Solvolytic Behaviors of *O*-Benzoyl, Cyclic *O,O*-Thionocarbonate, and *O,S*-Thiolcarbonate Groups in 3-*O*-Benzoyl-1,2-*O*-isopropylidene-α-D-glucofuranose Derivatives[1)]

Yoshisuke TSUDA* and Kenji SHIBAYAMA

Faculty of Pharmaceutical Sciences, Kanazawa University, 13–1 Takara-machi, Kanazawa 920, Japan.
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***O*-Benzoyl, cyclic thionocarbonate, and thiolcarbonate groups in 5,6-*O*-thiono-, 5,6-*O,S*-thiol-, and 5,6-*S,O*-thiolcarbonates of 3-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-glucofuranoses behaved differently on solvolysis under alkaline conditions. Generally, the 3-*O*-benzoyl group was the most vulnerable to NaOH in water or MeOH, while thionocarbonate and thiolcarbonate groups were more reactive than the *O*-benzoyl group toward methanolysis with NaOMe. In particular, methanolysis of the 5,6-*S,O*-thiolcarbonate with NaOMe gave a thiirane derivative very rapidly.**

Key words cyclic thiolcarbonate; solvolysis; thiirane; cyclic thionocarbonate; *O*-benzoyl group; glucofuranose

During the synthesis of ring-*S* thiosugars,[2)] we have observed that cyclic thiono- and thiol-carbonates groups are sometimes more susceptible than the *O*-benzoyl group in the same molecule to solvolysis with bases. This paper deals with this subject in detail. The substrates are 3-*O*-benzoyl-1,2-*O*-isopropylidene-glucofuranose derivatives, **1**, **6**, and **11**, whose preparation was reported previously.[2)]

Results and Discussion

Solvolysis of the 3-*O*-Benzoyl-5,6-*O*-thionocarbonate (1) The 3-*O*-benzoyl-thionocarbonate **1** was hydrolyzed with NaOH in water to give quantitatively the triol **3a**. In 5% K_2CO_3 solution, the reaction proceeded in a stepwise manner as shown in Chart 1, as proved by isolation of the mono-benzoate **2a**. This indicates that the thionocarbonate group is more vulnerable than the *O*-benzoyl group to alkaline hydrolysis in water.

The reaction of **1** with NaOH in MeOH at room temperature did not afford **3a**, but gave a different compound in 97% yield. The product was identified as the previously reported 3,6-ether **5a**.[2)] This result indicates that, in MeOH, the *O*-benzoyl group is solvolyzed firstly and the resulting hydroxyl anion in **4** attacks the C-6 position of the thionocarbonate group in an *SN*2 manner, giving rise to the ring-opened product **5a**.

Solvolysis of the 3-*O*-Benzoyl-5,6-*O,S*-thiolcarbonate (6) Hydrolysis of the 3-*O*-benzoyl-5,6-*O,S*-thiolcarbonate **6** in water with K_2CO_3 gave an intractable mixture. The reaction with 10% NaOH again gave a mixture, in which the presence of the triol **3a** was suggested by thin-layer chromatography (TLC) and by TLC of the derived acetate, suggesting that an *SN*2 type attack of hydroxide ion on the 6-*S* group had partially occurred.

Reaction of **6** with NaOH in methanol gave a different result, that is, formation of the 3,6-cyclic ether **5a** in >80% yield; this indicates that the 3-*O*-benzoyl group was solvolyzed firstly and the resulting hydroxyl anion intramolecularly attacked the C-6 position of the thiol-carbonate **7**.

