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Note

Thermodynamic stabilities and conformational analyses of 4,6-*O*-acetalized 1,5-anhydro-5-thio-DL-*threo*-2-enitols

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ABSTRACT

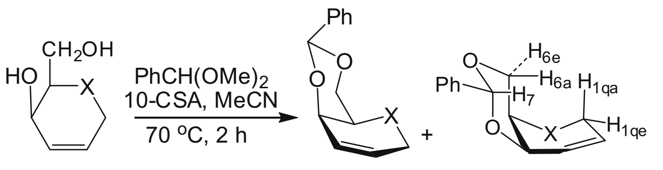
4,6-*O*-Methylidene and 4,6-*O*-neopentylidene derivatives of 1,5-anhydro-2,3-dideoxy-5-thio-DL-*thero*-hex-2-enitol having the C-inside form were found to be thermodynamically more stable than the corresponding O-inside conformers. Thermodynamic stabilities, as well as the conformation of sulfoxide and sulfone derivatives of the 4,6-*O*-neopentylidene compound were examined by experiment and ab initio MO and DFT calculations. These thermodynamic stabilities, and the most stable conformations determined by NMR data, were corroborated by calculations.

The conformational preference for an equatorial substituent compared to an axial substituent in a monosubstituted cyclohexane ring is well known. This steric substituent parameter, which is equal to the ΔG^o in kcal/mol for the equilibration of the cyclohexane ring conformers, is known as the *A* value, and is widely used in organic chemistry.[1] According to these values, a hydroxymethyl group (*A* value: 1.78) is larger than the methoxyl (0.55–0.75) or hydroxyl group (0.60).[2] In fact, benzylidenation of sugar **1** and **5a**-carba sugar **2** almost exclusively afforded the thermodynamically more stable O-inside **4** and **5** (O-inside: O-4 is placed inside of the pyranose ring), respectively, because conventional acidic acetalization is controlled thermodynamically. However, to our surprise, benzylidenation of 5-thiosugar **3** gave a 1.0:1.6 equilibrium mixture of the O-inside conformer **6** and the C-inside conformer **7** (C-inside: alternative half-chair conformer of O-inside).[3] As judged from a stereomodel, the C-inside conformer **7** is sterically more crowded. In fact, a correlation between H-6a and H-1qa was observed in the NOESY spectrum of **7**. These thermodynamic stabilities of 4,6-*O*-benzylidene derivatives of **1**, **2**, and **3** agreed qualitatively with DFT (B3LYP/6-31+G* level) calculations.[3] To confirm the generality of the exceptional stabilities observed in the 4,6-*O*-benzylidene derivatives of 5-thio sugars, we have performed methylidenation and neopentylidenation reactions of 5-thio sugar **3** and the latter was oxidized to the sulfoxide and sulfone derivatives (see Fig. 1).

Treatment of **3** with dimethoxymethane in the presence of (±)-10-camphorsulfonic acid (10-CSA) gave 4,6-*O*-methylidene derivative **8**. As expected from previous data,[3] this compound occupied the C-inside form, at least predominantly, as judged from NMR data ($J_{5,6a}$ = 8.9 Hz, $J_{5,6e}$ = 4.7 Hz), and the correlation between H-7a (axial hydrogen atom at the methylidene group) and H-3 in the NOESY spectrum.

Next, we performed neopentylidenation, because a bulky *tert*-butyl group, frequently used to fix ring conformation, is suitable for calculations because it is symmetrical. Treatment of **3** with pivalaldehyde diethylacetal in the presence of 10-CSA gave a 2.7:1.0 mixture of the C-inside conformer **9** and the O-inside conformer **10**. The conformations of **9** and **10** were determined from NMR data.

4,6-*O*-Neopentylidene derivatives **9** and **10** were oxidized by MCPBA, which led to the corresponding sulfoxide(s) and sulfone. Oxidation of C-inside **9** gave sulfone **13** (5%) and two sulfoxides **11** (33% yield) and **12** (60%) due to the chirality at sulfur atom of sulfoxide. The identification of the C-inside conformation for these



1 X = O
2 X = CH$_2$
3 X = S

4 X = O
5 X = CH$_2$
6 X = S

7 X = S

Figure 1. Benzylidenation of 1,5-anhydro-*threo*-2-enitol derivatives.

