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Asymmetric Induction to *meso*-Cyclohexane-1,2-diol Based on Diastereoselective Elimination

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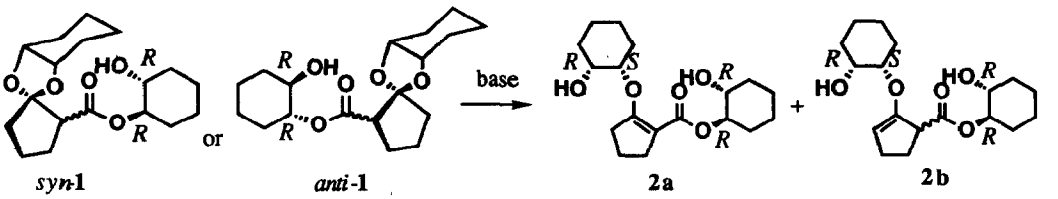
Abstract: Diastereoselective elimination of *syn*- and *anti*-**1** under basic condition, and subsequent protection of the hydroxy group followed by acid hydrolysis of the enol ether function gave (1*S*,2*R*)-**3** of 72% e.e.

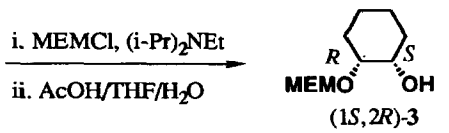
Our recent study on the chemistry of the asymmetric reaction using cycloalkane-1,2-diols as a chiral auxiliary[1] has led to a new method for chiral induction from *meso*-cyclohexane-1,2-diol[2] based on diastereoselective elimination of chiral 2,2-(cyclohexanedioxy)cyclopentane-1-carboxylates.

Starting substrates (*syn*- and *anti*-**1**) having the *cis*-cyclohexane-1,2-dioxy component were prepared as a 2 to 3 diastereomeric mixture at C1.[3] Reaction conditions were studied using a 9 to 1 mixture of *syn*-**1** and *anti*-**1**.[3] Treatment of the substrate (1 eq.) with a base (5 eq.) at -78 °C in THF under an Ar atmosphere for 0.5-1 h afforded the conjugated enol ether **2a** and the deconjugated enol ether **2b**.[4] Since the diastereomeric excess (d.e.) of **2a** could not be directly determined, it was converted into the MEM ether **3** in 80-85% yield *via* protection of the newly generated hydroxy group as MEM ether (MEMCl / $(i\text{-}Pr)_2NEt$ / CH_2Cl_2 / r.t., 24 h) and subsequent acid-hydrolysis (AcOH-THF-H_2O (1:1:1) / r.t., 24 h) of the enol ether function. The enantiomeric excess (e.e.) of **3** was determined by Mosher's method.[5] The absolute configuration of **3** was unambiguously determined to be 1*S*,2*R* by comparison of its specific rotation with an authentic sample[6] derived from (*S*,*S*)-cyclohexane-1,2-diol. The deconjugated enol ether **2b** obtained in 20-30% yields in each entry of Table I was also converted to **3**, which was found to have the same absolute configuration and e.e. value as that from **2a**. Table I shows the results relative only to the conjugate type product **2a**. Among the attempted reaction conditions in Table I, the diastereoselectivity of the elimination reaction was found to be affected by addition of HMPA (5 eq.) (entries 1 and 2, 5 and 6). In the case of using bis(trimethylsilyl)amides with HMPA (entries 3, 4 and 6), the effect of counter metal cation was observed, that is to say, potassium cation (entry 6) afforded the best result in connection with the e.e. of **3** (72% e.e.).

Next, *syn*- and *anti*-**1**, which were diastereomerically pure at least in terms of *syn*/*anti* stereochemistry, were subjected to the reaction conditions of entry 6. Surprisingly, both *syn*- and *anti*-**1** gave the same product (1*S*,2*R*)-**3** of 72% e.e. (Table II, entries 1 and 2). Further attempts to apply this reaction for chiral induction to *meso*-5 and 7-membered 1,2-diols proved unsatisfactory.[7]



syn-1 *anti*-1 **2a** **2b**



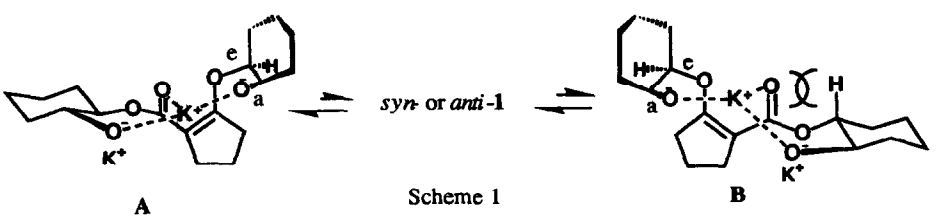
(1*S*,2*R*)-3

Table I. Reaction of a 9 to1 mixture of *syn*-**1** and *anti*-**1** with bases

Entry	Reagents	Isolated yield of **2a** (%) (Conversion yield)	% E.e. of (1*S*,2*R*)-**3** from **2a**
1	LDA	30 (33)	29
2	LDA, HMPA	30 (34)	61
3	$(TMS)_2NLi$, HMPA	20 (60)	41
4	$(TMS)_2NNa$, HMPA	34 (65)	62
5	$(TMS)_2NK$	55 (63)	54
6	$(TMS)_2NK$, HMPA	41 (65)	72