Methanolysis of **6** with NaOMe in MeOH gave two products, which were separated, after acetylation, into a crystalline compound (mp 83—85 °C) and an oil. The crystalline acetate contained three acetyl Me groups. The mass spectrum (MS) suggested its structure to be **9b**.[3)] The oil was assigned as the dimer **10b** on the basis of MS, as well as ^{1}H-, and ^{13}C-NMR spectra, being derived from **9a** by air oxidation. Lithium aluminum hydride (LAH) reduction of **6** followed by air oxidation and acetylation

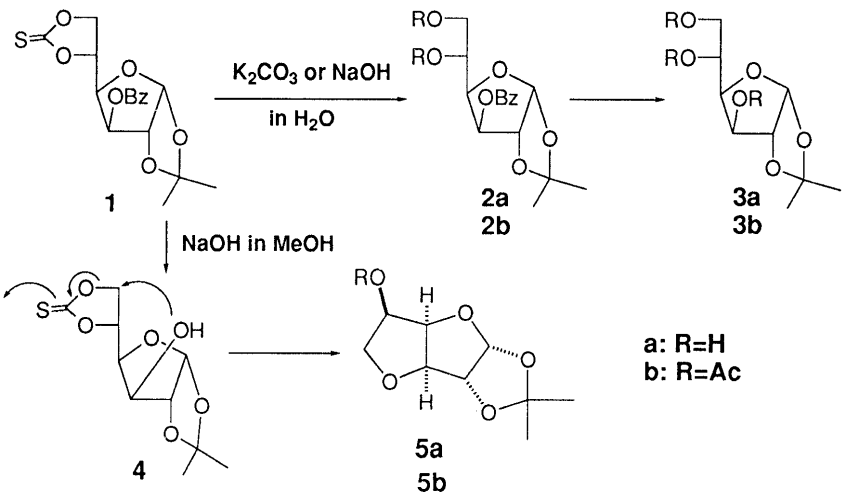

Chart 1

* To whom correspondence should be addressed.

