

ACCURATE DETERMINATION OF THE INTRINSIC RACEMIZATION IN CHIRAL SYNTHESIS VIA ENANTIOMER RESOLUTION OF UNDERIVATIZED VICINAL DIOLS

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Summary: The accurate assessment of the intrinsic racemization (down to 0.01%), inherent to reactions typically applied in chiral synthesis, demands for (i) a precursor of almost 100% e.e. (e.g., S-1a, e.e. $\geq 99.99\%$), and (ii) a reliable method for the determination of e.e. of the product (e.g., the derivatization-free enantiomer resolution of the vicinal diol 3a by GC on Chirasil-Val).

Vicinal diols are useful intermediates in chiral synthesis¹. The enantiomeric purity (e.e.) is usually determined after derivative formation. Thus, enantiomeric pairs of cyclic boronates², acetals², and carbonates³ were separated by GC. Mosher's esters were separated by HPLC on either achiral⁴ or chiral⁵ phases, N-TFA-glycyl esters⁶ and perfluoroacyl esters^{7,8} by GC on chiral phases. However, these derivatization reactions are time consuming and include the danger of side reactions and racemization. Therefore, we investigated the direct enantiomer resolution of the underivatized diols by GC on deactivated glass capillary columns coated with Chirasil-Val⁹. This technique allowed (i) to conveniently determine the e.e. of diols obtained from chiral synthesis, and (ii) to assess the degree of racemization during derivatization.

Diol samples of almost 100% enantiomeric purity were prepared, as follows. Diazotization of 1 mol S-valine¹⁰ or S-leucine¹¹ with 3 mol NaNO₂ in 0.85 L 4N H₂SO₄ for 5 h at 5°C and recrystallization of the dicyclohexyl ammonium salts from ethyl acetate gave the hydroxy acids S-1a and S-1b, respectively, e.e. $\geq 99.99\%$ for the 3-pentyl ester¹² S-2a, as determined by GC on D-Chirasil-Val, cf. Figure 1, and e.e. $99.85 \pm 0.01\%$ for the derivative¹³ S-2b, as determined on L-Chirasil-Val, cf. Table 1. Reduction of 0.1 mol 1 with 0.25 mol LiAlH₄ in 150 mL diethyl ether for 5 h at 25°C, quenched by the addition of 15 mL water and 250 mL 2 N H₂SO₄, gave the diols S-3a, e.e. $\geq 99.96\%$, and S-3b, e.e. $\geq 99.98\%$, as determined by direct enantiomer resolution on L-Chirasil-Val, cf. Figure 1, resolution factors $\alpha(50^\circ\text{C}) = 1.029$ and 1.090, respectively.

The exceedingly high enantiomeric purity of the key compound S-1a served to establish the small, but significant degree of racemization encountered, with unprecedented sensitivity. Almost no apparent inversion of configuration ($\leq 0.01\%$) was observed in two frequently used reactions, i.e., the acid catalyzed esterification of S-1a to S-2a, and the LiAlH₄ reduction of S-1a to S-3a. The multi step formation of the amide S-2b was accompanied by a small, but detectable degree of inversion (appr. 0.07%). Similar results, but with less certainty, were obtained for the R-antipodes, cf. Table 1.

Derivatization of the free diols 3 with N-TFA-glycyl chloride in dichloromethane⁶ to the esters 4 gave up to 0.2% inversion. As judged from the derivative 4c, the fairly high e.e. of commercial S-ethyl lactate (FLUKA, e.e. 99.0%) was almost completely preserved during LiAlH₄ reduction^{1a,2} to S-propanediol 3c, too.

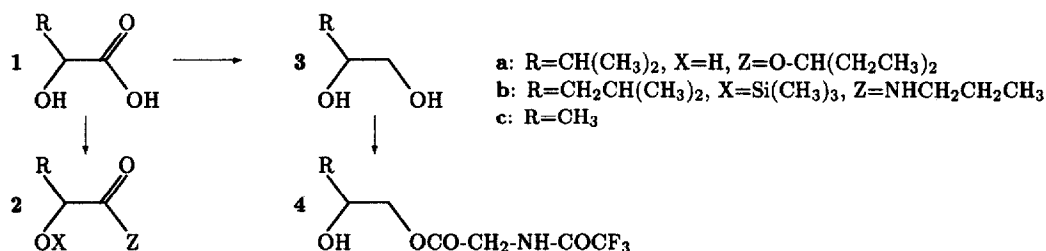


Figure 1: Enantiomeric purity of **2a** on D-Chirasil-Val (capillary column U5, 20 m x 0.3mm); **3a**, **3b**, and **4b** on L-Chirasil-Val (capillary column G7, 25 m x 0.3mm); FID; 0.45 kg/cm² H₂; split ratio 1 : 50; isothermal 45°C for **3a**, 56°C for **3b**, 60°C for **2a**, and 115°C for **4b**, respectively.

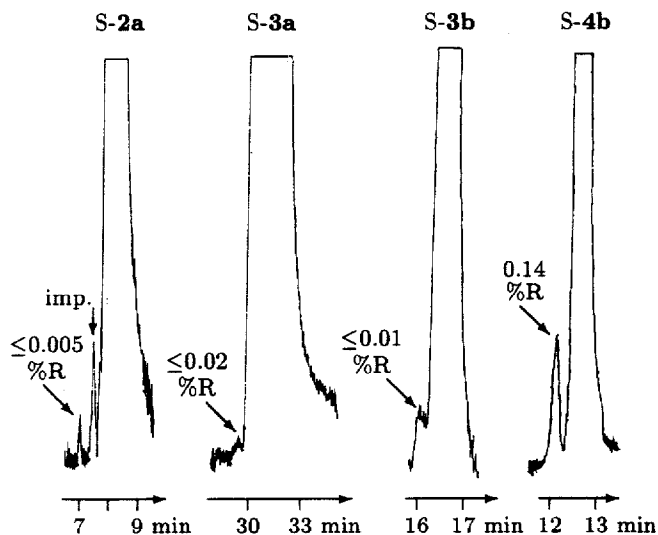


Table 1: Chiroptical Properties of Hydroxy Acids, Diols, and Derivatives thereof.

Hydroxy Acid	$[\alpha]_D^{20}$ (c 1 CHCl ₃)	
S-1a	+18.3°	
R-1a	-18.3°	
S-1b	+5.5°	
R-1b	-5.5°	
Diol	α_D^{20} (neat, 1 dm)	e.e. [%]
S-3a	+7.39°	≥99.96
R-3a	-7.29°	
S-3b	-13.75°	≥99.98
R-3b	+13.82°	99.51 ±0.06
Deriv.	e.e. [%]	
S-2a	≥99.99	
R-2a	99.49	±0.03
S-2b	99.85	±0.01
R-2b	99.49	±0.03
S-4a	99.95	±0.03
R-4a	99.39	±0.01
S-4b	99.69	±0.03
R-4b	99.33	±0.04
S-4c	98.96	±0.04

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