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A Novel Bicyclic Orthoester as a Chiral Auxiliary: Application to the Synthesis of α-Hydroxy Acids

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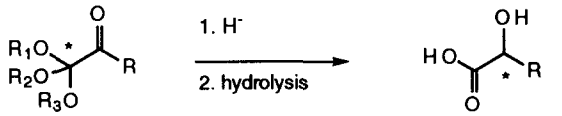
Abstract: Chiral α-keto orthoesters derived from tartaric acid can be reduced diastereoselectively. Hydrolysis affords optically active α-hydroxy acids and the recovered auxiliary.

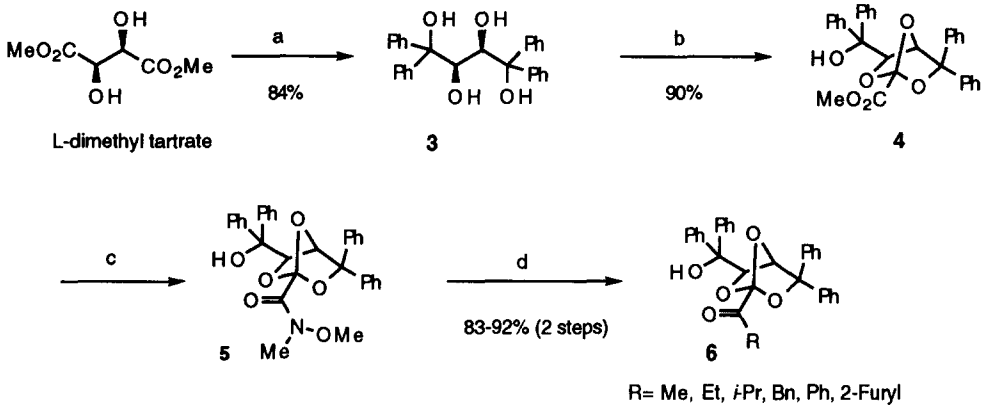
Our interest in the design of a new auxiliary for asymmetric synthesis led us to investigate orthoesters[1] as a possible complement to the more conventional approaches (chiral ester, amide etc.).[2,3] Chiral orthoesters have recently been reported as acylating agents,[4] but the idea of using them as an auxiliary has not been explored to date. We chose to test this concept in the stereoselective synthesis of α-hydroxy acids because they are important chirons or building blocks in organic synthesis.[5,6] Herein, we disclose the first successful application of this approach. The level of stereoselection in the reduction of α-keto orthoesters reported here is as good or exceeds the results obtained with other auxiliaries in similar applications.[7]



chiral *chiral*

A simple and efficient method for the preparation of α-keto orthoesters **6** was developed from enantiomerically pure dimethyl tartrate, commercially available in both (+) and (-) forms. As illustrated in Scheme 1, (+)-dimethyl tartrate was treated with phenyl magnesium bromide and then reacted with commercially available methyl 2-methoxy-2,2-dichloroacetate in anhydrous pyridine to afford the desired methyl ester **4** in greater than 75% yield for 2 steps. The required ketones **6** can then be made via addition of an alkylmagnesium or aryllithium reagent to the corresponding *N,O*-dimethyl amide **5**. This amide could be obtained in good yield from the ester **4** using the magnesium salt of *N,O*-dimethylhydroxylamine.

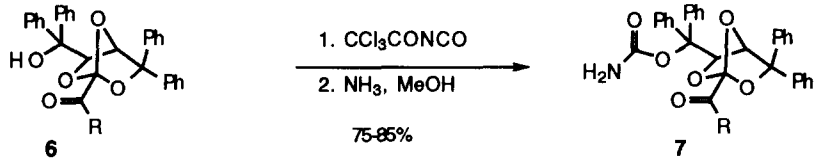
Scheme 1



(a) PhMgBr (b) $MeO(Cl)_2CCO_2Me$, Pyridine (c) MeO(Me)NMgBr, THF, -78°C to 0°C (d) RMgX or RLi, THF

