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Sugar-derived 2-*S*-substituted-2*H*-pyran-3(6*H*)-ones: synthesis and reactivity

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Abstract—A practical procedure for the preparation of chiral 2-*S*-substituted-2*H*-pyran-3(6*H*)-ones is described. According to the reaction conditions, 1,5-anhydro-2,3,4-tri-*O*-acetyl-D-*threo*-pent-1-enitol (**1**) reacted with thiophenol under Lewis acid catalysis to afford the polysubstitution product 1,5-anhydro-2,3,4-tri-*S*-phenyl-2,3,4-trithio-D,L-*threo*-pent-1-enitol (**2**) or phenyl 2,4-di-*O*-acetyl-3-deoxy-1-thio-α- and β-D-*glycero*-pent-2-enopyranoside (**3** and **4**, respectively). The iodine-promoted addition of thiophenol or α-toluenethiol to **1** gave (2*S*)-2-phenylthio-2*H*-pyran-3(6*H*)-one (**5**) or its 2-benzylthio analogue **6**, but these products showed low enantiomeric excesses (ee ~40–60%). However, dihydropyranone **5** with high optical purity (ee >94%) was successfully obtained by treatment of **4** with iodine in acetonitrile. On the other hand, it was established that the benzylthio group of **5** exerts high stereocontrol in reduction and cycloaddition reactions performed on the α,β-unsaturated carbonyl system.

Keywords: Dihydropyranone; Glycosylations; Iodine; Lewis acids; Thiols

1. Introduction

Sugar-derived dihydropyranones are useful intermediates in the synthesis of natural products and biologically active molecules.[1] The usefulness of the dihydropyranones as versatile building blocks relies on the reactivity of the α,β-unsaturated carbonyl system present in their molecules, to which a variety of well-known reactions may be applied. These reactions are usually highly diastereoselective due to the presence of the stereocenters located in the pyranone ring.[1d,e]

Furthermore, thioglycosides are known to be inhibitors of glycosylhydrolases,[2] and have been employed as glycosyl donors in oligosaccharide synthesis.[3]

Recently, we have described practical and large-scale procedures for the synthesis of 2-alkoxy-2*H*-pyran-3(6*H*)-ones from pentoses.[4,5] Such pyranones proved to be active dienophiles in Diels–Alder cycloadditions, which took place with high stereocontrol similar to other addition reactions involving their α,β-unsaturated carbonyl system.[4,6] They have been also employed as Michael acceptors of thiols in the synthesis of glycosides of 3-deoxy-4-thiopyranosid-2-uloses and 3-deoxy-4-thiopentopyranosides.[7] The presence of a thioglycoside functionality in the last compounds would facilitate the activation of the anomeric center for the synthesis of disaccharides of thio sugars.[3] Therefore, we report here the preparation of 2-*S*-substituted-2*H*-pyran-3(6*H*)-ones as precursors of thioglycosides of 4-thiopentopyranosides. Also, we describe the synthesis of carbocyclic derivatives by Diels–Alder cycloadditions to these pyranones, and the stereochemical outcome of the addition reactions was studied.

2. Results and discussion

Treatment of 1,5-anhydro-2,3,4-tri-*O*-acetyl-D-*threo*-pent-1-enitol (2-acetoxy-3,4-di-*O*-acetyl-D-xylal, **1**) with