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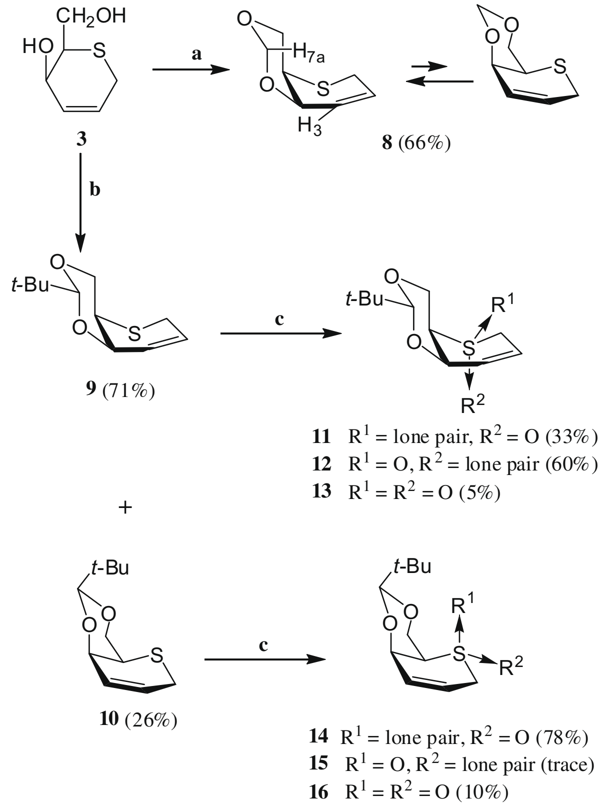

11 R^1 = lone pair, R^2 = O (33%)
12 R^1 = O, R^2 = lone pair (60%)
13 $R^1 = R^2$ = O (5%)

14 R^1 = lone pair, R^2 = O (78%)
15 R^1 = O, R^2 = lone pair (trace)
16 $R^1 = R^2$ = O (10%)

Scheme 1. Reagents and conditions: (a) $CH_2(OMe)_2$, 10-CSA, LiBr, reflux, overnight, (b) t-BuCH(OEt)$_2$, 10-CSA, MeCN, 70 °C, 10 min: (c) MCPBA, CH_2Cl_2, 0 °C.

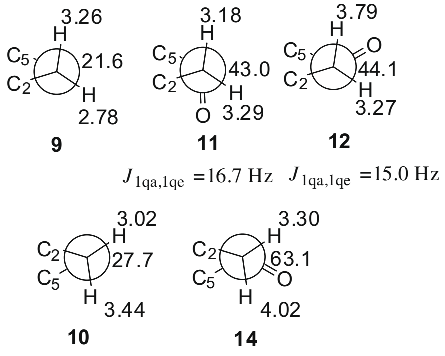

Figure 2. Newman projection of **9**, **11**, **12**, **10**, and **14** view from C-1 to S-5. Chemical shift (δ) of H-1a and H-1e as well as that of C-1 (δ) was shown.

three compounds was assigned by large coupling constants ($J_{5,6a} \geqslant 10.3$ Hz). It is noteworthy that sulfoxide **11** adopted the C-inside conformation in spite of the axial orientation of the sulfoxide oxygen atom. Similar oxidation of **10** gave sulfoxide **14** (78%) and sulfone **16** (10%), along with a trace amount of an unknown compound. Predominant attack from the lower side (α-side) of **10** could be attributed to steric hindrance mainly due to O-4 and O-6 (see Scheme 1).

The chirality at sulfur atom of the sulfoxides was assigned by NMR data. The chemical shift of a proton gauche to the S=O bond moves to a lower field than that of an antiperiplanar proton.[4] As shown in Figure 2, both protons at C-1 of **12** shift to a lower field than those of precursor sulfide **9**. For 11 h one proton shifts to lower field, but the other one does not. Thus, sulfoxides **11** and **12** were assigned to have axial and equatorial oxygen atom, respectively. It is reported that a methylene group adjacent to a sulfoxide having an axial oxygen atom has a larger geminal coupling constant than the other one. In fact, sulfoxide **11** has a larger geminal coupling constant ($J_{1qa,1qe}$ = 16.7 Hz) than **12** ($J_{1qa,1qe}$ = 15.0 Hz).[†] That **14** adopted the O-inside conformation with an equatorial sulfoxide oxygen was determined by small coupling constants, ($J_{5,6a}$ = 4.2, $J_{5,6e}$ = 3.3 Hz), and chemical shifts of H-1qa and H-1qe compared with those of the precursor sulfide **10** (Fig. 2).

