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Synthesis of polyhydroxylated cyclohexenyl sulfides and sulfoxides. Evaluation of their inhibitory activity on α- and β-D-glucosidases

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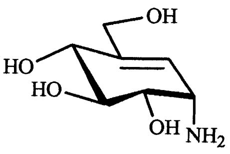
Abstract

Racemic polyhydroxylated sulfides and sulfoxides have been prepared as potential transition-state analogs of the glucoside hydrolysis reaction, through a reaction sequence involving transformations of a ketone group into thioacetal, followed by partial oxidation to sulfoxide then regioselective thermal elimination of the sulfoxide to vinyl sulfide. These sulfides with two, three or four hydroxyl groups have been oxidized to the corresponding diastereoisomeric sulfoxides. All compounds, summarily tested as inhibitors of α- and β-glucosidases, were found to be very weak inhibitors and thus their biological properties were not studied in depth. Curiously, however, their inhibitory properties, which are in the 10 mM range, do not really depend upon the number of hydroxyl groups or upon the presence of polar sulfoxide. In order to get more insights, 2-phenyl sulfoxide-3,4,5-trihydroxycyclohex-1-ene (**9a**) was studied in more detail using Brewers yeast α-glucosidase and was shown to give a mixed-type inhibition with a high K_i of 45 mM. © 1999 Elsevier Science Ltd. All rights reserved.

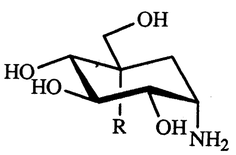
Keywords: Carbasugars; Cyclohexenyl sulfides and sulfoxides; Glycosidase inhibitors; Glycoside hydrolysis transition state

1. Introduction

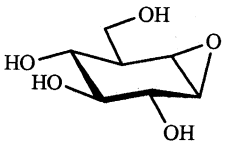
In connection with a program directed toward antibody catalysis of glycosidic bond hydrolysis, we were interested in carbasugar-type inhibitors, some of them being reported as good α- and β-D-glucosidase inhibitors. Thus, the valienamine **1**, the validamine **2** and the valiolamine **3** were shown to be strong inhibitors of α-D-glucosidases [1]. The inhibitory activity of these compounds rests on their configuration, their basic character or their conformation, which mimics in part the flattened anomeric region and/or the partial charge development around the anomeric carbon atom in the transition state along the hydrolysis pathway. As a result, many N-substituted derivatives of **1**–**3** and some of their



1: Valienamine



2: R = H Validamine
3: R = OH Valiolamine



4: Cyclophellitol

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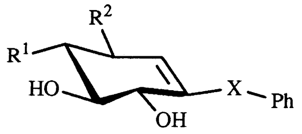
epimers have been synthesized, giving rise to numerous other glucosidase inhibitors [2,3].

More recently, the natural carbasugar cyclophellitol **4** [4] has been isolated and described as a specific inhibitor of β-D-glucosidases [5]. The cyclophellitol **4** is a fully oxygenated D-*gluco*-configured cyclohexane, which possesses a flattened conformation imposed by an epoxide [6] and acts as an inactivator of β-D-glucosidases. As reported by Withers and Umezawa, the epoxide **4** is first protonated by the carboxylic acid residue in the active site of the enzyme, then attacked by the nucleophile carboxylate residue to form a covalent derivative that inactives the 'retaining' β-D-glucosidase [7]. In order to provide some additional information about the interactions of such an epoxide with glucosidases, the 1,6-*epi*-cyclophellitol [8] and some related derivatives (aziridine [9] and thiirane [10]), possessing various configurations, have also been prepared. Thus, transposed in the area of catalytic antibodies, the design of the hapten could result from two different strategies: one based on the half-chair transition-state analogs and the other based on positively charged compounds expected to induce functional group in the antibody-combining site that would stabilize the delocalized positive charge of the transition state.

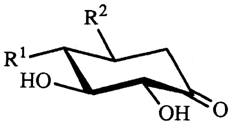
We now describe, for evaluation of their inhibition properties, the syntheses of the polyhydroxylated cyclohexenyl sulfides **5**–**7** and sulfoxides **8a/8b**–**10a/10b** as new carbasugar-type derivatives. Similarly to the cyclophellitol **4**, these compounds are uncharged derivatives; however, they possess a double bond in a correct position corresponding to that in the oxocarbenium ion, which should impose a flattened half-chair conformation. On the one hand, we were interested in the comparison of the inhibition activities between both series, the vinyl sulfides **5**–**7** and the more polarized vinyl sulfoxides **8a/8b**–**10a/10b**, which could induce some charge interactions in spite of the lack of basic center as found in valienamine-type inhibitors. At the same time, we considered evaluating the contribution of hydroxy groups in the inhibition and prepared the corresponding unsubstituted cyclohexene derivatives for comparison. We chose in a first approach to prepare the racemic derivatives for rapid evaluation of their biological behavior, bearing in mind that the complete determination of the exact inhibitory power would require the pure enantiomeric form. Indeed, their potential use as hapten for monoclonal antibody preparation does not require the pure enantiomer as each isolated monoclonal antibody must recognize only one enantiomeric form in the antigenic racemic mixture.

The syntheses of vinyl sulfides **5**–**7** and vinyl sulfoxides **8a/8b**–**10a/10b** were performed from the corresponding racemic cyclohexanones **11**–**13** in five and six steps, respectively. The key step in all the syntheses was a regioselective sulfoxide elimination that led to the substituted cyclohexene. We also describe the inhibitory potencies of vinyl sulfides **5**–**7** and vinyl sulfoxides **8a/8b**–**10a/10b** toward α-D-glucosidase (Brewers yeast) and β-D-glucosidase (sweet almonds).



5 R^1=R^2= H, X=S
6 R^1=OH, R^2= H, X=S
7 R^1= OH, R^2= CH$_2$OH, X=S

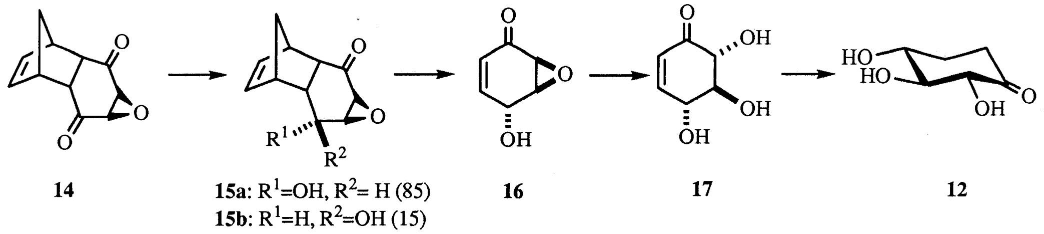
8a/8b R^1=R^2= H, X=SO
9a/9b R^1=OH, R^2= H, X=SO
10a/10b R^1= OH, R^2= CH$_2$OH, X=SO



11 R^1=R^2= H
12 R^1= OH, R^2= H
13 R^1= OH, R^2= CH$_2$OH

2. Results and discussion

Preparation of the starting ketones **11**–**13**.— The dihydroxyketone **11** was readily obtained in two steps from the commercial cyclohexenone according to a known procedure [11]. The trihydroxyketone **12** was prepared in four steps (Scheme 1) from the epoxide **14**, easily available from 1,4-benzoquinone and cyclopentadiene (two steps) [12]. The diastereo- and regioselective reduction of **14** with tetrabutylammonium borohydride [13] at low temperature afforded a mixture of diastereoisomers **15a/15b** in an 85:15 ratio as determined by ^{13}C NMR and ^{1}H NMR spectrometry. The diastereoisomers **15a/15b** could



Scheme 1.

not be separated from each other by flash chromatography; the configuration assignment was therefore performed on the diastereoisomeric mixture. Analysis of the multiplicity and coupling constants associated with H-3 of **15a/15b** showed that the major isomer **15a** had a trans configuration (**15a**: dd, J 4.5 and 3.5 Hz; **15b**: d, J 4.5 Hz). This assignment was later confirmed after acetylation of **15a/15b** followed by separation of both diastereoisomers by flash chromatography (data not shown).