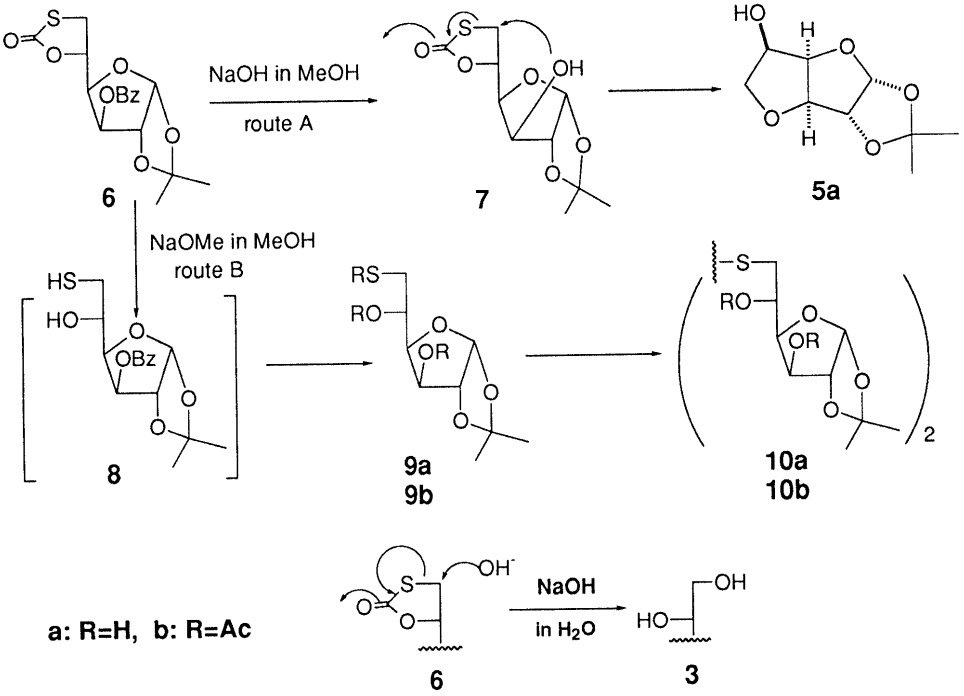

Chart 2

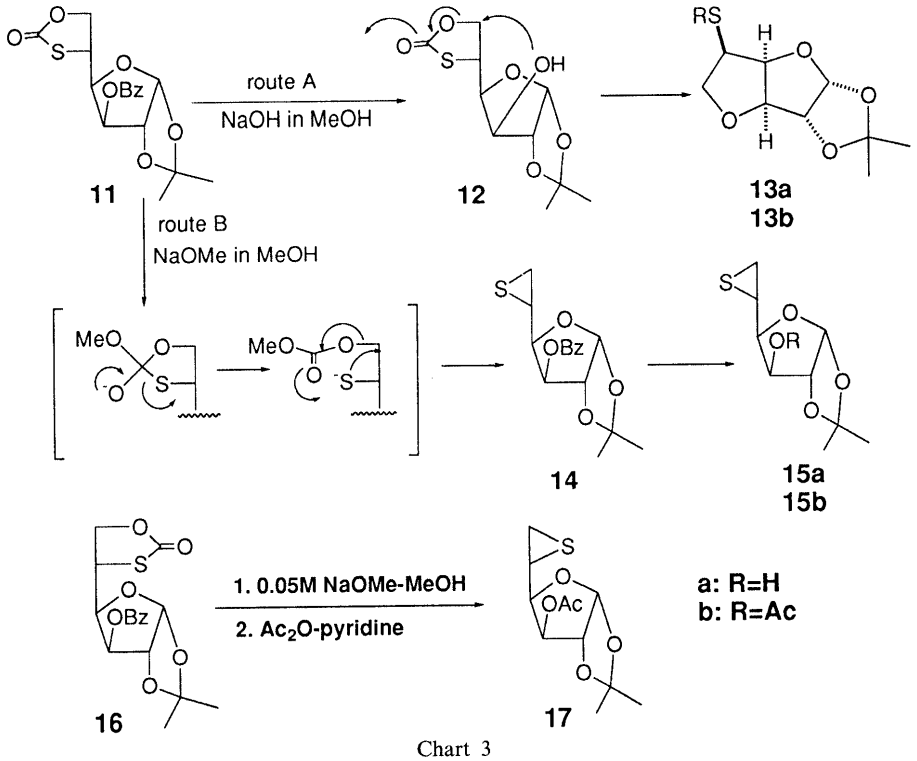

Chart 3

yielded **10b**, confirming this assignment. The thiirane (see below) was not formed in this methanolysis. The above results indicate that the thiolcarbonate group had been solvolyzed, in methanol, to a thiol group faster than the 3-*O*-benzoyl group was.

Solvolysis of the 3-*O*-Benzoyl-5,6-*S*,*O*-thiolcarbonate (11) Treatment of the 5,6-*S*,*O*-thiolcarbonate **11** with 5% NaOH in methanol at room temperature gave, after acetylation, an oily product. The molecular ion of this compound appeared at *m*/*z* 260 suggesting its formula to be $C_{11}H_{16}O_5S$. The ^{1}H-NMR spectrum exhibited only one Ac peak together with a characteristic multiplet at δ 3.99 (1H) attributable to >C<u>H</u>–SAc. The other peaks were very similar to those of **5b**, thus leading to the 3,6-ether structure **13b**. The ^{13}C-NMR spectrum exhibited a peak at δ 44.8, which was observed in the corresponding *O*-acetate **5b** at δ 69.1, supporting the assigned structure. The above results again indicate that the 3-*O*-benzoyl group was solvolyzed firstly and the resulting hydroxyl anion attacked the C-6 position of 5-*S*-thiolcarbonate.

Methanolysis of **11** with NaOMe in MeOH gave an entirely different result. When **11** was treated with 0.05 M

Table 1. ^{13}C-NMR Data for Compounds in This Paper (in $CDCl_3$)[a]

Compd.	C-1	C-2	C-3	C-4	C-5	C-6
2a[b]	106.0	86.2	75.1	81.1	68.2	67.7
9b	105.0	83.3	74.7	78.7	67.5	30.4
10a[c]	105.0	85.2	75.4	81.1	68.7	43.2
10b	105.0	83.4	74.7	78.7	67.7	41.3
15a	105.5	86.0	76.4	84.9	29.6	25.1
15b	105.4	84.8	77.3	83.2	28.8	24.6
14	105.5	85.1	77.9	83.3	29.0	24.6
17	104.6	84.0	83.7	83.6	30.5	30.5
13b	106.7	84.9	86.2	83.6	44.8	71.0

a) The data for isopropylidene and other protecting groups are omitted. *b*) In acetone-d_6. *c*) In CD_3OD.

