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Short communication

Simultaneous direct high-performance liquid chromatographic enantioseparation of 2-methylglycidol-1-benzyl ether and 2-methylglycerol-1-benzyl ether using a solvent-switching technique

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Abstract

Simultaneous HPLC separation of the enantiomers of 3-benzyloxy-2-methyl-1,2-propanediol and the corresponding 3-benzyloxy-2-methyl-1,2-propene oxide could be accomplished on amylose derived Chiralpak AD switching between 10% 2-propanol and 3% 1,2-dimethoxyethane as polar modifier in *n*-heptane. © 2001 Elsevier Science B.V. All rights reserved.

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1. Introduction

Carbaldehyde **1**, which is an important building block [1], can be prepared starting from mannitol [2]. This approach has the disadvantage of leading only to the (*R*)-enantiomer (six steps, total yield 13%). A biocatalytic kinetic resolution by lipase led to high enantiomeric excess (ee>95%) but again only with low yield [3]. Sharpless epoxidation of 2-methyl-3-propenol [4] and dihydroxylation of 3-benzyloxy-2-methylpropene [5] lead to products with rather low enantiomeric excesses (ee=85% and 77%, respectively). In the course of our investigation of an enantioconvergent chemo-enzymatic way to prepare (*S*)-**1** [1] we decided to investigate the enzymatic resolution of *O*-benzyl protected 2-methylglycidol **2**, which can be easily converted to **1** (Fig. 1). Protected hydroxymethyl epoxides are common substrates in biotransformation steps [6]. The development of an analytical method to determine the enantiomeric excess of epoxide **2** and diol **3** posed a problem. Previous successfully employed gas chromatographic methods to analyze chiral analogues containing a secondary carbon in position 2 [6] or tertiary substituted analogues containing a longer aliphatic chain [7] failed in the case of both benzyl ethers **2** and **3**. The gas-liquid chromatographic separation of the enantiomers of simple glycidol and glycerol analogues **4** and **5** (the latter derivatized as carbonate or acetonide) is known [8] but high-performance liquid chromatographic separation of **2** and **3** has not been described in the literature. Separation of the enantiomers of 3-tosyloxy-2-methylpropene

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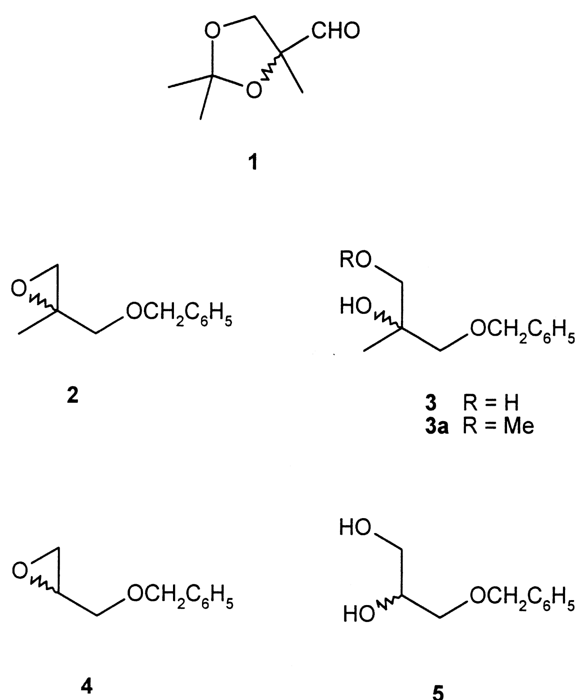

Fig. 1. Structures of carbaldehyde **1** and the investigated benzyl ethers.

oxide [9] and 2-methylglycerol as 1-(4-methoxybenzoate) [10] has been reported.

In this paper we describe our results using gas-liquid chromatography (GLC) and high-performance liquid chromatography (HPLC) chiral stationary phases and the optimized simultaneous liquid chromatographic resolution of **2** and **3** on amylose derived Chiralpak AD.

2. Experimental

2.1. Chemicals and reagents

Synthesis of **1** [2], **2**, **3** and **3a** [6] has been reported.

Compound **4** was obtained from Sigma–Aldrich (Vienna, Austria). *n*-Heptane, 2-propanol (for liquid chromatography) and 1,2-dimethoxyethane were obtained from Merck (Darmstadt, Germany).