Fortunately the mixture **15a/15b**, when submitted to a retro Diels–Alder reaction (diethylphthalate, 190 °C), led to a mixture of both epoxides **15b** and **16** [14] from which the epoxide **16** could be isolated in 80% yield. Heating epoxide **16** in water at 80 °C for 4 days led to the trihydroxycyclohexenone **17** [15] in 41% yield[1]. According to the coupling constants determined by ^{1}H NMR ($J_{4,5}$ 8.0 Hz, $J_{5,6}$ 10.5 Hz), the hydroxy groups possessed a trans relative configuration. Epoxide **16**, when treated in acidic conditions, also gave the trihydroxycyclohexenone **17** but in a lower yield (ca. 30%). Alkaline conditions to open such an epoxide could not be used here since aromatization might occur [16]. The cyclohexenone **17** was further reduced under catalytic hydrogenation in the presence of Pd–C to give **12** in 80% yield. The tetrahydroxylated ketone **13** was prepared in 11 steps from furan and acrylic acid using a method developed by Ogawa and co-workers [17] (data not shown).

Preparation of vinyl sulfides (**5–7**) *and vinyl sulfoxides* (**8–10**) *(Scheme 2).*—The dihydroxy ketone **11** was used as a model for the synthesis of polyhydroxylated cyclohexenyl sulfides **5**–**7** and sulfoxides **8a/8b**–**10a/10b**. Treatment of **11** with thiophenol in concd aq hydrochloric acid [18] followed by acetylation gave the acetylated dithioacetal **18** in 65% yield. Then, **18** was treated with mercuric acetate [19] and regioselectively gave the cyclohexenyl sulfide **19** but only in low yield (40%). So, an alternative route has been developed. First the dithioacetal **18** was selectively oxidized to a diastereomeric mixture of sulfoxides using 1 equiv of *m*-chloroperoxybenzoic acid[2] at −30 °C. Then, the sulfoxide mixture was directly heated at 80 °C in the presence of calcium carbonate [20] to provide the unique vinylic sulfide **19** in 90% yield (two steps). Then, deacetylation (MeOH, NaOMe) gave the expected dihydroxy cyclohexenyl sulfide **5** in 95% yield. Using 1 equiv of *m*-chloroperoxybenzoic acid, the oxidation of **19** to get the diastereomeric sulfoxides **20a**/**20b** was not selective, and further oxidation to the sulfone[3] **21** (35%) was observed. The sulfoxides **20a**/**20b** (ratio 60:40) and the sulfone **21** were obtained in a 65:35 ratio and could not be separated by flash chromatography at this stage. Pure samples of **8a** and **8b** were obtained after deacetylation of the mixture (MeOH, NaOMe).

A similar strategy was used to prepare the vinylic sulfides **6** and **7** and the vinylic sulfoxides **9a/9b** and **10a/10b** from either ketone **12**

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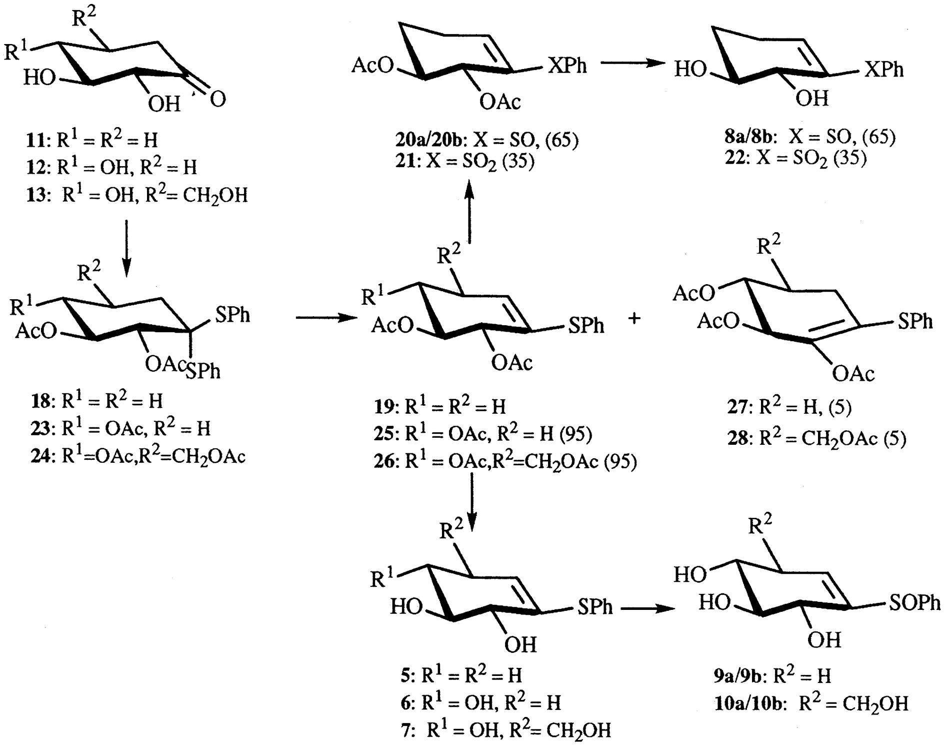
[1] After heating the epoxide **16** in water at 80 °C for 4 days, hydrolysis was not complete. The crude product also contained the starting material (ca. 39%) and the product resulting of the 1,4-addition of water on the double bond of **17** (ca. 17%). Increasing temperature or reaction time did not improve the yield.

[2] Titration of the *m*-chloroperoxybenzoic acid solution was performed (KI, $NaHCO_3$, AcOH–water, then titration with sodium thiosulfate) before use.

[3] Formation of the sulfone **17** as by-product was observed at low temperature, even before the complete conversion of **15** in the expected sulfoxides **16a/16b**.



Scheme 2.

or **13** (Scheme 2). Reaction of the ketones **12** or **13** with thiophenol and concd aq HCl followed by acetylation gave acetylated dithiophenylacetal **23** or **24** but only in low yield (ca. 30%). In fact, activation of **12** or **13** with borontrifluoride etherate [21] in the presence of thiophenol in dichloromethane at low temperature (−5 °C) gave the best results, resulting in **23** (85%) and **24** (66%) after acetylation. As expected, the cyclohexenyl sulfides **25** and **26** were the major regioisomers formed in the course of the sulfoxide elimination step. The vinylic sulfides **25** and **26** were obtained in 80 and 75% yields, respectively, although a small amount (4%) of the others regioisomers **27** and **28** was formed. Deacetylation of **25** and **26** (MeOH, NaOMe) yielded the tri- and tetrahydroxylated vinylic sulfides **6** (84%) and **7** (95%), respectively. Direct oxidation of both vinylic sulfides **2** and **3** with an excess of *t*-butylhydroperoxide at 60 °C gave a diastereomeric mixture (ratio 1:1) of vinylic sulfoxides **9a/9b** (84%) and **10a/10b** (78%), respectively. It is worth pointing out that further oxidation to the sulfones using *t*-butylhydroperoxide as oxidant instead of *m*-chloroperoxybenzoic acid was not observed. Pure samples of the trihydroxylated vinylic sulfoxides **9a** and **9b** were obtained after flash chromatography, while only partial separation of the tetrahydroxylated vinylic sulfoxides **10a/10b** (ca. 9:1, 1:1 and 1:4) was obtained.

Biological evaluations.—The cyclohexenyl sulfides **5**–**7** and sulfoxides **8a/8b**–**10a/10b** are very weak inhibitors of Brewers yeast α-D-glucosidase (EC 3.2.1.20) and sweet-almond β-D-glucosidase (EC 3.2.1.21). The IC_{50} (50% inhibition) was observed against yeast α-D-glucosidase at 10 mM for the cyclohexenyl sulfides **6** and **7**, at 8 mM for the cyclohexenyl sulfoxide **9a**, and at 2.5 mM for the cyclohexenyl sulfides **5**, while the K_m values of yeast α-D-glucosidase and sweet-almonds β-D-glucosidase for their corresponding substrate[4] were 0.16 and 2.4 mM, respectively. For all the other derivatives and with both glucosidases, the IC_{50} was not reached at 10 mM. The number of hydroxy groups in either sulfide or sulfoxide derivatives does not have the expected effect on the inhibition. Thus, the

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[4] The substrates used for the β-D-glucosidase (sweet almonds) and for the α-D-glucosidase (Brewers yeast) were *p*-nitrophenyl-β- and α-D-glucopyranosides, respectively.

