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Enzyme-Catalyzed Synthesis of Optically Pure β-Sulfonamidopropionic Acids. Useful Starting Materials for P-3 Site Modified Renin Inhibitors.

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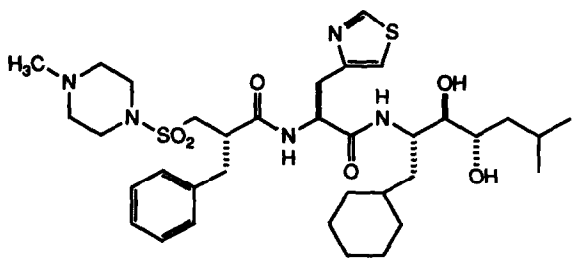
Abstract: The novel and efficient preparation of several racemic β-sulfonamidopropionate esters is described. Treatment of the racemic esters with Chymotrypsin or Subtilisin Carlsberg (purified or detergent grade) provided the corresponding (S)-carboxylic acids in 60-90% yield. These acids (75 to >98 % e.e.) are useful starting materials for the synthesis of P-3 site modified renin inhibitors.

Recently a series of orally active renin inhibitors have been disclosed for use in the control of hypertension and related illnesses.[1] A member of this series, A-72517 (Figure 1), was needed in substantial quantities for clinical development. This letter describes the synthesis of the optically pure β-sulfonamidopropionic acid **3b** which is a synthetic intermediate used in the preparation of the final inhibitor. Several related compounds containing the sulfonamide moiety were also prepared by the same route.

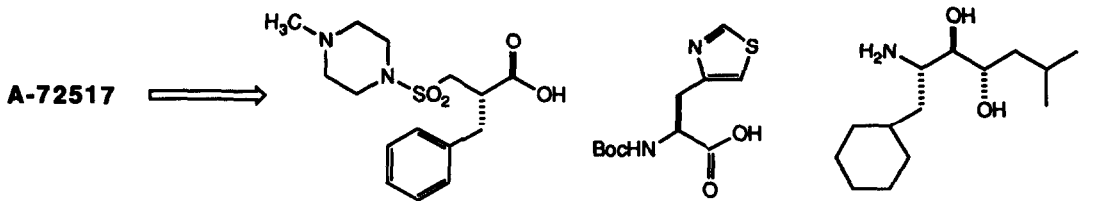


A-72517

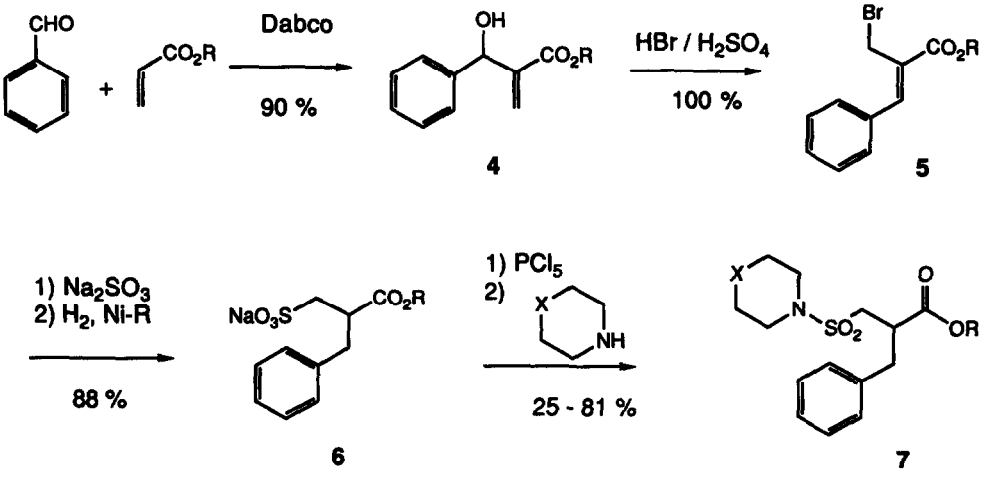
Figure 1

A-72517 was synthesized from the diol hook **1**, (Boc)-L-thiazoylalanine **2**, and the β-sulfonamidopropionic acid **3b** (Scheme 1). Syntheses of **1** and **2** were known, [2,3] however, at the time our work was started, the synthesis of **3b** or related compounds had not been reported. After this work was nearly completed, a patent application describing the synthesis of **3c** was published. [4]

Based on work reported by Cohen and Milovanovic dealing with the enzymatic resolution of succinate esters, we felt that the enzymatic resolution of racemic ester **7b** should provide the required optically pure (S) acid. [5,6] Therefore, an efficient synthesis of the racemic ester was devised.



