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A New Approach to the Protection of 1,2-Diols

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The 1,2-dihydroxy function is a frequently occurring structural feature of many biologically active compounds: such a moiety is present in natural compounds like saccharides, polyhydroxy amino acids, and polyketide and shikimic acid derivatives. The 1,2-diols protection still is a critical point in organic synthesis:[1] the principal, often difficult demand for the protective group is its stability under multiple reaction conditions, when functionally manipulating the rest of the molecule, and also the feasibility of an easy removal. Generally, the protection of glycols is performed through the formation of alkylidene cyclic acetals,[2] or, alternatively, cyclic carbonates.[3] The subsequent reactions on the protected molecule and the required conditions for removal of the protective group are to be taken into account. In this sense, the difference between these two types of protective groups is quite substantial and such as to make their use almost complementary.[4] The present paper deals with a new method for the protection of glycols, exploiting in the same reaction strategy the potentialities offered by the two above mentioned protective functionalities. We have considered a reaction sequel where the protective group could be easily, structurally transformed from an acidic to an alkaline stable moiety, or, under a different point of view, could be initially hydrolyzed in basic media, or, after modification, under acidic conditions. This sort of protection, "orthogonal" with respect to the acid and base stability, is offered by the thionocarbonate[5] and methylene acetal[4,6] groups.

In this frame we found 1,2:5,6-di-*O*-isopropylidene-D-mannitol **1a**, carrying two free hydroxy functions at carbons 3 and 4, to be a good candidate for initially testing this strategy. Scheme 1 shows the two-step synthetic pathway, foreseeing the protection of the glycol **1a** as thionocarbonate **2a**,[7a] which, in turn, can be reduced to the methylene derivative **3a**: the two reactions occur in high yields under mild, neutral conditions (Table 1). On the other hand, acid hydrolysis of **2a** generates the mannitol derivative **4a** with the two hydroxy functions at C-3 and C-4 protected as a cyclic thionocarbonate. Similar behavior is observed for 1,4-*O*-isopropylideneerythritol **1b**.

Scheme 1

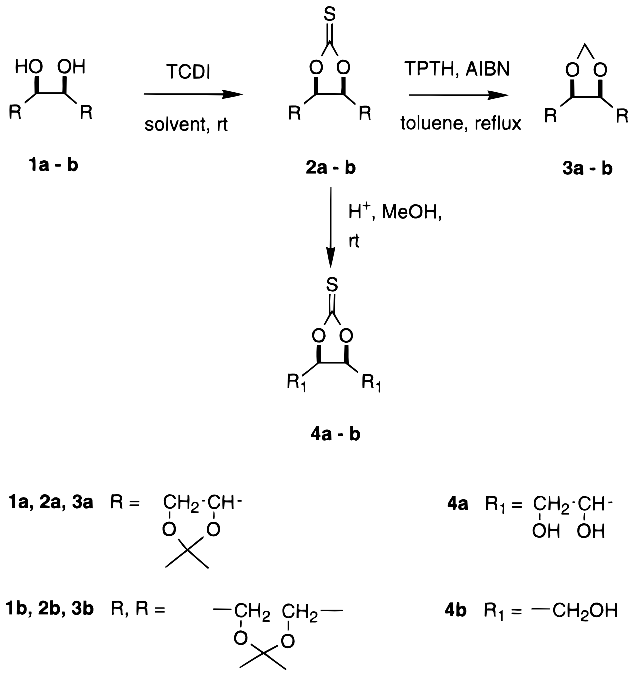

Table 1. Protection of 1,2-Diols as Thionocarbonates and Their Conversion to Methylene Acetals

substrate	product	overall yield,[a] %
1a	**3a**	83
1b	**3b**	82
1a	**4a**	80
1b	**4b**	90
5	**9**[b]	36
5	**6** + **7**	85
10	**12**	51

[a] The reactions were performed on a 1.0 mmol scale; yields are given after purification by crystallization or column chromatography. [b] Thionocarbonate **7** is formed in a 60% yield after column chromatography; conversion from **7** to **9** is accomplished in a 60% yield.