tetrahydroxylated vinylic sulfide **7** or the tetrahydroxylated vinylic sulfoxides **10a/10b** do not inhibit the α- or the β-D-glucosidase better than the corresponding di- or trihydroxylated derivatives **5**, **8a/8b** or **6**, **9a/9b** did. From these preliminary inhibition studies, it appears that neither the polyhydroxylated cyclohexenyl sulfides **5**–**7** nor the polyhydroxylated cyclohexenyl sulfoxides **8a/8b**–**10a/10b** possess the complete structural requirement to interact efficiently as inhibitors with the carboxylic acid residue in the active side of the tested glucosidases. While Khiar et al. [22] reported that only one diastereoisomer (S isomer) from a phenyl sulfoxide β-D-galactopyranoside diastereomeric mixture could be hydrolyzed by a β-D-galactosidase (*E. coli*), no significant discrimination has been observed during the inhibition assay using the sulfoxides **8a**, **9a** or **10a** as compared with the diastereoisomeric derivatives **8b**, **9b** or **10b**. To get more insights into the biochemical behavior of vinyl sulfoxides, 2-phenysulfoxide-3,4,5-trihydroxycyclohex-1-ene (**9a**) was studied in more detail using Brewers yeast α-glucosidases. The Lineweaver–Burke plots of α-glucosidase inhibition by **9a** showed a mixed-type inhibition, which could indicate the participation of covalent linkage between the enzyme and **9a**, which could behave as a Michael acceptor. Then, K_m(app)/V_{max} was plotted against the **9a** concentration to give K_i (45 mM).

Although the cyclohexenyl sulfoxides **8a/8b**–**10a/10b** possess a flattened conformation with a planar pseudo anomeric center, the sulfoxide group may not be basic enough, and also not at the optimal distance from the carboxylic acid residue in the active site, to interact by forming a strong hydrogen bond with the latter [23,24].

In conclusion, we have shown that the inhibitory properties of vinyl sulfides and sulfoxides do not depend upon the number of hydroxyl groups in the cyclohexenyl moiety and that the polar vinyl sulfoxide functionality does not bring any additional interaction with the active sites of the tested enzymes. In particular, among all the tested compound, the simplest vinyl sulfide **5** with only two hydroxyl groups behaves as the best inhibitor.

3. Experimental

General methods.—^{1}H (200 and 250 MHz) and ^{13}C (50 and 63 MHz) NMR spectra were recorded with Bruker AC 200 and 250 spectrometers. Chemical shifts were given relative to Me_4Si in $CDCl_3$; for NMR spectra in CD_3OD, δ 3.16 ppm was used as reference. Flash chromatography was performed with Silica Gel 60A CC 6–35 μm (SDS). Melting points were measured on a Reichert apparatus and were uncorrected. Optical rotations were measured on an Electronic Digital Jasco DIP-370 Polarimeter. IR spectra were recorded on a FT-IR Bruker IFS 66 spectrometer. Mass spectra were realized in EI mode on a Finnigan Mat 95S. Dry DME was distillated from sodium and benzophenone, and dry CH_2Cl_2 from CaH_2. Enzymes (Brewers yeast α-glucosidase (EC 3.2.1.20) and sweet almond β-glucosidase (EC 3.2.1.21)) were purchased from Sigma Chemical Co and used without further purification. Elemental analyses were performed at the Service Central de Microanalyses du CNRS (Gif sur Yvette, France)

4-Hydroxy-5,8-methylene-10-oxa-tricyclo-[4-4-0^{4a,8a}-4-1-0^{2,3}]-undeca-6-ene-1-one (**15a/15b**).—A solution of **14** (1.5 g, 7.9 mmol) in 1:1 CH_2Cl_2–MeOH (80 mL) at −78 °C was treated with tetrabutylammonium borohydride (1.0 g, 3.95 mmol) over 2 h. The temperature was slowly warmed up to 0 °C (2.5 h), then the mixture was diluted with CH_2Cl_2 and treated with a satd NH_4Cl soln (100 mL). The combined organic phases, filtered through a phase separator filter, were concentrated. Flash chromatography (7:3 hexane–EtOAc) of the residue gave **15a/15b** (85:15, 1.2 g, 81%) as a white amorphous solid (ratio determined by ^{13}C NMR). IR **15a/15b** (KBr) cm^{-1}: 3378 (OH), 3058 and 2989 (CH double bond), 1710 (CO). Data for **15a**: ^{1}H NMR ($CDCl_3$) δ: 6.21 (m, 2 H, H-6 and H-7), 4.66 (ddd, 1 H, J 9.0 Hz, $J_{4a,4}$ 5.0 Hz, $J_{4,3}$ 3.5 Hz, H-4), 3.59 (dd, 1 H, $J_{3,2}$ 4.5 Hz, H-3), 3.30 (d, 1 H, H-2), 3.17 (dd, 1 H, $J_{8a,4a}$ 11.0 Hz, $J_{8a,8}$ 3.5 Hz, H-8a), 3.03, 3.09 (2 br s, 2 H, H-5 and H-8), 2.96 (ddd, 1 H, $J_{4a,5}$ 3.0 Hz, H-4a), 1.41 (br, 1 H, d, $J_{9a,9b}$ 8.5 Hz, H-9a), 1.31 (br d, 1 H, H-9b). ^{13}C NMR ($CDCl_3$) δ: 208.1 (C-1), 135.6, 135.3 (C-7, C-6), 66.94 (C-4), 59.4 and 54.6 (C-2, C-3), 51.2, 49.4, 44.9, 44.8, 42.5 (C-8, C-8a, C-5, C-4a, C-9). Data for **15b**: ^{1}H NMR ($CDCl_3$) δ: 6.18 (m, 1 H, H-6 or H-7), 6.02 (dd, 1 H, $J_{6,7}$ 6.0 Hz, J 3.0 Hz, H-6 or H-7), 3.52 (d, 1 H, $J_{2,3}$ 4.5 Hz, H-3), 3.28 (d, 1 H, H-2), 2.64 (ddd, 1 H, $J_{4a,8a}$ 11.0 Hz, $J_{4a,4}$ 9.0 Hz, $J_{4a,5}$ 3.5 Hz, H-4a), 1.53 (dt, 1 H, $J_{9a,9b}$ 8.5 Hz, $J_{9a,8} = J_{9a,5}$ 2.0 Hz, H-9a), 1.45 (dt, 1 H, $J_{9b,5} = J_{9a,8}$ 2.0 Hz, H-9b). δ_C ($CDCl_3$): 138.6, 134.5 (C-7, C-6), 70.7 (C-4), 61.5, 55.4 (C-2, C-3), 49.7, 47.5, 44.5, 43.8, 42.8 (C-8, C-8a, C-5, C-4a, C-9). Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.72; H, 6.29; O, 24.97. Found: C, 68.69; H, 6.25; O, 24.92.

5-Hydroxy-7-oxabicyclo-[4-1-0^{1,6}]-hept-3-ene-2-one (**16**).—A solution of **15a**/**15b** (85:15, 2.0 g, 10 mmol) in diethylphthalate (30 mL) was stirred at room temperature (rt) under nitrogen bubbling for 30 min, then warmed (still under bubbling) at 190 °C for 2.5 h. The reaction mixture was then cooled to rt and filtered through Silica Gel (70–200 μm). Diethylphthalate was eluted with 9:1 → 4:1 hexane–EtOAc and the crude product with 3:2 hexane–EtOAc. After evaporation of the solvents, flash chromatography (99:1 → 19:1 CH_2Cl_2–MeOH, 1% gradient) of the residue gave **16** (1.02 g, 80%) as white crystals, mp 56–57 °C (Lit. [14] 56–58.5 °C). **15b** did not react under those conditions. IR (KBr) cm^{-1}: 3375 (OH), 2929 (CH double bond), 1676 (CO). ^{1}H NMR ($CDCl_3$) δ: 6.71 (ddd, 1 H, $J_{4,3}$ 10.5 Hz, $J_{4,5}$ 4.0 Hz, $J_{4,6}$ 2.5 Hz, H-4), 6.00 (dt, 1 H, $J_{3,5} = J_{3,1}$ 1.5 Hz, H-3), 4.69 (br dd, 1 H, $J_{5,OH}$ 8.0 Hz, $J_{5,4}$ 4.0 Hz, $J_{5,6}$ 1.0 Hz, H-5), 3.81 (ddd, 1 H, $J_{6,1}$ 3.5 Hz, H-6), 3.46 (m, 1 H, H-1), 2.87 (d, 1 H, OH). δ_C ($CDCl_3$) :194.2 (C-1), 144.5 (C-4), 126.7 (C-3), 62.8, 57.7, 53.2 (C-2, C-5 and C-6). Anal. Calcd for $C_6H_6O_3$: C, 57.14; H, 4.80; O, 38.06. Found: C, 57.93; H, 4.94; O, 36.99.

