Novel Method for Deracemization: Transformation of Racemic *syn*-1,3-Polyols to Enantiomerically Pure *anti*-1,3-Polyols by Enantiodifferentiating Inversion of Stereogenic Centers

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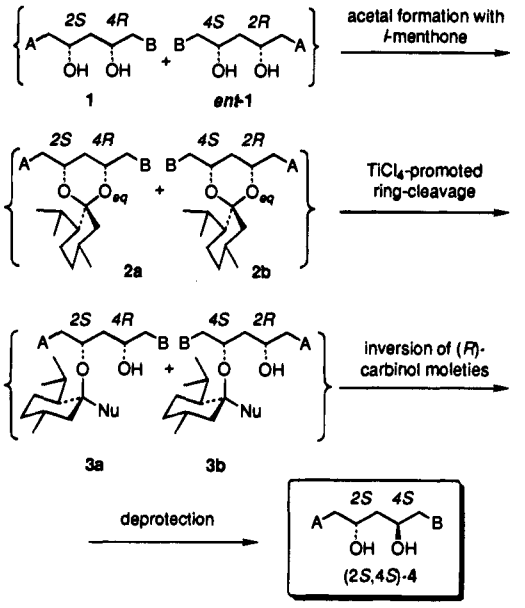
Enantiodifferentiating reactions of racemic substrates are of increasing importance in asymmetric synthesis, expanding the scope of potential substrates, which has been limited to prochiral compounds. Kinetic resolution[1] is an example, but it suffers from a theoretical yield of 50%. Dynamic kinetic resolution[2] in which racemic substrates undergo in situ racemization during reaction allows, in principle, conversion to enantiomerically pure products in 100% yield, but the substrates are limited to those possessing chirally labile stereogenic centers. We report here a transformation of racemic *syn*-1,3-diols to the enantiomerically pure *anti*-1,3-diols, a novel example of a third type in which racemic substrates are transformed to enantiomerically pure products by enantiodifferentiating inversion of stereogenic centers.[3]

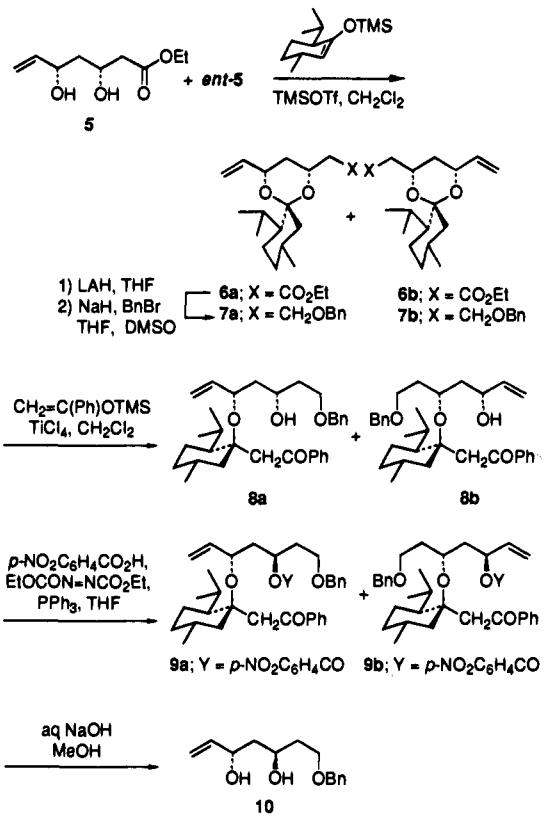
As shown in Scheme 1, enantiomers of *syn*-diols (2*S*,4*R*)-**1** and (2*R*,4*S*)-*ent*-**1** are transformed to the same *anti*-diols (2*S*,4*S*)-**4** by selective inversion of the *R* stereogenic centers (4*R* for **1** and 2*R* for *ent*-**1**).[4] Such transformation can be realized in a stepwise manner by enantiodifferentiating protection of the (*S*)-carbinol moieties and subsequent inversion of the free (*R*)-carbinol moieties. In our approach using *l*-menthone as a chiral template,[5] the racemic diols are first converted into a mixture of menthonides **2a** and **2b** derived respectively from **1** and *ent*-**1**.[6] The mixture is then subjected to a $TiCl_4$-promoted ring-cleavage reaction. Selective cleavage of the equatorial carbon−oxygen bonds[5,8] leads to the formation of **3a** and **3b**, in which the (*S*)-carbinol moieties are protected in an enantiodifferentiating manner. Finally, enantiomerically pure *anti*-diol (2*S*,4*S*)-**4** is obtained by inversion of the free (*R*)-carbinol moieties and deprotection. Asymmetric synthesis of *anti*-heptenetriol derivative **10** starting from racemic *syn*-diol *rac*-**5** (Scheme 2) exemplifies the approach.

