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Preparation of isopropylidene acetals from butane-1,2,4-triol and its cyclopropane congeners

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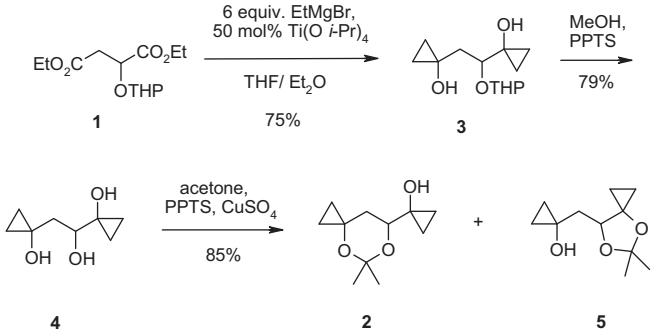
ABSTRACT

Features of isopropylidene acetal synthesis from butane-1,2,4-triol and its cyclopropane congeners were studied. Procedures for the preparation and purification of the respective acetonides have been developed.

Building blocks prepared by transformation of functional groups in malic acid are of interest for organic synthesis because of the commercial availability of both enantiomers and relatively low cost of (*S*)-malic acid.[1] A cyclopropanol approach, involving cyclopropanation of the ester moiety and subsequent ring cleavage, has been widely used in our research group for the synthesis of naturally occurring and biologically active compounds.[2] Recently, we used the cyclopropanation of THP-protected diethyl malate (**1**) to prepare several useful building blocks.[3a] One of the latter, namely, the (*S*)-form of acetonide **2** (Scheme 1), was applied in the synthesis of the C13–C21 fragment of epothilones.[3b] The enantiomeric purity of the product, determined using Mosher's method,[4] was more than 99%. The key step of this synthesis was differentiation between the two cyclopropanol moieties of biscyclopropanol **3** by removal of the THP-group followed by transformation of triol **4** into isopropylidene acetal **2** (Scheme 1).[3] It is worth noting that, in contrast to the analogous acetalization of butane-1,2,4-triol (easily available from malic acid) leading to the corresponding five-membered acetonide,[5] acetalization of triol **4** gave a mixture of products **2** and **5** in the ratio 11:1 in favour of the six-membered acetonide **2**, in a total yield of 85%.[3,6]

Later, this reaction series was used in this laboratory for the synthesis of (+)-disparlure[7] and the C17–C21 fragment of laulimalide.[8] In the course of this study we reproduced the acetonide **2** synthesis many times and, in some cases, the content of undesired acetal **5** was as high as 15%. In view of this fact, and in connection with the demonstrated synthetic potential of building block **2**,[3b,7,8] and the anticipated necessity for the synthesis of similar derivatives (see below), we have attempted to improve the yield and regioselectivity of the formation of acetonide **2**. These investigations were performed using racemic triol **4**.[3a]

Investigation of the influence of the reaction time on the ratio of isomeric acetonides **2** and **5** (determined by ^{1}H NMR[6]) showed that immediately after complete or almost complete consumption of triol **4** (as monitored by TLC) the ratio of **2** and **5** was equal to 11:1. However, if the reaction mixture was stirred for an additional 72 h, the ratio of isomers decreased to 3:1 in favour of the six-membered isopropylidene acetal **2** and did not change further. Thus, the ratio 3:1 corresponds to the thermodynamic equilibrium state.



Scheme 1.