Relative thermodynamic stabilities of the C-inside and O-inside conformers of the 4,6-*O*-neopentylidene derivatives were determined. When sulfide **9** was treated with pivalaldehyde diethyl ether in the presence of 10-CSA for 2 h at 70 °C, a 1.9:1.0 mixture of **9** and **10** was formed. The same equilibrium mixture was obtained from **10**. Thus, the C-inside conformer **9** was slightly more stable than the O-inside conformer **10**. The same trend was observed in the case of the 4,6-*O*-benzylidene derivatives: the equilibrium mixture of **6** and **7** was 1.0:1.6.[3] Similar treatment of sulfoxides **11** and **14**, respectively, gave a 1.0:9.6 mixture of **11** and **14**. As shown in Table 1, the C-inside conformer **11** having the axial sulfoxide oxygen atom was dramatically less stable than the O-inside conformer **14**, which has an equatorial oxygen atom. Although O-inside **15**, with an axial sulfoxide oxygen atom, was not obtained, C-inside **12**, with an equatorial sulfoxide oxygen atom should be thermodynamically more stable, because similar treatment of **12** even after 20 h gave almost pure **12**. Thus, the axial orientation of the sulfoxide oxygen atom was found to be unfavorable. In the case of sulfones **13** and **16**, the C-inside conformer **13** was the major product at equilibrium (**13**:**16** = 5.7:1.0). Isomerization of the sulfoxide oxygen atom, that is, change of the chirality at the sulfur atom of sulfoxides, was not observed in these reactions.

In the case of the 4,6-*O*-benzylidene derivatives of 5-thio sugars **6** and **7**, the thermodynamic stabilities were qualitatively corroborated by DFT calculations. Therefore, we examined whether or not the experimental results were reproduced by ab initio MO and DFT calculations. For this purpose, several conformers were calculated and two examples are shown in Figure 3. As shown in Tables 2 and 3, the most stable conformers calculated were in qualitative agreement with these determined from NMR data. As indicated by experiment, sulfoxides **12** and **14**, which have an equatorial oxygen atom, are more stable than the alternative conformers **15** and **11** by 3.4 and 3.3 kcal/mol (DFT), respectively (Table 2, entries 2 and 3). In the case of sulfones, C-inside conformer **13** is more stable than O-inside conformer **16** by 2.7 kcal/mol (DFT, entry 4). Thus, thermodynamic stabilities determined herewith were qualitatively corroborated by calculations, but not quantitatively because calculations were performed at 0 K in vacuo.

It was therefore found that C-inside conformers, **7**, **8**, and **9**, were more stable than the corresponding O-inside ones. To get some information about this observation, we performed calculations on the 4,6-*O*-methylidene derivatives of **5a**-carba **17**, 5-thio sugar **8**, sugar **18**, and 5-seleno sugar **19** as shown in Table 3, although the favorable conformation for the latter two compounds is not reported.

The predominance of the O-inside conformation for **5a**-carba **17** and that of the C-inside one for 5-thio sugar **8** agreed with the experimental data (Table 3, entries 3 and 1). Calculations indicated that the O-inside conformation was favorable for sugar **18** (entry 2). This is reasonable from the conformational analysis of 4,6-*O*-benzylidene derivative **4**.[3] If the conformational exception observed in 5-thio sugars is caused by steric repulsion, the C-inside conformation for 5-seleno sugar **19** should be more favorable compared with 5-thio sugar **8**, because the C–Se bond is longer than a C–S bond, and the C–Se–C bond angle is close to C–S–C angle. In

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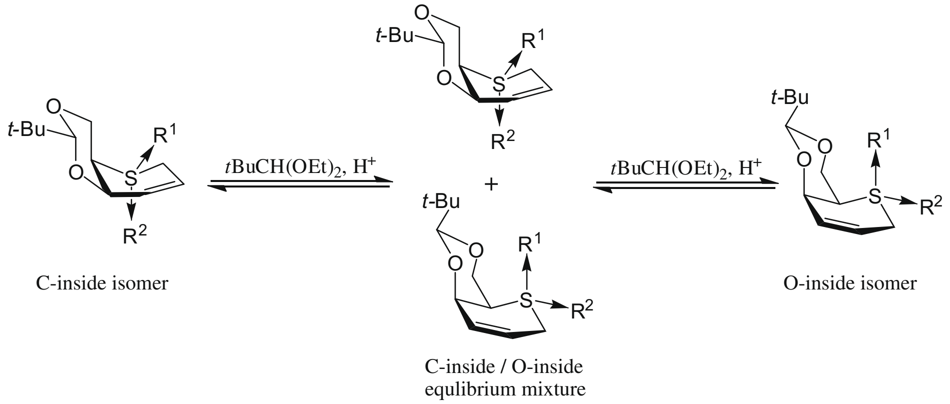
[†] According to Ref. 4b, carbon signals adjacent to the sulfur atom having the axial oxygen atom appeared at higher field than those having equatorial one. However, the C-1 signals of **11** and **12** were δ 43.0 and δ 44.1, respectively.