In general, cyclic thionocarbonates **2** are obtained by reacting 1,2-diols **1** with 1,1′-thiocarbonyldiimidazole[7] (TCDI) in organic solvents at room temperature; they possess properties similar to carbonates, *i.e.* they are stable in an acid medium while they are converted to the starting diols by basic hydrolysis (more easily than the corresponding carbonates).[5]

We have also evaluated the stability of the thionocarbonate moiety under the most commonly used cleavage conditions for the acetonide protective group.[2] Results referred to products **2a** and **2b** are reported in Table 2.

Reduction of **2** leads to the formation of the methylene acetal **3**, which is highly stable in an alkaline medium while it is labile by acid treatment.[2] We have performed this kind of conversion by radical reduction with triphenyltin hydride[8] (TPTH) in the presence of AIBN, in organic solvent at the reflux temperature. TPTH is a totally selective reducing agent: it only allows the desulfurization reaction while, on the other hand, the formation of

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[1] Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis, 2nd ed.*; John Wiley & Sons, Inc.: New York, 1991; pp 118−142, and references given therein.

[2] See ref 1, pages 118−135 and references given therein.

[3] See ref 1, pages 140−141, and references given therein. Burk, R. M.; Roof, M. B. *Tetrahedron Lett.* **1993**, *34*, 395−398. Allainmat, M.; Plusquellec, D. *Tetrahedron Lett.* **1991**, *32*, 2751−2754.

[4] See ref 1, pages 422−424, and references given therein.

[5] Hough, L.; Priddle, J. E.; Theobald, R. S. *Adv. Carbohyd. Chem.* **1960**, *15*, 91−158.

[6] See ref 1, pages 119−120, and references given therein.

[7] Lee, K. J.; Boyd, S. A.; Radin, N. S. *Carbohyd. Res.* **1985**, *144*, 148−145. Funaki, K.; Takeda, K.; Yoshii, E. *Tetrahedron Lett.* **1982**, *23*, 3069−3072.

[8] Krosley, K. W.; Gleicher G. J.; Clapp G. E. *J. Org. Chem.* **1992**, *57*, 840−844, and references given therein.

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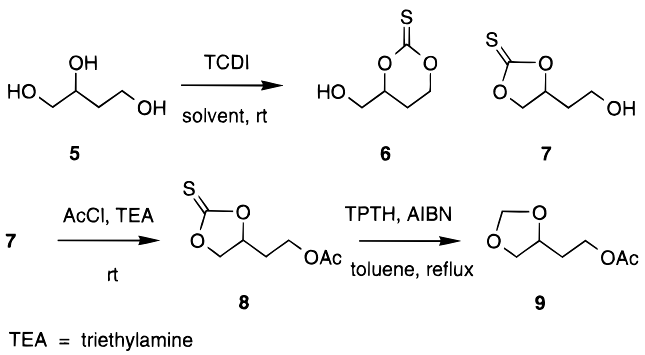
Table 2. Selective Removal of the Acetonide Group in the Presence of a Cyclic Thionocarbonate Function

substrate	product	condition[a]	yield,[b] %
2a	**4a**	1 N HCl, THF/H_2O (1:1), 18 h	100
2b	**4b**	1 N HCl, THF/H_2O (1:1), 30 min	95
2a	**4a**	I_2 cat., MeOH, 24 h	95
2a	**4a**	AcOH, reflux, 24 h	10[c]
2a	**4a**	TsOH cat., MeOH, 3 h	80[c]
2a	**4a**	2 N HCl, 30 min	95[d]
2a	**4a**	A-15(H^+),[e] MeOH, 18 h	100
2b	**4b**	A-15(H^+),[e] MeOH, 30 min	100
2a	**4a**	TFA/$CHCl_3$, 24 h	95

[a] The reactions were performed on a 1.0 mmol scale at room temperature, unless otherwise specified. The reaction conditions used are those cited in ref 1, pages 125 and 246. [b] Yields are calculated on the basis of the ^1H-NMR spectra of the crude reaction mixture. [c] Monoacetonide thionocarbonate derivatives are the only byproducts formed. [d] **4a** was completely hydrolyzed to mannitol in 3 h time. [e] Amberlyst 15 ion-exchange resin.

