Diastereomer-Differentiating Hydrolysis of 1,3-Diol-Acetonides: A Simplified Procedure for the Separation of *syn*- and *anti*-1,3-Diols
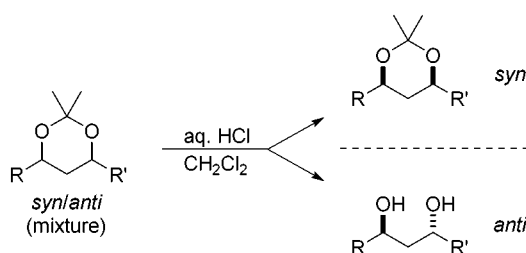
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ABSTRACT

A new method to facilitate the separation of diastereomeric *syn*- and *anti*-1,3-diols is described. The method relies on the different hydrolysis rates of the corresponding diastereomeric acetonides. Treatment of a dichloromethane solution of *syn*- and *anti*-1,3-diol-acetonide with a catalytic amount of diluted aqueous hydrochloric acid leads to the selective cleavage of the *anti* diastereomer. The resulting *anti*-1,3-diol can be easily separated from the unchanged *syn*-1,3-diol-acetonide.

Substituted 1,3-diols are valuable intermediates in the synthesis of drugs and natural products.[1] These useful building blocks are often obtained as mixtures of *syn* and *anti* diastereomers in varying diastereomeric ratios. The separation of 1,3-diol diastereomers can be a difficult task, even at the stage of cyclic derivatives such as the corresponding acetals.[2] This applies especially for noncrystallizing 1,3-diols and when the separation has to be conducted on a large scale. Here we report a general and simple method of efficiently separating diastereomeric 1,3-diols. The crucial step is a diastereomer-differentiating hydrolysis of the corresponding 1,3-diol-acetonides (2,2-dimethyl-1,3-dioxanes).

Recently, we developed a stereoselective synthesis of the enantiopure β,δ-dihydroxy ester *syn*-(3*R*,5*S*)-**1**, which comprises a highly enantioselective enzymatic reduction, a *syn*-selective borohydride reduction, and a crystallization step.[3] This chiral dihydroxy ester is an advanced building block for HMG-CoA-reductase inhibitors of the mevinic acid type.[4] From a 200 g campaign, the stereoisomerically pure crystallized main product *syn*-(3*R*,5*S*)-**1** was collected along with considerable quantities of mother liquor residues.


syn-(3*R*,5*S*)-**1**   *anti*-(3*S*,5*S*)-**1**

Although these residues still mainly consisted of the desired *syn*-β,δ-dihydroxy ester *syn*-(3*R*,5*S*)-**1**,[5] a second crop

(1) (a) Oishi, T.; Nakata T. *Synthesis* **1990**, 635−645. (b) Rychnovsky, S. D. *Chem. Rev.* **1995**, *95*, 2021−2040. (c) Schneider, C. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1375−1378.
(2) (a) Tamaru, Y.; Hojo, M.; Kawamura, S.; Sawada, S.; Yoshida, Z. *J. Org. Chem.* **1987**, *52*, 4062−4072. (b) Jung, M. E.; Kretschik, O. *J. Org. Chem.* **1998**, *63*, 2975−2981. (c) Trieselmann, T. Dissertation, University of Marburg, Germany, 1999. (d) Trieselmann, T., Hoffmann, R. W. *Org. Lett.* **2000**, *2*, 1209−1212.

(3) (a) Wolberg, M.; Hummel, W.; Wandrey, C.; Müller, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4306−4308. (b) Wolberg, M.; Hummel, W.; Müller, M. *Chem. Eur. J.* **2001**, *7*, 4562−4571.

of crystalls could not be obtained. Separation of the diastereomers *syn*-(3*R*,5*S*)-**1** and *anti*-(3*S*,5*S*)-**1** by column chromatography is ineffective as a result of marked coelution, and the same holds for the cyclic derivatives *syn*-(3*R*,5*S*)-**2** and *anti*-(3*S*,5*S*)-**2**.[6]