Table 1
Equilibrium experiments of **9**–**16**



Entry	Compound (sulfur oxidation)	R^1	R^2	Product ratio[a]	
				C-inside	O-inside
1	**9**,**10** (sulfide)	Lone pair	Lone pair	**1.9**	1
2	**11**,**14** (sulfoxide)	Lone pair	→O	1	**9.6**
3	**12**,**15** (sulfoxide)[b]	→O	Lone pair	**>10**	1
4	**13**,**16** (sulfone)	→O	→O	**5.7**	1

[a] Determined by NMR spectroscopy.

[b] Even after about 20 h, compound **12** was recovered. Epimerization of **15** could not be performed, because of its lack of availability.

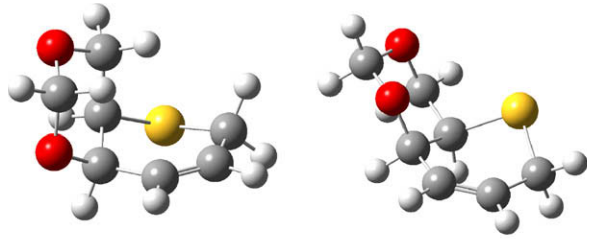
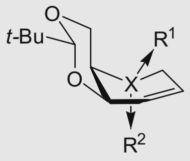
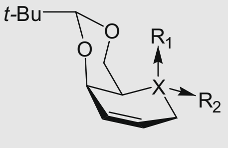
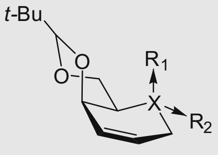
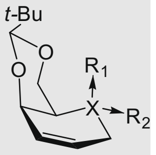

C-Inside conformation of **8**   O-Inside conformation of **8**

Figure 3. DFT Optimized structure of **8** having the C-inside and O-inside conformation.

fact, the bond length of the C5–Se (1.959 Å) and C1–Se (1.973 Å) bonds, as calculated by the DFT method for the C-inside form of **19** is longer than C5–S (1.833 Å) and C1–S (1.839 Å) bonds for **8** and the C5–Se–C1 angle (96.5° is close to the C5–S–C1 (100.2°) angle. Although in the case of **19** the C-inside conformer is more stable than the O-inside one, by 1.6 kcal/mol, the difference is slightly smaller than that for **8** (Table 3, entries 1 and 4). In the case of the 4,6-*O*-neopentylidene derivatives, the energy difference for the 5-thio and 5-seleno sugars was 1.6 and 0.8 kcal/mol, respectively (Table 2, entries 1 and 5). The O-inside conformation suffers from electrostatic repulsion between axially orientated lone pairs on both O-4 and O-6 and that of the ring hetero atom (Fig. 3). The extent of its electron cloud increases according to the order of O < S < Se; however, its electron density decreases according to the sequence of Se < S < O. As a result, electrostatic repulsion should be severest in the case of the 5-thio sugars. It is likely that the conformation observed herewith is determined by such an electrostatic repulsion as well as by steric hindrance (see Fig. 4).

In conclusion, we elucidated that, in contrast to the corresponding sugar and **5a**-carba sugar, the C-inside conformation of the 5-thio sugars was more stable than O-inside one regardless of substituent at C-7 (H, Ph, *tert*-Bu). The same trend was observed for the sulfones, whereas in the case of the sulfoxides, the orientation of the sulfoxide oxygen in the equatorial position was more stable

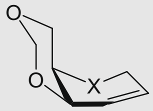
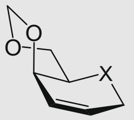
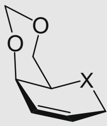
Table 2
Stabilities of conformers of neopentylidene derivatives calculated at HF/6-31+G* as well as B3LYP/6-31+G* level[a]

Entry		 C-inside	 O-inside axial *t*Bu group	 O-inside twisted dioxan ring	 O-inside equatorial *t*Bu group
1	X = S, $R_1 = R_2$ = lone pair	0.0 (0.0)	11.0 (11.7)	5.7 (5.7)	1.6 (1.6)
2	X = S, R_1 = O, R_2 = lone parir	0.0 (0.0)	13.0 (7.2)[b]	5.8 (6.1)	3.4 (4.2)
3	X = S, R_1 = lone pair, R_2 = O	3.3 (3.2)	9.6 (10.5)	5.3 (5.1)	0.0 (0.0)
4	X = S, $R_1 = R_2$ = O	0.0 (0.0)	12.3 (13.0)	5.8 (5.4)	2.7 (2.6)
5	X = Se, $R_1 = R_2$ = lone pair	0.0 (0.0)	10.3 (11.1)	4.6 (5.4)	0.8 (0.8)

[a] Energy differences (figures in parentheses derived by HF/6-31+G*) are shown (kcal/mol).

