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A DIRECT HPLC METHOD FOR THE DETERMINATION OF ENANTIOMERIC EXCESS OF SOME HIGHLY ENANTIOMERICALLY ENRICHED DERIVATIVES OF CHIRAL GLYCIDOLS

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Abstract: *A newly developed HPLC method which requires no derivatization is used to determine accurately the enantiomeric purity of some glycidol-based derivatives that have been enantiomerically enriched by recrystallization or lipase-catalyzed kinetic resolution after the Sharpless Asymmetric Epoxidation.*

The Sharpless Asymmetric Epoxidation (SAE) reaction has found wide applications in organic synthesis since its discovery in 1980.[1] While the homochiral 2,3-epoxy alcohols made from the allylic alcohols by this invention are themselves versatile, chiral synthons,[2] they also provide an entry to the synthesis of a variety of glycidol-based derivatives from which many optically active, complex organic molecules can be constructed. One attractive feature of these derivatives is their high enantiomeric purity achievable from enrichment in the recrystallization steps exemplified by some of the crystalline arenesulfonate derivatives.[3] As a manufacturer of derivatives of homochiral 2,3-epoxy alcohols, we are particularly interested in the exploitation of recrystallization technique for upgrading the enantiomeric purity of these compounds. This necessitates the development of a highly accurate and convenient analytical method for the determination of their enantiomeric excess. The most commonly employed derivatization method[3] using Mosher acid chloride not only is tedious but also requires very careful preparative column chromatography to ensure complete recovery of the Mosher ester made. We report here the enantiomeric resolution of nine representative compounds by a direct HPLC method which altogether utilizes a combination of only two commercially available columns and four organic solvents to achieve complete, baseline separations. With this method, which requires no derivatization, we were able to determine accurately and unambiguously the enantiomeric purity of

these synthetically useful derivatives of chiral glycidols that had been enantiomerically enriched to >96% ee by the recrystallization technique or the lipase-catalyzed kinetic resolution method.

The glycidyl arenesulfonate derivatives (**1-8**) and trityl glycidol (**9**) were synthesized from the corresponding homochiral 2,3-epoxy alcohols according to published procedures.[4,5] Conditions for the chromatographic separation of these compounds are summarized in Table I. The two normal phase columns used are a Chiralpak® AS column and a Chiralcel® OB-H column purchased from Chiral Technologies, Inc. No derivatization is necessary to achieve baseline separation of these enantiomers with the selected isocratic solvent mixtures (Figure 1). Hence, even the actual sulfonation reaction mixtures can be conveniently analyzed by this direct method prior to product isolation. It is noteworthy that our method is significantly better than the one previously reported [6] for the separation of glycidyl tosylate (**1**) and glycidyl 3-nitrobenzenesulfonate (**2**) in terms of resolution and speed of the analyses.

Table I. Enantiomeric Separation of Derivatives of Chiral Glycidols by HPLC

Compd[a]	Config	Enrich. Method[b]	%ee	Column[c]	r[d]	Eluent[e] (v/v)		T_r (min)[f]	Elution Order	α[g]	R_s[h]
1	2S	A	96.3	OB-H	0.8	7/3	H/E	20.1, 23.7	S, R	1.18	2.52
2	2S	A	97.7	AS	1.2	8/2	H/I	28.4, 31.8	R, S	1.12	1.82
3	2S	A	89.7	AS	0.6	95/5	C/I	30.4, 33.5	S, R	1.10	1.08
3	2R	B	97.6	AS	0.6	95/5	C/I	30.4, 33.5	S, R	1.10	1.08
4	2R	A	94.1	OB-H	1.0	8/2	H/I	28.2, 32.3	S, R	1.15	2.01
4	2R	B	97.3	OB-H	1.0	8/2	H/I	28.2, 32.3	S, R	1.15	2.01
5	2R	A	88.0	AS	1.2	8/2	H/I	19.5, 22.8	S, R	1.17	1.96
5	2R	B	96.6	AS	1.2	8/2	H/I	19.5, 22.8	S, R	1.17	1.96
6	2S,3S	A	98.0	AS	1.0	95/5	H/I	24.4, 28.5	RR, SS	1.22	3.36
7	2R,3R	A	96.1	AS	1.2	8/2	H/I	17.5, 25.1	SS, RR	1.44	5.22
8	2S,3R	A	93.8	AS	1.2	98/2	H/I	26.3, 30.1	SR, RS	1.14	1.78
8	2S,3R	B	96.4	AS	1.2	98/2	H/I	26.3, 30.1	SR, RS	1.14	1.78
9	2S	A	97.0	AS	0.6	99/1	H/I	10.7, 12.7	S, R	1.19	2.85

[a] **1**, glycidyl tosylate; **2**, glycidyl 3-nitrobenzenesulfonate; **3**, glycidyl 4-iodobenzenesulfonate; **4**, 2-methylglycidyl tosylate; **5**, 2-methylglycidyl 3-nitrobenzenesulfonate; **6**, 3-methylglycidyl tosylate; **7**, 3-methylglycidyl 3-nitrobenzenesulfonate; **8**, cis-3-ethylglycidyl tosylate; **9**, trityl glycidol. [b] A, recrystallization method; B, lipase-catalyzed kinetic resolution method. [c] OB-H, Chiralcel® OB-H , 5 μm, 4.6 x 250 mm; AS, Chiralpak® AS, 10 μm, 4.6 x 250 mm. [d] r, flow rate, ml/min. [e] H, hexane; E, ethanol; I, isopropyl alcohol; C, cyclohexane. [f] T_r, retention time. [g] α, separation factor. [h] R_s, resolution.

