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Short Communication

High-performance liquid chromatographic separation of racemic and diastereomeric mixtures of 2,4-pentadienoate–iron tricarbonyl derivatives

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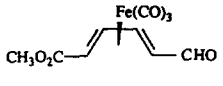
ABSTRACT

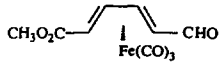
β-Cyclodextrin chiral stationary phase facilitates the chiral separation of the (±)-methyl-5-formyl-2,4-pentadienoate–iron tricarbonyl (*1*) racemic mixture. The separation of oxazolidine derivatives *2* and *3* diastereomers were achieved with a C_{18} column but the compounds underwent in-column hydrolysis to give (−)- and (+)-*1*, respectively. This hydrolysis was exploited for the determination of *2* and *3* by the β-cyclodextrin column, namely *2* and *3* were initially and completely hydrolyzed in the column to give (−)- and (+)-*1* and this racemic mixture was then separated by this chiral column.

INTRODUCTION

Methyl-5-formyl-2,4-pentadienoate–iron tricarbonyl (**1**) has been proved to be an important intermediate in the syntheses of many chiral compounds, for instance chiral polyenes [1,2]. Introduction of the iron tricarbonyl to the formyl pentadienoate produces a chiral center on the molecule which is very useful in asymmetric syntheses [3]. The absolute configuration of enantiomers **1** has been determined by X-ray crystallography [4]. The structures of (−)- and (+)-**1** are given below:



(-)-1



(+)-1

Several chemical resolutions of racemic mixture (±) **1** into enantiomers have been reported [5,6]. For example, the racemic mixture **1** can be resolved by the initial

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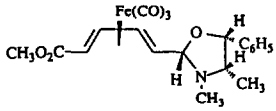
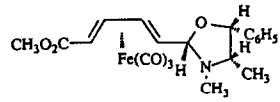
conversion of **1** into diastereomeric oxazolidine derivatives **2** and **3** through a reaction with a chiral compound (−)-ephedrine and the subsequent isolation of **2** and **3** through fractional crystallization in diethyl ether and *n*-hexane, respectively.



2



3

The final hydrolyses of the diastereomers **2** and **3** in the presence of silica gel and water give the optically active (−)- and (+)-**1**. This procedure is tedious, time consuming and more importantly, cannot be easily performed with a small amount of sample. It is thus, important to develop a novel separation method which can separate not only the (−)- and (+)-**1** enantiomers but also the **2** and **3** diastereomers as well.

Cyclodextrin (CD)-bonded stationary phases are well known for their efficient in the separation of chiral compounds [7–10]. The chiral separation is accomplished because CDs which are the optically active, doughnut shaped molecules, selectively form inclusion complexes with the analyte. Since **1**, **2** and **3** are relatively hydrophobic and have the required functional groups to interact with CDs, it is expected their separation can be achieved with the use of the chiral stationary phase CD column. It will be reported, for the first time, in this communication that (−)- and (+)-**1** enantiomers can be separated by a β-CD column. The diastereomeric **2** and **3** can also be separated by the same column by initially allowing this compounds to undergo in-column hydrolysis to give a racemic mixture of (±)-**1**.

EXPERIMENTAL

Reagents and materials

High-performance liquid chromatography (HPLC)-grade methanol was obtained from Burdock & Jackson (Muskegon, MI, U.S.A.). Deionized water was distilled from all glass distillation apparatus. Mobile phase was filtered through a nylon 0.45-μm membrane filter and degassed with sonication and vacuum.

Chiral compound (−)-**1**, (+)-**1** and their racemic mixture as well as diastereomers **2**, **3** and their mixture were synthesized and purified according to ref. 5. Optical rotations in methanol were determined to be $[\alpha]_D^{25} = -62°$ and $+62°$ for (−)- and (+)-**1**, and $-365°$ and $+100°$ for **2** and **3**, respectively. These values are in agreement with the literature data [5]. The melting points of **2** and **3** were found to be 111.0°C and 104.0°C which agree well with the literature values of 111.0°C and 104.0°C, respectively [5]. All samples were dissolved in absolute methanol prior to injection.

Apparatus and procedure

The HPLC separations were performed with a Shimadzu isocratic pump (Model LC-600), a Rheodyne Model 7125 sample injector equipped with a 20-μl loop, and a variable-wavelength detector operated at 351 nm.

