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ASYMMETRIC SYNTHESIS OF NAPROXEN VIA A PINACOL-TYPE REACTION*

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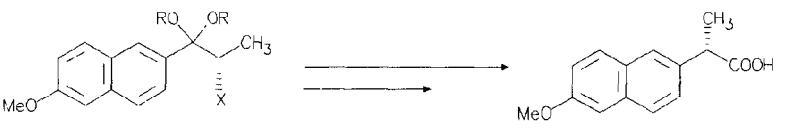
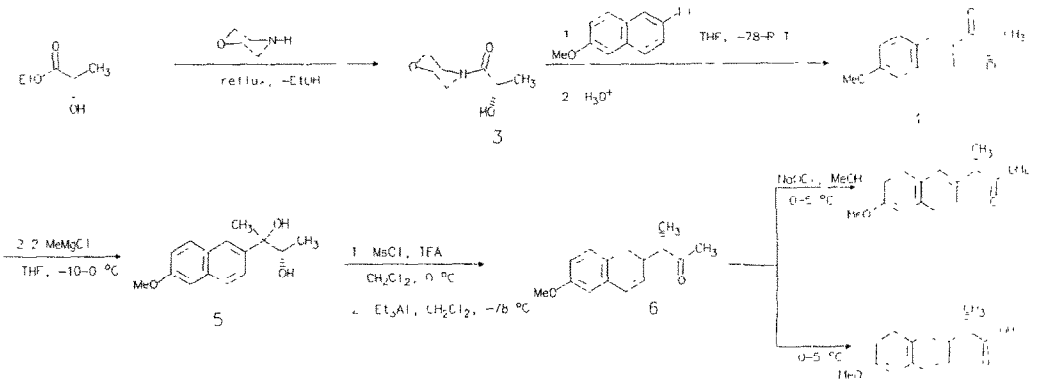
Abstract: An asymmetric pinacol-type rearrangement was used in the synthesis of (S)-naproxen. The pinacol-type reaction of a *sec-tert* vicinal diol provided an α-aryl ketone which was oxidized with sodium hypochlorite in the presence of methanol to the methyl ester of naproxen.

Recently, there has been a great deal of attention focused on the use of a ketal rearrangement in the synthesis of optically active 2-arylpropanoic acids. Most of these syntheses utilize either optically active starting materials or in some cases, an asymmetric bromination for the source of chirality[1] (see below). The use of an asymmetric pinacol-type reaction for the synthesis of 2-arylpropanoic acid acid has never been described before. The synthesis described herein was based on the use of an asymmetric pinacol-type reaction to make a chiral 3-arylbutan-2-one which was oxidized via a haloform reaction to give the desired methyl 2-arylpropanoate. This work was stimulated by the report of Tsuchihashi and coworkers[2] who reported the synthesis of optically pure 2-aryl ketones. The use of this work for the synthesis of (S)-Naproxen will be described herein.



X=OH
X=Br

The synthesis of (S)-naproxen starts by first forming the morpholino amide of (S)-ethyl lactate. This was accomplished by refluxing 1.2 equivalents of morpholine with (S)-ethyl lactate for 12 hours. The product was purified by vacuum distillation to give the desired amide (3) in 95% yield. The amide was reacted with 2.1 eq. of 2-litho-6-methoxynaphthalene (generated from 2-bromo-6-methoxynaphthalene and *n*-butyllithium) at -20 °C to give the known intermediate (4) in 90% yield (after chromatography). The melting point and spectral properties of the hydroxy ketone (4) were identical to those reported earlier[3]. The hydroxy ketone (4) was reacted with 2.2 eq. of methyl magnesium chloride to give the *sec-tert* vicinal diol (5) in 87% yield. The diol was transformed to the mesylate with 1.2 eq. of methanesulfonyl chloride in the presence of 1.5 eq. of triethylamine. The resulting mesylate was reacted without purification with 1.2 eq. of triethylaluminium. This gave the desired (S)-3-(6-methoxy-2-naphthalenyl)butan-2-one (6)[4] in 63% overall yield from (5). The ketone (6) was utilized in the final step without determination of its optical purity. The final step in the synthesis was the haloform reaction of ketone (6) using sodium hypochlorite in methanol at 0-5 °C[5]. This reaction gave (S)-methyl naproxen in 85% chemical yield and the enantiomeric excess was determined to be 97.3% by chiral phase HPLC (Chiralcel OD with 2.5% isopropanol and 0.5% TFA in heptane). This is the first report of the use of a haloform reaction in the synthesis of optically active α-aryl propanoic acids.[6]



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References and Notes

* Dedicated to Professor A. I. Meyers on the occassion of his 60 th birthday

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6 After completion of this work, it was found that the haloform reaction has been utilized to make racemic naproxen. Oe, T.; Tsuruta, M. Jp. Pat. 51056436 (1976), cf. CA: 85:108456x (1976); Valero Clavero, M J ; Gonzalez Guerrero, A.J. Span. ES 550,362, (1986) cf. CA: 108:37410h (1988).