 2.25 (1 H, m, HS1), 2.43 (1 H, m, HS2), 3.94 (2 H, m, HS3), 4.14 (1 H, dd, J 4.4, 13, 6, HS4), 5.25 (1 H, d, J 5.3, HS5), 5.42 (1 H, d, J 5.3, HS6), 5.72 (1 H, d, J 5.3, HS4), 6.43 (1 H, m, HS5), 7.19 (1 H, m, HS6), 7.79 (1 H, m, HS6').

5f. Following the general procedure B, the title compound was isolated as a byproduct in the above reactions as a pale yellow oil. Yield: 20 mg, 14%; Rf 0.52 (Et₂O/hexane, 1:1); [α]D +89.0 (c 0.9, CHCl₃); HRMS (LC-TOFMS) (Found: M+ 190.0401. C₆H₁₂Cl₂O₄ requires 190.0391); δ-H (400 MHz, CDCl₃) 3.81 (3 H, s, OH) 2.25 (1 H, m, HS1), 2.43 (1 H, m, HS2), 3.94 (2 H, m, HS3), 4.14 (1 H, dd, J 4.4, 13, 6, HS4), 5.25 (1 H, d, J 5.3, HS5), 5.42 (1 H, d, J 5.3, HS6), 5.72 (1 H, d, J 5.3, HS4), 6.43 (1 H, m, HS5), 7.19 (1 H, m, HS6), 7.79 (1 H, m, HS6').

(1S,2R)-3-(Trifluoromethyl)cyclohex-3-ene-1,2-cyclic sulfate 3b.

Following the general procedure B, diol 1b gave a crude product, which was purified by PLC and then crystallised from Et₂O to give cyclic sulfate 3b as colourless solid. Yield: 95 mg, 72%; m. p. 73-74 °C; δ-H (400 MHz, CDCl₃) 3.07 (3 H, s, OH) 2.20 (1 H, m, HS1), 2.40 (1 H, d, J 4.4, HS2), 4.04 (1 H, d, J 4.4, HS3), 5.04 (1 H, d, J 4.4, HS4), 5.29 (1 H, d, J 4.4, HS5), 5.43 (1 H, d, J 4.4, HS6), 5.54 (1 H, d, J 4.4, HS5'), 5.96 (1 H, d, J 4.4, HS6').
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Sodium azide (31 mg, 0.48 mmol) was added to a solution of cyclic sulfate 3a (50 mg, 0.24 mmol) in a mixture of acetone:water (6:1, 5 mL) at 0 °C. The solution was stirred for 12 h and then allowed to warm to room temperature. The solvent was removed in vacuo, the white solid residue obtained was treated with a mixture of 20% H₂SO₄ and Et₂O (1:1, 6 mL) and the reaction mixture stirred for a further 8 h. It was diluted with Et₂O (20 mL), washed withaq. NaHCO₃ (2 x 15 mL), brine (15 mL), dried (Na₂SO₄) and concentrated in vacuo. The crude product, obtained as a yellow oil, was purified by PLC (EtOAc:hexane, 3:7) to furnish azide 9a as a colourless oil. Yield: 28 mg, 68%; R₆ 0.48 (EtOAc:hexane, 3:7); [α]D +198.0 (c 0.7, CHCl₃); HRMS (LCTOFMS) (Found: [M+Na]+, 196.0245. C₆H₇ClN₃NaO requires 196.0248); ¹H-NMR (400 MHz, CDCl₃) δH 7.17 (1 H, m, H-6), 1.89 (1 H, m, H-6′), 1.96 (1 H, s, OH), 2.21-2.28 (2H, m, H-5, H-5′), 3.87 (1 H, br d, J 5.6, H-2), 3.91 (1 H, ddd, J 8.5, 5.6, 3.1, H-1), 6.07 (1 H, t, J 4.1, H-3); ¹³C-NMR (100 MHz, CDCl₃) δC 22.8, 26.3, 67.6, 71.0, 128.3, 129.3; LRMS (EI) 173 (7), 146 (25), 144 (78), 131 (81), 129 (72), 118 (73), 116 (82), 103 (64), 101 (100); νmax/cm⁻¹ (thin film) 3367, 2932, 2103, 1662, 1257.

A solution of cyclic sulfite 2a (2.01 g, 10.3 mmol) and sodium diol (0.24 mmol) in DCM (10 mL) was heated with stirring at 60 °C for 4 h. After cooling the mixture, it was diluted with water (40 mL) and extracted with ethyl acetate (60 mL). The organic phase was washed with brine (3 x 50 mL), dried (Na₂SO₄) and concentrated to give the crude product (1.67 g, 93%) as an inseparable mixture (3:1) of azides 9a and 10a. In addition to the NMR signals for the major isomer 9a, additional signals for the compound 10a were also present. ¹H-NMR (300 MHz, CDCl₃) δH 6.07 (1 H, d, J 4.6, H-2), 4.25 (1H, m, H-1), 3.93 (1 H, t, J 4.9, H-4) 2.30-2.30 (2H, m, H-5), 1.93-1.80 (2H, m, H-6); ¹³C-NMR (100 MHz, CDCl₃) δC 131.33, 128.51, 65.35, 61.19, 27.67, 26.29. The above data matched with that reported in the literature.²²

Triethylamine (0.34 mL, 2.42 mmol) was added to solution of (1R,2S)-cis-diol 11b (100 mg, 0.61 mmol) and DMAP (0.03 g, 0.24 mmol) in DCM (10 mL). The mixture was cooled to -78 °C and stirred for 10 min. Sulfuryl chloride (0.09 mL, 1.15 mmol) was added dropwise over a period of 1 h and the mixture allowed to stir for a further 30 min at -78 °C. The reaction mixture was quenched with a saturated solution of sodium bicarbonate (3 mL), diluted with DCM (5 mL), and water (15 mL). The organic layer was separated, washed with water, dried (Na₂SO₄), and concentrated on a rotary evaporator, to give a brown-coloured oil. The crude product was passed through a short silica gel column with Et₂O as eluent. This sample was further purified by PLC (EtOAc:hexane, 1:1), to give the chlorohydrin 13b as a colourless oil. Yield: 81 mg, 73%. Its spectral properties were in general agreement with the literature values.²³ R₆ 0.42 (EtOAc:hexane, 1:1); [α]D +39 (c 0.7, CHCl₃); lit²⁴ [α]D -39 (c 0.7, CHCl₃); ¹H-NMR (400 MHz, CDCl₃) δH 1.89 (1 H, m, H-3), 2.33 (1 H, ddd, J 14.4, 5.8, 3.3, H-3), 2.43 (1 H, s, OH), 2.94 (2 H, appr t, J 6.2, H-4), 4.15 (1 H, ddd, J 9.6, 6.9, 3.3, H-2), 5.02 (1 H, d, J 6.9, H-1), 7.11 (1 H, m, Ar), 7.23 (2 H, m, Ar), 7.53 (1 H, m, Ar); ¹³C-NMR (100 MHz, CDCl₃) δC 26.33, 27.69, 46.56, 72.84, 126.54, 128.14, 128.54, 130.17, 133.92, 135.91. *Signals are within 0.2 ppm except for signal at 72.84 does not match the literature value of 69.1 ppm.

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