The chromatograms of (±)-, (−)- and (+)-**1** were obtained using a β-CD

bonded column (250 × 4.6 mm I.D., ASTEC, Whippany, NJ, U.S.A.) at 23°C as a chiral stationary phase and water–methanol (9:1, v/v) as a mobile phase. The chromatograms of diastereomeric mixture, their single component **2** and **3** were performed with a C_{18} bonded column (250 × 4.6 mm I.D., Custom LC, Houston, TX, U.S.A.) at 23°C and a mobile phase which consists of methanol–0.06 *M* phosphate buffer pH 8.0 (85:15, v/v). The flow-rate of 1.0 ml/min was used in all the experiments. The void volume of the columns was determined by injecting 20 μl pure methanol or water when pumping with a mixture mobile phase. The change of reflective index caused by the injected solvents was used as the marker.

RESULTS AND DISCUSSION

The chromatogram in Fig. 1a shows a near base-line separation of the racemic mixture (±)-**1**. The chromatograms of the pure optically active (−)- and (+)-

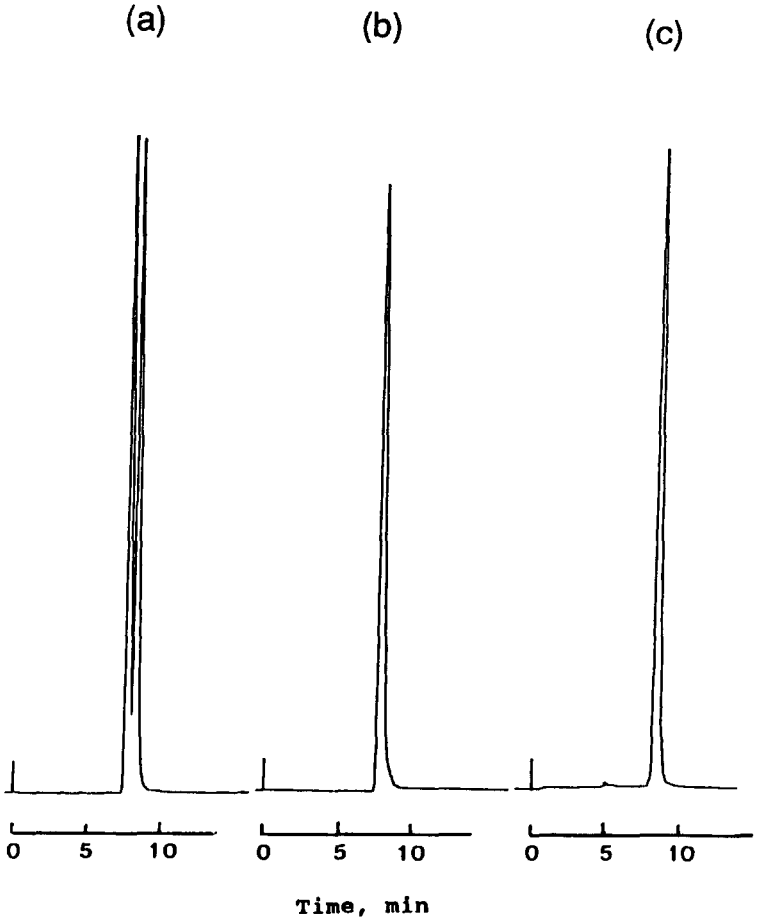


Fig. 1. Chiral separation of (±)-methyl-5-formyl-2,4-pentadienoate–iron tricarbonyl (compound **1**) on a β-CD bonded chiral stationary phase. Mobile phase: water–methanol (9:1, v/v); flow-rate: 1.0 ml/min. (a) Racemic mixture; (b) (−)-enantiomer; (c) (+)-enantiomer.

enantiomers, which are given in Fig. 1b and c, confirm the chiral resolution and enable the assignment of the peaks. Accordingly, the first peak, eluted with a retention time at 7.5 min is due to the (−)-enantiomer following by the (+)-enantiomer with a retention time of 8.1 min. The separation factor α and the resolution R_s are calculated to be 1.11 and 0.93.

The β-CD column was also used to separate the diastereomeric mixture of **2** and **3**. The results, obtained with the mobile phase consists of water–methanol (9:1, v/v) at pH 6.5, is shown in Fig. 2a. For reference, the chromatogram of the pure **2** and **3**