4,5,6-Trihydroxycyclohex-2-ene-1-one (**17**).—A solution of **16** (0.53 g, 4.2 mmol) in water (21 mL) was kept at 80 °C for 4 days. Water was then co-evaporated with MeCN and the residue adsorbed on Silica Gel (70–200 μm) and deposited on a Silica Gel column. Elution (19:1 → 4:1 CH_2Cl_2–MeOH) gave a first fraction (210 mg, 39%) containing the starting material **16** principally, a second one containing **17** (249 mg, 41%) as brown amorphous solid and a last fraction that contained the product resulting from the 1,4-addition of water on **17**. The epoxide **17** was recrystallized in EtOH, mp 158–160 °C (Lit. [15] 156–158 °C). IR (KBr) cm^{-1}: 3434 (OH), 2889 (CH double bond), 1684 (CO). ^{1}H NMR (CD_3OD) δ: 6.80 (dd, 1 H, $J_{3,2}$ 10.0 Hz, $J_{3,4}$ 2.0 Hz, H-3), 5.91 (dd, 1 H, $J_{2,4}$ 2.0 Hz, H-2), 4.24 (dt, 1 H, J 3.5 Hz, $J_{4,5}$ 8.0 Hz, H-4), 3.90 (d, 1 H, $J_{6,5}$ 10.5 Hz, H-6), 3.45 (dd, 1 H, H-5). ^{13}C NMR (D_2O) δ: 211.3 (C-1), 163.2(C-2), 137.3 (C-3), 88.3, 86.9, 82.1 (C-4, C-5, C-6). Anal. Calcd for $C_6H_8O_4$: C, 49.99; H, 5.60, O, 44.42. Found C, 49.75; H, 5.67; O, 44.52.

2,3,4-Trihydroxycyclohexanone (**12**).—A solution of **17** (0.38 g, 2.92 mmol) in MeOH (9 mL) was stirred for 2 h under hydrogen (1 atm) in the presence of Pd–C 10% (35 mg). Water was then added, and the mixture was filtered through a Celite pad and eluted with 1:1 MeOH–water and the resulting aq soln was concentrated. The residue was adsorbed on Silica Gel (70–200 μm) and deposited on a Silica Gel column. Elution (49:1 → 22:3, CH_2Cl_2–MeOH, 2% gradient) gave **12** (0.31 g, 80%) as a white amorphous solid. IR (KBr) cm^{-1}: 3418 (OH), 2967, 2929, 2883 (CH), 1708 (CO). ^{1}H NMR (CD_3OD) δ: 3.90 (dd, 1 H, $J_{2,3}$ 9.5 Hz, $J_{2,6a}$ 1.5 Hz, H-2), 3.68 (ddd, 1 H, $J_{4,5a}$ 11.5 Hz, $J_{4,3}$ 9.0 Hz, $J_{4,5b}$ 4.5 Hz, H-4), 3.13 (dd, 1 H, H-3), 2.41 (tdd, 1 H, $J_{6a,5a}$ 14.5 Hz, $J_{6a,5b}$ 6.0 Hz, H-6a), 2.21 (ddd, 1 H, $J_{6b,5b}$ 4.5 Hz, $J_{6b,5a}$ 2.5 Hz, H-6b), 1.98 (dddd, 1 H, $J_{5b,5a}$ 12.5 Hz, $J_{5b,4}$ 4.5 Hz, H-5b), 1.35 (m, 1 H, H-5a). ^{13}C NMR (CD_3OD) δ: 153.0 (C-1), 80.9, 79.4, 72.5 (C-2, C-3, C-4), 36.5, 29.9 (C-5, C-6). Anal. Calcd for $C_6H_{10}O_4$: C, 49.31; H, 6.90, O, 43.79. Found C, 49.15; H, 6.95; O, 43.75.

1,1′-Bis(phenylthio)-2,3-diacetoxycyclohexane (2α, 3β)/(2β, 3α) (**18**).—A solution of **11** (1.0 g, 7.7 mmol) in PhSH (15 mL) was treated with a concd HCl soln (36%, 0.13 mL) for 60 h. The mixture was then neutralized with Et_3N, diluted by Et_2O (100 mL), and treated with a NaOH soln (10%, 100 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The crude product was crystallized in hexane–AcOEt to give the dihydroxy dithioacetal intermediate (1.67 g) as white crystals, mp 92 °C. The mother liquor was concentrated and flash chromatography (7:3 hexane–EtOAc) of the residue gave an additional crop (152 mg). Total yield: 1.83 g, 72%. IR (KBr) cm^{-1}: 3453 (OH), 2953 and 2922 (CH Ar). ^{1}H NMR (CDCl$_3$) δ: 7.75 (m, 2 H, H Ar), 7.20–7.65 (m, 8 H, H Ar), 4.21 (ddd, 1 H, $J_{3,4a}$ 11.0 Hz, $J_{3,2}$ 9.0 Hz, $J_{3,4b}$ 4.0 Hz, H-3), 3.62 (br s, 1 H, OH), 3.43 (d, 1 H, H-2), 2.94 (br s, 1 H, OH), 1.55–2.07, 0.94–1.46 (2 m, 6 H, CH$_2$). ^{13}C NMR (CDCl$_3$) δ: 137.5, 137.1 (CH Ar), 130.0 (Cq Ar), 129.7, 129.3, 129.0, 128.6 (CH Ar), 78.1, 70.5 (C-2, C-3), 70.9 (C-1), 33.5, 31.6, 19.7 (C-4, C-5, C-6). Anal. Calcd for $C_{18}H_{20}O_2S_2$: C, 64.63; H, 6.63; O, 9.57. Found: C, 64.63; H, 6.41; O, 9.44.

A solution of the dihydroxy dithioacetal (0.75 g, 2.26 mmol) in pyridine (6 mL) was treated with Ac$_2$O (1.27 mL), 2,4-dimethylaminopyridine (70 mg, 0.6 mmol) and kept at rt overnight. After co-evaporation with toluene several times, flash chromatography (9:1 → 9:2 hexane–EtOAc) of the residue gave **18** (0.85 g, 90%) as white crystals, mp 142–144 °C. IR (KBr) cm^{-1}: 3065, 2937, 2863 (CH Ar) and 1758 (CO). ^{1}H NMR (CDCl$_3$) δ: 7.85 (m, 2 H, H Ar), 7.57 (m, 2 H, H Ar), 7.26–7.44 (m, 6 H, H Ar), 5.41 (ddd, 1 H, $J_{3,4a}$ 11.0 Hz, $J_{3,2}$ 9.5 Hz, $J_{3,4b}$ 5.0 Hz, H-3), 5.20 (d, 1 H, H-2), 2.16 (s, 3 H, AcO), 2.01 (s, 3 H, AcO), 2.08, 1.85, 1.59, 1.34 and 1.15 (4 m, 6 H, CH$_2$). ^{13}C NMR (CDCl$_3$) δ: 170.3, 170.2 (O*C*OCH$_3$), 137.6, 137.0 (CH Ar), 130.8 (Cq Ar), 129.6, 129.4, 128.8, 128.6 (CH Ar), 72.3, 72.1 (C-2, C-3), 67.9 (C-1), 33.9, 29.9, 19.2 (C-4, C-5, C-6), 21.03, 20.86 (OCO*C*H$_3$). Anal. Calcd for $C_{22}H_{24}O_4S_2$: C, 63.44; H, 5.81; O, 15.36; S, 15.39. Found: C, 63.74; H, 5.52; O, 15.34; S, 15.44.