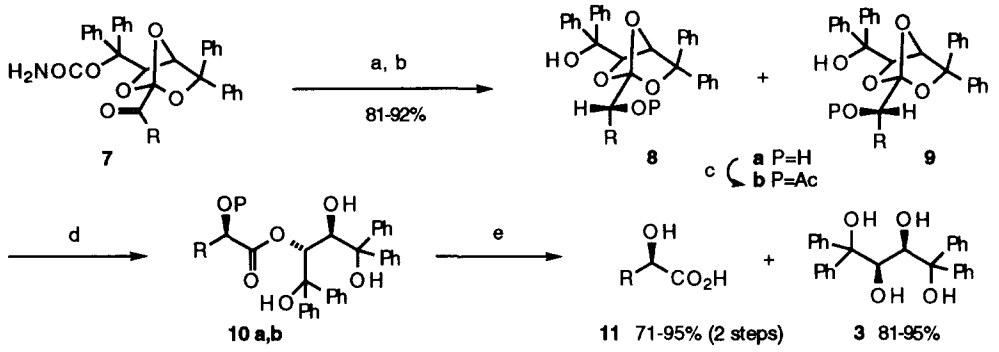
We investigated conditions leading to the asymmetric reduction of **6** by varying the size of the R group, hydride sources,[8] solvents and the nature of the substitution on the tertiary alcohol. In summary, we found that optimum selectivity was obtained with L-Selectride® in THF at -78°C. When the tertiary alcohol is not derivatised, we observed maximum stereoselection with bulky α-substituted ketones (R=*i*-propyl; 99:1, R=benzyl; 98:2). The selectivity decreases proportionately with the size of the substituents (R=Et; 86:14, R=Me; 53:47, R=Ph; 95:5, R=2-furyl; 69:31). In order to enhance the diasteroselectivity for less hindered α-substituted ketones, the alcohol was protected as its carbamate (Scheme 2).

Scheme 2



Diastereoselection in the reduction of carbamate **7** (Scheme 3) is excellent with all ketones studied (Table 1). Other derivatives of the tertiary alcohol, such as the *t*-butyl carbonate (OBOC), also gave rise to excellent diastereoselection. However, we chose to use carbamate **7** because it can be easily removed with catalytic NaOEt in EtOH at room temperature in a one pot reaction. Using the auxiliary derived from (+)-tartrate, we consistantly obtained the unnatural *R*-isomer for the newly formed chiral center.

Scheme 3



(a) L-Selectride®, THF, -78°C, (1.1 equiv.) (b) NaOEt / EtOH , 21°C (c) Ac_2O, DMAP
(d) THF:MeOH:H_2O:TFA (4:4:1:0.1) (e) LiOH, THF

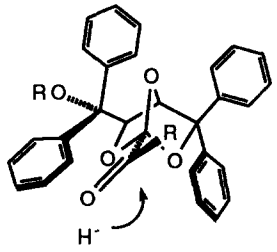
Attempted hydrolysis of the orthoester **8a** directly to the corresponding acid **11** in strong acidic media led to partial or total racemisation of the newly formed chiral center. A milder, more reliable two step sequence was thus developed. The cleanest and fastest hydrolyses were obtained using aqueous TFA in THF / MeOH, which effected opening of the α-acetoxy orthoester **8b** to the ester **10b**[9] (Scheme 3). The ester **10b** was then treated with LiOH, giving the desired α-hydroxy acid **11** without any racemisation when R is an alkyl group (Table 1, entry 1-4) and the recovered auxiliary **3**.[10]

Table **1** Diastereoselective Reduction of Chiral α-Keto Orthoester **7** and Hydrolysis to the Free Acid **11**

entry	R	isomer ratio[a] **8b : 9b**	enantiomeric purity after hydrolysis[b] **11** (*R:S*)[c]
1	methyl	97:3	≥ 99:1[d]
2	ethyl	≥ 99:1	≥ 99:1
3	benzyl	≥ 99:1	≥ 99:1
4	*i*-propyl	≥ 99:1	≥ 99:1
5	phenyl	≥ 99:1	99:1
6	2-furyl	≥ 99:1	98:2[e]