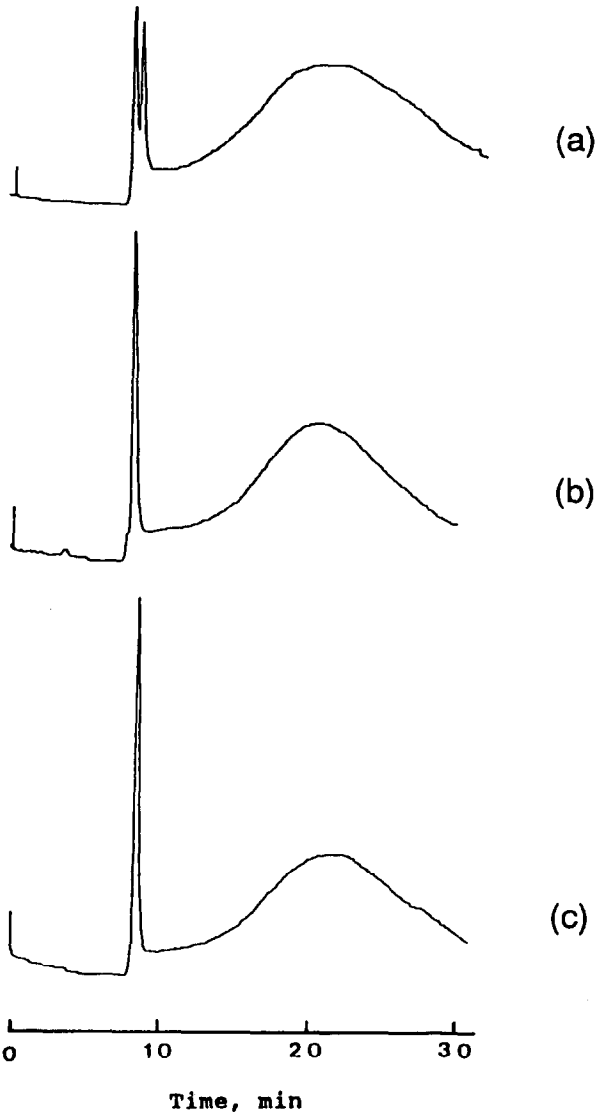


Fig. 2. Separation of diastereomeric oxazoline derivatives **2** and **3** on the β-CD chiral stationary phase. Mobile phase: water–methanol (9:1, v/v), pH 6.5; flow-rate: 1.0 ml/min. (a) Mixture of **2** and **3**; (b) pure **2**; (c) pure **3**.

obtained using the same conditions, are also shown in Fig. 2b and c. Based on the optical rotations, melting points and NMR data, **2** and **3** are considered to be pure. It is therefore, possible that they undergo decomposition in the column. In fact, it is likely that compounds **2** and **3** decompose in the column to give (−)- and (+)-**1** in the column because: (1) there is some unreacted silica in the β-CD column and (2) as explained earlier, these diastereomers are known to undergo hydrolysis in the presence of silica gel and water. From Fig. 2a–c and the chromatograms of the optically pure (−)- and (+)-**1** shown in Fig. 1a–c, it is evident that the broad peaks in Fig. 2 are due to the diastereomers **2** and **3**. These compounds decomposed in the column to give (−)- and (+)-**1**, respectively. The decomposed product (±)-**1** are then undergone chirally separated by the β-CD column to give a chromatogram (Fig. 2a) similar to those of the pure racemic mixture (±)-**1**. Moreover, the similarity between the peak at 7.5 min in Fig. 2b [from the (−)-**1** generated by **2**] and that of the pure (−)-**1** shown in Fig. 1b, and between the peak at 8.1 min in Fig. 2c [from the (+)-**1** generated by **3**] and that of the pure (+)-**1** shown in Fig. 1c further confirms our explanation. Since the in-column hydrolysis of **2** and **3** is unavoidable, it may be possible to quantitatively determine **2** and **3** by selecting experimental conditions in such a way that **2** and **3** undergo completely hydrolysis to give (−)- and (+)-**1**. The hydrolyzed products can then be determined by the β-CD column. We have, in fact, successfully implemented this possibility by performing the separation at pH 4.5 and the results obtained for the mixture of **2** and **3**, and also for the pure **2** and **3** are shown in Fig. 3. As shown in these figures, **2** and **3** underwent complete hydrolysis to give (−)- and (+)-**1** which were then quantitatively and chirally separated by the β-CD column.

The diastereomeric mixture of **2** and **3** was also separated on a C_{18} bonded phase using methanol containing 15% phosphate buffer at pH 8.0 as mobile phase. The chromatogram obtained, shown in Fig. 4a, is rather complex. For reference, the chromatograms of the pure **2**, **3** and **1** are also given in Fig. 4b, c and d. From these chromatograms it is evident that **2** and **3** also underwent hydrolysis in this column. The peaks having retention times of 6.7 and 8.1 min in Fig. 2a are due to compounds **2** and **3**, respectively, while the peak at 3.1 min is similar to the single chromatogram peak of the pure compound **1** (Fig. 4d) and is due to the hydrolyzed product **1**. There is only one peak in Fig. 4a which corresponds to compound **1** in spite of the fact that **2** and **3** are known to undergo hydrolysis to give (−)- and (+)-**1**, respectively. This is hardly surprising because while (−)- and (+)-**1** enantiomers are produced by **2** and **3**, they cannot be separated by the achiral C_{18} column used.