Scheme 2

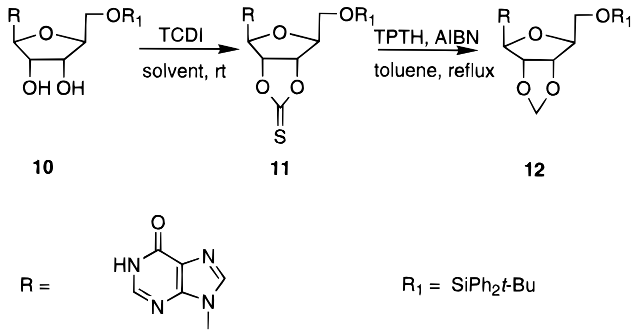


deoxygenation products was not observed. This behavior is quite peculiar for this reagent, since tributyltin hydride[9] is generally used to convert cyclic thionocarbonates into the corresponding alkenes,[10] under the same reaction conditions we used in our TPTH reduction.

In the effort to evaluate the range of applicability of our method, we examined also some other polyol derivatives. Ring closure on 1,2-diols is preferred to the alternative 1,3-diol functionality. In fact, when 1,2,4-butanetriol **5** was treated with TCDI (Scheme 2, see also Table 1), the five-membered cyclic thionocarbonate **7** was the major isolated product (60% yield), while the six-membered cyclic thionocarbonate **6** was formed only in 25% yield. **7** was then converted into the methylene acetal **9** by acetylation of the remaining hydroxyl group to give **8** and reduction with TPTH.

A further example is the following: (−)-inosine **10**, protected at the hydroxy function at 5′ as *tert*-butyldiphenylsilyl derivative, was treated with TCDI (see Scheme 3 and Table 1); the 2′ and 3′ hydroxy groups were thus selectively protected by the cyclization reaction, the five-membered cyclic thionocarbonate **11** being the only isolated compound (65% yield). **11** was in turn converted to the methylene derivative **12** by TPTH reduction. All attempts to form the thionocarbonate derivative starting from unprotected inosine failed, leading only to decomposition products.

Scheme 3



An additional point of interest of the described procedure is represented by the possibility of discriminating cyclic *cis*- from *trans*-1,2-diols, due to the fact that thionocarbonate formation occurs exclusively with *cis*-diols. For instance, the same protection we realized on the erythritol derivative **1b** failed when applied on 1,4-*O*-isopropylidenethreitol, where the two remaining hydroxy groups are in a *trans* geometry. It follows that a pure *cis* methylene derivative can be obtained by reduction of the thionocarbonate moiety. The *cis*-diol selectively is in contrast with preparation of methylene acetals by treatment with formaldehyde and acid which protects both *cis*- and *trans*-diol.[2]

Finally, the protecting procedure for 1,2-diols we have described in this paper can be, in principle, widely extended to many substrates. It allows an easy access to the corresponding thionocarbonate-type derivatives and, in sequence, to the methylene-type derivatives, following an easy and highly efficient reaction strategy.

Experimental Section

Analytical. Melting points were determined by the capillary method on an electrothermal Büchi apparatus and are uncorrected. ^1H-NMR spectra were taken at 300 MHz; chemical shifts were expressed in δ values downfield from TMS. ^{13}C-NMR spectra were taken at 75 MHz; chemical shifts were expressed in ppm values downfield from TMS. IR spectra were recorded on FT-IR instrument as 2% KBr pellets: all thionocarbonates derivatives give the expected assorbances at 1820, 1800, 1710 cm^{-1} typical of the thiono carbonate function. Elemental analyses (C, H, N) were performed by using elemental analyzer, while S element was determined by automatic titration. Mass analyses were performed by using the fast atom bombardment technique, with glycerol as the matrix.

Materials. Triphenyltin hydride (TPTH) and anhydrous solvents were purchased from Aldrich. **1a, 5**, and the other commercial reagents were purchased from Fluka. Thin layer chromatography was performed on 0.25 mm silica gel 60 F254 plates. Flash chromatography was performed using silica gel 60 (40−63 mesh).