1,1′-Bis(phenylthio)-2,3,4-triacetoxycyclohexane (2α, 3β, 4α)/(2β, 3α, 4β) (**23**).—A solution of **12** (0.105 g, 0.72 mmol) in CH$_2$Cl$_2$ (5 mmol) at −5 °C was treated with PhSH (1.5 mL, 14.4 mmol) and BF$_3$·Et$_2$O (0.266 mL, 2.16 mL) for 4 h. Et$_3$N (0.62 mL) was then added and CH$_2$Cl$_2$ was evaporated under nitrogen flushing. The crude product was washed with hexane (3 × 15 mL) then 5:1 hexane–Et$_2$O (2 × 15 mL). The resulting white solid was dissolved in MeOH (20 mL), adsorbed on Silica Gel (70–200 μm), deposited at the top of a Silica Gel column and eluted (19:1, CH$_2$Cl$_2$–MeOH). After evaporation and drying in vacuo, pyridine (7 mL), Ac$_2$O (1 mL) and 2,4-dimethylaminopyridine (13 mg, 0.11 mmol) were added and the mixture was stirred overnight. After evaporation, CH$_2$Cl$_2$ (25 mL) was added and the solution was washed with water (25 mL), filtered on a phase separator filter and concentrated. Flash chromatography (9:1 hexane–EtOAc) of the residue gave **23** (0.29 g, 85%) as a white solid. IR (KBr) cm^{-1}: 3061, 2946 (CH Ar), 1752 (CO). ^{1}H NMR (CDCl$_3$) δ: 7.82 (m, 2 H, CH Ar), 7.54 (m, 2 H, CH Ar), 7.37 (m, 6 H, CH Ar), 5.67 (t, 1 H, $J_{3,2} = J_{3,4}$ 9.5 Hz, H-3), 5.22 (d, 1 H, H-2), 4.58 (ddd, 1 H, $J_{4,5a}$ 11.5 Hz, $J_{4,5b}$ 5.0 Hz, H-4), 2.16 (s, 3 H, OAc), 2.00 (br s, 6 H, OAc), 1.96 (m, 1 H, H-6a), 1.70 (m, 2 H, H-6b and H-5a), 1.26 (m, 1 H, H-5b). ^{13}C NMR (CDCl$_3$) δ: 170.1, 169.8 (O*C*OCH$_3$), 137.5, 136.9, 130.1, 129.9, 129.6, 129.0, 128.7 (CH Ar and Cq Ar), 75.4, 72.7, 72.1 (C-2, C-3, C-4), 66.4 (C-1), 29.8, 24.9 (C-5, C-6), 20.8, 20.6 (OCO*C*H$_3$). Anal. Calcd for $C_{24}H_{26}O_6S_2$: C, 60.74; H, 5.52; O, 20.23. Found: C, 60.58, H, 5.61; O, 20.19.

1,1′-Bis(phenylthio)-2,3,4-triacetoxy-5-acetoxymethylcyclohexane (2α, 3β, 4α, 5β)/(2β, 3α, 4β, 5β) (**24**).—Tetrahydroxylated ketone **13** (0.15 g, 0.85 mmol) was treated at 0 °C with BF$_3$·Et$_2$O (0.315 mL, 2.55 mmol) and PhSH (1.75 mL) for 48 h as described for the preparation of **23**. After workup, pyridine (7 mL), Ac$_2$O (1.6 mL) and 2,4-dimethylaminopyridine (15 mg, 0.13 mmol) were added to the residue and the mixture was stirred for 12 h. After workup, flash chromatography (9:1, hexane–EtOAc) gave **24** (0.30 mg, 66%) as a white amorphous solid. IR (KBr) cm^{-1}: 2931 (CH Ar), 1754 (CO). ^{1}H NMR (CDCl$_3$) δ: 7.55 and 7.86 (2 br d, 2 H, CH Ar), 7.30–7.50 (m, 8 H, CH Ar), 5.65 (t, 1 H, $J_{3,4} = J_{3,2}$ 9.5 Hz, H-3), 5.26 (d, 1 H, H-2), 4.72 (dd, 1 H, $J_{4,5}$ 10.5 Hz, H-4), 3.50 (d, 2 H, $J_{7,5}$ 4.0 Hz, H-7a and H-7b), 2.52 (m, 1 H, H-5), 2.16 (s, 3 H, AcO), 2.02 (s, 3 H, AcO), 1.98 (3 H, AcO), 1.78 (s, 3 H, AcO), 1.65 (dd, 1 H, $J_{6a,6b}$ 15.0, $J_{6a,5}$ 3.0 Hz, H-6a), 1.21 (dd, 1 H, $J_{6b,5}$ 12.0 Hz, H-6b). ^{13}C NMR (CDCl$_3$) δ: 170.4, 169.9, 169.8, 169.7 (4 O*C*OCH$_3$), 137.6, 136.8, 129.9, 129.7, 129.0, 128.8 (CH, Cq Ar), 74.9, 73.2, 71.2 (C-2, C-3, C-4), 65.3 (C-1), 62.6 (C-7), 35.4, 33.6 (C-5, C-6), 20.6, 20.5, 20.4 (OCO*C*H$_3$). Anal. Calcd for $C_{27}H_{30}O_8S_2$: C, 59.32; H, 5.53; S, 11.73. Found: C, 59.32; H, 5.68; S, 11.06.

2-Phenylthio-3,4-diacetoxycyclohex-1-ene (3α, 4β)/(3β, 4α) (**19**).—A solution of **18** (0.75 g, 1.8 mmol) in CH_2Cl_2 (4 mL) at −30 °C was treated with a 0.28 M *m*-chloroperoxybenzoic acid (*m*CPBA) soln in CH_2Cl_2 (7.04 mL, 1.97 mmol). The mixture was then slowly warmed up to rt (1 h), diluted with CH_2Cl_2 (20 mL), washed with a phosphate buffer (0.2 M, pH 7.6, 20 mL), filtered through a phase separator filter and concentrated. The residue was taken up in DME (15 mL), treated with $CaCO_3$ (0.9 g, 9 mmol) and kept at 80 °C for 15 h. The solution was cooled to rt, diluted with CH_2Cl_2 (50 mL), filtered, washed with water (60 mL), dried ($MgSO_4$), filtered and concentrated. Flash chromatography (9:1 hexane–EtOAc) of the residue gave **19** (0.5 g, 90%) as a colorless syrup. IR (NaCl) cm^{-1}: 2934 (CH Ar and double bond), 1743 (CO). ^{1}H NMR ($CDCl_3$) δ: 7.25 (m, 5 H, CH Ar), 6.39 (t, 1 H, $J_{1,6a} = J_{1,6b}$ 4.0 Hz, H-1), 5.33 (br d, 1 H, $J_{3,4}$ 4.5 Hz, H-3), 5.04 (q, 1 H, $J_{4,5a} = J_{4,5b}$ 4.5 Hz), 2.32 (m, 2 H, H-6a and H-6b), 2.04 (s, 3 H, AcO), 1.92 (s + m, 5 H, AcO, H-5a and H-5b). ^{13}C NMR ($CDCl_3$) δ: 169.9, 169.7 (O*C*OCH$_3$), 134.5, 128.5 (Cq Ar, C-2), 130.1, 128.9 (CH Ar), 139.4, 126.8 (CH Ar, C-1), 70.7, 69.5 (C-3, C-4), 23.3, 22.7 (C-5, C-6), 21.0, 20.6 (OCO*C*H$_3$). Anal. Calcd for $C_{16}H_{18}O_4S$: C, 62.73; H, 5.92; O, 20.89; S, 10.46. Found: C, 62.65; H, 5.81; O, 20.72; S, 10.53.