Table II. Reaction of *syn*- and *anti*-**1** with $(TMS)_2NK$, HMPA in THF

Entry	Substrate	Combined yield of **2a,b** (%) (Conversion yield)	Optical purity of **3** from **2a,b** Product	% e.e.
1	*syn*-**1**	67 (88)	(1*S*,2*R*)-**3**	72
2	*anti*-**1**	65 (90)	(1*S*,2*R*)-**3**	72



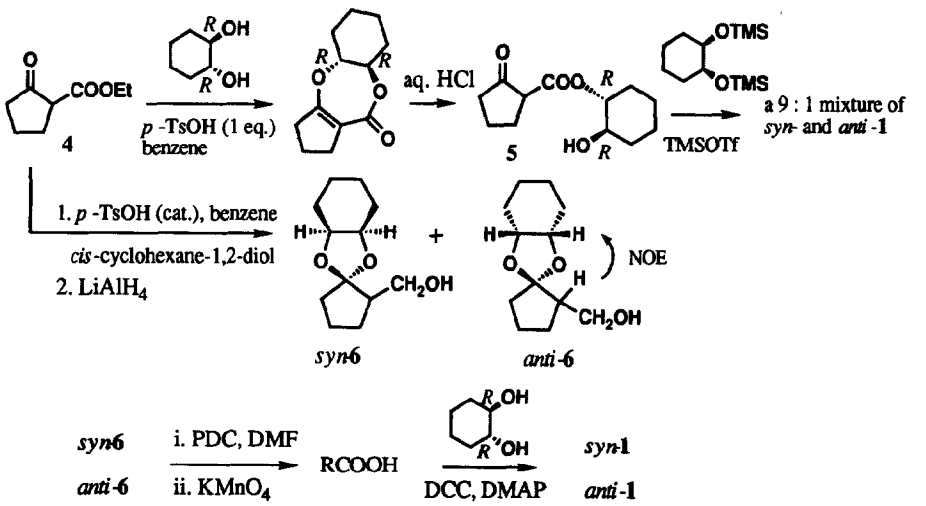
A **B**

Scheme 1

The possible reaction pathway was considered to be as follows. An equilibrium between chelated enol ethers (**A** and **B** in Scheme 1) *via* acetal substrates was assumed judging from the following experimental results. 1) *Syn*- and *anti*-substrates gave the same products as regards absolute configuration and e.e. value. 2) In all the cases of reaction in Table I and II, starting material was recovered in 5-25% yields. 3) Treatment of **2a** with NaH in THF gave a mixture of *syn*- and *anti*-**1**. The chelation intermediate **B** might be unfavorable because of steric hindrance between the carbonyl function and C1'-axial-H. That is to say, the reaction might proceed *via* the favorable intermediate **A** in thermodynamically controlled fashion to afford finally (1*S*,2*R*)-**3** predominantly.

References and Notes

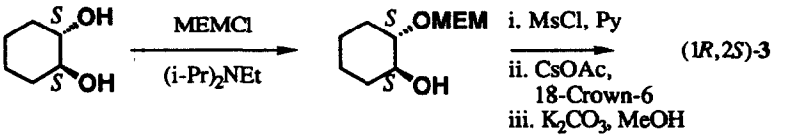
1. *a*) Fang, C.-L.; Ogawa, T.; Suemune, H.; Sakai, K. *Tetrahedron: Asymmetry*, **1991**, 2, 389; *b*) Fang, C.-L.; Suemune, H.; Sakai, K. *J. Org. Chem.*, **1992**, 57, 4300; *c*) Kato, K.; Suemune, H.; Sakai, K. *Tetrahedron Lett.*, **1992**, 33, 247 and 3481.
2. Harada, T.; Wada, I.; Oku, A. *J. Org. Chem.*, **1989**, 98, 2599.
3. Starting substrates were synthesized by two different methods. Acetalization of chiral β-keto ester **5** derived from the corresponding ethyl ester **4** *via* a tricyclic lactone, with *cis*-1,2-bis(trimethylsilyloxy)-cyclohexane by Noyori's method[8] afforded an inseparable 9 to 1 mixture of *syn*- and *anti*-**1** in 91% yield. Acetalization of **4** with *cis*-cyclohexane-1,2-diol under azeotropic conditions (*p*-TsOH, benzene) and subsequent $LiAlH_4$ reduction of the ester function afforded separable alcohols (*syn*- and *anti*-**6**) in 27 and 52% yields from **4**, respectively. The relative stereochemistry was confirmed by $^1H,^1H$-NOESY spectra, in which the NOE was observed between 2-H and 1'-H of *anti*-**6**. Each isolated alcohol was converted to the corresponding *syn*- and *anti*-**1** *via* two-step oxidation (i. PDC, DMF; ii. $KMnO_4$) and subsequent esterification with (*R*,*R*)-cyclohexane-1,2-diol (DCC, DMAP) in 52 and 55% yields, respectively.