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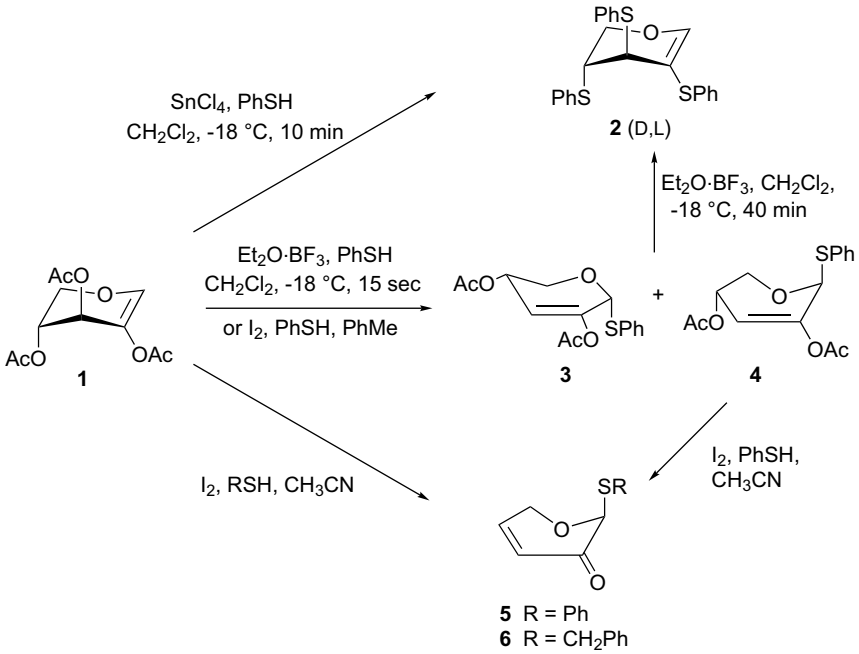
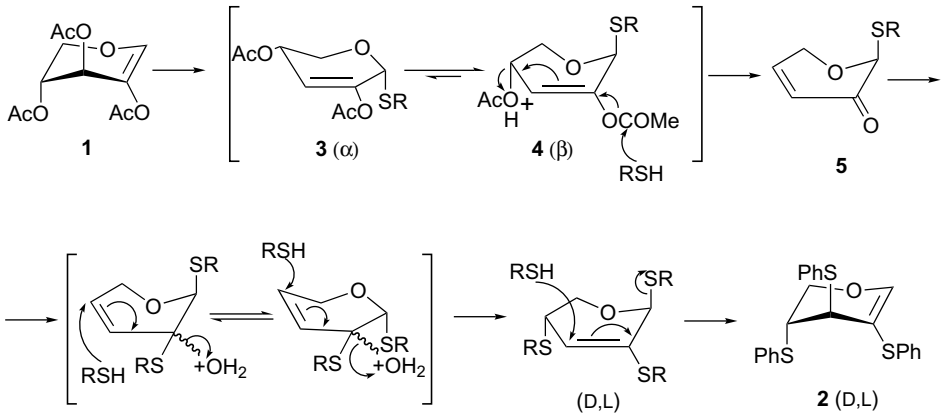


Scheme 1.

thiophenol in the presence of tin(IV) chloride as catalyst, under the conditions employed for the synthesis of 2-alkoxy-2*H*-pyran-3(6*H*)-ones,[4] afforded the 2,3,4-tri-*S*-phenyl-2,3,4-trithio-D,L-*threo*-pent-1-enitol (**2**) instead of the expected 2-phenylthio dihydropyranone **5** (Scheme 1). The ^{1}H NMR spectrum of the reaction mixture showed, together with **2**, the presence of pyranone **5** as a minor byproduct, but the other diastereoisomers of **2** were not detected. Compound **2** was isolated by column chromatography in 57% yield. The integral of the aromatic signals (15 protons) in the ^{1}H NMR spectrum of **2** indicated that this is a product of polysubstitution, in which all the acetoxy groups of **1** have been replaced by phenylthio. The small values for $J_{3,4}$ (<1 Hz), $J_{4,5}$ and $J_{4,5'}$ were indicative of a trans disposition between H-3 and H-4 in the preferred $^5H_4$ (D) conformation found for structurally related glycal derivatives.[4,8] The fact that **2** is optically inactive in contrast to its analogue **1**, which shows a large optical rotation value ($[\alpha]_D$ −272.3),[4] suggests that **2** is a racemic product.

To prevent the formation of **2**, the glycosylation of **1** with thiophenol catalyzed by a weaker Lewis acid was attempted. When the reaction was conducted with $Et_2O{\cdot}BF_3$ for a short time (15 s) the pent-2-enopyranosides **3** and **4** were obtained as main products (65% yield). The longer reaction times led to variable ratios of **3** and **4**, and the formation of increasing amounts of polysubstituted **2** (the presence of **5** was also detected in the reaction mixtures). In this case, the behavior of glycal **1** is similar to that of analogous nonsubstituted glycals at C-2, which react with alcohols or thiols in the presence of a Lewis acid to give, via a Ferrier rearrangement,[9] the 2,3-unsaturated derivatives as kinetic products. At equilibrium, 2-unsubstituted glycals react with thiols to give 3-thio-substituted glycals as major products,[9,10] whereas **1** leads to **2**. It was also determined that treatment of **4** with $Et_2O{\cdot}BF_3$ yielded **2**, under the same conditions employed in the glycosylation but in the absence of thiophenol. Together with **2** the formation of degradation products having $R_f = 0$ (probably a polymeric material) was detected by TLC. The efficiency of the conversion of **2** into **4** was relatively high (23% or 70% of theoretical), and no other phenylthio substituted derivatives from **1** were isolated. This result indicated that, under Lewis acid catalysis, the dihydropyranones could not be obtained because the intermediate pent-2-enopyranoside rapidly reacts releasing thiophenol, which is captured by an unsaturated intermediate (probably the enone **5**, see later) to afford **2**.