[b] Optimized structure derived by B3LYP/6-31+G* had chair dioxane ring, however, that derived by HF/6-31+G* had between O-inside and twisted dioxane ring

Table 3
Stabilities of conformers of methylene and neopentylidene derivatives calculated at HF/6-31+G* as well as B3LYP/6-31+G* level[a]

Entry		 C-inside	 O-inside twisted dioxan ring	 O-inside
1	**8** X = S	0.0 (0.0)	4.7 (4.3)	1.8 (1.9)
2	**18** X = O	1.5 (1.5)	2.4 (1.7)	0.0 (0.0)
3	**17** X = CH_2	1.5 (1.4)	3.7 (3.3)	0.0 (0.0)
4	**19** X = Se	0.0 (0.0)	5.1 (4.9)	1.6 (1.8)

[a] Energy differences (figures in parentheses derived by HF/6-31+G*) are shown (kcal/mol).

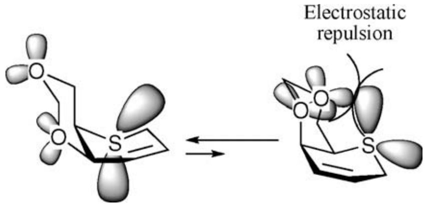


Figure 4. Schematic electrostatic repulsion between axially occupied lone pair on the ring hetero atom and those on both O-4 and O-5 (shown in the case of compound **8**).

than the alternative one. These results were qualitatively corroborated by ab initio MO and DFT calculations.

1. Experimental

1.1. General methods

Melting points are uncorrected. Most of the reactions were monitored by TLC using silica gel coated on glass. Products were purified by flash column chromatography and recrystallized if necessary. NMR spectra were measured by Bruker AVANCE 400 at 400 MHz/(^{1}H) or 100 MHz (^{13}C) with TMS as an internal standard. Some signals were assigned by the use of COSY, HMQC, HMBC, and/or NOESY experiments. IR spectra were recorded as KBr pellets on a Perkin–Elmer Spectrum One FT-IR spectrometer. Silica gel (C-60, Kanto or 40–63 μm, Merck) was used for column chromatography.

1.2. 1,5-Anhydro-4,6-*O*-methylidene-2,3-dideoxy-5-thio-DL-threo-hex-2-enitol (8)

A solution of **3** (292 mg, 2.0 mmol) in dimethoxymethane (3 mL) was heated at reflux under an Ar atmosphere, to which 10-CSA (30 mg, 0.13 mmol) and LiBr (30 mg, 0.35 mmol) were added and the mixture was kept stirring overnight. After addition of Et_3N (1 mL) and then water, the products were extracted with EtOAc. The aqueous layer was extracted with EtOAc (10 mL × 3). The combined organic layers were washed with satd NaCl solution, dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with toluene to give **8** (210 mg, 66%). Mp 28–30 °C. IR (KBr): ν 1656, 1482, 1455. ^{1}H NMR ($CDCl_3$): δ 3.19 (ddd, 1H, $J_{1qa,1qe}$ 18.1 Hz, $J_{1qa,2}$ 2.6 Hz, $J_{1qa,3}$ 2.6 Hz, H-1qa), 2.97 (ddd, 1H, $J_{1qe,2}$ 2.1 Hz, $J_{1qe,3}$ 2.1 Hz, H-1qe), 6.13 (ddd, 1H, $J_{2,3}$ 10.9 Hz, H-2), 5.80 (dddd, 1H, $J_{3,4}$ 2.4 Hz, H-3), 4.61 (dd, 1H, $J_{4,5}$ 2.3 Hz, H-4), 3.18 (ddd, 1H, $J_{5,6e}$ 4.7 Hz, $J_{5,6a}$ 8.9 Hz, H-5), 4.08 (dd, 1H, $J_{6a,6e}$ 11.5 Hz, H-6e), 3.84 (dd, 1H, H-6a), 4.85 (d, 1H, $J_{7a,7e}$ 6.4 Hz, H-7e), 4.78 (d, 1H, H-7a); ^{13}C NMR ($CDCl_3$): δ 23.0 (C-1), 129.1 (C-2), 127.7 (C-3), 69.0 (C-4), 34.6 (C-5), 67.3 (C-6), 89.4 (–O*CH*$_2$O–); NOESY correlation: H-1qa and H-6a, H-3 and H-7a. Anal. Calcd for $C_{11}H_{18}O_2S$: C, 53.14; H, 6.37; S, 20.27. Found: C, 52.92; H, 6.67; S, 19.97.