It has been demonstrated that the racemic mixture of the compound **1** can be near baseline separated into enantiomers by use of the β-CD chiral stationary column. The corresponding diastereomers **2** and **3** were also separated by this chiral column. However, these diastereomers undergo in-column hydrolysis to give a racemic mixture of **1**. However, the diastereomers can be determined by this method by performing the separation at pH 4.5 because at this pH, they undergo complete hydrolysis to give a racemic mixture of **1** which is then quantitatively and chirally separated. A C_{18} column can also separate the diastereomers. However, since the in-column hydrolysis is unavoidable and this column cannot chirally separate the racemic mixture of **1**, it is not as useful as the β-CD chiral stationary phase column.

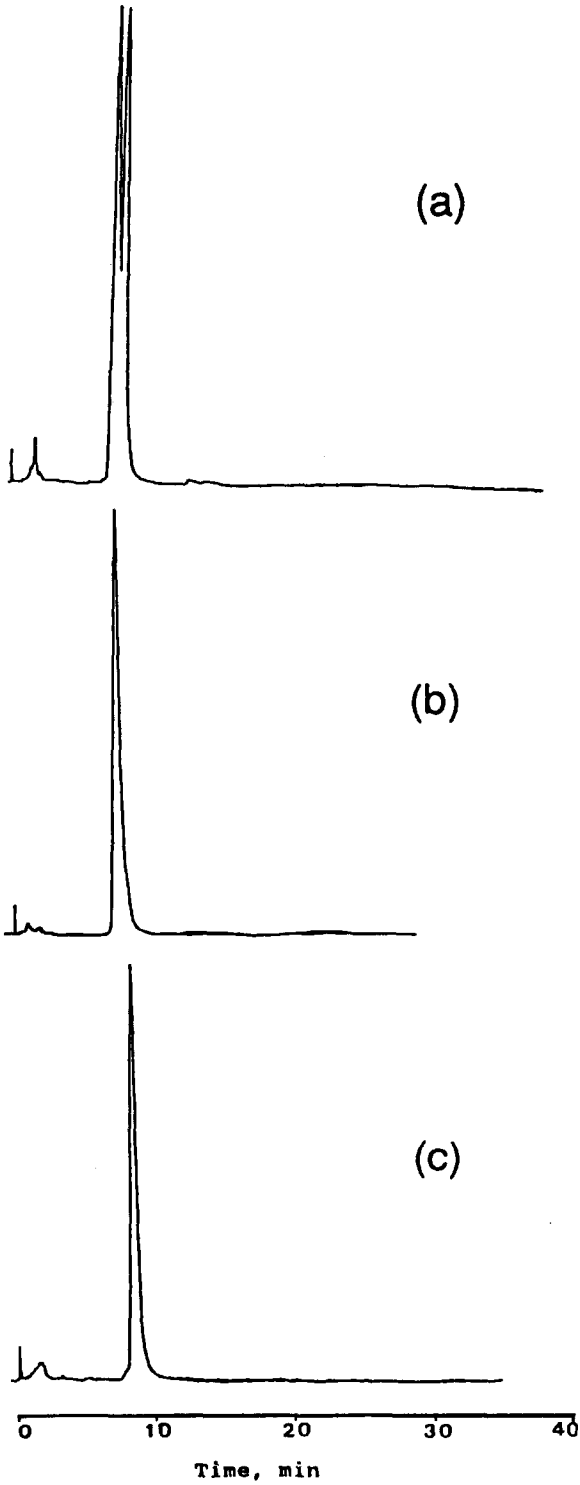


Fig. 3. Separation of diastereomeric oxazoline derivatives **2** and **3** on the β-CD chiral stationary phase. Same conditions as in Fig. 2 except pH was 4.5. (a) Mixture of **2** and **3**; (b) pure **2**; (c) pure **3**.

Fig. 4. Separation of diastereomeric oxazolidine derivatives **2** and **3** on a C_{18} column. Mobile phase: methanol–0.06 *M* phosphate buffer pH 8.0 (85:15, v/v); flow-rate: 1.0 ml/min. (a) Mixture of **2** and **3**; (b) pure **2**; (c) pure **3**; (d) pure **1**.

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