Facile Synthesis of Enantiopure 1,2-Diols and Terminal Epoxides from Chiral β-Hydroxy Sulfides

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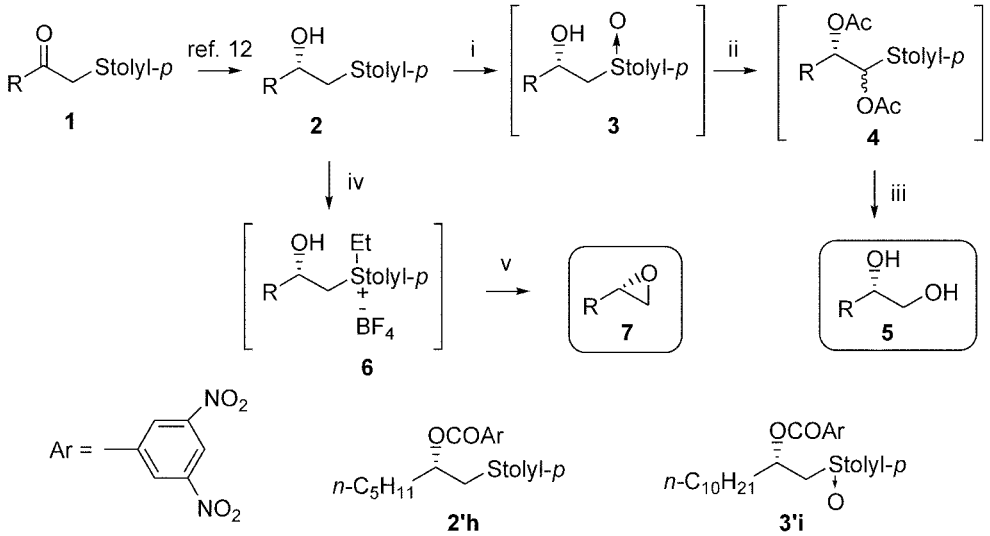
Enantiomerically pure terminal 1,2-diols are important synthetic intermediates.[1] A number of synthetic methods for these compounds have been extensively investigated.[2] Foremost among these methods is the catalytic asymmetric dihydroxylation of olefins.[2a] Another potentially powerful route into optically active 1,2-diols is the asymmetric reduction of α-hydroxy (or α-protected hydroxy) ketones.[3] Also, enantiopure aromatic and aliphatic terminal epoxides are extremely useful chiral building blocks for the synthesis of a variety of pharmaceutical products[4] and can be used as key intermediates for the synthesis of other biologically active substances[5] and chiral ligands.[6] In recent years, many chemical and biological methods for the synthesis of optically active epoxides, such as asymmetric epoxidation of olefins, resolution of racemic epoxides and indirect chemical transformation, have been reported. However, the direct asymmetric epoxidation of terminal olefins such as styrene analogues catalyzed by salen and porphyrin ligands,[7] or chiral dioxiranes[8] has been only moderately successful to give 50-70% ee. The resolution method of racemic epoxides with biocatalytic hydrolysis[9] and chemically hydrolytic resolution methods,[10] both suffer from the fact that the theoretical yield is limited to 50%. Recently we reported an efficient synthesis of chiral terminal epoxides with high enantiomeric purity *via* asymmetric reduction of α-sulfonyloxy ketones.[11] This method was very effective for the synthesis of aromatic and hindered aliphatic epoxides to give very high enanioselectivity, whereas less effective for the case of unhindered aliphatic epoxides, such as 40% ee for 1,2-epoxynonane. Very recently, we successfully achieved asymmetric reduction of β-keto sulfides to give β-hydroxy sulfides, which provided good enantioselcectivity (73-74% ee) for even unhindered aliphatic analogues.[12] These β-hydroxy sulfides could be used as starting materials for the preparation of non-racemic 1,2-diols and epoxides *via* Pummerer reaction[13] and intramolecular S_N2 reaction.[14] We wish to report here an efficient synthesis of enantiopure 1,2-diols and epoxides from non-racemic β-hydroxy sulfides.