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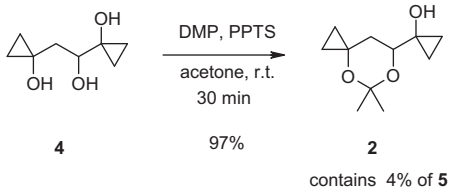
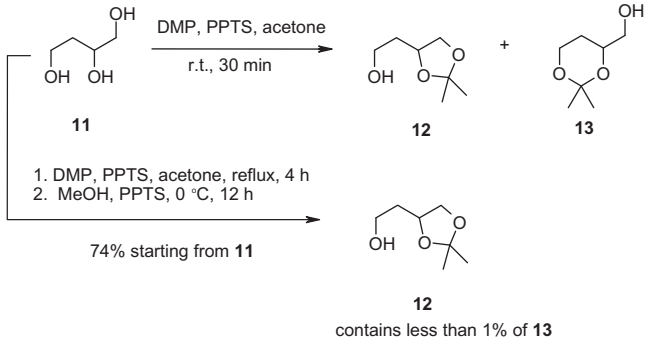


Scheme 2.

The use of 2,2-dimethoxypropane (DMP)[9] or isopropenyl methyl ether[10] in acetone in the presence of pyridinium *p*-toluenesulfonate (PPTS) to obtain the isopropylidene acetal from **4** was found to provide a rapid and quantitative formation of acetonide **2**, with a **2**:**5** isomeric ratio of 25:1 (Scheme 2).[11] This can be explained by the formation of a less reactive carbocation intermediate (a 1-methoxy-1-methylethyl cation) in contrast to the 1-hydroxy-1-methylethyl cation formed in the case of the acetone/$CuSO_4$/PPTS system.

Since we intended to apply the cyclopropanol approach[2] to (*S*)-2-hydroxybutyrolactone[1] which was to be used for the synthesis of epothilones and other natural compounds, it appeared of interest to study isopropylidene acetal formation from triol **6**[12] (Scheme 3). The latter can be prepared by cyclopropanation of lactone **7**[13] with subsequent removal of the THP-protecting group from the product **8** obtained.[14] The acetalization regioselectivity for triol **6** was found to be similar to that for compound **4**. Thus, using acetone/$CuSO_4$/PPTS led to the formation of compound **9**, which contained about 10% of the isomeric five-membered acetonide **10**, while the use of 2,2-dimethoxypropane or isopropenyl methyl ether in acetone in the presence of PPTS gave isomeric compounds **9** and **10** in a ratio of about 100:1.[15,16]

It is worth noting, however, that keeping the reaction mixture at room temperature for an additional 72 h, or heating it under reflux for three hours, led to the formation of a thermodynamic mixture of **9** and **10** in a ratio of 1:2 in favour of the five-membered acetonide **10**. This observation was interesting since it allows compound **10** to be synthesized in pure form. Indeed, we have found that it is possible to obtain almost pure acetonide **10** via a one-pot partial removal of the isopropylidene acetal-protecting group from the thermodynamic mixture of acetonides **9** and **10** at low temperature.[17] Thus, triol **6** can be transformed into either the six-membered acetonide **9** or the corresponding five-membered derivative **10**. The latter can be prepared in acceptable yield by acetalization of triol **6** under thermodynamically controlled conditions followed by one-pot partial deacetalization at low temperature. This observation is in accordance with the known more rapid deprotection of six-membered acetonides.[18]

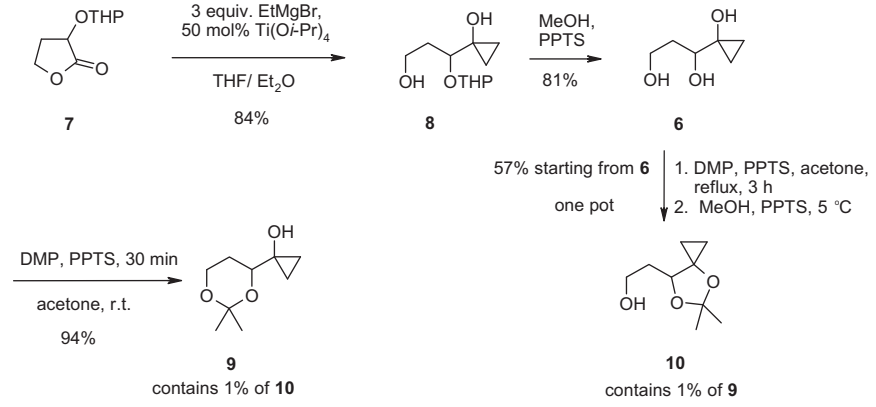


Scheme 4.