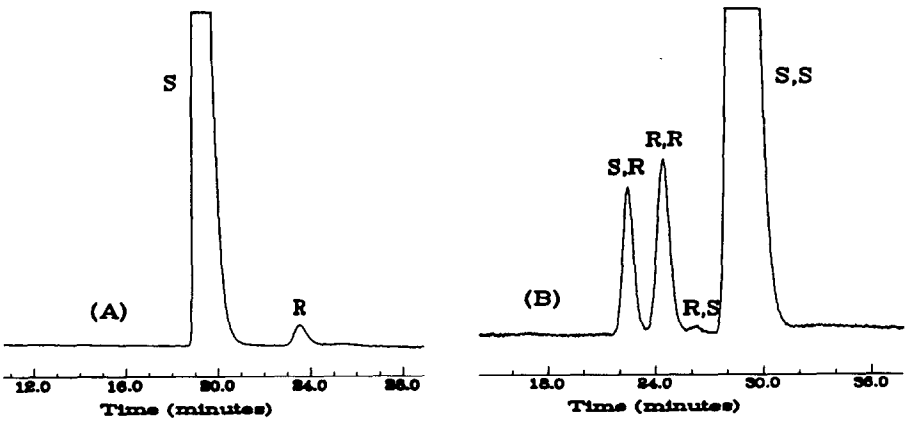

Figure 1. Chromatographic Separation of Chiral Glycidol Arenesulfonates: (A) Recrystallized Glycidyl Tosylate **1** and (B) Crude 3-Methylglycidyl Tosylate **6**.

The chromatographic separation of the sulfonation products of 3-methylglycidol obtained from asymmetric epoxidation of the commercial grade crotyl alcohol actually involves four isomers.[7] As shown in Figure 1B, all four isomers of 3-methylglycidyl tosylate (**6**) can be effectively resolved on a Chiralpak® AS column under the specified conditions. It would be very difficult to determine accurately the enantiomeric purity of the minor tosylate derived from cis-epoxide by the traditional Mosher ester method.

With the successful development of this HPLC method, we were able to evaluate the efficacy of using the recrystallization and lipase-catalyzed kinetic resolution approaches for the synthesis of these compounds in high enantiomeric purity (>96% ee). Absolute ethanol was found to be a particularly good solvent for the recrystallization of glycidyl arenesulfonates. Compounds **1**, **2**, and **9** prepared from (R)-glycidol of 89% ee can be enriched to >96% ee by two recrystallizations. The one compound that is most effectively enriched by recrystallization is **6**. In this case, a single recrystallization in hot ethanol is sufficient to upgrade the enantiomeric purity from 93% ee to 98% ee. Except for **5**, in which a loss of enantiomeric purity was actually observed upon recrystallization, **3**, **4**, **7**, and **8** all showed higher enantiomeric purity after multiple recrystallizations.[8]

Compounds **3**, **4**, **5**, and **8** which are less susceptible to enrichment by the recrystallization method can be enantiomerically enriched to >96% ee by an alternative approach. The lipase derived from *Pseudomonas sp.* had been used to catalyze the enantioselective esterification of glycidol in organic solvents.[9] Although this reaction is not highly enantioselective on short-chain aliphatic epoxy alcohols, it can be easily integrated into the Sharpless asymmetric epoxidation process to afford highly

enantiomerically enriched epoxy alcohols and glycidyl derivatives. We found that (S)-glycidol and (S)-2-methylglycidol obtained from SAE can be conveniently upgraded to >98% ee by carrying out this lipase-catalyzed esterification in methylene chloride at ambient temperature. In a typical reaction, (S)-glycidol (20 g, 90% ee) in methylene chloride (100 g) was stirred at ambient temperature with vinyl acetate (11.6 g, 0.5 equivalent) and lipase P (2 g, available from Amano). The resolution was monitored by gas chromatographic analysis[10] of the enantiomeric purity of the resolved (S)-glycidol. After reaching a satisfactory ee level, the lipase was filtered off, and the entire reaction mixture was used without further purification for the synthesis of the arenesulfonate derivatives. Cis-epoxy alcohols, which are typically obtained in significantly lower enantiomeric purity by SAE,[11] can also be resolved to >96% ee by this approach, and subsequently tosylated to obtain enantiomerically pure product as illustrated by **8**.

In summary, compounds **1-9**, as shown in Table I, can all be enantiomerically enriched to >96% ee and accurately analyzed by our direct HPLC method. This should be the standard method for the determination of enantiomeric purity of derivatives of homochiral glycidols especially in view of the complexity and ambiguity involved in the traditional Mosher ester derivatization method and the relatively small rotation values from polarimetric measurement.

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References and Notes

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7. Although the cis-allylic alcohol present in the commercial grade crotyl alcohol reacts slower than the trans-crotyl alcohol in the SAE, a 3-5% yield of the (R,S) and (S,R) epoxy alcohols is typical.
8. Compounds **4**, **5**, and **8** crystallized out from ethanol on cooling to -30° C, but their melting points are below ambient temperature.
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11. The cis-3-ethylglycidol obtained from epoxidation of cis-2-penten-1-ol has an ee of 87%, based on gas chromatographic analysis on its trifluoroacetylated derivative using an α-cyclodextrin-based column.

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