Synthesis of the Cyclic Thionocarbonates. General Procedure. To a solution of diol (1 mmol) in anhyd solvent (10% solution) was added TCDI (2 mmol) under stirring and at 0 °C. After stirring for 2−3 days at rt, most of the solvent was removed under vacuum. The yellow-orange residue was poured onto ethyl acetate (50 mL) and washed with 1 N HCl (10 mL) and then water and brine. The organic layer was dried over $MgSO_4$ and filtered and the solvent evaporated under reduced pressure. All crude products have been purified by gravity or flash column chromatography.

1,2:5,6-Di-*O*-isopropilydene-D-mannitol 3,4-Thionocarbonate (2a) (known compound).[11] THF was used as solvent. The crude product was purified by crystallization from ethyl ether (80% yield) or column chromatography (98% yield), obtaining **2a** as a white solid (mp = 162−163 °C)(literature reference, mp = 160−162 °C). $[\alpha]_D = -14$ ($c = 1$ in CH_2Cl_2). TLC (CH_2Cl_2) $R_f = 0.4$. MS (FAB) m/z 305 $(M + H)^+$. ^1H-NMR ($CDCl_3$)

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δ 4.66−4.60 (m, 2H), 4.26−4.16 (m, 2H), 4.14 −4.06 (dd, 2H, J,J' = 6.1,4.5 Hz), 3.98−3.94 (dd, 2H, J,J' = 6.1, 2.4 Hz), 1.40 (s, 6H), 1,28 (s, 6H). ^{13}C-NMR ($CDCl_3$) ppm 119.6, 91.4, 82.4, 74.2, 35.1, 33.0. Anal. Calcd for $C_{13}H_{20}O_6S$: C, 51.30; H, 6.62; S, 10.53. Found: C, 51.25; H, 6.60; S, 10.32.

1,4-*O*-Isopropylidene-*meso*-erythritol 2,3-Thionocarbonate (2b). CH_3CN was used as solvent. The pure product was obtained as a white solid (90% yield) (mp = 158−160 °C). TLC (ethyl ether/*n*-hexane 8:2) $R_f = 0.44$. MS (FAB) m/z 205 (M + H)$^+$. ^{1}H-NMR ($CDCl_3$) δ 4.58−4.56 (m, 2H), 4.07−3.96 (m, 2H), 3.93−3.85 (m, 2H), 1.48 (s, 6H). ^{13}C-NMR ($CDCl_3$) ppm 103.2, 81.0, 57.8, 24.4, 23.2. Anal. Calcd for $C_8H_{12}O_4S$: C, 47.04; H, 5.92; S, 15.69. Found: C, 46.81; H, 5.94; S, 15.61.

(*R*,*S*)-1,3,4-Butanetriol 1,3-Thionocarbonate(6) and (*R*,*S*)-1,3,4-Butanetriol 3,4-Thionocarbonate (7). THF was used as solvent. **6** and **7** were obtained as oils, after separation by flash chromatography of the crude mixture (**6**, 25%; **7**, 60%). **6**: TLC (ethyl acetate/*n*-hexane 1:1) $R_f = 0.25$. MS (FAB) m/z 149 (M + H)$^+$. ^{1}H-NMR ($CDCl_3$) δ 5.10−5.00 (m, 1H), 4.80−4.66 (dd, 1H), 4.66−4.45 (m, 2H), 4.40−4.25 (dd, 1H), 2.36−2.10 (m, 2H), 1.78−1.60 (br, 1H). ^{13}C-NMR ($CDCl_3$) ppm 194.8, 78.7, 72.6, 67.8, 31.7. Anal. Calcd for $C_5H_8O_3S$: C, 40.52; H, 5.44; S, 21.63. Found: C, 40.15; H, 5.65; S, 21.20. **7**: TLC (ethyl acetate/*n*-hexane 1:1) $R_f = 0.10$. MS (FAB) m/z 149.1 (M + H)$^+$. ^{1}H-NMR ($CDCl_3$) δ 5.20−5.00 (m, 1H, J =7 Hz), 4.84−4.60 (t, 1H, J = 8.5 Hz), 4.40−4.20 (t, 1H, J = 8.5 Hz), 3.90−3.70 (m, 2H), 2.20−1.80 (m, 2H), 1.80−1.40 (br, 1H). ^{13}C-NMR ($CDCl_3$) ppm 191.6, 80.0, 73.2, 58.0, 35.0. Anal. Calcd for $C_5H_8O_3S$: C, 40.52; H, 5.44; S, 21.63. Found: C, 40.21; H, 5.40; S, 21.30.

