Tetrahedron: Asymmetry Vol. 3, No. 6, pp. 731-734, 1992
Printed in Great Britain

0957-4166/92 $5.00+.00

An Efficient Preparation of Tetrahydropyran-(3*R*)-Carboxaldehyde, a Key Intermediate for the Synthesis of a Novel 5-Lipoxygenase Inhibitor.

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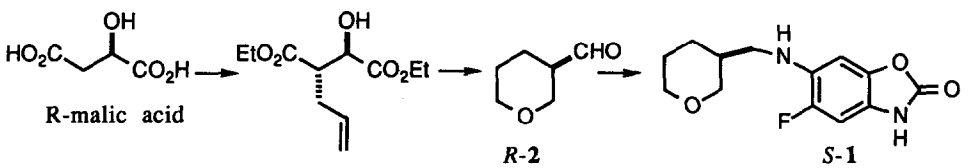
(*Received* 10 *April* 1992)

Abstract: A novel process based on the efficient resolution of *rac*-**2** and suitable for preparing kilogram quantities of the chemically sensitive aldehyde tetrahydropyan-3*R*-carboxaldehyde *R*-**2** of ≥98% ee is described.

Tetrahydropyran-(3*R*)-carboxaldehyde *R*-**2** is a key intermediate in the synthesis of 5-fluoro-6-(tetrahydropyran-3*S*-yl)-methylamino-2-benzoxazolone *S*-**1**, a novel 5-lipoxygenase inhibitor discovered at Pfizer Central Research in Nagoya, Japan.[1] Both compound *S*-**1** and its enantiomer were synthesized from *R*- and *S*- malic acid, respectively via lengthy syntheses[2] (Scheme 1). To prepare larger quantities of *S*-**1** for preclinical evaluation, a more efficient synthesis of *R*-**2** was required.

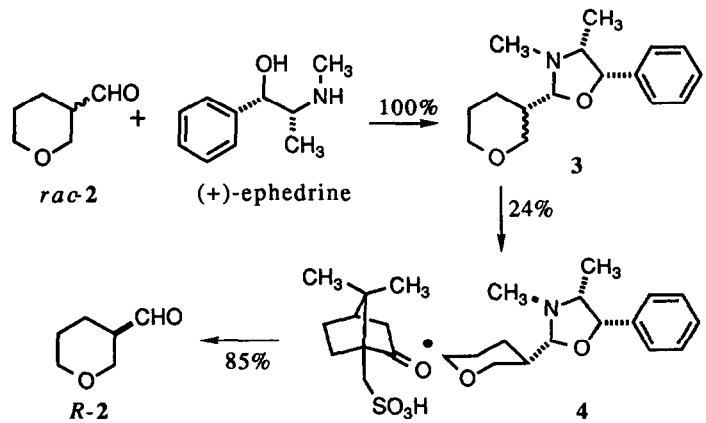
Scheme 1



The racemic aldehyde *rac*-**2** was readily available in two steps through the acid catalyzed dimerization of acrolein[3] to yield 3,4-dihydro[2H]pyran-5-carboxaldehyde which was hydrogenated. In the literature, resolution of aldehydes has been accomplished through the formation of covalent compounds with optically active reagents.[4] We were attracted by the work of Kelly and VanRheenen[5] who used fractional crystallization to separate the diastereomeric oxazolidines which resulted from condensation of several aldehydes or ketones with ephedrine. Initially, reaction of ephedrine with aldehyde *rac*-**2** in methylene chloride did give a mixture of two diastereomeric oxazolidines which could be readily seen in the nmr spectrum. However, unlike the literature examples which were separable via fractional crystallization, the mixture of oxazolidines **3** was an oil. However, it was found that treatment of **3** with (+)-camphorsulfonic acid allowed the separation of the diastereomeric

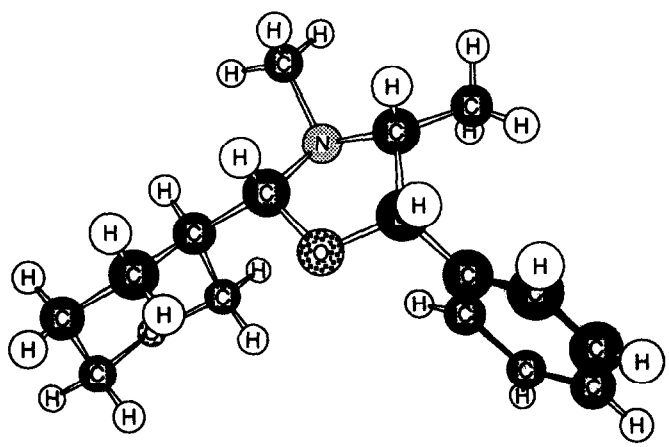
camphorsulfonate salt *R*-**4** by crystallization from methylene chloride/isopropyl ether solution. (Scheme 2)

Scheme 2



Upon recovery of the resolved free base of oxazolidine **3**, the optically active material was found to be crystalline and allowed for a single crystal x-ray analysis to provide the absolute stereochemistry for the compound. (See Figure 1)[6] All three substituents on the ring carbons of resolved oxazolidine **3** were in a cis relationship.

Figure 1.