2-Phenylthio-3,4,5-triacetoxycyclohex-1-ene (3α, 4β, 5α)/(3β, 4α, 5β) (**25**) *and 1-phenylthio-2,3,4-triacetoxycyclohex-1-ene (3α, 4β)/(3β, 4α)* (**27**).—Compound **23** (0.387 g, 0.81 mmol) was treated, as described for the preparation of **19**, with a 0.145 M *m*CPBA soln in CH_2Cl_2 (6 mL, 0.87 mmol) at −40 °C, yielding 392 mg of the intermediate sulfoxide. The residue was dissolved in DME (7 mL), treated with $CaCO_3$ (0.57 g, 5.7 mmol), and stirred overnight at 85 °C. After normal workup, flash chromatography (17:3 hexane–EtOAc) gave **25** (0.24 g, 80%) and **27** (5 mg, 4%), both as white solids. Data for **25**: IR (KBr) cm^{-1}: 3069, 2946 (CH Ar and double bond), 1730, 1752 (CO). ^{1}H NMR ($CDCl_3$): 7.20–7.40 (m, 5 H, CH Ar), 6.61 (ddd, 1 H, $J_{1,6a}$ 5.5 Hz, $J_{1,6b}$ 3.0 Hz, $J_{1,3}$ 1.5 Hz, H-1), 5.61 (ddd, 1 H, $J_{3,4}$ 7.0 Hz, $J_{3,6a}$ 3.0 Hz, $J_{3,6b}$ 1.5 Hz, H-3), 5.35 (dd, 1 H, $J_{4,5}$ 9.5 Hz, H-4), 5.13 (ddd, 1 H, $J_{5,6b}$ 8.5 Hz, $J_{5,6a}$ 5.5 Hz, H-5), 2.73 (dt d, 1 H, $J_{6a,6b}$ 17.5 Hz, H-6a), 2.36 (ddt, 1 H, H-6b), 2.05 (s, 3 H, OAc), 2.02 (s, 3 H, OAc), 1.89 (s, 3 H, OAc). ^{13}C NMR ($CDCl_3$) δ: 170.0, 169.8, 169.7 (O*C*OCH$_3$), 133.8, 132.8, 131.7, 131.1, 131.0, 129.0, 127.5 (CH Ar, Cq Ar, C-1, C-2), 128.3, 126.5 (CH Ar), 72.6, 71.8, 68.0 (C-3, C-4, C-5), 30.5 (C-6), 20.8, 20.6, 20.4 (OCO*C*H$_3$). Anal. Calcd for $C_{18}H_{20}O_6S$: C, 59.33; H, 5.53. Found: C, 59.49; H, 5.76. Data for **27**: ^{1}H NMR ($CDCl_3$) δ: 7.68–7.39 (m, 2 H, CH Ar), 7.38–7.28 (m, 3 H, CH Ar), 5.54 (br d, 1 H, $J_{3,4}$ 9.5 Hz, H-3), 5.06 (ddd, 1 H, $J_{4,5a}$ 6.5 Hz, $J_{4,5b}$ 3.0 Hz, H-4), 2.21 (m, 2 H, H-6a and H-6b), 2.17 (s, 3 H, OAc), 2.10 (s, 3 H, OAc), 2.09 (s, 3 H, OAc) and 1.89 (m, 2 H, H-5a and H-5b).

2-Phenylthio-3,4,5-triacetoxy-6-acetoxymethylcyclohex-1-ene (3α, 4β, 5α, 6β)/(3β, 4α, 5β, 6α) (**26**) *and 1-phenylthio-2,3,4-triacetoxy-5-acetoxymethylcyclohex-1-ene (3α, 4β, 5α)/(3β, 4α, 5β)* (**28**).—Compound **24** (0.163 g, 0.3 mmol) was treated, as described for the preparation of **19**, with a 0.16 M *m*CPBA soln in CH_2Cl_2 (2.06 mL, 0.3 mmol) to give 168 mg of the sulfoxide intermediate. This residue, dissolved in DME, was treated with $CaCO_3$ (0.21 g, 2.13 mmol) and kept at 85 °C overnight. After workup, flash chromatography (17:3 hexane–EtOAc) of the residue gave **26** (92 mg, 75%) and **28** (5 mg, 4%) as white solids. Data for **26**: IR (KBr) cm^{-1}: 3059, 2957, 2935 (CH Ar and double bond), 1750 (CO). ^{1}H NMR ($CDCl_3$) δ: 7.40–7.23 (m, 5 H, CH Ar), 5.84 (t, 1 H, $J_{1,3} = J_{1,6}$ 2.0 Hz, H-1), 5.69 (ddd, 1 H, $J_{3,4}$ 7.0 Hz, $J_{3,6}$ 3.0 Hz, H-3), 5.38 (dd, 1 H, $J_{4,5}$ 10.0 Hz, H-4), 5.26 (dd, 1 H, $J_{5,6}$ 9.0 Hz, H-5), 4.06 (dd, 1 H, $J_{7a,7b}$ 11.0 Hz, $J_{7a,6}$ 4.0 Hz, H-7a), 4.01 (dd, 1 H, $J_{7b,6}$ 5.0 Hz, H-7b), 2.87 (m, 1 H, H-6), 2.06 (br s, 6 H, OAc), 2.00 (s, 3 H, OAc), 1.93 (s, 3 H, OAc). ^{13}C NMR ($CDCl_3$) δ: 170.3, 170.6, 170.9, 169.8 (O*C*OCH$_3$), 133.5, 131.7, 131.6, 129.3, 127.9 (CH Ar, Cq Ar, C-1, C-2), 73.4, 71.9, 68.4, 62.8 (C-3, C-4, C-5, C-7), 41.6 (C-6), 20.6, 20.5 (OCO*C*H$_3$). Anal. Calcd for $C_{21}H_{24}O_8S$: C, 57.79; H, 5.54; O, 29.32. Found: C, 57.49; H, 5.56; O, 29.48. Data for **28**: ^{1}H NMR ($CDCl_3$) δ: 7.45–7.23 (m, 5 H, CH Ar), 5.68 (dt, 1 H, $J_{3,4}$ 6.0 Hz, $J = J_{3,5}$ 2.0 Hz, H-3), 5.24 (dd, 1 H, $J_{4,5}$ 9.0 Hz, H-4), 4.12 (dd, 1 H, $J_{7a,7b}$ 11.0 Hz, $J_{7a,5}$ 4.0 Hz, H-7a), 3.89 (dd, 1 H, $J_{7b,5}$ 4.0 Hz, H-7b), 2.23–2.41 (m, 3 H, H-6a, H-6b and H-5), 2.13 (s, 3 H, OAc), 2.07 (s, 3 H, OAc), 2.05 (s, 3 H, OAc) and 1.97 (s, 3 H, OAc). ^{13}C NMR ($CDCl_3$) δ: 170.6, 170.3, 169.9, 168.1 (O*C*OCH$_3$), 140.1, 131.2, 125.3 (Cq Ar, C-1, C-2), 132.7, 129.2, 128.1 (CH Ar), 71.3, 71.2, 62.6 (C-3, C-4, C-7), 36.9, 29.3 (C-5, C-6), 20.8, 20.4 (OCO*C*H$_3$).

2-Phenylthio-3,4-dihydroxycyclohex-1-ene (3α, 4β)/(3β, 4α) (**5**).—A solution of **19** (0.33 g, 1.08 mmol) in MeOH (5 mL) was treated at rt with a 0.5 M NaOMe soln in MeOH (0.4 mL) for 1.5 h. The mixture was then neutralized with AcOH and concentrated. Flash chromatography (3:2 hexane–EtOAc) of the residue gave **5** (226 mg, 95%) as a white foam. IR (KBr) cm^{-1}: 3381, 3056, 2926 (CH Ar and double bond). ^{1}H NMR ($CDCl_3$) δ: 7.39–7.15 (m, 5 H, CH Ar), 6.08 (t, 1 H, $J_{1,6a} = J_{1,6b}$ 3.0 Hz, H-1), 3.98 (m, 1 H, H-3), 3.81 (ddd, 1 H, $J_{4,5a}$ 11.0 Hz, $J_{4,5b}$ 3.0 Hz, $J_{4,3}$ 6.0 Hz, H-4), 3.40 (br s, 2 H, 2 OH), 2.26 (m, 2 H, H-6a and H-6b), 1.95, 1.71 (2 m, 2 H, H-5a and H-5b). ^{13}C NMR ($CDCl_3$) δ: 133.9, 132.6 (Cq Ar, C-2), 130.2, 129.1 (CH Ar), 135.7, 126.9 (CH Ar, C-1), 72.9, 72.5 (C-3, C-4), 27.1, 24.9 (C-5, C-6). Anal. Calcd for $C_{12}H_{14}O_2S$: C, 64.84; H, 6.35; O, 14.39. Found: C, 64.15; H, 6.36; O, 14.06.