Treatment of *rac*-**5** with *l*-menthone enol trimethylsilyl ether (1.8 equiv)[9] in the presence of TMSOTf (0.2 equiv) gave a 1:1 mixture of menthonides **6a** and **6b**, derived respectively from **5** and *ent*-**5**, in 91% yield. Without separation, **6a**,**b** were converted into the benzyl ether derivatives **7a**,**b** in two steps (80% yield). Upon treatment of the mixture of **7a** and **7b** with $TiCl_4$ (1.1 equiv) and acetophenone enol trimethylsilyl ether (1.1 equiv), the ring cleavage took place exclusively at the equatorial carbon oxygen bonds[5,8] to afford a 1:1 mixture of **8a** and **8b** in 80% yield. Inversion of the free carbinol moieties

Scheme 1



Scheme 2



in **8a**,**b** was achieved by esterification with *p*-nitrobenzoic acid[10] under the conditions of the Mitsunobu reaction[11] to give a 1:1 mixture of **9a** and **9b** in 79% yield. Finally, treatment of **9a**,**b** under basic conditions furnished *anti*-heptenetriol **10** ($[\alpha]^{25}_D$ −17.9° (*c* 1.19, $CHCl_3$)) of >95% ee in 85% yield.[12] The *anti* stereochemistry of **10** was confirmed by ^{13}C NMR analysis of

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(2) Kitamura, M.; Tokunaga, M.; Noyori, R. *J. Am. Chem. Soc.* **1993**, *115*, 144 and references cited therein.
(3) Harada, T.; Kurokawa, H.; Oku, A. *Tetrahedron Lett.* **1987**, *28*, 4847.
(4) Groups A and B are arbitrarily chosen as highest-priority groups in Scheme 1.
(5) For review, see; Harada T, Oku A. *Synlett* **1994**, 95.
(6) Formation of diastereomeric menthonides is not feasible for steric reasons. For a relevant discussion, see refs 5 and 7.
(7) Harada, T.; Kurokawa, H.; Kagamihara, Y.; Tanaka, S.; Inoue, A.; Oku, A. *J. Org. Chem.* **1992**, *57*, 1412.
(8) Harada, T.; Hayashiya, T.; Wada, I.; Iwa-ake, N.; Oku A. *J. Am. Chem. Soc.* **1987**, *109*, 527.
(9) Harada, T.; Tanaka, S.; Oku, A. *Tetrahedron* **1992**, *48*, 8621.
(10) Dodge, J. A.; Trujillo, J. I.; Presnel, M. *J. Org. Chem.* **1994**, *59*, 234 and references cited therein.
(11) (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Hughes, D. L. *Org. React. (N.Y.)* **1992**, *42*, 335.
(12) The ee was determined by ^1H NMR analyses of the derived bis-(*R*)- and -(*S*)-MTPA esters.
(13) Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511.

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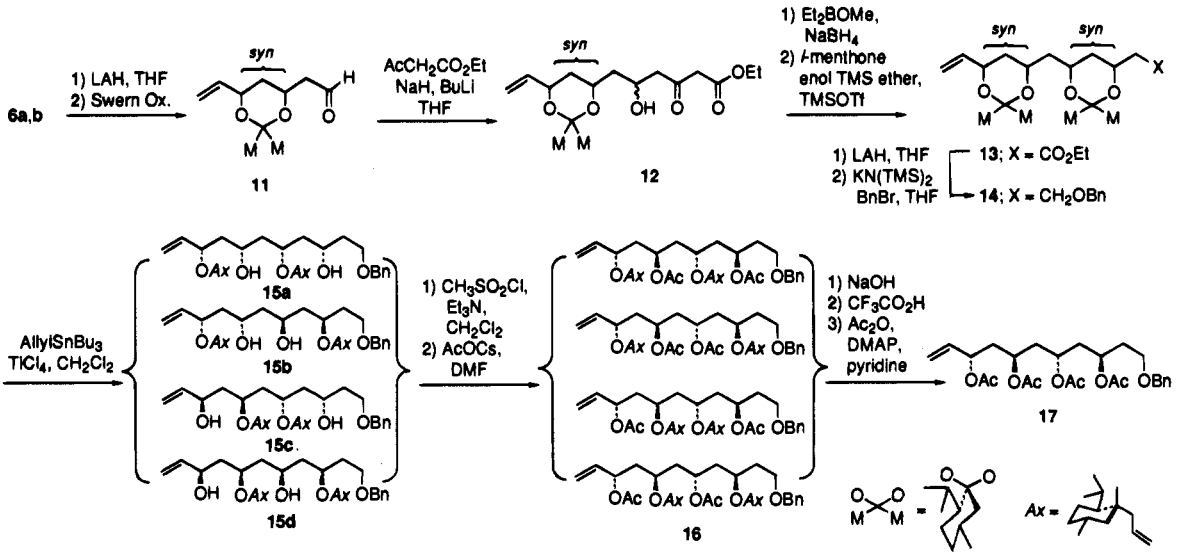
Scheme 3