On deprotecting a *syn/anti* mixture of acetonide **2** with a catalytic amount of diluted aqueous hydrochloric acid in dichloromethane solution, we observed that the *anti* diastereomer hydrolyses much faster than the *syn* diastereomer. Premature quenching of the acid catalyst with aqueous sodium bicarbonate solution resulted in a mixture of the diols *syn*-(3*R*,5*S*)-**1** and *anti*-(3*S*,5*S*)-**1** and highly enriched *syn*-acetonide *syn*-(3*R*,5*S*)-**2** (Scheme 1). Because of the great
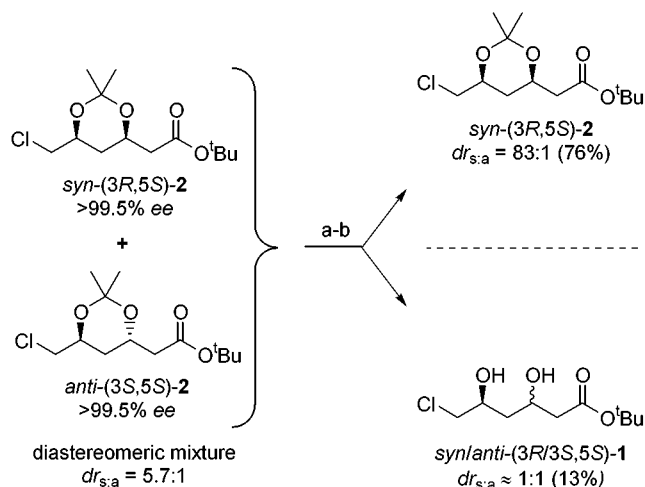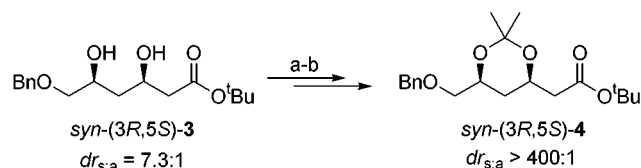
differences in polarity, the diastereomeric diols **1** can be easily removed from the corresponding acetonides **2** by flash chromatography. Thus, the diastereomer-differentiating acetonide hydrolysis turns the difficult *syn/anti* diastereomer separation into a separation of nonstereoisomeric compounds, which show great differences in their physical properties and can therefore be readily separated.

On the basis of these observations, we developed a workup procedure for the mother liquor residues of the large-scale synthesis of dihydroxy ester *syn*-(3*R*,5*S*)-**1**. To this end, the residues are treated with excess 2,2-dimethoxypropane in the presence of camphor sulfonic acid to generate the acetonides *syn*-(3*R*,5*S*)-**2** and *anti*-(3*S*,5*S*)-**2**. The crude product, obtained by merely evaporating the volatiles, is subjected to the

(4) (a) Thottathil, J. K.; Pendri, Y.; Li, W. S.; Kronenthal, D. R. U.S. Patent 5,278,313, 1994; *Chem. Abstr.* **1994**, *120*, 217700. (b) Kizaki, N.; Yamada, Y.; Yasohara, Y.; Nishiyama, Y.; Miyazaki, M.; Mitsuda, M.; Kondo, T.; Ueyama, N.; Inoue, K. Eur. Patent Application 1,024,139, 2000; *Chem. Abstr.* **2000**, *132*, 166230.

(5) Diastereomeric ratio (dr$_{s:a}$) *syn*-(3*R*,5*S*)-**1**:*anti*-(3*S*,5*S*)-**1** =5:1 up to 9:1, *ee* > 99.5%.

(6) For the sake of clarity, the relative configuration of the acetonides **2**, **4**, **5**, and **6** is expressed by adopting the *syn/anti* descriptors of the underlying 1,3-diols instead of using the *cis/trans* nomenclature.

diastereomer-differentiating hydrolysis as described above. At 20 °C and a substrate concentration of 0.2 mol L^{-1}, the hydrolysis is slow enough to be conveniently monitored by means of gas chromatography.[7] In a representative example,[8] a noncrystallizing mother liqour residue, consisting mainly of dihydroxy esters *syn*-(3*R*,5*S*)-**1** and *anti*-(3*S*,5*S*)-**1** in a diastereomeric ratio *syn/anti* (dr$_{s:a}$) of 9:1, gave acetonide *syn*-(3*R*,5*S*)-**2** with dr$_{s:a}$ = 221:1. The unreacted acetonide *syn*-(3*R*,5*S*)-**2** was isolated by flash chromatography, which removed the other polar impurities originating from the preceding synthesis steps as well (67% isolated yield; 75% based on the *syn* diastereomer present in the starting material). Apart from the minute content of remaining *anti* diasteremoer (<0.5%), the product *syn*-(3*R*,5*S*)-**2** was pure according to NMR and GC−MS analysis. Remarkably, the acid-sensitive *tert*-butyl ester group is not significantly affected under these conditions.

