Synthesis of Naproxen *via* Regioselective Ring Opening of (2*S*,3*S*)-Epoxy-1-butanol

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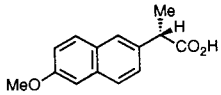
Received December 14, 1992

(*S*)-Naproxen was synthesized by the regioselective and stereospecific epoxide ring opening of (2*S*,3*S*)-epoxy-1-butanol (**2**) with diethyl-2-(6-methoxynaphthyl)aluminium (**5**) as the key step. Thus, treatment of diethylaluminate of **2** with **5** at 0° afforded (2*S*,3*S*)-3-(6-methoxy-2-naphthyl)butan-1,2-diol (**6**), which was oxidized by sequential treatment with sodium periodate and potassium permanganate in a mixture of *tert*-butyl alcohol and phosphate buffer (*p*H 7.0) to give naproxen in high enantiomeric purity.

J. Heterocyclic Chem., **30**, 825 (1993).

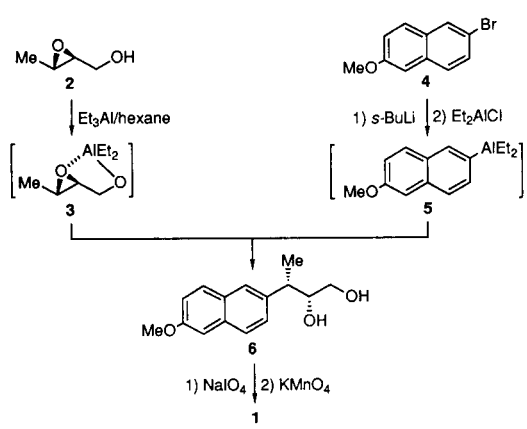
Naproxen (**1**), one of most widely used antiinflammatory agent [1], is an optically active 2-naphthylpropanoic acid with *S*-absolute stereochemistry. Its enantiomer is much less potent [1,2]. Because of this stereoselective antiinflammatory activity of naproxen associated with (*S*)-stereochemistry, the enantioselective synthesis of the compound has long been the subject of intensive researches [3]. Our approach described in this note starts with readily available (2*S*,3*S*)-epoxy-1-butanol and 2-bromo-6-methoxynaphthalene making use of the previous observation that *trans*-2,3-epoxy alcohols undergo ring opening reactions with aryl nucleophiles in highly regioselective and stereospecific manners [4].



1 (Naproxen)

As shown in Scheme I, the epoxy alcohol **2** [5] which was prepared from *E*-crotyl alcohol by the method of the Sharpless-Katsuki epoxidation reaction was converted to alkoxyaluminum complex **3** by the treatment with triethylaluminum at 0°. The aryl nucleophile **5** [6] was generated by treating 2-bromo-6-methoxynaphthalene (**4**) with 2 molar equivalents of *sec*-butyllithium at 0°, followed by the transmetallation of the aryllithium thus obtained with an equimolar amount of diethylaluminum chloride also at 0°. The treatment of the activated epoxide **3** with five molar equivalent amounts of the aryldiethylaluminum (**5**) at 0° cleaved the epoxide ring regioselectively at the 3-position to afford diol **6** in 75% yield [7].

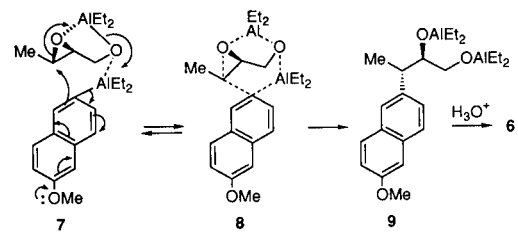
Scheme I



The regioselectivity of this reaction is found to be better than 50:1 when determined by the ^{1}H nmr spectral analysis of the product after acetylation with acetic anhydride, and the optical purity was determined to be higher than 98% also by the analysis of the ^{1}H nmr spectrum of the Mosher esters of the corresponding 2-arylpropanol that was obtained by treating the product with sodium periodate followed by sodium borohydride reduction. It appears that the intramolecular liganding of the oxygen of the epoxide to the alkoxyaluminum as shown by **3** not only activates the ring for the nucleophilic cleavage reaction, but also causes the epoxide ring opening reaction to occur selectively at the 3-position with an inversion of configuration.