2-Phenylthio-3,4,5-trihydroxycyclohex-1-ene (3α, 4β, 5α)/(3β, 4α, 5β) (**6**).—A solution of **25** (156 mg, 0.43 mmol) in MeOH (8.6 mL) was treated at rt with NaOMe (11 mg, 0.21 mmol) for 30 min. The mixture was neutralized with Dowex (AC50Wx8) (H^+ form) and filtered. The crude product was adsorbed on Silica Gel (70–200 μm) and deposited at the top of a Silica Gel column. Elution (49:1 → 24:1 CH_2Cl_2–MeOH) gave **6** (86 mg, 84%) as a white powder after filtration through a polyacrylamide gel and lyophilization. IR (KBr) cm^{-1}: 3202 (OH), 2890 (CH Ar and double bond). ^{1}H NMR (CD_3OD) δ : 7.77 (m, 1 H, CH Ar), 7.41–7.04 (m, 4 H, CH Ar), 5.44 (m, 1 H, H-1), 3.62 (m, 1 H, H-3), 3.52 (dt, 1 H, $J_{5,6a}$ 5.5 Hz, $J_{5,6b} = J_{5,4}$ 9.0 Hz, H-5), 3.36 (dd, 1 H, $J_{4,3}$ 7.0 Hz, H-4), 2.31 (dtd, 1 H, $J_{6a,6b}$ 17.5 Hz, $J_{6a,1}$ 1.5 Hz, J 5.5 Hz, H-6a) and 1.94 (ddt, 1 H, $J_{6b,1} = J$ 3.0 Hz). ^{13}C NMR (CD_3OD) δ: 137.1, 135.3 (Cq, C-2), 133.0, 130.2, 128.4 (CH Ar, C-1), 78.9, 74.6, 70.1 (C-3, C-4, C-5) and 34.7 (C-6). Anal. Calcd for $C_{12}H_{14}O_3S$: C, 60.48; H, 5.92; O, 20.14. Found: C, 60.44; H, 5.94; O, 20.41.

2-Phenylthio-3,4,5-trihydroxy-6-hydroxymethylcyclohex-1-ene (3α, 4β, 5α, 6β)/(3β, 4α, 5β, 6α) (**7**).—Compound **26** (92 mg, 0.2 mmol) was treated as described for the preparation of **6** with NaOMe (6 mg, 0.135 mmol) in MeOH (4.5 mL). Flash chromatography of the crude reaction mixture (24:1 → 46:3 CH_2Cl_2–MeOH) gave **7** (54 mg, 95%) as a white powder after filtration through a polyacrylamide gel and lyophilization. IR (KBr) cm^{-1}: 3395 (OH), 2889 (CH Ar and double bond). ^{1}H NMR (CD_3OD) δ: 6.92–7.33 (m, 5 H, CH Ar), 5.57 (t, 1 H, $J_{1,6} = J_{1,3}$ 1.5 Hz, H-1), 3.86 (m, 1 H, H-3), 3.63 (dd, 1 H, $J_{7a,7b}$ 10.5 Hz, $J_{7a,6}$ 4.0 Hz, H-7a), 3.45 (dd, 1 H, $J_{7b,6}$ 6.0 Hz, H-7b), 3.28–3.43 (m, 2 H, H-4 and H-5), 2.16 (m, 1 H, H-6). ^{13}C NMR (CD_3OD) δ: 137.6, 135.6 (Cq Ar, C-2), 132.8, 131.3, 130.2, 128.3 (CH Ar, C-1), 79.1, 74.4, 71.4, 63.1 (C-3, C-4, C-5, C-7), and 48.0 (C-6). Anal Calcd for $C_{13}H_{16}O_4S \cdot 0.25\ H_2O$: C, 57.23; H, 6.09; O, 24.92; S, 11.75. Found: C, 56.67; H, 6.01; O, 24.12; S, 11.64.

2-Phenyl sulfoxide-3,4-diacetoxycyclohex-1-ene (3α, 4β)/(3β, 4α) (**20a/20b**) *and 2-phenyl sulfone-3,4-diacetoxycyclohex-1-ene (3α, 4β)/(3β, 4α)* (**21**).—A solution of **19** (0.804 g, 0.26 mmol) in CH_2Cl_2 (20 mL) was treated at −40 °C with a 0.102 M *m*CPBA soln in CH_2Cl_2 (28.3 mL, 2.88 mmol). The solution was slowly warmed to rt (2 h), diluted with CH_2Cl_2 (50 mL), then washed with a phosphate buffer (0.1 M, pH 7.6, 70 mL). The organic phase was filtered through a phase separator filter then concentrated. Flash chromatography (3:2 hexane–EtOAc) of the residue gave 3 fractions: **21** (50 mg), a mixture (7:13) of **21** and **20a/20b** (3:2, 593 mg), and **20a/20b** (3:2, 50 mg) as colorless oils (overall yield 82%). Data for **21**: ^{1}H NMR ($CDCl_3$) δ: 7.80–7.90 (m, 2 H, CH Ar), 7.48–7.49 (m, 4

H, CH Ar and H-1), 5.59 (d, 1 H, $J_{3,4}$ 3.0 Hz, H-3), 4.98 (m, 1 H, H-4), 2.47 (m, 2 H, H-6a and H-6b), 1.93 (m and s, 4 H, H-5a and OAc), 1.83 (m, 1 H, H-5b) and 1.72 (s, 3 H, OAc). ^{13}C NMR ($CDCl_3$) δ: 169.2, 168.5 (O*C*OCH$_3$), 139.5, 135.6 (Cq Ar, C-2), 144.8, 133.1 (CH Ar, C-1), 128.8, 127.8 (CH Ar), 67.7, 62.7 (C-3, C-4), 21.4, 20.4, 20.1 (OCO*C*H$_3$, C-5, C-6). **20a/20b** were characterized after deacetylation and separation (see below).

2-Phenyl sulfoxide-3,4-dihydroxycyclohex-1-ene (3α, 4β)/(3β, 4α) (**8a** *and* **8b**).—A solution of the mixture of **20a/20b** and **21** (15:7, 0.2 g, 0.39 mmol of **20a/20b** and 0.21 mmol of **21**) in MeOH (10 mL) was treated at rt, with a 0.5 M NaOMe soln in MeOH (0.43 mL, 0.215 mmol) for 5 h. The reaction mixture was neutralized with AcOH (12 μL) and concentrated. Flash chromatography (CH_2Cl_2–MeOH) of the residue gave four fractions: **22** (47 mg), **8a** (16 mg), **8a/8b** (28 mg) and **8b** (38 mg) as white foams (overall yield 88%). IR (KBr) cm^{-1} (mixture **8a/8b**): 3400 (OH), 2930 (CH Ar and CH double bond), 1083 (SO).

Data for **8a**: ^{1}H NMR (CD_3OD) δ: 7.55 (m, 2 H, CH Ar), 7.43 (m, 3 H, CH Ar), 6.59 (t, 1 H, $J_{1,6a} = J_{1,6b}$ 3.8 Hz, H-1), 3.91 (br d, 1 H, $J_{3,4}$ 4.5 Hz, H-3), 3.63 (ddd, 1 H, $J_{4,5a}$ 6.8 Hz, $J_{4,5b}$ 2.3 Hz, H-4), 2.23 (m, 2 H, H-6a and H-6b), 1.81 (m, 1 H, H-5b), and 1.56 (br dt, 1 H, H-5a). ^{13}C NMR (CD_3OD) δ: 143.3, 139.0, 132.3 (Cq Ar, CH Ar, C-1, C-2), 130.2, 126.5 (CH Ar), 71.3, 68.9 (C-4, C-3), 25.6, 23.7 (C-6, C-5). Anal. Calcd for $C_{12}H_{14}O_3S \cdot 0.25\ H_2O$: C, 59.36; H, 6.02; O, 21.41; S, 13.20. Found C, 58.62, H, 5.99; O, 20.36; S, 11.91.

Data for **8b**: ^{1}H NMR (CD_3OD) δ: 7.60 (m, 2 H, CH Ar), 7.44 (m, 3 H, CH Ar), 6.5 (br t, 1 H, $J_{1,6a} = J_{1,6b}$ 3.0 Hz, H-1), 3.62 (ddd, 1 H, $J_{4,5a}$ 10.0 Hz, $J_{4,3}$ 6.0 Hz, $J_{4,5b}$ 3.5 Hz, H-4), 3.36 (br d, 1 H, H-3), 2.31 (m, 2 H, H-6a and H-6b), 1.82 (m, 1 H, H-5b), 1.47 (ddt, 1 H, $J_{5a,5b}$ 13.0 Hz, $J_{5a,6a} = J_{5a,6b}$ 7.0 Hz, H-5a). ^{13}C NMR (CD_3OD): δ143.9, 143.1, 132.9, 131.4 (Cq Ar, CH Ar, C-1, C-2), 130.4, 127.1 (CH Ar), 73.4, 70.8 (C-3, C-4), 28.7, 24.7 (C-5, C-6). Anal. Calcd for $C_{12}H_{14}O_3S$: C, 60.48; H, 5.92; O, 20.14. Found C, 60.39; H, 5.98; O, 19.92.