(*R*,*S*)-1,3,4-*O*-Acetyl-butanetriol 3,4-Thionocarbonate (8). To a solution of **7** (1 mmol) and triethylamine (1.1 mmol) was added AcCl (1.1 mmol) dropwise at 0 °C. The reaction mixture was stirred for 30 min. The organic solution was washed with water and dried over $MgSO_4$. After removing the solvent under vacuum, **8** was isolated as an oil in 94% yield.TLC (ethyl acetate/*n*-hexane 1:1) $R_f = 0.40$. MS (FAB) m/z 191 (M + H)$^+$. ^{1}H-NMR ($CDCl_3$) δ 5.02−4.92 (m, 1H), 4.74−4.66 (t, 1H, J = 4.3 Hz), 4.32−4.20 (m, 2H), 4.18−4.06 (m, 1H), 2.20−2.00 (m, 2H), 2.06 (s, 3H). ^{13}C-NMR ($CDCl_3$) ppm 191.6, 170.8, 80.0, 73.2, 60.0, 32.4, 21.0. Anal. Calcd for $C_7H_{10}O_4S$: C, 44.20; H, 5.30; S, 16.85. Found: C, 43.65; H, 5.19; S, 16.60.

5′-*O*-(*tert*-Butyldiphenylsilyl)inosine 2′3′-Thionocarbonate (11). DMF was used as solvent. Crude product was triturated with ethyl ether and filtered to give **11** as a white solid (85% yield) (mp = 225−227 °C). $[\alpha]_D = -20$ (c = 1 in $CHCl_3$). TLC (CH_2Cl_2/MeOH 1:1) $R_f = 0.35$. MS (FAB) m/z 549 (M + H)$^+$. ^{1}H-NMR (DMSO-d_6) δ 8.22 (s, 1H), 7.90 (s, 1H), 7.58−7.28 (m, 10H), 6.61−6.58 (d, 1H, J = 2.3 Hz), 6.30−6.24 (dd, 1H, J,J' = 7.8, 1.8 Hz), 5.84−5.81 (dd, 1H, J,J' = 7.8, 2.8 Hz), 4.66−4.60 (m, 1H), 3.86−3.78 (dd, 1H, J,J' = 11, 5.5 Hz), 3.76−3.70 (dd, 1H, J,J' = 11, 6.3 Hz), 0.96 (s, 9H). ^{13}C-NMR (DMSO-d_6) ppm 190.3, 156.5, 147.4, 146.2, 139.6, 135.1, 135.1, 132.5, 132.4, 130.1, 130.1, 128.0, 127.9, 88.4, 88.3, 88.2, 86.1, 63.1, 26.7, 18.9. Anal. Calcd for $C_{27}H_{28}N_4O_5SiS$: C,59.10; H, 5.14; N, 10.21; S, 5.84. Found: C, 58.51; H, 5.20; N, 10.10; S, 5.78.

Desulfuration. General Procedure. Cyclic thionocarbonate (1 mmol), TPTH (2 mmol), and AIBN (10 mg) were dissolved in anhyd toluene (25 mL). The reaction mixture was stirred at the reflux temperature until it was completed (2−4 h)(TLC analysis). The solvent was removed under vacuum and the residue dissolved in CH_3CN. The solution was then washed with small portions of *n*-hexane and the solvent evacuated under vacuum. The remaining oil was purified by column chromatography.