The triols **6** and **4** can be considered as the respective mono- and bis-cyclopropane congeners of butane-1,2,4-triol (**11**).[19] The synthesis of five-membered acetonide **12** from the latter (Scheme 4) was studied in detail as compound **12** can serve as a convenient intermediate in organic synthesis.[1] Thus, according to the literature,[5] acetalization of butane-1,2,4-triol (**11**) initially gives a kinetic mixture of acetonides **12** and **13** in a ratio of 2:1, while on subsequent heating of the reaction mixture under reflux for several hours the ratio of **12**:**13** changes to 9:1 in favour of the five-membered derivative **12**.[5] This corresponds to the thermodynamic equilibrium state. The isomeric acetonides **12** and **13** could not be separated chromatographically.[5a,b,e] Separation of **12** from **13** is possible by recrystallization of the corresponding 3,5-dinitrobenzoates.[5b,e] However, this method is time consuming (three recrystallizations) and the yield of the target acetonide **12** is poor (about 30%). Alternatively, pure acetonide **12** could be synthesized from malic acid in a more complicated way in comparison with acetalization of commercially available butane-1,2,4-triol.[20]

We supposed that the procedure employed earlier for the purification of **10** involving partial removal of the isopropylidene acetal-protecting group at low temperature could also be applied to purify derivative **12**. Indeed, acetalization of triol **11** using 2,2-dimethoxypropane or isopropenyl methyl ether in acetone, followed by heating under reflux for four hours and then one-pot partial deprotection at low temperature, gave practically pure **12** (the content of the corresponding six-membered derivative **13** was less than 1%).[21,22]

Thus, the advantages of 2,2-dimethoxypropane or isopropenyl methyl ether as reagents over the acetone/$CuSO_4$/PPTS system for the acetalization of cyclopropane-containing congeners of butane-1,2,4-triol and the applicability of partial deacetalization for the purification of five-membered acetonides have been demon-



Scheme 3.

strated.[23] The homochiral forms of the intermediates prepared in this study are intended to be used for the synthesis of natural products.