NaOMe in MeOH at room temperature, it rapidly changed into a compound (**14**) which was highly mobile on TLC and was then transformed into a less mobile compound (**15a**). The latter compound was isolated as colorless needles of mp 151—153 °C in 97% yield. It formed a mono-acetate **15b** on acetylation. In the ^{1}H-NMR spectrum, **15a** showed two doublets at δ 2.45 and 2.67, each corresponding to 1H. The mass spectrum (MS) and elementary analysis of **15a** afforded the formula $C_9H_{14}O_4S$. These data lead to the thiirane structure for **15a**.[4,5] Benzoylation of **15a** gave the benzoate, which was identical with the above intermediary compound **14**, thus indicating that the above methanolysis proceeded through route B illustrated in Chart 3; the cyclic 5-*S*-thiolcarbonate is therefore more vulnerable than the *O*-benzoyl group to methanolysis with NaOMe.

The 5-*S*-thiolcarbonate of *ido*-configuration **16** similarly gave the corresponding thiirane **17**[4] in high yield.

The above findings provide a facile route to the thiirane **15a**, a key intermediate to 5-thioglucose, from a mixture of **6** and **11**, which was prepared by a radical-promoted *O*-*S* rearrangement of **1**.[2] Although **6** and **11** were hardly separable by usual column chromatography and could be separated by recycling HPLC, the methanolysis products from that mixture, **9a** (or **10a**) and **15a**, in contrast, were easily separated by column chromatography. Thus, a short-step synthesis of 5-thioglucose from 1,2-*O*-isopropylidene-glucofuranose became possible.

Experimental

Melting points were determined on a Yanaco micro hot stage melting point apparatus and are uncorrected. IR spectra were taken as KBr disks on a Jasco IR-G spectrometer and data are given in cm^{-1}. ^{1}H-NMR spectra were taken with a JEOL GX 500 (500 MHz) spectrometer in $CDCl_3$ solutions with tetramethylsilane as an internal standard and the chemical shifts are given in δ values. MS and high-resolution MS (HRMS) were taken with a Hitachi M-80 machine and M^+ and/or $M^+ - Me$ are indicated as *m/z*. Column chromatography was carried out with silica gel (Wacogel C-200). For TLC, Merck precoated plates GF_{254} were used and spots were monitored under UV light (254 nm), then developed by spraying 10% H_2SO_4 and heating the plate at 100 °C until coloration took place. All organic extracts were washed with brine and dried over anhydrous sodium sulfate before concentration. Identities were confirmed by mixed melting point determination (for crystalline compounds) and also by comparisons of TLC behavior and ^{1}H-NMR spectra.

Hydrolysis of the 3-*O*-Benzoyl-5,6-*O*-thionocarbonate (1) 1) The benzoate **1** (110 mg, 0.3 mmol) in 10% NaOH–H_2O (4 ml) was heated at 80 °C for 1 h with stirring. The mixture was neutralized with Ambelite IR-120-H^+ and concentrated to dryness. Chromatography of the residue in EtOAc gave **3a**, which was characterized as the triacetate **3b** (88 mg, 83% yield), colorless needles, mp 74—76 °C.

2) The benzoate **1** (110 mg) was treated with 5% K_2CO_3 (4 ml) at 50 °C for 0.5 h and worked up as above to give **2a** (14 mg, 14.4%) and **3a** (18.4 mg, 27.9%).