1.3. 1,5-Anhyro-4,6-O-neopentylidene-2,3-dideoxy-5-thio-DL-threo-hex-2-enitols

To a solution of **3** (200 mg, 1.37 mmol) and pivalaldehyde diethylacetal (320 mg, 2.00 mmol) in MeCN (10 mL), 10-CSA (30 mg, 0.13 mmol) was added at 70 °C. The mixture was stirred for 10 min at the same temperature. After addition of Et_3N (1 mL), the mixture was extracted with EtOAc and the aqueous layer was extracted with EtOAc three times. The combined organic layer was washed with brine solution, dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by silica gel column chromatography (toluene) to give 208 mg of C-inside **9** (71%) and 76 mg of O-inside **10** (26%).

1.3.1. Physical data for C-inside 9

Mp 31–32 °C. IR (KBr): ν 1656, 1483. ^{1}H NMR ($CDCl_3$): δ 3.23 (ddd, 1H, $J_{1qa,1qe}$ 13.0 Hz, $J_{1a,2}$ 3.2 Hz, $J_{1qa,3}$ 2.1 Hz, H-1a), 2.78 (ddd, 1H, $J_{1qe,2}$ 2.3 Hz, $J_{1qe,3}$ 1.7 Hz, H-1qe), 6.05 (ddd, 1H, $J_{2,3}$ 11.0 Hz, H2), 5.73 (dddd, 1H, $J_{3,4}$ 2.5 Hz, H3), 4.79 (dd, 1H, $J_{4,5}$ 2.1 Hz, H4), 3.11 (ddd, 1H, $J_{5,6a}$ 11.2 Hz, $J_{5,6e}$ 5.4 Hz, H-5), 4.04 (dd, 1H, $J_{6a,6e}$ 11.6 Hz, H-6e), 3.76 (dd, 1H, H-6a), 4.20 (s, 1H, H-7), 0.91(s, 9H, *t*-Bu); ^{13}C NMR ($CDCl_3$): δ 21.6 (C-1), 129.2 (C-2), 127.9 (C-3), 69.6 (C-4), 32.7 (C-5), 66.7 (C-6), 101.2 (*t*-Bu*CH*), 35.1, 25.4 (*t*-Bu). NOESY correlation: H-1qa and H-6a, H-3 and H-7. Anal. Calcd for $C_{11}H_{18}O_2S$: C, 61.64; H, 8.47; S, 14.96. Found: C, 61.92; H, 8.23; S, 15.10.

1.3.2. Physical data for O-inside 10

Mp 71–73 °C (recrystallized from EtOH). IR (KBr): ν 1659, 1485. ^{1}H NMR ($CDCl_3$): δ 3.44 (ddd, 1H, $J_{1qa,1qe}$ 17.6 Hz, $J_{1qa,2}$ 4.3 Hz, $J_{1qa,3}$ 2.1 Hz, H-1qa), 3.02 (dd, $J_{1qe,2}$ 6.3 Hz, 1H, H-1qe), 6.16 (ddd, 1H, $J_{2,3}$ 9.7 Hz, 1H, H-2), 5.86–5.82 (m, 1H, H-3), 4.22–4.11 (m, 3H, H-4, H-6), 2.86 (br s, 1H, H-5), 4.20 (s, 1H, H-7), 0.94 (s, 9H, *t*-Bu); ^{13}C NMR ($CDCl_3$): δ 27.7 (C-1), 130.2 (C-2), 127.9 (C-3), 69.1 (C-4), 39.5 (C-5), 70.3 (C-6), 108.5 (*t*-Bu*CH*), 35.3, 25.1 (*t*-Bu). Anal. Calcd for $C_{11}H_{18}O_2S$: C, 61.64; H, 8.47; S, 14.96. Found: C, 61.48; H, 8.22; S, 15.26.