2-Phenyl sulfoxide-3,4,5-trihydroxycyclohex-1-ene (3α, 4β, 5α)/(3β, 4α, 5β) (**9a/9b**).—A solution of **6** (0.13 g, 0.54 mmol) in water (2.5 mL) and MeOH (1 mL) was treated with a 7.3 M *t*-BuOOH soln in water (3.7 mL) and kept at 60 °C for 24 h. The reaction mixture was concentrated, and two successive flash chromatographies (19:1 → 9:1 CH_2Cl_2–MeOH) of the residue gave **9a** and **9b** in three fractions after filtration through a polyacrylamide gel and lyophilization: **9a** (49 mg), **9a/9b** (3:7, 32 mg) and **9b** (34 mg) as white powders. Data for **9a**: IR (KBr) cm^{-1}: 3341 (OH), 2901 (CH Ar and CH double bond), 1082 and 1023 (SO). ^{1}H NMR (CD_3OD) δ: 7.56 (m, 2 H, CH Ar), 6.40 (m, 2 H, CH Ar), 6.31 (m, 1 H, H-1), 4.13 (m, 1 H, H-3), 3.51 (td, 1 H, $J_{5,6a}$ 5.0 Hz, $J_{5,6b} = J_{5,4}$ 9.0 Hz, H-5), 3.36(dd, 1 H, $J_{4,3}$ 7.0 Hz, H-4), 2.53 (dtd, 1 H, $J_{6a,6b}$ 18.0 Hz, $J_{6a,3}$ 7.0 Hz, H-6a) and 2.13 (ddt, 1 H, $J_{6b,3} = J_{6b,1}$ 3.0 Hz, H-6b). ^{13}C NMR (CD_3OD) δ: 144.8, 143.7 (CqAr, C-2), 133.2, 132.5 (CH Ar, C-1), 130.3, 126.8 (CH Ar), 78.1, 72.5, 69.6 (C-3, C-4, C-5), 34.0 (C-6). Anal. Calcd for $C_{12}H_{14}O_4S \cdot 0.5\ H_2O$: C, 54.74; H, 5.74. Found: C, 54.67; H, 5.68. Data for **9b**: IR (KBr) cm^{-1}: 3355 (OH), 2897 (CH Ar and double bond), 1082 and 1020 (SO). ^{1}H NMR (CD_3OD) δ: 7.60 (m, 2 H, CH Ar), 7.41 (m, 3 H, CH Ar), 6.31 (m, 1 H, H-1), 3.23–3.50 (m, 3 H, H-3, H-4, H-5), 2.66 (br dt, 1 H, $J_{6a,6b}$ 19.0 Hz, $J_{6a,5} = J_{6a,1}$ 5.0 Hz, H-6a), 2.14 (m, 1 H, H-6b). ^{13}C NMR (CD_3OD) δ: 144.8, 142.9 (Cq Ar, C-2), 130.6, 127.1 (CH Ar), 133.1, 127.0 (CH Ar, C-1), 79.2, 79.3, 69.9 (C-3, C-4, C-5) and 34.1 (C-6). Anal. Calcd for $C_{12}H_{14}O_4S \cdot 0.5\ H_2O$: C, 54.74; H, 5.74. Found: C, 54.91; H, 5.75.

2-Phenyl sulfoxide-3,4,5-trihydroxy-6-hydroxymethylcyclohex-1-ene (3α, 4β, 5α, 6β)/(3β, 4α, 5β, 5α) (**10a/10b**).—A solution of **7** (0.094 g, 0.35 mmol) in water (2 mL) was treated with a 7.3 M *t*-BuOOH soln in water (2 mL) as previously described for the preparation of **9a/9b**. Flash chromatography (19:1 → 9:1 CH_2Cl_2–MeOH) gave **10a** and **10b** in three fractions after filtration through a polyacrylamide gel and lyophilization, **10a**/**10b** (9:1, 23 mg), **10a/10b** (1:1, 31 mg) and **10a**/**10b** (1:4, 24 mg) (overall yield 78%). Data for **10a**: IR (KBr) cm^{-1}: 3397 (OH), 2888 (CH Ar and double bond), 1081 and 1029 (SO). ^{1}H NMR (D_2O) δ: 7.76 (m, 2 H, CH Ar), 7.42 (m, 3 H, CH Ar), 6.53 (t, 1 H, $J_{1,6} = J_{1,3}$ 2.0 Hz, H-1), 4.46 (m, 1 H, H-3), 3.94 (dd, 1 H, $J_{7a,7b}$ 11.0 Hz, $J_{7a,6}$ 4.0 Hz, H-7a), 3.81 (dd, 1 H, $J_{7b,6}$ 5.0 Hz, H-7b), 3.55–3.71 (m, 2 H, H-4 and H-5), 2.61 (m, 1 H, H-6). ^{13}C NMR (D_2O) δ: 142.5, 140.9 (Cq Ar, C-2), 134.1, 132.8, 130.0, 126.5 (CH Ar, C-1), 76.8, 71.2, 69.3, 60.7 (C-3, C-4, C-5, C-7), 46.1 (C-6). Anal Calcd for **10a/10b** (ca. 9:1) $C_{13}H_{16}O_5S{\cdot}H_2O$: C, 51.64; H, 6.00. Found: C, 51.44; H, 6.96. Data for **10b**: IR (KBr) cm^{-1}: 3331 (OH), 2881 (CH Ar and double bond), 1080 and 1023 (SO). ^{1}H NMR (D_2O) δ: 7.78 (m, 2 H, CH Ar), 7.66 (m, 3 H, CH Ar), 6.52 (m, 1 H, H-1), 4.00 (dd, 1 H, $J_{7a,7b}$ 10.5 Hz, $J_{7a,6}$ 4.0 Hz, H-7a), 3.84 (dd, 1 H, $J_{7b,6}$ 5.0 Hz, H-7b), 3.50–3.76 (m, 3 H, H-3, H-4 and H-5), 2.66 (m, 1 H, H-6). ^{13}C NMR (D_2O) δ: 141.6, 139.0 (Cq Ar, C-2), 133.5, 130.6, 1303, 127.3 (CH Ar, C-1), 77.2, 70.8, 69.3, 60.9 (C-3, C-4, C-5, C-7), 46.3 (C-6). Anal. Calcd for **10a**/**10b** (ca. 1:4) $C_{13}H_{16}O_5S{\cdot}0.75\ H_2O$: C, 52.43; H, 5.92; O, 30.89. Found: C, 52.03; H, 5.97; O, 31.19. High-resolution EI-MS for **10a**/**10b** (ca. 1:1) M^+ Calcd for $C_{13}H_{16}O_5S$: 284.0718. Found: 284.0729.

Enzyme and activity measurements.—Enzyme assays were performed at 37 °C in a phosphate buffer (50 mM, pH 6.8). Using *p*-nitrophenyl α-D-glucopyranoside and *p*-nitrophenyl β-D-glucopyranoside as substrates, the hydrolytic activity of α-D-glucosidase (Brewers yeast) and β-D-glucosidase (sweet almonds), respectively, was followed by measuring the formation of *p*-nitrophenol at 410 nm. In those conditions, the K_m was 0.16 mM for the α-D-glucosidase and 2.40 mM for the β-D-glucosidase.

To determine the IC_{50}, each derivative (at the following concentrations: 0.1, 1, 5 and 10 mM) was preincubated with the glucosidase at 37 °C for 15 min before the addition of the substrate (concentration near to the K_m). The K_i of **9a** towards Brewers yeast α-glucosidase was determined using Lineweaver–Burke plots of the initial reaction velocities against the reciprocals of *p*-nitrophenyl β-D-glucoside concentration (0.08, 0.1, 0.2, 0.5 and 1 mM) in the presence of 0, 8 and 12 mM of compound **9a**, followed by plotting $K_m(\text{app})/V_{\max}$ against **9a** concentration.

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