2a: Colorless needles from hexane–EtOAc, mp 194—196 °C. IR: 1719. ^{1}H-NMR (acetone-d_6): 8.09—7.49 (5H, m, Ph-H), 5.89 (1H, d, J=3.4 Hz, H-1), 4.60 (1H, dd, J=11.2, 2.0 Hz, H-6), 4.52 (1H, d, J=3.4 Hz, H-2), 4.35 (1H, dd, J=11.2, 6.4 Hz, H-6), 4.31 (1H, d, J=2.9 Hz, H-3), 4.29 (1H, m, H-5), 4.18 (1H, dd, J=8.3, 2.9 Hz, H-4), 1.42, 1.27 (each 3H, s, Me). MS: 309 ($M^+ - Me$, 17). *Anal.* Calcd for $C_{16}H_{20}O_7 \cdot H_2O$: C, 56.13; H, 6.48. Found: C, 56.43; H, 6.23.

Acetylation of **2a** with Ac_2O–pyridine gave the diacetate **2b** as an oil (79%). IR: 1747, 1725. ^{1}H-NMR: 8.03—7.41 (5H, m, Ph-H), 5.95 (1H, d, J=3.4 Hz, H-1), 5.39 (1H, d, J=3.1 Hz, H-3), 5.37 (1H, m, H-5), 4.80 (1H, d, J=12.8, 2.4 Hz, H-6), 4.53 (1H, dd, J=8.5, 3.1 Hz, H-4), 4.51 (1H, d, J=3.4 Hz, H-2), 4.40 (1H, dd, J=12.8, 5.9 Hz, H-6), 2.08, 2.01 (each 3H, s, OAc), 1.53, 1.32 (each 3H, s, Me). MS: 393 ($M^+ - Me$, 38).

Reaction of 1 with NaOH in MeOH The benzoate **1** (110 mg) in 5% NaOH–MeOH (4 ml) was stirred at room temperature for 1 h. The mixture was quenched with NH_4Cl, then concentrated to dryness, and the residue was subjected to chromatography with EtOAc to give **5a** (59 mg, 97%), which was identical with the specimen reported in a previous paper.[2]

Hydrolysis of the 3-*O*-Benzoyl-5,6-*O*,*S*-thiolcarbonate (6) 1) The thiolcarbonate **6** (110 mg, 0.3 mmol) in 2.5% K_2CO_3 in H_2O–dioxane (1 : 1, 4 ml) was stirred at 80 °C for 1 h, and worked up as in **1** to give an oil. Although the product showed a single spot on TLC, its ^{1}H-NMR spectrum indicated that it is a mixture of several compounds, whose chromatographic separation was unsuccessful.

2) The thiolcarbonate **6** (110 mg) in 10% NaOH was stirred at 80 °C for 1 h, and worked up as above to give an oily mixture, which showed several spots on TLC. Chromatographic separation was unsuccessful. One of these spots was identical with that of **3a**. Acetylation of this mixture gave acetates. One of the spots was identical with that of **3b**.

Reaction of 6 with NaOH in MeOH The benzoate **6** (110 mg) in 5% NaOH–MeOH (4 ml) was stirred at room temperature for 1 h. The mixture was neutralized with Ambelite IR-120-H^+ and concentrated to dryness. Chromatography of the residue in EtOAc gave **5a** (58 mg, 96%), which was identical with the compound reported previously.[2]

Methanolysis of 6 with NaOMe The thiolcarbonate **6** (73 mg) in 0.05 M NaOMe–MeOH (4 ml) was stirred for 1 h at room temperature. The reaction was quenched with NH_4Cl, then the mixture was concentrated, and the residue was acetylated as usual (Ac_2O–pyridine, overnight). Chromatography of the resulting acetate with hexane–EtOAc (1 : 1) gave **9b** (22 mg, 30.4%) and **10b** (4 mg, 6.3%).