For preparative purposes the resolved aldehyde *R*-**2** was regenerated directly from salt **4** by hydrolysis in water. The course of the hydrolysis could be monitored by a pH change from an initial

3.4 to a final value of 4.6 since the pH of **4** and ephedrine camphorsulfonate were different. The aldehyde *R*-**2** was recovered by extraction into methylene chloride and assayed by chiral HPLC (see experimental). *R*-**2** was generated and used in the reductive alkylation as needed since it was found to have poor chiral stability. A fresh sample of 98%ee upon storage neat at O°C was found to be 70%ee after three weeks.

By using the process in Scheme 2 it was possible to prepare kilogram quantities of aldehyde *R*-**2** which was successfully used in the reductive alkylation to provide *S*-**1**. It was found that p-toluenesulfonic acid could be used in place of camphorsulfonic acid; however, the yield for the resolution was lower as an additional recrystallization was required to achieve acceptable optical purity.

Experimental

N-Methyl 2R-(3'S-tetrahydropyranyl)-4R-methyl-5S-phenyloxazolidinium (+)-camphorsulfonate **4**.

Tetrahydropyran-3-carboxaldehyde (139 g, 1.22 mol) and (+)-ephedrine (201 g, 1.22 mol) were combined in methylene chloride (2 L) and refluxed for 2 hours. The solution was cooled, magnesium sulfate (240 g, 2 mol) was added. The mixture was stirred for one hour, then filtered and the solids washed with methylene chloride (1 L). (+)-Camphorsulfonic acid (2.84 g, 1.22 mol) was added to the filtrate and the solution was diluted with isopropyl ether (3 L). After stirring at room temperature overnight, the crystalline solids were collected and recrystallized from a 1:1 mixture of methylene chloride and isopropyl ether (1.6 L) as described above to provide the title compound, 144 g, 24% yield. mp 167-8°C; $[\alpha]_D$ + 77 (c= 1.4, methanol). Anal. Calcd. for $C_{26}H_{39}NO_6S$: C, 63.26; H, 7.96; N, 2.84. Found: C, 63.24; H, 7.79; N, 2.84.

N-Methyl 2R-(3'S-tetrahydropyranyl)-4R-methyl-5S-phenyloxazolidine **3**

The resolved salt **4** (5.55 g, 11.2 mmol) was added to a mixture of hexanes (100 ml) and aqueous sodium carbonate (5.25 g, 50 mmol in 100 ml water). After stirring for one hour the hexane layer was separated and the aqueous layer was extracted with hexanes. The combined organic layers were washed with water, dried over sodium sulfate, and evaporated in vacuo to a colorless crystalline solid, 2.9 g, 99% yield. mp 68-69.5°C; $[\alpha]_D$ + 68 (c= 0.75, methanol). Anal. Calcd. for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.81; H, 9.02; N, 5.46. 300MHz-^{1}H-NMR($CDCl_3$): δ(ppm)= 7.28 (m, 5), 4.90 (d, 1), 4.25 (m, 1), 3.94 (m, 1), 3.73 (d, 1), 3.58 (t, 1), 3.35 (dt, 1), 2.74 (m, 1), 2.28 (s, 3), 2.0 (m, 1), 1.84 (m, 1), 1.66 (m, 3), 0.67 (d, 3).

Slow evaporation of a hexane solution of **3** provided a crystal suitable for single crystal x-ray analysis.

Tetrahydropyran-(3*R*)-carboxaldehyde *R*-**2**.

The resolved camphorsulfonic acid salt **4** (17 g, 34.4 mmol) was stirred with water (344 ml) for four hours during which time the solid dissolved and the pH rose from 3.2 to 4.6. The aqueous was extracted three times with methylene chloride. The combined organics were washed with water and

dried over magnesium sulfate. Evaporation of the methylene chloride provided the aldehyde as a colorless oil, 3.36 g, 85% yield. $[\alpha]_D$ + 3 (c= 0.64, chloroform) 300MHz-^{1}H-NMR($CDCl_3$): δ (ppm)= 9.68(s, 1), 3.95(q, 1), 3.70 (q, 1), 3.69 (m, 1), 3.53 (m, 1), 1.96-1.75 (m, 2), 1.72-1.48 (m, 2). The chiral purity was assayed by capillary GLC on a 20 m x 0.25mm I.D. Chiraldex G-TA column with the following settings: oven temp. 100°C; injector temp. 125°C; detector temp. 125°C; helium 14 cm/sec; split 200:1; detection FID (range = 1); injection vol. 1mL.[7] The aldehyde was dissolved in acetonitrile for the analysis.

Acknowledgment: We thank Dr. Jon Bordner of Pfizer Central Research for the determination of the single crystal x-ray structure of 3.

References and Notes:

1 M. Nakane; K. Satake; K. Ando; N. Asai; T. Mano; K. Shimada; and F. Ito, European patent application 409484A, **1990**.

2 M. Nakane; K. Satake; K. Ando; N. Asai; T. Mano; K. Shimada; and F. Ito, Unpublished results.

3 H. Eckhardt; K Halbritter; N. Goetz; and G. Heilen, U.S. Patent 4,532,337 **1985**.

4 J.Jacques; A. Collet; S.A. Wilen, Enantiomers, Racemates and Resolutions, John Wiley and Sons., N.Y., **1981**, p 335-339.

5 R. Kelly and V. VanRheenen *Tetrahedron Letters*, **1973**, 1709.

6 Figure 1 was prepared by using the experimentally determined x-ray coordinates in Chem3D Plus®.

7 We thank Dr. J.G. Stroh and V.V. Papov of Analytical Chemistry, Pfizer Central Research for these analyses.