(a) Ratios were determined by 400 MHz ^{1}H NMR. (b) Ratios were determined, after treatment with CH_2N_2 , by ^{1}H and / or ^{19}F NMR of the corresponding Mosher's ester (ref. 11). (c) Absolute configuration was confirmed by the sign of $[\alpha]_D$ and / or by comparison of the ^{1}H NMR of their corresponding Mosher's ester with authentic samples (see also ref.12,13). (d) Prior to hydrolysis, the product mixture (**8b+9b**, white solid) was purified by stirring vigorously in hexane / ether and then filtered; this could have resulted in further enrichment of major isomer. (e) Hydrolysis was conducted on **8a**.

Partial racemisation can be observed when R is an aryl group (Table 1, entry 5,6). We observed significant racemisation (ratio 91:9) with **8b** when R=2-furyl, but hydrolysis of α-hydroxy analog **8a** was more rapid and gave rise to less racemisation (ratio 98:2).



One hypothesis to rationalize the observed diastereoselectivity involves a restricted rotation about the C-C bond between the carbonyl and the orthoester. The favoured conformation is as depicted, which minimizes steric interactions between the R group and the sterically demanding substituents on the bicyclo [2.2.1] nucleus. Hydride then approaches from the bottom face of the carbonyl, away from the bulky tertiary carbinol which shields the top face of the carbonyl, leading to the observed diastereoisomer **8**.

In conclusion, we have shown that bicyclic orthoesters are efficient new chiral auxiliaries and can be a useful complement to the standard methods available for asymmetric synthesis.

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8. With LAH, DIBAL-H, $LiAlH[OC(Et)_3]_3$, BH_3, $NaBH_4$, N or K-Selectride®, we observed lower diastereoselectivity and longer reaction time.
9. Small amounts (≤ 5%) of the deacetylated hydroxy ester **10a** were also produced during hydrolysis.
10. A typical experimental procedure for reduction and hydrolysis is as follows:
    (a) To a solution of **7** (1.5 mmol) in anh. THF (40 mL) at -78°C was added L-Selectride® (1M, THF, 1.7 mL, 1.7 mmol) dropwise. After 15 min, NaOEt/EtOH (0.25M, 2.0 mL, 0.5 mmol) was added and the reaction mixture was warmed to 21°C, stirred for 2 h and quenched with a saturated NH_4Cl solution. After standard workup, the crude diol **8a** in CH_2Cl_2 (30 mL) was treated with Ac_2O (0.29 mL, 3 mmol), pyridine (0.25 mL, 3 mmol) and DMAP (20 mg, 0.15 mmol) for 1 h. After standard workup, the residue was purified by flash chromatography to afford **8b** as a white solid (81-92% yield).
    (b) To the orthoester **8b** (0.35 mmol) in THF/MeOH/H_2O (4:4:1, 12 mL) was added TFA (0.13 mL, 1.7 mmol). After 3 h at 21°C, the reaction mixture was quenched with a saturated $NaHCO_3$ solution. After standard workup, the crude esters **10ab** were dissolved in THF (6mL) and a solution of LiOH (1N, 0.7 mL, 0.7 mmol) was added. After 24 h at 21°C, the mixture was diluted with Et_2O (10 mL) and H_2O (2 mL). The organic phase decanted, the aqueous phase stirred vigorously with Et_2O and decanted again (2x). The combined organic phases were evaporated and the residue purified by flash chromatography to afford the recovered auxiliary **3** (81-95%). The aqueous phase was lyophilized, the salts obtained were suspended in EtOAc and a HCl solution was added (1N, 0.8 mL, 0.8 mmol). The resulting mixture was dried with NaCl and $MgSO_4$ and the solvant evaporated to afford the desired α-hydroxy acid **11** (71-95%) as a white solid.
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