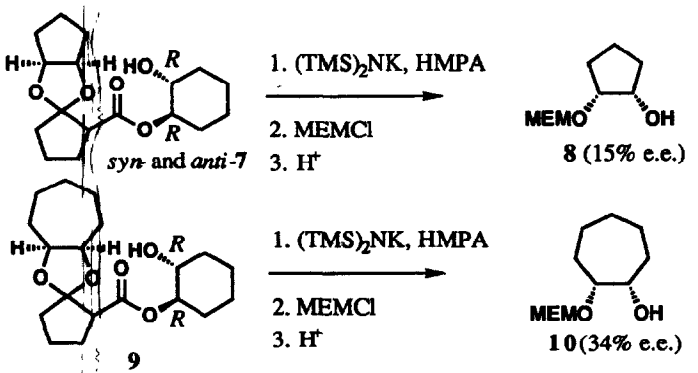
Selected spectral data for *syn*- and *anti*-**1**. *Syn*-**1** (1 to 1 diastereomeric mixture at C1): ^1H-NMR δ ($CDCl_3$) 2.89 (0.5 H, dd, *J*=3.5, 8.6 Hz), 3.05 (0.5 H, dd, *J*=7.3, 8.3 Hz), 3.52 (1H, m), 3.68, 3.77

(0.5 H each, s), 4.00-4.16 (2H, m). 4.66, 4.77 (0.5 H each, m). *Anti*-**1** (10 to 1 diastereomeric mixture at C1): ^{1}H-NMR δ ($CDCl_3$) for major isomer 2.83 (1H, dd, *J*=4.0, 8.7 Hz), 3.48 (1H, m), 3.50 (1H, br.s), 4.10-4.20 (2H, m), 4.75 (1H, m). The diastereomeric ratio was confirmed by ^{13}C-NMR.

4. Selected spectral data for **2a** and **2b**. **2a**: ^{1}H-NMR δ ($CDCl_3$) 3.25, 3.35 (1H each, br.s), 3.59 (1H, m), 3.79 (1H, m), 4.15 (1H, m), 4.62 (1H, m). MS *m/z* 324 (M^+), 295, 227. **2b**: ^{1}H-NMR δ ($CDCl_3$) 3.50-3.65 (2H, m), 3.98 (1H, m), 4.64 (1H, m), 4.66 (1H, dd, *J*=2.3, 4.2 Hz).
5. Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.*, **1973**, 95, 512. 270 MHz ^{1}H-NMR for (+)-MTPA ester of (1*S*,2*R*)-**3**: δ ($CDCl_3$) 3.56 (3H, q), 4.67, 4.68 (1H each, d,*J*=15.0 Hz), 5.38 (1H, m), 7.57 (2H, m). ^{1}H-NMR for (+)-MTPA ester of (1*R*,2*S*)-**3**: δ ($CDCl_3$) 3.59 (3H, q), 4.76, 4.78 (1H each, d,*J*=15.0 Hz), 5.43 (1H, m), 7.64 (2H, m).
6. The authentic (1*R*,2*S*)-**3** ($[\alpha]_D^{24}$ +27.1 (*c*=0.7, $CHCl_3$)) was synthesized from (*S*,*S*)-cycloalkane-1,2-diols[9] *via* monoprotection of the hydroxy group and subsequent inversion of the hydroxy function by Ikegami's method.[10] Obtained (1*S*,2*R*)-**3** (72% e.e.) in entry 1 of Table II: $[\alpha]_D^{24}$ -20.1 (*c*=0.7, $CHCl_3$). ^{1}H-NMR δ ($CDCl_3$) 2.73 (1H, br.s), 3.40 (3H,s), 3.57 (2H, t, *J*=4.3 Hz), 3.68 (1H, m), 3.73 (1H, t, *J*=4.3 Hz), 3.77-3.85 (2H, m), 4.80 (2H, s).



7. The application of this reaction to *meso*-cyclopentane-1,2-diol derivatives (*syn*- and *anti*-**7**) and cycloheptane derivative **9** (one of four possible diastereomers) gave products **8** and **10** of low e.e. The absolute configuration of these products was not determined.



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