As the previous Lewis acid-promoted additions to **1** did not produce the desired dihydropyranone **5**, a different type of catalyst was tested. Iodine and electrophilic iodine-releasing agents have been used for the anomeric activation of glycals,[11] and we have found that alkyl 2-enopyranosides and 2-alkoxy-2*H*-pyran-3(6*H*)-ones were the major products in the *N*-iodosuccinimide- and iodine-mediated additions of alcohols to glycals.[12] The iodine-promoted glycosylations of **1** with thiophenol and ω-toluenethiol in acetonitrile (room temperature, 40 min) gave good yields (>63%) of the respective dihydropyranones **5** and **6**. To establish the enantiomeric excess (ee) of these enones, NMR experiments were conducted using a chiral lanthanide shift reagent



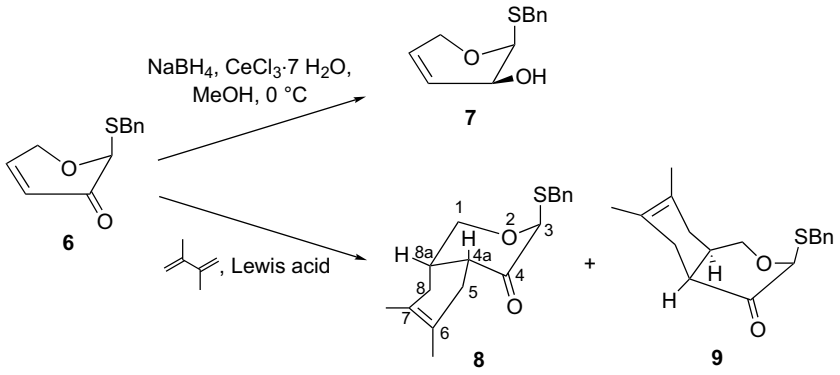
Scheme 2.

(ytterbium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate]).[13] Such experiments indicated that **5** and **6** were obtained with rather low and nonreproducible enantiopurities (ee ranging from 40% to 60%, for different preparations conducted under practically identical conditions). On the other hand, the large negative value of their optical rotations ($[\alpha]_D$ between −170 and −270) suggested that the enantiomer in excess in **5** and **6** had the *S* configuration at the C-2 stereocenter.[4] The formation of the dihydropyranone should involve a second allylic rearrangement in **3** or **4**. This type of rearrangement was shown to be promoted by the anhydrous hydrogen iodide generated by oxidation of the thiol by iodine.[14]

We observed that the solvent had a remarkable influence on the rate of the rearrangements that led to the dihydropyranone under iodine-catalyzed conditions. The reaction conducted in acetonitrile and dichloromethane showed by TLC faster disappearance of the starting glycal than additions performed in carbon tetrachloride or toluene. In the last solvent, the second Ferrier rearrangement was slow enough to allow the isolation of the 2-enopyranosides **3** and **4**. In acetonitrile, even at very short times (10–60 s), were obtained mixtures of 2-enopyranosides **3** and **4** along with the dihydropyranone **5**. It is noteworthy that the observed ratios of **3** and **4** were variable, and they do not correlate with the enantiomeric composition of **5**, obtained after longer reaction times. Moreover, treatment of the β-pent-2-enopyranoside **4** with iodine in acetonitrile led to **5**, and this product showed a large negative optical rotation ($[\alpha]_D$ −433.6) and high optical purity in favor of the *S* enantiomer (ee >94%). The same reaction when applied to a mixture of **3** and **4** (2.4:1) led also to **5**, having a small excess (ee >2%) of the enantiomer with *S* configuration. This result suggests that during the rearrangement that leads to **5**, the equilibrium between the 2-enopyranosides is shifted toward the β isomer **4**. Moreover, the enone **5** converts rapidly into racemic **2** on treatment with thiophenol–$Et_2O{\cdot}BF_3$.

A general mechanism for the acid-catalyzed thioglycosylation of **1**, which accounts for the formation of the main products under different conditions, is depicted in Scheme 2. The enopyranosides **3** and **4** are the primary products formed via a Ferrier rearrangement, under smooth reaction conditions (catalysis with $Et_2O{\cdot}BF_3$ during short times or with iodine in nonpolar solvents). Attack of the thiol to the vinylic acetoxy group in **3** or **4** promotes a second allylic rearrangement to the dihydropyranone **5**.[12] This rearrangement is efficiently catalyzed by iodine in polar solvents, whereas it occurs slowly in nonpolar solvents, and **3** and **4** can be isolated. Probably, the polar solvent is able to stabilize the intermediate ionic species by solvation, facilitating the reaction. During this rearrangement equilibration between **3** and **4** takes place, **4** being the favored isomer. The enopyranoside **4** is expected to be more stable than **3**, as it is stabilized by the anomeric effect (as **3**) and additionally by the axially oriented acetoxy group ('allylic effect'). From the precursor **5**, the successive additions of the thiol to the carbonyl and double bonds of the intermediates would lead to **2** as the final product. The fact that optically active **5** afforded racemic **2**, under $Et_2O{\cdot}BF_3$ catalysis, suggests that isomerization of the stereocenter of the enone takes place during the rearrangements. As shown in the scheme, the configuration of C-2 in **5** would determine the stereochemical course of the additions of thiol that leads to **2**. Furthermore, as the proposed disubstituted intermediates were not detected in the reaction mixture, it suggests that these species are unstable with respect to the trisubstituted **2**.