This workup procedure was successfully applied to benzyloxy-substituted *β*,*δ*-dihydroxy ester *syn*-(3*R*,5*S*)-**3**[9] as well (Scheme 2). Treating a diastereomeric mixture of this

compound as described above led to an increase of the diastereomeric ratio *syn/anti* from 7.3:1 to more than 400:1 (GC−MS analysis). Acetonide *syn*-(3*R*,5*S*)-**4** was obtained in a 77% yield after flash chromatography (88% yield with regard to the amount of *syn* diastereomer present in the starting material).

To confirm the general applicability of this method, we investigated the hydrolysis of two other 1,3-diol-acetonides. For that purpose, diastereomeric mixtures of the racemic acetonides *syn/anti*-**5** (dr$_{s:a}$ = 1.2:1) and *syn/anti*-**6** (dr$_{s:a}$ =

(7) At higher concentrations (>0.3 mol L^{-1}) the reaction is impracticably slow, whereas at a lower concentrations (<0.1 mol L^{-1}) the reaction is too fast to be reasonably monitored by GC.

(8) To a solution of *β*,*δ*-dihydroxy ester *syn*-(3*R*,5*S*)-**1** [34.5 g, mother liquor residue, chemical purity ∼85% (^{1}H NMR), ee > 99.5%, dr$_{s:a}$ = 9:1] in acetone/2,2-dimethoxypropane (210 mL, 50:50 v/v) was added camphor sulfonic acid (0.5 g, 2.2 mmol). The solution was stirred at room temperature for 2 h and then concentrated in vacuo. The oily residue was dissolved in dichloromethane (0.7 L), and hydrochloric acid (2 mol L^{-1}, 3.2 mL, 6.4 mmol) was added. After vigorously stirring at 20 °C for 3 h, the solution was washed with saturated aqueous NaHCO$_3$ solution and water, dried over MgSO$_4$, and evaporated in vacuo. Flash chromatography of the residue (ethyl acetate/isohexane 10:90 v/v, 10 cm Ø column, 0.38 kg SiO$_2$) gave acetonide *syn*-(3*R*,5*S*)-**2** as a weakly yellow oil: yield 23.2 g (67%); dr$_{s:a}$ 221:1 [GC−MS, HP-5MS column (Hewlett-Packard), 120 °C]. ^{1}H and ^{13}C NMR data of this compound are described elsewhere.[3b]

(9) Beck, G.; Jendralla, H.; Kesseler, K. *Synthesis* **1995**, 1014−1017.

1.4:1) were prepared by sodium borohydride reduction of the corresponding β-diketones and subsequent ketalization with 2,2-dimethoxypropane. The acetonides were subjected to hydrolysis conditions as described above, except for the application of a lower reaction temperature in the case of *syn/anti*-**6** (0 °C). Quenching with sodium bicarbonate solution after partial conversion was followed by a usual aqueous workup procedure, and the crude products were analyzed by GC−MS[10] and NMR spectroscopy. As can be seen from eqs 1 and 2, the hydrolysis is highly selective in both cases; only traces of the respective *anti* diastereomer were found in the remaining acetonide fractions.

The application of Lewis acids as the hydrolysis catalyst led to a high selectivity as well. Using 5 mol % $FeCl_3 \cdot 6H_2O$[11] instead of hydrochloric acid under otherwise identical conditions, we observed an increase of the diastereomeric ratio *syn/anti* from 3:1[12] to 238:1 within 1 h in the case of acetonide *syn/anti*-**6** (0 °C, 36% conv). Obviously, the presented diastereomer-differentiating hydrolysis of 1,3-diol-acetonides is of general scope. Moreover, it can be applied to generate highly enriched *anti*-1,3-diol from a diastereomeric mixture of 1,3-diol-acetonides as well (eq 2). To obtain optimal results with regard to selectivity and yield, careful monitoring of the hydrolysis is necessary.