1.4. Oxidation of sulfur atom of 9

MCPBA powder (88 mg, 0.5 mmol) was gradually added to a solution of **9** (100 mg, 0.47 mmol) in CH_2Cl_2 (5 mL) at 0 °C until the TLC spot of **9** had disappeared. The reaction was quenched by the addition of 10% aq $Na_2S_2O_3$, and poured into satd aq $NaHCO_3$, the mixture was extracted with EtOAc three times and combined organic layer was washed with brine, dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed on silica gel eluting with EtOAc to give **11** (36 mg, 33%) and **12** (65 mg, 60%) and **13** (6 mg, 5%).

1.4.1. Physical data for 11

Mp 159–160 °C. IR (KBr): ν 1647. ^{1}H NMR ($CDCl_3$): δ 3.29 (ddd, 1H, $J_{1qa,1qe}$ 16.7 Hz, $J_{1qe,2}$ 2.3 Hz, $J_{1qe,3}$ 0.9 Hz, H-1qe), 3.18 (ddd, 1H, $J_{1qa,2}$ 2.4 Hz, $J_{1qa,3}$ 1.2 Hz, H-1qa), 5.91 (ddd, 1H, $J_{2,3}$ 11.1 Hz, H-2), 5.99 (br dd, 1H, $J_{3,4}$ 1.0 Hz, H-3), 5.05 (dd, 1H, $J_{4,5}$ 2.6 Hz, H-4), 3.73 (ddd, 1H, $J_{5,6e}$ 4.9 Hz, $J_{5,6a}$ 11.1 Hz, H-5), 4.17 (dd, 1H, $J_{6a,6e}$ 10.8 Hz, H-6e), 3.53 (dd, 1H, H-6a), 4.31 (s, 1H, H-7), 0.91 (s, 9H, *t*-Bu); ^{13}C NMR ($CDCl_3$): δ 43.0 (C-1), 120.3 (C-2), 129.5 (C-3), 65.6 (C-4), 50.3 (C-5), 62.4 (C-6), 102.8 (*t*-Bu*CH*), 35.2, 24.9 (*t*-

Bu). Anal. Calcd for $C_{11}H_{18}O_3S$: C, 57.36; H, 7.88; S, 13.92. Found: C, 57.12; H, 7.89; S, 13.89.

1.4.2. Physical data for 12

Mp 127–129 °C. IR (KBr): ν 1656. ^{1}H NMR ($CDCl_3$): δ 3.79 (ddd, 1H, $J_{1qa,1qe}$ 15.0 Hz, $J_{1qa,2}$ 2.3 Hz, $J_{1qa,3}$ 1.3 Hz, H-1qa), 3.27 (ddd, 1H, $J_{1qe,2}$ 2.3 Hz, $J_{1qe,3}$ 1.7 Hz, H-1qe), 5.91–5.84 (m, 2H, H-2 and H-3), 4.78 (br s, 1H, H-4), 3.86 (ddd, 1H, $J_{4,5}$ 3.5 Hz, $J_{5,6e}$ 4.2 Hz, $J_{5,6a}$ 10.8 Hz, H-5), 4.54 (dd, 1H, $J_{6a,6e}$ 11.5 Hz, H-6e), 3.95 (dd, 1H, H6a), 4.17 (s, 1H, H-7), 0.90 (s, 9H, *t*-Bu); ^{13}C NMR ($CDCl_3$): δ 44.1 (C-1), 121.3 (C-2), 130.9 (C-3), 69.6 (C-4), 49.4 (C-5), 61.2 (C-6), 102.7 (*t*-Bu*CH*), 35.1, 25.0 (*t*-Bu); Anal. Calcd for $C_{11}H_{18}O_3S$: C, 57.36; H, 7.88; S, 13.92. Found: C, 57.45; H, 7.91; S, 13.65.

1.4.3. Physical data for 13

Mp 188–190 °C. IR (KBr): ν 1654. ^{1}H NMR ($CDCl_3$): δ 3.54–3.53 (m, 2H, H-1), 5.94–5.91 (m, 2H, H-2, H-3), 5.06 (dd, 1H, $J_{3,4}$ 1.7 Hz, $J_{4,5}$ 2.2 Hz, H-4), 3.68 (ddd, 1H, $J_{5,6e}$ 4.5 Hz, $J_{5,6a}$ 10.3 Hz, H-5), 4.33 (dd, 1H, $J_{6a,6e}$ 12.0 Hz, H-6e), 3.73 (dd, 1H, H-6a), 4.18 (s, 1H, H-7), 0.90 (s, 9H, *t*-Bu); ^{13}C NMR ($CDCl_3$): δ 47.9 (C-1), 121.3 (C-2), 129.4 (C-3), 71.3 (C-4), 54.8 (C-5), 63.1 (C-6), 102.4 (*t*-Bu*CH*), 35.0, 24.9 (*t*-Bu). Anal. Calcd for $C_{11}H_{18}O_4S$: C, 53.68; H, 7.37; S, 13.02. Found: C, 53.44; H, 7.42; S, 12.79.