In order to compare the level of stereocontrol exerted by the benzylthio group of the pyranone with respect to the benzyloxy group of the respective analogues,[4] we conducted reduction and cycloaddition reactions to the enone system of **6**. Thus, the sodium borohydride reduction of the carbonyl group of **6** was highly facially selective to give the alcohol **7**, the product formed by attack of the hydride from the α face[15] of the pyranone



Scheme 3.

(Scheme 3). This selectivity was even higher than that observed for the 2-benzyloxy analogue of **6**,[4] as **7** was the only diastereomer detected in the NMR spectra of the crude reaction mixture.

As 2-alkoxydihydropyranones derived from pentoses have been shown to be reactive dienophiles in Diels–Alder cycloadditions to afford synthetically useful carbocyclic and polycyclic systems,[4,6] cycloadditions to **6** were conducted. The influence of the benzylthio substituent on C-2 of this pyranone on the stereochemistry of the reaction was established and compared with that of the benzyloxy group in the 2-benzyloxy analogue of **6**. The Diels–Alder cycloaddition of 2,3-dimethylbutadiene to **6**, under $Et_2O{\cdot}BF_3$ catalysis, was highly diastereofacially selective. Cycloadduct **8**, the product of addition of the diene from the α face, was the only isolated product. The ^{1}H NMR spectra of the crude reaction mixture showed only traces of other products, and a diastereomeric ratio **8**:**9** higher than 50:1. On the other hand, the Diels–Alder reaction under chelating $SnCl_4$ catalysis[16,17] showed the formation of **8** and **9** in a 1:1.9 ratio. Again in this case the selectivity in favor of the α-addition product was higher than that observed for the 2-benzyloxy analogue.[4] These results seem to indicate that the benzylthio group at C-2, bulkier than the benzyloxy substituent, hinders the β face of the pyranone more efficiently. The structures of **8** and **9** were established on the basis of their NMR spectra and confirmed by 2D COSY NMR experiments. They were also in excellent agreement with data already reported for related systems.[4,18] In the ^{1}H NMR spectrum of **8**, the small $J_{1,8a}$ (2.3 Hz) and $J_{1',8a}$ (1.7 Hz) values indicated that the C–H-8a bond bisects the dihedral angle of the H-1–C–H-1′ group, and the $J_{4a,8a}$ (5.3 Hz) value was consistent with a gauche axial–equatorial disposition for H-4a and H-8a. The relatively large $J_{1,8a}$ (6.3 Hz) and $J_{1',8a}$ (4.6 Hz) values in the spectrum of **9** suggested an axial disposition for H-8a, and the $J_{4a,8a}$ (5.9 Hz) value was compatible with an equatorial–axial relationship for H-4a and H-8a. These data showed that the cyclohexene ring is cis-fused to the pyranone from the α face in **8** and from the β-face in **9**.

In summary, we have described a procedure for the synthesis of 2-*S*-substituted-2*H*-pyran-3(6*H*)-ones starting from the readily accessible 2-acetoxy-3,4-di-*O*-acetyl-D-xylal. Dihydropyranone **5**, having high enantiomeric purity, could be obtained by treatment of the pent-2-enopyranoside **4** with iodine in acetonitrile. On the other hand, reduction of the carbonyl system of dihydropyranone **6**, as well as cycloaddition to the double bond, was highly diastereoselective due to the stereocontrol exerted by the C-2 stereocenter.

3. Experimental

3.1. General methods

Melting points are uncorrected. Optical rotations were measured at 25 °C. Column-chromatographic separations were performed with silica gel 60, 240–400 mesh. Analytical TLC was conducted on silica gel 60 F_{254} precoated plates (0.2 mm). Visualization of the spots was effected by exposure to UV light and charring with a solution of 5% H_2SO_4 in EtOH, containing 0.5% *p*-anisaldehyde. Solvents were reagent grade and, in most cases, were dried and distilled prior to use according to the standard procedures. The identity of the protons in the ^{1}H NMR spectra of the products was confirmed by 2D COSY NMR experiments; and for the assignment of the signals in the ^{13}C NMR spectra, DEPT experiments were conducted.