The synthetic routes for preparation of chiral 1,2-diols **5** and terminal epoxides **7** from chiral β-hydroxy sulfides **2** are outlined in Scheme 1. The starting material **2** was prepared by CBS-oxazaborolidine-catalyzed borane asymmetric reduction of β-keto sulfides **1** as previously reported.[11] The reduction of aromatic and hindered aliphatic analogues (**1a-**



a: R = Ph; **b**: R = *p*-MeC_6H_4; **c**: R = *p*-ClC_6H_4; **d**: R = *p*-FC_6H_4; **e**: R = 2-naphthyl; **f**: R = *t*-Bu; **g**: R = cyclohexyl; **h**: R = *n*-C_5H_{11}; **i**: R = *n*-$C_{10}H_{21}$

Scheme 1. Reaction conditions: i. *m*-chloroperbenzoic acid (1.1 eq), CH_2Cl_2, 0 °C, 96-99%. ii. NaOAc (2.5 eq), Ac_2O, reflux. iii. $NaBH_4$ (1.5 eq), 6 N NaOH, r.t., 68-75% from **2**. iv. Et_3OBF_4 (1.2 eq), r.t. v. NaOH, r.t., 84-93% from **2**.

Table 1. Synthesis of **5** and **7** from Chiral b-Hydroxy Sulfides **2**

2	**5**[a]			**7**[b]		
	Yield (%)[c]	% ee	Config.	Yield (%)[c]	% ee	Config.
2a	68	99[d]	*S*	89	99[h]	*S*
2b	70	99[e]	*S*	90	99[i]	*S*
2c	69	99[e]	*S*	89	99[j]	*S*
2d	70	99[e]	*S*	91	99[h]	*S*
2e	68	99[e]	*S*	93	99[h]	*S*
2f	75	99[f]	*S*		k	
2g	71	99[g]	*S*	84	99[g]	*S*
2h	73	96[g]	*S*		k	
2i	75	99[g]	*S*	86	99[l]	*S*

[a]**5** was obtained from sulfoxidation of **2** with *m*-chloroperbenzoic acid (1.2 eq), followed by Pummerer reacion and reduction with $NaBH_4$. [b]**7** was obtained from alkylation of **2** with Et_3OBF_4 (1.2 eq), followed by epoxidation with 0.5 *N* NaOH. IR, ^1H and ^{13}C NMR spectral data of **5** and **7** obtained were identical with those reported: ref. 3a, 3b, 11a, 17, and 18. [c]Isolated yields based on **2**. [d]By HPLC analysis using Chiralcel OB chiral column. [e]By HPLC analysis using Whelk-O1chiral column. [f]By GC analysis using α-Dex chiral column. [g]By GC analysis using G-TA chiral column. [h]By GC analysis using β-Dex chiral column. [i]By HPLC analysis using Chiralcel OD chiral column. [j]By HPLC analysis using Chiralpak OT chiral column. [k]Not examined. [l]By optical rotation value: ref. 5.

g) provided the corresponding β-hydroxy sulfides **2a**-**g** with 99% ee, whereas the case of unhindered aliphatic analogues, such as **1h** and **1i**, afforded **2h** with 74% ee and **2i** with 79% ee. Optical purity of **2h** was increased from 74% ee to 96% ee by recrystallization of its 3,5-dinitrobenzoate derivative (**2h**) from ethyl ether, followed by hydrolysis with 2 *N* NaOH. For the case of **2i**, its optical purity was upgraded to 99% ee by recrystallization of a diastereomeric mixture of the corresponding sulfinyl ester (**3i**) from dichloromethane-hexane, followed by hydrolysis and deoxygenation with $TiCl_3$.[15] When β-hydroxy sulfides **2** obtained were treated with 1.1 equiv of *m*-chloroperbenzoic acid in dichloromethane at 0 °C, the corresponding sulfoxides **3** were obtained in 96-99% yields. It was subsequently reacted with 2.5 equiv. of sodium acetate in acetic anhydride at reflux condition to give 1,2-diacetoxy sulfides **4**. Without further purification, these were directly treated with 1.0 equiv. of sodium borohydride in 6 *N* NaOH at room temperature to give nearly enantiopure 1,2-diols **5** in 68-75% yields from **2**. During sulfoxidation, Pummerer reaction and reduction, no racemizations were observed.