Scheme 1



Scheme 2

a: X = NH, R = CH_3
b: X = NCH_3, R = CH_3
c: X = O, R = CH_3
d: X = NCH_3, R = CH_2CH_3

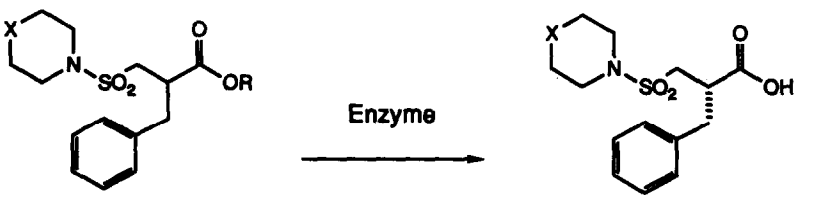
Our synthesis of the racemic ester (Scheme 2) starts with the Dabco mediated condensation of benzaldehyde and methyl acrylate as described by Drewes et. al. to provide methyl ester **4** in 90 % yield. [7] Treatment of **4** with HBr and H_2SO_4 led to the rearranged ester **5** in quantitative yield. Reaction of **5** with

sodium sulfite in aqueous methanol followed by Raney Nickel catalyzed hydrogenation afforded ester **6** in 88 % yield. Finally, chlorination of **6** with PCl_5 in toluene afforded the intermediate sulfonyl chloride which was then treated with a series of secondary amines to give the racemic resolution substrates **7 a-c** in 25 - 81 % yield for the two steps. The ethyl ester **7d** was prepared in the same way by replacing methyl acrylate with ethyl acrylate in the first step of the sequence. The synthesis of **7a, b,** and **7d** required no column chromatography, whereas the synthesis of **7c** required careful column purification after the final step.

The results of the enzymatic resolution of esters **7a-d** are shown in Table 1. [8] Treatment of ester **7a** with either chymotrypsin or Subtilisin Carlsberg provided the desired acid **3a** in 88-90 % yield and with 93-94 % e.e. . Resolution of methyl ester **7b** with Alcalase [R] (a commercially available detergent grade preparation of Subtilisin Carlsberg available from Novo Labs Inc.) afforded acid **3b** in 70 % yield and with 96 % e.e. . Similar treatment of the corresponding ethyl ester **7d** provided acid **3b** in 80 % yield and with > 98 % e.e. . Finally, resolution of ester **7c** with Subtilisin Carlsberg or Alcalase [R] afforded acid **3c** in 60-80 % yield and with 75 % e.e. . The % e.e. listed for acid **3a** was determined by converting the crude acid into the N-Boc methyl ester followed by HPLC determination of enantiomer ratios using a Chiracel OC column. The % e.e. values for the remaining acids were determined by chemical coupling of the crude acid to amine **8** [9] followed by chromatographic determination of the diastereomer ratios.

Table 1

Substrate	Enzyme	Solvent	Product	Yield	% e. e.
7a	Chymotrypsin	Acetone/ KCl aq	**3a**	88 %	93
7a	Subtilisin	Acetone/H_2O	**3a**	90 %	94
7b	Alcalase	Acetone/H_2O	**3b**	70 %	96
7c	Alcalase	Acetone/H_2O	**3c**	80 %	75
7c	Subtilisin	Acetone/H_2O	**3c**	60 %	75
7d	Alcalase	Acetone/H_2O	**3b**	80 %	>98



7 **3**

a: X = NH, R = CH_3
b: X = NCH_3, R = CH_3
c: X = O, R = CH_3
d: X = NCH_3, R = CH_2CH_3

a: X = NH
b: X = NCH_3
c: X = O

In conclusion, we have described the novel and efficient preparation of a series of chiral β-sulfonamido-propionic acids for use in the synthesis of P-3 site modified renin inhibitors. The 6-step route proceeded in good to excellent overall yield and provided the final acids in high optical purity. Moreover, this process has recently been scaled-up to afford bulk quantities of acid **3b**.

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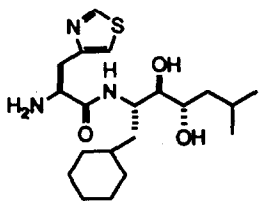
8. Ester **7b** (135g, 397 mmol) was suspended in acetone (300 ml) and water (900 ml). Alcalase ^{R} (10 ml) was added and the mixture was rapidly stirred for 3 days at 35° C. During this time, 6 N NaOH was added as needed to keep the pH at or around 7.5-8.0. Acetone was removed under reduced pressure and the aqueous phase was extracted with $CHCl_3$ (1L). The aqueous phase was acidified to pH 7 and was desalted by eluting through a column of XAD-16 (2Kg) eluting with a water to methanol/water gradient. Evaporation of the solvent afforded the desired product (46g, 70 %) as a colorless solid. mp = 184.5° C.

9. amine **8** :



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