9b: Colorless needles from MeOH, mp 83—85 °C (lit. 89—90 °C).[3] IR: 1746 (OAc), 1696 (SAc). ^{1}H-NMR: 5.91 (1H, d, J=3.4 Hz, H-1), 5.31 (1H, d, J=2.9 Hz, H-3), 5.20 (1H, m, H-5), 4.46 (1H, d, J=3.4 Hz, H-2), 4.33 (1H, dd, J=8.8, 2.9 Hz, H-4), 3.58 (1H, dd, J=14.7, 3.4 Hz, H-6), 3.04 (1H, dd, J=14.7, 6.6 Hz, H-6), 2.23, 2.05 (each 3H, s, Ac), 1.52, 1.31 (each 3H, s, Me). MS: 362 (M^+, 1).

10b: Colorless oil. IR: 1746. ^{1}H-NMR: 5.90 (1H × 2, d, J=3.9 Hz, H-1), 5.34 (1H × 2, d, J=2.9 Hz, H-3), 5.30 (1H × 2, m, H-5), 4.47 (1H × 2, d, J=3.9 Hz, H-2), 4.40 (1H × 2, dd, J=9.3, 2.9 Hz, H-4), 3.26 (1H × 2, dd, J=14.7, 2.9 Hz, H-6), 2.93 (1H × 2, dd, J=14.7, 6.9 Hz, H-6), 2.06, 2.02 (each 3H × 2, s, Ac), 1.52, 1.30 (each 3H × 2, s, Me). MS: 638 (M^+, 0.6).

LAH Reduction of 6 A mixture of **6** (110 mg, 0.3 mmol) and $LiAlH_4$ (23 mg, 0.6 mmol) in tetrahydrofuran (10 ml) was stirred for 2 h at room temperature. The reaction was quenched with water, the mixture was filtered and the residue was extracted with MeOH. The combined filtrate and extract was concentrated to dryness. Chromatography of the residue gave **10a** (41 mg, 29%) as a gum from the $CHCl_3$–MeOH (10 : 1) eluate. IR: 3430. ^{1}H-NMR (CD_3OD): 5.86 (1H × 2, d, J=4.0 Hz, H-1), 4.47 (1H × 2, d, J=4.0 Hz, H-2), 4.20 (1H × 2, d, J=3.0 Hz, H-3), 4.13 (1H × 2, m, H-5), 3.97 (1H × 2, dd, J=9.0, 3.0 Hz, H-4), 3.19 (1H × 2, dd, J=14.0, 3.0 Hz, H-6), 2.82 (1H × 2, dd, J=14.0, 9.0 Hz, H-6), 1.45, 1.29 (each 3H × 2, s, Me). MS: 470 (M^+, 17).

Acetylation of **10a** (5 mg) gave **10b** (6 mg, 94%), which was identical with the compound obtained above.

Reaction of 3-*O*-Benzoyl-5,6-*S*,*O*-*gluco*-thiolcarbonate (11) with NaOH in MeOH Compound **11** (37 mg, 0.1 mmol) in 5% NaOH–MeOH (3 ml) was stirred for 1 h at room temperature. After addition of NH_4Cl, the solvent was evaporated and the residue was acetylated in a usual manner.

Chromatography of the product gave the 3,6-ether **13b** (13 mg, 50%) as an oil. IR: 1694 (SAc). ^{1}H-NMR: 5.88 (1H, d, J=3.4 Hz, H-1), 4.89 (1H, t, J=3.4 Hz, H-4), 4.61 (1H, d, J=3.4 Hz, H-2), 4.57 (1H, d, J=3.4 Hz, H-3), 4.17, 3.57 (each 1H, dd, J=10.7, 8.3 Hz, H-6), 3.99 (1H, m, H-5), 2.35 (3H, s, SAc), 1.48, 1.32 (each 3H, s, Me). MS: 260 (M^+, 16).