Next we examined one-pot conversion of optically active sulfides **2** to terminal epoxides **7**. For this, we carried out reaction of **2** with 1.2 equiv of Et_3OBF_4 in dichloromethane at room temperature, followed by direct treatment of the resulting sulfonium salts **6** with 0.5 *N* NaOH in water.[16] The reaction provided **7** with 96-99% ee in 84-93% yields. Optical purities of product **7** were determined by GC or HPLC analysis using chiral column. The results are summarized in Table 1.

In summary, we have established a simple and efficient synthesis of enantiopure 1,2-diols and terminal epoxides starting from chiral β-hydroxy sulfides.

Experimental Section

General. The reactions were monitored by TLC using silica gel plates and the products were purified by flash column chromatography on silica gel (Merck; 230-400 mesh). NMR spectra were recorded at 200, 300 or 400 MHz for ^1H and 50, 75 or 100 MHz for ^{13}C using Me_4Si as the internal standard in $CDCl_3$. Optical rotations were measured with a high resolution digital polarimeter. Melting points were uncorrected. Enantiomeric excesses (e.e.s) of **2**, **5** and **7** were determined with a HPLC analysis using a 25 cm Whelk-O1 (Regis), Chiralcel OB, Chiralcel OD or Chiralpak OT (Daicel) chiral column and GC analysis using a 30 m α- or β-Dex 120 (Supelco) and G-TA (Astec) capillary chiral column. Most of organic compounds utilized in this study were commercial products of the highest purity. THF was distilled over sodium benzophenone ketyl and stored in ampules under nitrogen atmosphere. Chiral β-hydroxy sulfides **2** used as starting materials were prepared as previously reported.[12] IR, ^1H and ^{13}C NMR spectral data of **2** obtained were identical with those reported.[12]

Preparation of 5: **General procedure**. To a solution of **2** (2 mmol) in dichloromethane (10 mL) was added dropwise a solution of *m*-chloroperbenzoic acid (2.2 mmol) in dichloromethane (15 mL) for 10 min at 0 °C. After the mixture was stirred for 30 min at room temperature, organic layer was separated, washed with 2 *N* NaOH (2 × 10 mL) and brine (2 × 10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated to give **3**, which could be used for the following reaction without further purification. A stirred mixture of **3** and NaOAc (5 mmol) in acetic anhydride (6 mL) was heated to reflux for 3 h. After excess of acetic anhydride and acetic acid were removed under reduced pressure, the residue was suspended in benzene (10 mL) and passed through silica gel. Crude 1,2-diacetoxy sulfides **4** obtained from the evaporation of the solvent followed by drying under vacuum was dissolved in ethanol (10 mL). To this was added $NaBH_4$ (3 mmol) in 6 *N* NaOH (1 mL) and stirred for 4 h at room temperature. After the reaction mixture was extracted with ether (3 × 10 mL), the combined extracts are concentrated. to give 5, which was further purified by a flash column chromatography on silica gel (230-400 mesh) using ethyl acetate/hexane (2/1) as the eluent.. (*S*)-**5a**: 68% yield; mp 65-6 °C (lit.[3a] mp 65-7 °C); $[\alpha]_D^{22}$ +38.94 (*c* 3.62, EtOH) {lit.[3a] $[\alpha]_D^{22}$ +38.91 (*c* 3.81, EtOH), >99% ee, *S*}. (*S*)-**5b**: 70% yield; mp 75-7 °C (lit.[3a] mp 64-6 °C); $[\alpha]_D^{22}$ +69.14 (*c* 1.14, $CHCl_3$) {lit.[9b] $[\alpha]_D^{23}$ -67 (*c* 0.9, $CHCl_3$), 97% ee, *R*}. (*S*)-**5c**: 69% yield; mp 94-5 °C; $[\alpha]_D^{22}$ +64.31 (*c* 1.21, $CHCl_3$) {lit.[9b] $[\alpha]_D^{23}$ -60 (*c* 0.9, $CHCl_3$), 98% ee, *R*}. (*S*)-**5d**: 70% yield; mp 57-8 °C (lit.[9c] mp 55-7°C); $[\alpha]_D^{22}$ +64.83 (*c* 1.21, $CHCl_3$) {lit.[9b] $[\alpha]_D^{23}$ -63 (*c* 1.06, $CHCl_3$), 98% ee, *R*}. (*S*)-**5e**: 68% yield; mp 134-6 °C (lit.[3a] mp 133-5 °C); $[\alpha]_D^{22}$ +34.89 (*c* 1.00, EtOH) {lit.[9b] $[\alpha]_D^{23}$ =+32.60 (*c* 1.02, EtOH), 96% ee, *S*}. (*S*)-**5f**: 75% yield; mp 37-8 °C; $[\alpha]_D^{22}$ +21.92 (*c* 1.06, $CHCl_3$) {lit.[3b] $[\alpha]_D^{22}$ +21.51 (*c* 1.01, $CHCl_3$), 97% ee, *R*}. (*S*)-**5g**: 71% yield; mp 50-1 °C (lit.[3a] mp 50-2 °C); $[\alpha]_D^{22}$ +5.10 (*c* 1.15,