3.2. 1,5-Anhydro-2,3,4-tri-*S*-phenyl-2,3,4-trithio-D,L-*threo*-pent-1-enitol (2)

3.2.1. By $SnCl_4$-promoted addition of thiophenol to 1,5-anhydro-2,3,4-tri-*O*-acetyl-D-*threo*-pent-1-enitol (2-acetoxy-3,4-di-*O*-acetyl-D-xylal, 1). A solution of **1**[4] (122 mg, 0.47 mmol) and thiophenol (100 μL, 0.98 mmol) in anhydrous CH_2Cl_2 (5 mL) was cooled to −18 °C, and $SnCl_4$ (72 μL, 0.61 mmol) was added under argon. The mixture was stirred for 10 min and then

diluted with CH_2Cl_2. This solution was washed with saturated (satd) aqueous (aq) $NaHCO_3$, dried ($MgSO_4$), and concentrated. The resulting crude syrupy product showed (^{1}H NMR) the presence of **2** and the pyranone **5** (ratio 7:1) as main products. The syrup was purified by flash chromatography (70:1 hexane–EtOAc) to give oily **2** (111 mg, 57%); $[\alpha]_D$ 0.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51–6.92 (m, 15H, H-aromatic), 7.06 (br s, 1H, H-1), 4.63 (dd, 1H, $J_{4,5} = 2.2$ Hz, $J_{5,5'} = 11.5$ Hz, H-5), 4.28 (dt, 1H, $J_{3,5'} \sim J_{4,5'} \sim 2.1$ Hz, H-5′), 3.61 (m, 1H, H-3), 3.54 (td, 1H, H-4); ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.7 (C-1), 132.4, 131.6, 129.2, 129.1, 128.9, 128.6, 127.5, 127.2, 126.2 (C-aromatic, C-2), 64.5 (C-5), 49.0, 47.8 (C-3,4). Anal. Calcd for $C_{23}H_{20}OS_3$: C, 67.61; H, 4.93; S, 23.54. Found: C, 67.97; H, 4.70; S, 23.19.

3.2.2. By $Et_2O{\cdot}BF_3$-promoted conversion of 4 into 2. A solution of **4** (142 mg, 0.46 mmol) in anhydrous CH_2Cl_2 (5.4 mL) was cooled to −18 °C, and $Et_2O{\cdot}BF_3$ (74 μL, 0.59 mmol) was added under argon. The mixture was stirred for 40 min, when TLC showed no remaining starting material and the formation of a main compound having the same mobility as **2** and decomposition products ($R_f = 0$) were observed. The reaction mixture was diluted with CH_2Cl_2, washed with satd aq $NaHCO_3$, dried ($MgSO_4$) and concentrated. The residue was subjected to flash chromatography to afford **2** (43 mg, 23%); $[\alpha]_D$ 0.0 (*c* 1.0, $CHCl_3$).

3.3. Phenyl 2,4-di-*O*-acetyl-3-deoxy-1-thio-α- and β-D-*glycero*-pent-2-enopyranoside (3 and 4, respectively)

3.3.1. By $Et_2O{\cdot}BF_3$-promoted addition of thiophenol to 1. To a solution of **1**[4] (272 mg, 1.05 mmol) and thiophenol (107 mL, 1.05 mmol) in anhydrous CH_2Cl_2 (12 mL), cooled to −18 °C, was added $Et_2O{\cdot}BF_3$ (169 μL, 1.35 mmol) under argon. After 15 s of the addition of the Lewis acid, satd aq $NaHCO_3$ was added to the cool solution. The mixture was diluted with CH_2Cl_2, washed with water, and the organic extract dried ($MgSO_4$) and concentrated. Flash chromatography (30:1 hexane–EtOAc) of the crude product afforded first compound **3** (75 mg, 23%); $[\alpha]_D$ +142.5 (*c* 1.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52–7.25 (m, 5H, H-aromatic), 5.74 (ddd, 1H, $J_{1,3} = 1.1$ Hz, $J_{3,4} = 3.0$ Hz, $J_{3,5'} = 0.7$ Hz, H-3), 5.70 (dd, 1H, $J_{1,4} = 1.8$ Hz, H-1), 5.50 (dddd, 1H, $J_{4,5} = 8.0$ Hz, $J_{4,5'} = 5.9$ Hz, H-4), 4.07 (ddd, 1H, $J_{5,5'} = 11.4$ Hz, H-5ax), 4.01 (ddd, 1H, H-5′eq), 2.19, 2.07 (2s, 6H, 2 CH_3CO); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 168.2 (CH_3CO), 147.4 (C-2), 134.0, 131.9, 129.0, 127.7 (C-aromatic), 115.4 (C-3), 83.0 (C-1), 65.0 (C-4), 60.9 (C-5), 21.1, 21.0 (CH_3CO). Anal. Calcd for $C_{15}H_{16}O_5S$: C, 58.43; H, 5.23; S, 10.40. Found: C, 58.47; H, 5.31; S, 10.42.