It is known from the literature that *syn*-1,3-diol-acetonides preferentially adopt a chair conformation, while for steric reasons the acetonides of *anti*-1,3-diols are generally forced into a more strained twist-boat conformation.[13] Differences in the reactivity of diastereomeric *syn*- and *anti*-1,3-diol-acetonides are scarcely described, however. Paterson and Scott observed acetonide protection of an *anti*-1,3-diol building block to be too labile under several hydrogenolysis conditions while the acetonide moiety of the *syn*-configured counterpart proved to be inert under the same conditions.[14] In the course of a kinetic conformational analysis conducted on diastereomerically pure 1,3-dioxanes, Pihlaja showed that *anti*-2,4-pentandiol-acetonide hydrolyses 26 times faster than the corresponding *syn* diastereomer (diluted hydrochloric acid, 25 °C).[15] Pihlaja assigned the relief of strain in the ring cleavage step to account for this difference, and it is reasonable to assume that this explanation applys generally to the hydrolysis of *syn*- and *anti*-1,3-diol-acetonides. Relief of strain has been invoked as an accelerating factor in the hydrolysis of other strained acetals and ketals as well.[16]
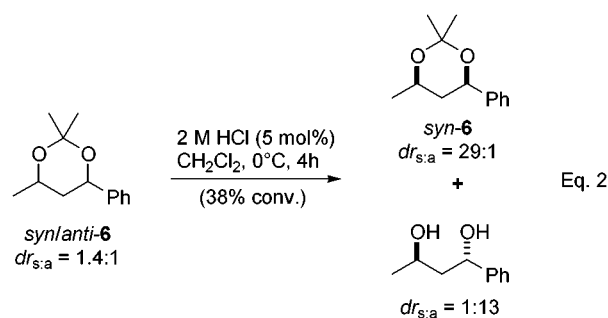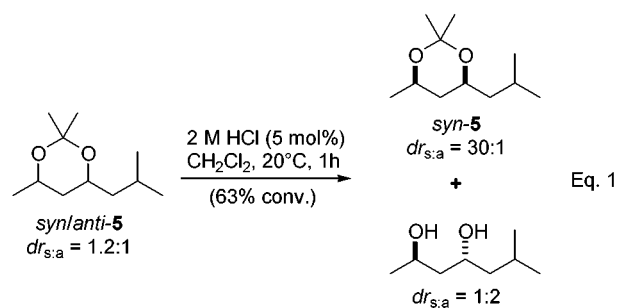
The differences in the hydrolysis rates of diastereomeric 1,3-diol-acetonides had been known in principle.[15] To the best of our knowledge, however, an intended utilization of these differences for the separation of *syn*- and *anti*-1,3-diols or *syn*- and *anti*-1,3-diol-acetonides has not yet been described in the literature.

In conclusion, we have developed a new procedure for the efficient separation of diastereomeric 1,3-diols that is based on a diastereomer-differentiating hydrolysis of the corresponding 1,3-diol-acetonides. The presented method is very mild and highly selective and can be easily applied on a large scale.

(10) Samples were acylated prior to GC−MS analysis (see ref 3b).

(11) Sen, S. E.; Roach, S. L.; Boggs, J. K.; Ewing, G. J.; Magrath, J. *J. Org. Chem.* **1997**, *62*, 6684−6686.

(12) This starting material was obtained from a hydrolysis experiment that had been terminated too early.

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(14) Paterson, I.; Scott, J. P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1003−1014.

(15) Pihlaja, K. *Ann. Univers. Turkuensis Ser. A1* **1967**, *114*; *Chem. Abstr.* **1968**, *69*, 76439.

(16) (a) Atkinson, R. F.; Bruice, T. C. *J. Am. Chem. Soc.* **1974**, *96*, 819−825 and references therein. (b) Fife, T. H.; Natarajan, R. *J. Am. Chem. Soc.* **1986**, *108*, 8050−8056.