$CHCl_3$) {lit.[3a] $[\alpha]_D^{22}$ 4.97 (*c* 1.21, $CHCl_3$), 97% ee, *R*}. (*S*)-**5h**: 73% yield; mp 47-9 ºC (lit.[17] mp 48-50 ºC); $[\alpha]_D^{22}$ +16.4 (*c* 2.7, EtOH) {lit.[17] $[\alpha]_D^{23}$ = -16.6 (*c* 11.9, EtOH), 100% ee, *R*}. (*S*)-**5i**: 75% yield; mp 67-69 ºC (lit.[18] mp 71-2 ºC); $[\alpha]_D^{20}$ = -12.1 (*c* 1.1, EtOH) {lit.[18] $[\alpha]_D^{23}$ = 10.1 (*c* 2.55, EtOH), 89% ee, *S*}.

Preparation of 7: **General procedure**. To a solution of **2** (2 mmol) in dichloromethane (2 mL) was added Et_3OBF_4 (2.4 mmol) and the reaction mixture was stirred for 1 h at room temperature. To this was added directly 0.5 *N* NaOH in water (12 mL, 6 mmol) and stirred for 10 h at the same temperature. After organic layer was separated, aqueous layer was extracted with ether. The combined extract was evaporated under reduced pressure. The crude oxiranes **7** obtained were further purified by a flash column chromatography on silica gel (230-400 ethyl acetate/hexane (1/2) as the eluent. (*S*)-**7a**: 89% yield; oil; $[\alpha]_D^{22}$ +44.12 (*c* 1.06, C_6H_6) {lit.[11a] $[\alpha]_D^{22}$ +44.5 (*c* 1.15, C_6H_6), 99% ee, *S*}. (*S*)-**7b**: 90% yield; oil; $[\alpha]_D^{22}$ -26.1 (*c* 1.12, C_6H_6) {lit.[11a] $[\alpha]_D^{22}$ -25.9 (*c* 1.02, C_6H_6), 97% ee, *S*}. (*S*)-**7c**: 89% yield; oil; $[\alpha]_D^{22}$ +25.8 (*c* 1.03, $CHCl_3$) {lit.[11a] $[\alpha]_D^{22}$ +25.5 (*c* 1.00, $CHCl_3$), 97% ee, *S*}. (*S*)-**7d**: 91% yield; oil; $[\alpha]_D^{22}$ +19.9 (*c* 1.25, $CHCl_3$) {lit.[11a] $[\alpha]_D^{22}$ +19.2 (*c* 1.20, $CHCl_3$), 98% ee, *S*}. (*S*)-**7e**: 89% yield; mp 66-8 ºC (lit.[11a] 68-9 ºC); $[\alpha]_D^{22}$ +11.2 (*c* 1.08, $CHCl_3$) {lit.[11a] $[\alpha]_D^{22}$ +11.4 (*c* 1.11, $CHCl_3$), 100% ee, *S*}. (*S*)-**7g**: 84% yield; oil; $[\alpha]_D^{20}$ +2.16 (*c* 0.93, $CHCl_3$) {lit.[11a] $[\alpha]_D^{22}$ +2.1 (*c* 0.88, $CHCl_3$), 96% ee, *S*}. (*S*)-**7i**: 86% yield; oil; $[\alpha]_D^{20}$ -6.67 (*c* 0.82, $CHCl_3$) {lit.[5] $[\alpha]_D$ -6.55 (*c* 1.10, $CHCl_3$), >95% ee, *S*}.

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