From further fractions of the column was isolated crystalline **4** (136 mg, 42%); mp 62 °C; $[\alpha]_D$ −23.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51–7.26 (m, 5H, H-aromatic), 5.87 (br d, 1H, $J_{3,4} = 5.8$ Hz, H-3), 5.82 (br s, 1H, H-1), 5.25 (dd, 1H, $J_{4,5} = 2.7$ Hz, H-4), 4.43 (dd, 1H, $J_{5,5'} = 13.2$ Hz, H-5ax), 3.93 (br d, 1H, H-5′eq), 2.20, 2.09 (2s, 6H, 2 CH_3CO); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 170.4, 167.8 (CH_3CO), 148.9 (C-2), 131.3, 129.0, 127.5 (C-aromatic), 112.5 (C-3), 83.0 (C-1), 64.8 (C-4), 61.6 (C-5), 21.0 (×2) (CH_3CO). Anal. Calcd for $C_{15}H_{16}O_5S$: C, 58.43; H, 5.23; S, 10.40. Found: C, 58.85; H, 5.16; S, 10.27.

The ^{1}H NMR spectra of the crude reaction mixture showed a 1.8:1 ratio for **4**:**3**. Signals of low intensity due to dihydropyranone **5** were also detected. Longer reaction times afforded mixtures having variable ratios of **3** and **4**, and increasing amounts of polysubstituted **2**.

3.3.2. By iodine-promoted addition of thiophenol to 1. A solution of **1** (156 mg, 0.60 mmol) and thiophenol (70 μL, 0.69 mmol) in dry toluene (5 mL) was treated in the dark with iodine (37 mg, 0.15 mmol, added in two equal portions over a period of 20 min) at room temperature for 40 min. After the usual workup for iodine reactions, the residue was subjected to flash chromatography (30:1 hexane–EtOAc) to afford three products: the dihydropyranone **5** (3 mg, 2%) and the pent-2-enopyranosides α (**3**, 18 mg, 10%) and β (**4**, 81 mg, 43%). Compounds **3** and **4** showed the same physical and spectroscopic properties as those already described. The ^{1}H NMR of the crude mixture showed a 21:4:1 ratio of **4**:**3**:**5**.

3.4. (2*S*)-2-Phenylthio-2*H*-pyran-3(6*H*)-one (5)

3.4.1. By iodine-promoted addition of thiophenol to 1. To a solution of **1** (200 mg, 0.77 mmol) and thiophenol (87 μL, 0.85 mmol) in anhydrous acetonitrile (6 mL) was added iodine (44 mg, 0.17 mmol). The mixture was stirred in the dark at room temperature for 40 min, and then diluted with CH_2Cl_2, washed with a 5:1 (v/v) mixture of satd aq $Na_2S_2O_3$ and satd aq $NaHCO_3$, dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (30:1 hexane–EtOAc) to afford **5** (109 mg, 68%). The enantiomeric composition of **5** was determined by ^{1}H NMR using ytterbium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate] as a chiral resolving reagent.[4,13] To a solution of **5** (0.05 mmol) in carbon tetrachloride containing 1% benzene-d_6 (0.5 mL) was added the ytterbium reagent. Upon addition of 0.05–0.6 M equiv, the ^{1}H NMR spectrum showed splitting of the H-2 signal. From the integral of these signals (3:1 ratio), the enantiomeric composition (ee >50%) was established for **5**. This product had $[\alpha]_D$ −228.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.56–7.30 (m, 5H, H-aromatic), 7.10 (ddd, 1H, $J_{4,5} = 10.5$ Hz, $J_{5,6} = 1.8$ Hz, $J_{5,6'} = 4.1$ Hz, H-5),

6.18 (dddd, 1H, $J_{2,4} = 0.4$ Hz, $J_{4,6} = 2.7$ Hz, $J_{4,6'} = 1.6$ Hz, H-4), 5.67 (s, 1H, H-2), 4.93 (ddd, 1H, $J_{6,6'} = 19.1$ Hz, H-6), 4.34 (ddd, 1H, H-6′); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 189.0 (C-3), 148.3 (C-5), 132.8, 132.6, 129.2, 128.1 (C-aromatic), 125.9 (C-4), 88.3 (C-2), 59.5 (C-6). Anal. Calcd for $C_{11}H_{10}O_2S$: C, 64.05; H, 4.89; S, 15.55. Found: C, 64.24; H, 4.85; S, 15.82.

Similar yields of **5** were obtained for various preparations under identical conditions starting from **1**. However, variable enantiomeric excesses (ranging from 40% to 60%) were obtained for such preparations.