2.2. Chromatography

GLC measurements were carried out on a Varian 3800 gas chromatograph equipped with a flame ionization detection (FID) system using H_2 as the carrier gas. Investigated columns were: Chrompak Chirasil-dex CB (β-cyclodextrin directly bonded to a dimethylpolysiloxane; 25 m×0.32 mm I.D., 0.25 μm film), ASTEC Chiraldex B-TA column (β-cyclodextrin, modified as 2,6-di-*O*-pentyl-3-trifluoroacetyl derivative; 30 m×0.25 mm I.D.), ASTEC Chiraldex G-PN (γ-cyclodextrin as the 2,6-di-*O*-pentyl-3-propionyl derivative; 30 m×0.25 mm I.D.), ASTEC Chiraldex G-PH [γ-cyclodextrin as (*S*)-2-hydroxypropyl methyl ether; 30 m×0.25 mm I.D.].

HPLC analyses were performed on a Jasco system containing a PU-980 pump equipped with an MD-910 multiwavelength detector. Investigated columns were: Daicel Chiralpak AD (250×4.6 mm), Daicel Chiralcel ODH (250×4.6 mm), Merck (3*S*,4*R*) Whelk-O1 (250×4 mm).

Hold-up times were determined using 1,3,5-tri-*tert*.-butylbenzene. Separation parameters for **3** were calculated as started from the moment of solvent switch in order to obtain relevant numbers.

3. Results and discussion

3.1. GLC approaches

Racemic secondary carbon containing compounds **4** and **5** could be separated via gas chromatography using literature conditions [8]. However, tertiary analogues **2** and **3** resisted several attempts on all four investigated columns (see Experimental). We could separate the enantiomers as 1-methoxy derivative **3a** on Chirasil-Dex [6], but the method was not practical due to many side products.

3.2. HPLC approaches

Attempts failed to separate **2** and **3** on Pirkle-type CSP Whelk-O1, which has shown previously enantioseparation abilities for compounds with these types of functional groups. [**2**: $k'_2=0.65$; **3**: $k'_2=1.05$; conditions: *n*-heptane–2-propanol (90:10), 0.5 ml/min, 20°C]. Better results were obtained using

cellulose 3,5-dimethylphenylcarbamate derived Chiralcel ODH. Diol **3** was partly separated [$k_2'=1.61$, $\alpha=1.08$, $R_s=0.88$; conditions: *n*-heptane–2-propanol (90:10), 0.5 ml/min, 20°C], epoxide **2** remained unresolved [$k_2'=0.36$; conditions: *n*-heptane–2-propanol (95:5), 0.5 ml/min, 20°C]. Use of less 2-propanol as polar modifier did not improve results.

Amylose 3,5-dimethylphenylcarbamate derived Chiralpak AD showed the relatively best performance: optimized flow and temperature conditions for diol **3** resulted in baseline separation [$k_2'=2.22$, $\alpha=1.12$, $R_s=1.85$; conditions: *n*-heptane–2-propanol (90:10), 0.5 ml/min, 20°C]. However, epoxide **2** remained poorly separated [Fig. 2A; $k_2'=0.96$, $\alpha=1.07$, $R_s=0.3$; conditions: *n*-heptane–2-propanol (98:2), 0.5 ml/min, 10°C].

Changing the polar modifier from routinely used 2-propanol to aprotic 1,2-dimethoxyethane (monoglyme), far better results for epoxide **2** could be obtained, especially after careful optimization of the temperature [Fig. 2B; $k_2'=3.50$, $\alpha=1.14$, $R_s=1.68$; conditions: *n*-heptane–monoglyme (98:2), 0.5 ml/min, 10°C].

In screening procedures it is highly desirable to observe both, educt and product simultaneously. This could be accomplished by using a solvent switching method starting with the less polar mobile phase containing monoglyme resolving **2** ($k_2'=2.49$, $\alpha=1.13$, $R_s=1.51$) and leaving the chiral diol **3** at the head of the column. Changing the mobile phase modifier to 2-propanol and optimizing flow-rates it was possible to elute baseline separated enantiomers of diol **3** [$k_2'=1.74$, $\alpha=1.16$, $R_s=1.31$; conditions: 10°C; 0-35 min: *n*-heptane–monoglyme (97:3), 0.5 ml/min, 35-45 min: *n*-heptane–2-propanol (90:10), 0.75 ml/min, 45-80 min: *n*-heptane–2-propanol