Acknowledgement

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11. *Synthesis of compound* **2**. A solution of 2,2-dimethoxypropane (0.90 ml, 7.3 mmol), triol **4** (0.50 g, 3.2 mmol) and PPTS (0.04 g) in acetone (10 mL) was stirred at room temperature for 30 min. The reaction was quenched with Et_3N (0.25 mL) and the solvent was removed under reduced pressure. The residue was diluted with petroleum ether/EtOAc mixture (10:1) and filtered through a small pad of silica gel. Evaporation of the solvent under reduced pressure gave acetonide **2** (0.61 g, 97%). Spectral data for compound **2** were identical to those reported previously.[3a]
12. *Compound* **6**. IR (neat) 3443 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 0.57–0.66 (m, 2H), 0.73–0.81 (m, 2H), 1.81–1.97 (m, 2H), 3.26 (dd, $J = 8.8$, 4.7 Hz, 1H), 3.69–3.79 (m, 2H); ^{13}C NMR (100 MHz, D_2O) δ 11.2, 12.0, 35.3, 57.9, 59.2, 73.9.
13. Compound **7** was prepared by a standard method using DHP/PPTS/CH_2Cl_2 starting from commercially available α-hydroxy-γ-butyrolactone. Both enantiomers of the latter are also commercially available.
14. *Compound* **8**. IR (CCl_4) 3586, 3508, 3095 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.39–0.50 (m, 1H), 0.64–0.72 (m, 1H), 0.75–0.88 (m, 2H), 1.49–1.60 (m, 4H), 1.75–2.06 (m, 4H), 2.60 (br s, 2H), 3.42–3.57 (m, 2H), 3.69–3.86 (m, 2H), 3.91–4.04 (m, 1H), 4.67–4.71 (m, 0.5H), 4.81–4.85 (m, 0.5H). Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 61.04; H, 9.43.
15. The signals of the protons of the methine groups at $\delta = 3.42$ ppm for acetonide **9** and $\delta = 4.20$ ppm for **10** were used to determine ratio of **9**:**10**.
16. *Synthesis of compound* **9**. A solution of 2,2-dimethoxypropane (2.90 mL, 23.6 mmol), triol **6** (1.05 g, 8.0 mmol) and PPTS (0.10 g) in acetone (20 mL) was stirred for 30 min. The reaction was quenched with Et_3N (0.5 mL) and the solvent was removed under reduced pressure. The residue was diluted with petroleum ether/EtOAc mixture (6/1) and filtered through a small pad of silica gel. Evaporation of the solvent under reduced pressure gave acetonide **9** (1.29 g, 94%). IR (CCl_4) 3585, 3092 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.43–0.53 (m, 2H), 0.70–0.79 (m, 2H), 1.38 (s, 3H), 1.39 (s, 3H), 1.91–2.02 (m, 2H), 2.97 (br s, 1H), 3.42 (dd, $J = 12.0$, 2.5 Hz, 1H), 3.82 (ddd, $J = 12.0$, 6.0, 2.0 Hz, 1H), 3.82 (td, $J = 12.0$, 3.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.6, 12.4, 19.2, 26.3, 29.7, 57.0, 59.5, 73.7, 98.4. Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.54; H, 9.21.
17. *Synthesis of compound* **10**. A solution of 2,2-dimethoxypropane (1.8 mL, 14.6 mmol), triol **6** (0.66 g, 5.0 mmol) and PPTS (0.10 g) in acetone (15 mL) was stirred at room temperature for 30 min and then heated under reflux for 3 h. The solvent was removed under reduced pressure and the residue was dissolved in MeOH (15 mL). After standing for 12 h at 5 °C, the reaction was quenched with Et_3N (0.5 mL). The solvent was removed under reduced pressure. Column chromatography of the residue (8 g of silica gel, eluent: from petroleum ether/EtOAc 5/1 to EtOAc) gave acetonide **10** (0.49 g, 57%) and the starting triol **6** (0.15 g, 23%). IR (CCl_4) 3639, 3560, 3095 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.54–0.60 (m, 1H), 0.64–0.70 (m, 1H), 0.84–0.91 (m, 1H), 0.97–1.03 (m, 1H), 1.46 (s, 3H), 1.48 (s, 3H), 1.50–1.57 (m, 1H), 1.69–1.78 (m, 1H), 2.41 (br s, 1H), 3.80 (t, $J = 5.6$ Hz, 2H), 4.20 (dd, $J = 9.5$, 3.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.3, 8.6, 25.9, 27.1, 34.8, 60.4, 64.1, 77.2, 108.3. Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.60; H, 9.27.
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21. The signals of the protons of the methyl groups at $\delta = 1.36$ and 1.42 ppm for acetonide **12** and $\delta = 1.39$ and 1.47 ppm for **13** were used to determine ratio of **12**:**13**.
22. Compound **12** was synthesized according to the procedure employed in the synthesis of acetonide **10**.[17] Product **12** is slightly volatile. In this connection removal of the majority of the solvents was performed under atmospheric pressure using a Vigreux column. A pentane/Et_2O mixture (2:1) was used instead of the petroleum ether/EtOAc system. The spectral data for the obtained product were identical with those reported in the literature.[5]
23. We failed to obtain compound **5** in pure form using this methodology due to the unfavourable ratio of compounds **2** and **5** in the mixture under thermodynamic equilibrium conditions (3:1). Moreover, the rate of deacetalization of acetonide **2** exceeds that of acetonide **5**, but not as much as in the case of compounds **9** and **10**.