Methanolysis of 11 with NaOMe 1) Compound **11** (50 mg, 0.14 mmol) in 0.05 M NaOMe–MeOH (3 ml) was stirred for 10 min at room temperature. The reaction was quenched by NH_4Cl, and the mixture was concentrated. The residue was extracted with EtOAc and the extract was washed with brine and concentrated. Chromatography of the residue gave the thiirane **15a** (29 mg, 97.4%) from the hexane–EtOAc (1 : 1) eluate as colorless needles, mp 153—154 °C (lit. 140—141 °C).[5] IR: 3400. ^{1}H-NMR: 5.98 (1H, d, J=3.9 Hz, H-1), 4.54 (1H, d, J=3.9 Hz, H-2), 4.23 (1H, br s, H-3), 3.62 (1H, dd, J=8.8, 2.9 Hz, H-4), 3.12 (1H, m, H-5), 2.67, 2.45 (each 1H, d, J=5.4 Hz, H-6), 2.09 (1H, br d, J=4.9 Hz, OH), 1.46, 1.31 (each 3H, s, Me). MS: 218 (M^+, 6). *Anal.* Calcd for $C_9H_{14}O_4S$: C, 49.54; H, 6.47. Found: C, 49.34; H, 6.38.

Acetylation of **15a** with Ac_2O–pyridine as usual gave the acetate **15b** as an oil. IR: 1744 (OAc). ^{1}H-NMR: 5.94 (1H, d, J=3.4 Hz, H-1), 5.25 (1H, d, J=2.9 Hz, H-3), 4.54 (1H, d, J=3.4 Hz, H-2), 3.69 (1H, dd, J=8.8, 2.9 Hz, H-4), 3.00 (1H, m, H-5), 2.60, 2.40 (each 1H, d, J=7.3 Hz, H-6), 2.14 (3H, s, OAc), 1.48, 1.30 (each 3H, s, Me). MS: 260 (M^+, 46).

Benzoylation of **15a** gave the benzoate **14** as an oil (lit. syrup).[5] ^{1}H-NMR: 7.40—8.08 (5H, m, Ph-H), 6.02 (1H, d, J=3.7 Hz, H-1), 5.51 (1H, d, J=2.8 Hz, H-3), 4.68 (1H, d, J=3.7 Hz, H-2), 3.84 (1H, dd, J=9.8, 2.8 Hz, H-4), 3.10 (1H, m, H-5), 2.61 (1H, d, J=6.0 Hz, H-6), 2.43 (1H, d, J=4.0 Hz, H-6), 1.52, 1.32 (each 3H, s, Me).

2) Compound **11** (7 mg, 0.02 mmol) was treated with 0.05 M NaOMe–MeOH (1 ml) for 2 min and worked up as described above to give a mixture. The TLC, ^{1}H-NMR, and ^{1}H–^{1}H correlation spectroscopy (COSY) revealed that this mixture consists of **14** and **15a**.

Methanolysis of 3-*O*-Benzoyl-5,6-*S*,*O*-*ido*-thiolcarbonate (16) with NaOMe Compound **16** (36 mg, 0.1 mmol) was treated with 0.05 M NaOMe–MeOH (1 ml) and the mixture was worked up as described above. The product was acetylated and purified as usual to give the *ido*-thiirane–acetate **17** (19 mg, 73%) as colorless needles, mp 73—75 °C (lit. 77—78 °C).[4] IR: 1742 (OAc). ^{1}H-NMR: 5.96 (1H, d, J=3.9 Hz, H-1), 5.25 (1H, d, J=3.4 Hz, H-3), 4.57 (1H, d, J=3.9 Hz, H-2), 3.83 (1H, dd, J=7.8, 3.4 Hz, H-4), 2.92 (1H, m, H-5), 2.42 (1H, dd, J=6.4, 1.5 Hz, H-6), 2.25 (1H, dd, J=5.4, 1.5 Hz, H-6), 2.13 (3H, s, OAc), 1.48, 1.31 (each 3H, s, Me). MS: 260 (M^+, 7).

Thiirane (15a) from a Mixture of 6 and 11 A mixture of **6** and **11** (1 : 2, 61 mg) was treated with 0.05 M NaOMe–MeOH (2 ml) for 10 min at room temperature and worked up as described above. Chromatography of the product gave the thiirane **15a** (14 mg). This result means that **11** was converted to **15a** in 71% yield.

References and Notes

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