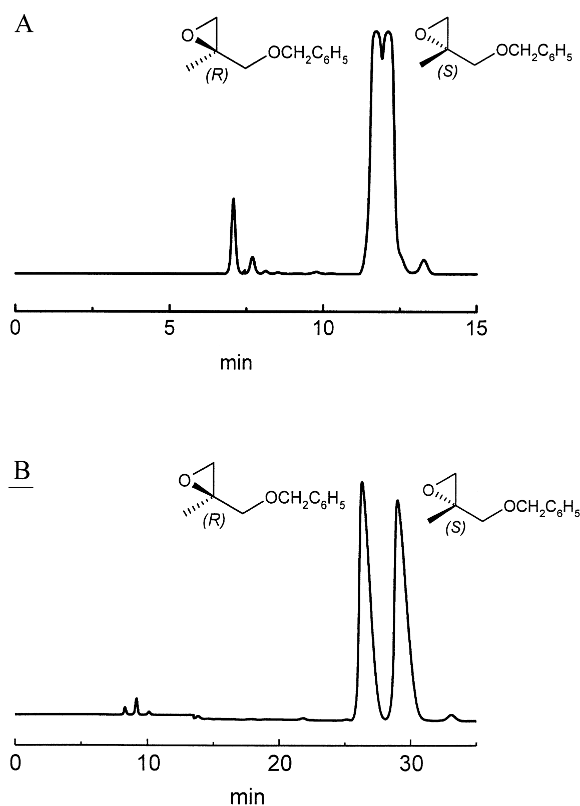

Fig. 2. Effects on the separation of racemic epoxide **2** using 2% 2-propanol (A) or monoglyme (B) as polar modifier in *n*-heptane (Chiralpak AD, conditions see Results and discussion).

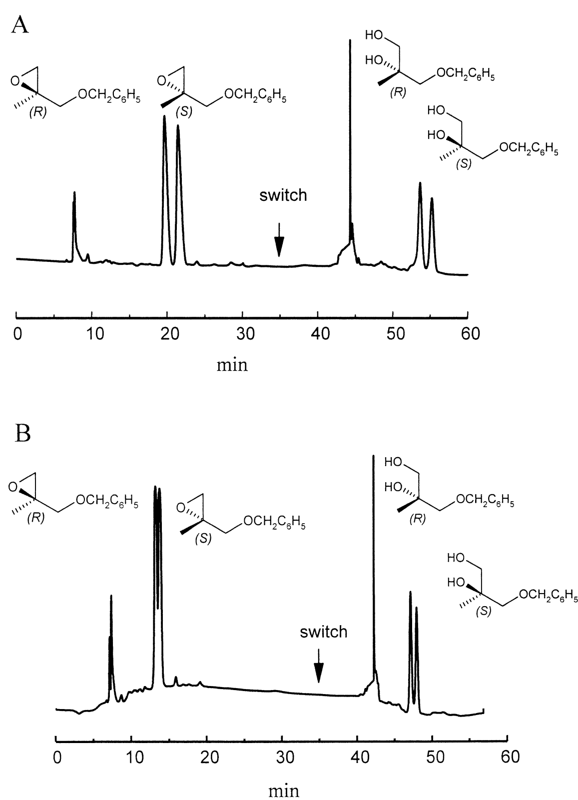

Fig. 3. Separation of epoxide **2** and diol **3** on Chiralpak AD using optimized conditions (A) and slightly different conditions (B) (see Results and discussion).

(90:10), 0.5 ml/min, Fig. 3A]. We can show in Fig. 3B, that small changes of the optimized protocol give far less useful results [**2**: $k'_2=1.27$, $\alpha=1.09$, $R_s=0.88$; **3**: $k'_2=0.89$, $\alpha=1.12$, $R_s=1.13$; conditions: 10°C, 0-35 min: *n*-heptane–monoglyme (96:4), 0.5 ml/min, 35-55 min: *n*-heptane–2-propanol (90:10), 0.75 ml/min, 55-80 min: *n*-heptane–2-propanol (90:10), 0.5 ml/min].

4. Conclusions

We have shown, that carefully chosen separation conditions in combination with a solvent switching technique lead to a simultaneous HPLC enantioseparation of 2-methylglycidol-1-benzyl ether **2** and 2-methylglycerol-1-benzyl ether **3** facilitating enzymatic hydrolysis studies.

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