the acetonide derivatives ($(CH_3)_2C(O-)_2$, δ 24.57 and 25.23 ppm in C_6D_6).[13]

One of the characteristic features of the present approach is that the sequence of reactions can be performed without separation of isomeric intermediates. The feature is advantageous especially in the asymmetric synthesis of alternating polyol chains found in polyene macrolide antibiotics[14,15] as illustrated in the asymmetric synthesis of (3*S*,5*R*,7*S*,9*R*)-pentol derivative **17** (Scheme 3).[16]

A 1:1 mixture of menthonides **6a**,**b** was converted into the aldehyde derivative **11** (78% yield) in two steps. Treatment of **11** with the dianion of ethyl acetoacetate yielded hydroxy keto ester **12** as a mixture of four possible diastereomers (*ca.* 6:6:4:3, 62% yield). Chelation-controlled reduction (Et_2BOMe, $NaBH_4$)[17] and the subsequent acetalization of the resulting *syn*-diols afforded dimenthonides **13a**–**e** (50% overall yield),[18] which were then converted into the benzyl ethers **14** in 97% yield.

Ring-cleavage reaction of **14** was examined first by use of acetophenone enol silyl ether as a nucleophile. However, the reaction mainly afforded the corresponding monocleavage products (83%) and the dicleavage products were obtained only in 10% yield.[19] We then examined the use of more powerful nucleophiles in combination with $TiCl_4$. Reaction using ketene *S*,*O*-acetal CH_2=C(OTMS)S^{t}Bu gave the corresponding dicleavage products in 51% yield together with monocleavage products (16%). The best result was obtained when allyltributyltin (1.8 equiv) was employed as a nucleophile at −40 °C. The reaction afforded dicleavage products **15** in 60% yield together with the monocleavage products (22%).[20] Mesylation of the mixture followed by treatment with cesium acetate in DMF at 50 °C[21] furnished diacetates **16** in 52% yield.[22] Finally, saponification of the mixture followed by removal of the allylneomenthyl group upon treatment with trifluoroacetic acid in CH_2Cl_2[23] and subsequent acetylation afforded tetraacetate **17** ($[\alpha]^{25}_D$ +2.94° (*c* 0.34, MeOH)) in 59% overall yield. It should be noted that intermediates of the present synthesis (**12**–**16**) are mixtures of stereo- and/or regioisomers exhibiting complex overlapping signals in their ^{1}H NMR spectra, but the final products showed clear resonaces of a single diastereomer **17** in ^{1}H and ^{13}C NMR analysis. The 1,3-*anti* and 5,7-*anti* stereochemistry of **17** was confirmed by ^{13}C NMR analysis of the diacetonide derivatives ($(CH_3)_2C(O-)_2$, δ 24.94, 25.15, 25.20, and 25.53 ppm in C_6D_6).[13]

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Supporting Information Available: Experimental procedures and spectral data for **5**–**17** and acetonide derivatives of **10** and **17** as well as the determination of the ee of **10** (10 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(16) Polyol chains of the same configurations are found in polyene macrolides such as lienomycin, mycoticin A and B, and roxaticin.

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(19) ^{1}H-NMR analysis of the dicleavage products showed that one of the four possible isomers was produced preferentially.

(20) The stereoselctivity of the reaction, i.e., equatorial vs. axial C–O bond cleavage, was uncertain at this point. A model reaction of menthonides **7a**,**b** with allyltributyltin under similar conditions gave exclusively the corresponding two isomeric, equatorial C–O bond cleavage products in 94% yield.

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