1.5. Oxidation of sulfur atom of 10

MCPBA powder (88 mg, 0.5 mmol) was gradually added to a solution of **10** (100 mg, 0.47 mmol) in CH_2Cl_2 (5 mL) at 0 °C until the TLC spot of **10** had disappeared. The reaction was quenched by the addition of 10% aq $Na_2S_2O_3$, and poured into satd aq $NaHCO_3$, the mixture was extracted with EtOAc three times. The combined organic layer was washed with brine, dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed on silica gel eluting with EtOAc to give **14** (84 mg, 78%) and **16** (12 mg, 10%).

1.5.1. Physical data for 14

Mp 153–155 °C (recrystallized from EtOH and *n*-hexane). IR (KBr): ν 1665, 1480. ^{1}H NMR ($CDCl_3$): δ 3.30 (br d, 1H, $J_{1qa,1qe}$ 15.6 Hz, H-1qe), 4.02 (br d, 1H, H-1qa), 5.91 (m, 1H, H-2), 5.79 (m, 1H, H-3), 4.59 (dd, 1H, $J_{3,4}$ 3.0 Hz, $J_{4,5}$ 1.2 Hz, H-4), 2.75 (br s, 1H, H-5), 4.81 (dd, 1H, $J_{5,6a}$ 4.2 Hz, $J_{6a,6e}$ 12.9 Hz, H-6a), 3.97 (dd, 1H, $J_{5,6e}$ 3.3 Hz, H-6e), 4.27 (s, 1H, H-7), 0.92 (s, 9H, *t*-Bu); ^{13}C NMR ($CDCl_3$): δ 63.1 (C-1), 129.7 (C-2), 122.5 (C-3), 60.7 (C-4), 50.6 (C-5), 73.4 (C-6), 108.5 (*t*-Bu*CH*), 35.5, 24.9 (*t*-Bu). Anal. Calcd for $C_{11}H_{18}O_3S$: C, 57.36; H, 7.88; S, 13.92. Found: C, 57.46; H, 8.01; S, 13.70.

1.5.2. Physical data for 16

Mp 228–231 °C (recrystallized from $CHCl_3$ and EtOH). IR (KBr): ν 1658. ^{1}H NMR($CDCl_3 + CD_3OD$): δ 3.69 (dd, 1H, $J_{1qa,1qe}$ 17.3 Hz, $J_{1qe,2}$ 2.1 Hz, H-1qe), 3.77 (br d, 1H, $J_{1qa,2}$ 5.3 Hz, H-1qa), 6.07–5.99 (m, 2H, H-2, H-3), 4.77 (dd, 1H, $J_{3,4}$ 3.6 Hz, $J_{4,5}$ 1.1 Hz, H-4), 3.07 (dd, 1H, $J_{4,5}$ 1.2 Hz, $J_{5,6a}$ 4.0 Hz, $J_{5,6e}$ 0 Hz, H-5), 4.92 (br d, $J_{6a,6e}$ 13.2 Hz, 1H, H-6a), 4.00 (dd, 1H, H-6e), 4.20 (s, 1H, H-7), 0.94 (s, 9H, *t*-Bu); ^{13}C NMR ($CDCl_3 + CD_3OD$): δ 54.2 (C-1), 127.7 (C-2), 124.1 (C-3), 61.2 (C-4), 50.9 (C-5), 73.1 (C-6), 108.1 (*t*-Bu*CH*), 35.4 (*t*-Bu), 24.8 (*t*-Bu). Anal. Calcd for $C_{11}H_{18}O_4S$: C, 53.68; H, 7.37; S, 13.02. Found: C, 53.42; H, 7.27; S, 12.97.

1.6. Equilibration experiment

A solution of 4,6-*O*-acetal **9–16** (20 mg) in distilled MeCN (3 mL) and pivalaldehyde diethyl acetal (1.0 equiv) was heated at reflux under an Ar atmosphere, to which 10-CSA (0.1 equiv) was added and the mixture kept for 2 h at 70 °C. After addition of Et_3N (1 mL), water was added and the mixture was extracted with EtOAc. Extracts were washed with water, dried over $MgSO_4$ and concentrated. The product ratios were determined by ^{1}H NMR spectroscopy

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2009.02.028.

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