3.4.2. By iodine-promoted conversion of 4 into 5. A solution of **4** (148 mg, 0.48 mmol) in acetonitrile (4 mL) was treated in the dark with iodine (27 mg, 0.11 mmol) at room temperature for 25 min. After the usual workup for iodine reactions, the residue was subjected to flash chromatography (30:1 hexane–EtOAc) to afford the dihydropyranone **5** (73 mg, 74%) having $[\alpha]_D$ −433.6 (*c* 1.0, $CHCl_3$), which corresponded to an ee >94% (calculated from the ^{1}H NMR spectra recorded in the presence of the Yb chiral resolving agent).

The same reaction applied to a mixture of **3** and **4** (2.4:1 ratio, 100 mg, 0.32 mmol) afforded the enone **5** (48 mg, 72%) having $[\alpha]_D$ −11.4 (*c* 1.0, $CHCl_3$) and ee >2%.

3.5. (2*S*)-2-Benzylthio-2*H*-pyran-3(6*H*)-one (6)

Dihydropyranone **6** was prepared following the procedure described for **5** in the previous item. Thus, reaction of **1** (200 mg, 0.77 mmol) with ω-toluenethiol (100 μL, 0.85 mmol) afforded **6** (108 mg, 63%) as an amorphous yellowish solid. The ee of **6** was established as indicated for **5**. Compound **6** (ee >42%) had $[\alpha]_D$ −179.7 (*c* 1.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36–7.24 (m, 5H, H-aromatic), 7.04 (ddd, 1H, $J_{4,5} = 10.5$ Hz, $J_{5,6} = 1.8$ Hz, $J_{5,6'} = 4.0$ Hz, H-5), 6.12 (dddd, 1H, $J_{2,4} = 0.5$ Hz, $J_{4,6} = 2.7$ Hz, $J_{4,6'} = 1.6$ Hz, H-4), 5.29 (br s, 1H, H-2), 4.72 (ddd, 1H, $J_{6,6'} = 18.8$ Hz, H-6), 4.24 (ddd, 1H, H-6′), 3.92, 3.83 (2d, 2H, $J = 13.3$ Hz, PhCH_2S); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 190.0 (C-3), 148.0 (C-5), 137.0, 129.0, 128.6, 127.4 (C-aromatic), 125.8 (C-4), 83.4 (C-2), 59.0 (C-6), 34.8 (Ph*C*H_2S). Anal. Calcd for $C_{12}H_{12}O_2S$: C, 65.43; H, 5.49; S, 14.56. Found: C, 65.67; H, 5.51; S, 14.43.

3.6. *S*-Benzyl 3,4-dideoxy-1-thio-α-L-*glycero*-pent-3-enopyranoside (7)

To a solution of **6** (155 mg, 0.70 mmol, ee >42%) in dry MeOH (14 mL) was added cerium(III) chloride heptahydrate (96 mg, 0.26 mmol).[16] The solution was stirred for 5 min at room temperature and then cooled to 0 °C. Sodium borohydride (29 mg, 0.77 mmol) was added and the stirring was maintained for 15 min, when TLC (2:1 hexane–EtOAc) showed formation of a more polar product ($R_f = 0.33$) and no starting material remaining ($R_f = 0.53$). The mixture was diluted with a large excess of CH_2Cl_2, washed with satd aq NaCl, dried ($NaSO_4$), and concentrated. The residue, which showed by ^{1}H NMR signals of a single product, was purified by flash chromatography to afford **7** as a syrup (134 mg, 86%, ee >42%); $[\alpha]_D$ −90.8 (*c* 1.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35–7.23 (m, 5H, H-aromatic), 5.85, 5.82 (2br d, 2H, $J_{3,4} = 10.7$ Hz, H-3,4), 4.81 (d, 1H, $J_{1,2} = 3.4$ Hz, H-1), 4.35 (d, 1H, $J_{5,5'} = 16.2$ Hz, H-5), 4.12 (br d, 1H, H-2), 4.06 (dd, 1H, H-5′), 3.90, 3.84 (2d, 2H, $J = 13.4$ Hz, PhCH_2S); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 137.9, 128.9, 128.4, 128.3 (C-aromatic), 127.1, 126.9 (C-3,4), 84.1 (C-1), 64.4 (C-2), 63.7 (C-5), 34.3 (Ph*C*H_2S). Anal. Calcd for $C_{12}H_{14}O_2S$: C, 64.83; H, 6.35; S, 14.42. Found: C, 65.14; H, 6.31; S, 14.57.

The ^{1}H NMR spectra of the crude reaction mixture showed signals of **8** and no other diastereomers.