1,2:5,6-Di-*O*-isopropilydene-D-mannitol 3,4-Methylene Acetal (3a). **3a** was obtained as a white solid (mp = 39−42 °C) in 85% yield. $[\alpha]_D = +18.7$ (c = 0.5 in $CHCl_3$). TLC (*n*-hexane/ethyl ether 7:3) $R_f = 0.62$. MS (FAB) m/z 275.1 (M + H)$^+$. ^{1}H-NMR ($CDCl_3$) δ 5.00 (s, 2H), 4.18−3.90 (m, 4H), 3.90−3.82 (m, 4H), 1.42 (s, 6H), 1.32 (s, 6H). ^{13}C-NMR ($CDCl_3$) ppm 109.6, 95.5, 78.1, 75.5, 66.3, 26.6, 25.2. Anal. Calcd for $C_{13}H_{22}O_6$: C, 56.92; H, 8.08. Found: C, 56.45; H, 7.80.

1,4-*O*-Isopropylidene-*meso*-erythritol 2,3-Methylene Acetal (3b). The product was obtained as a white solid (91% yield) (mp = 42−44 °C). TLC (*n*-hexane/ethyl ether 7:3) R_f = 0.3. ^{1}H-NMR ($CDCl_3$) δ 5.20 (s, 1H), 4.86 (s, 1H), 4.01−3.94 (m, 2H), 3.90−3.80 (m, 2H), 3.78−3.68 (m, 2H), 1.34 (s, 6H). ^{13}C-NMR ($CDCl_3$) ppm 102.0, 76.0, 58.9, 24.8, 23.5. Anal. Calcd for $C_8H_{14}O_4$: C, 55.15; H, 8.10. Found: C, 54.75; H, 7.81.

(*R*,*S*)-1-Acetyl-3,4-methylidenebutanetriol (9). **9** was an oil (50% yield). TLC (*n*-hexane/ethyl ether 6:4) $R_f = 0.35$. ^{1}H-NMR ($CDCl_3$) δ 4.96 (s, 1H), 4.80 (s, 1H), 4.22−3.98 (m, 2H),3.98−3.88 (t, 1H, J = 3.7 Hz), 3.50−3.40 (t, 1H, J = 3.7 Hz), 2.00 (s, 3H), 1.98−1.74 (m, 2H). ^{13}C-NMR ($CDCl_3$) ppm 171.3, 96.6, 73.3, 69.3, 61.3, 31.3, 20.1. Anal. Calcd for $C_7H_{12}O_4$: C, 52.49; H, 7.55. Found: C, 52.30; H, 7.45.

5′-*O*-(*tert*-butyldiphenylsilyl)inosine 2′3′-Methylene Acetal (12). **12** was isolated as a white solid in 60% yield (mp = 190 °C, dec). $[\alpha]_D = -3.5$ (c = 0.5 in $CHCl_3$). TLC (CH_2Cl_2/MeOH 1:1) $R_f = 0.30$. ^{1}H-NMR ($CDCl_3$) δ 8.00 (s, 1H), 7.94 (s, 1H), 7.63−7.26 (m, 10H), 6.08 (d, 1H, J = 2.3 Hz), 5.22 (s, 1H), 5.15 (s, 1H), 5.20−5.14 (dd, 1H, J,J' = 3.2, 1.2 Hz), 5.00−4.94 (dd, 1H, J,J' = 3.2, 1.6 Hz), 4.38−4.32 (m, 1H), 3.92−3.76 (m, 2H), 1.00 (s, 9H).^{13}C-NMR ($CDCl_3$) ppm 148.2, 144.8, 138.9, 135.5, 135.5, 132.7, 132.6, 129.9, 129.9, 127.8, 127.7, 125.4, 96.4, 90.2, 85.4, 84.0, 81.1, 63.8, 26.8, 19.2. Anal. Calcd for $C_{27}H_{30}N_4O_5Si$: C, 62.52; H, 5.83; N, 10.80. Found: C, 62.05; H, 5.78; N, 10.79.

Supporting Information Available: Spectra (^{1}H-NMR and ^{13}C-NMR) for compounds **2a**, **2b**, **3a**, **3b**, **6**, **7**, **8**, **9**, **11**, and **12** and FAB-mass spectra for **2a**, **2b**, **3a**, **6**, **7**, **8**, and **11** (47 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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