3.7. Diels–Alder cycloadditions of 2,3-dimethylbutadiene to 6: synthesis of (3*S*,4a*R*,8a*S*)-3-benzylthio-6,7-dimethyl-4a,5,8,8a-tetrahydro-1-*H*-2-benzopyran-4(3*H*)-one (8) and (3*S*,4a*S*,8a*R*)-3-benzylthio-6,7-dimethyl-4a,5,8,8a-tetrahydro-1-*H*-2-benzopyran-4(3*H*)-one (9)

3.7.1. $Et_2O{\cdot}BF_3$-promoted cycloaddition. A solution of **6** (129 mg, 0.59 mmol, ee >42%) in dry toluene (1.2 mL) was cooled to −18 °C and $Et_2O{\cdot}BF_3$ (74 μL, 0.50 mmol) was added under argon. The vial was sealed and the mixture was stirred at −18 °C for 15 min, then 2,3-dimethylbutadiene (113 μL, 1.00 mmol) dissolved in anhydrous toluene (0.5 mL) was slowly injected into the solution. When the addition was finished, the mixture was stirred at −18 °C for 15 min. The reaction mixture was diluted with ethyl ether, washed with satd aq $NaHCO_3$, dried ($MgSO_4$), and concentrated. The ^{1}H NMR spectrum of the crude reaction mixture showed only traces of other products (a diastereomeric ratio for **8** >50:1). The mixture was subjected to flash chromatography (60:1 hexane–EtOAc) to afford cycloadduct **8** (132 mg, 75%, ee >42%) as a white amorphous solid; $[\alpha]_D$ −152.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34–7.22 (m, 5H, H-aromatic), 5.07 (s, 1H, H-3), 4.53 (dd, 1H, $J_{1,1'} = 11.6$ Hz, $J_{1,8a} = 2.3$ Hz, H-1), 3.90, 3.81 (2d, 2H, $J = 13.3$ Hz, PhCH_2S), 3.59 (dd, 1H, $J_{1',8a} = 1.7$ Hz, H-1′), 3.09 (dd, 1H, $J_{4a,5'} = 6.5$ Hz, $J_{4a,8a} = 5.3$ Hz, H-4a), 2.53 (d, 1H, $J_{5,5'} = 17.6$ Hz, H-5), 2.35 (m, 1H, H-8a), 2.21 (br dd, 1H, $J_{8a,8} = 11.7$ Hz, $J_{8,8'} = 17.3$ Hz, H-8), 1.96 (br d, 1H, H-5′), 1.83 (br dd, 1H, H-8′), 1.62, 1.56 (2 br s, 6H, 2 CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 203.7 (C-4), 137.1, 129.1, 128.6, 127.4 (C-aromatic), 123.5, 122.9 (C-6,7), 85.9 (C-3), 64.4 (C-1), 44.4 (C-4a), 36.6 (C-8a), 35.3, 31.4, 28.8 (C-5,8, Ph*C*H_2S), 19.1, 18.7 (2CH_3). Anal. Calcd for $C_{18}H_{22}O_2S$: C, 71.49; H, 7.33; S, 10.60. Found: C, 71.63; H, 7.27; S, 10.76.

3.7.2. $SnCl_4$-promoted cycloaddition. The same procedure described for the preceding cycloaddition was followed using $SnCl_4$ instead of $Et_2O{\cdot}BF_3$. Thus, starting from **6** (150 mg, 0.68 mmol, ee >42%), the reaction promoted by $SnCl_4$ (80 μL, 0.68 mmol) afforded a crude mixture containing mainly **9** and **8** (1.9:1 ratio, according to the ^{1}H NMR spectrum). Column chromatography gave adducts **8** (54 mg, 26%, ee >42%) and **9** (101 mg, 49%). Compound **9** (ee >42%) had $[\alpha]_D$ −95.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35–7.22 (m, 5H, H-aromatic), 5.06 (s, 1H, H-3), 4.05 (dd, 1H, $J_{1,1'} = 11.5$ Hz, $J_{1,8a} = 6.3$ Hz, H-1), 3.89, 3.80 (2 d, 2H, $J = 13.2$ Hz, PhCH_2S), 3.82 (dd, 1H, $J_{1',8a} = 4.6$ Hz, H-1′), 2.87 (dd, 1H, $J_{4a,5} \sim J_{4a,8a} = 5.9$ Hz, $J_{4a,5'} \sim 5.7$ Hz, H-4a), 2.56 (br d, 1H, $J_{5,5'} = 17.4$ Hz, H-5), 2.52 (m, 1H, H-8a), 2.02 (br s, 2H, H-8,8′), 1.96 (dd, 1H, H-5′), 1.62, 1.58 (2br s, 6H, 2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.3 (C-4), 137.2, 129.2, 128.6, 127.3, 123.2, 122.8 (C-aromatic, C-6,7), 85.2 (C-3), 65.7 (C-1), 45.7 (C-4a), 34.9 (C-8a), 34.6 (Ph*C*H$_2$S), 32.6 (C-8), 29.1 (C-5), 19.0, 18.7 (2CH_3).

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