The above oxirane ring opening reaction may be envisioned to go through a cyclic six-centered transition state, **8** (Scheme II). Precedents of this type of transition state are found in the literature. Thus, Evans has invoked a

Scheme II



similar bimetallic six-centered species as an energetically favorable transition state in the reductive reaction of ketones to carbinols with trimethylaluminum [8]. Such a reaction path may possibly be initiated by the lone pair electrons on the methoxy oxygen of the naphthyl moiety

(Scheme II). The decreased regioselectivity which we observed previously [4] in the ring opening reaction of *trans*-2,3-epoxy alcohols with aryldiethylaluminum having no methoxy group on the ring may now be understood. Thus, when there is no methoxy group present on the nucleophilic aryl moiety, the generation of the six-centered transition state becomes difficult, and consequently an alternative intermolecular reaction [9] in which the aryl nucleophile attacks at the C-2 position becomes important.

Attempts at the improvement of the yield for the reaction of **3** with **5** met with only a limited success. When an equimolar amount of **5** was used for the coupling reaction, **6** was obtained persistently in 40% yield [4]. The use of **5** in a 2.5-fold excess enhanced the yield only to 58%, and as described above 4 molar excess of **5** gave the product in 75% yield. An additional 2.5 molar excess of **5** was needed to improve the yield to 80%. We attribute the less than satisfactory yield of **6** to the tendency of **5** to form coordination complexes with the oxy radical present in the product and the reactant as well. Attempts at the improvement of the yield by using an excess of **3** were in vain. When the reaction was carried out in methylene chloride, to our surprise, the reaction failed.

The oxidation of the diol to naproxen was carried out in 70% yield in a one-pot two stage process. Thus, **6** was converted using periodate to the corresponding aldehyde which was then oxidized to naproxen under the conditions described by Abiko *et al.* [10].

The present synthesis of naproxen is conceptually novel and convergent in its approach, affording the product in high enantiomeric purity. Furthermore, it exemplifies a new synthetic method which introduces a glycol moiety directly on an aromatic ring with desired stereochemistry.

EXPERIMENTAL

Melting points are uncorrected. The ^{1}H nmr spectra were determined at 300 MHz (Bruker FT-NMR) in deuteriochloroform and are expressed as a down field shift from internal tetramethylsilane. The ir spectra were obtained in a potassium bromide pellet using a Perkin-Elmer Model 843 FT-IR. Mass spectra were recorded on a Kratos MS 25 spectrometer. Elemental analysis was performed by the Korea Basic Science Center.

(2*S*,3*S*)-3-(6-Methoxy-2-naphthyl)butan-1,2-diol (**6**).

To a benzene-hexane (1:1) solution of 6-methoxy-2-naphthyllithium prepared from 6-methoxy-2-bromonaphthalene (4.0 g, 16.9 mmoles) by dropwise addition of *sec*-butyllithium (1.3 *M* in *n*-hexane, 13.0 ml) at 0° for 30 minutes was added diethylaluminum chloride (16.9 ml, 1.0 *M* in *n*-hexane) at 0° under a nitrogen atmosphere. The resulting mixture was stirred at 0° for 40 minutes. To the chilled arylaluminum complex **5** thus obtained was added the activated epoxide **3** which was prepared by adding at 0° triethylaluminum (3.4 ml, 1.0 *M* in *n*-hexane) to (2*S*,3*S*)-epoxy-1-butanol [5] (**2**, 0.30 g, 3.4 mmoles). The reaction mixture was stirred at 0° for 1 hour, then was poured into 20% aqueous tartaric acid solution, and stirred for 2 hours at room temperature. The product was extracted with ethyl acetate, and purified by column chromatography (silica gel) to give diol **6** (630 mg, 75% yield), mp 143-145° (dichloromethane-methanol); $[\alpha]_D^{24}$ −22.5° (*c* 0.4 in acetone); ^{1}H nmr (300 MHz, deuteriochloroform): δ 7.71-7.11 (m, 6H), 3.91 (s, 3H), 3.85 (m, 1H), 3.50 (dd, J = 2.8, 11.1 Hz, 1H), 3.40 (dd, J = 7.5, 11.1 Hz, 1H), 2.95 (m, 1H), 2.45-2.15 (br s, 1H), 1.95-1.65 (br s, 1H), 1.45 (d, J = 7.1, 3H); ir (potassium bromide): 3550-3300 (ν_{OH}), 1620-1595 ($\nu_{C=C}$); ms: (EI) m/z 115, 128, 141, 153, 170, 185, 215, 246 (M^+).

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.20; H, 7.62.

Naproxen (**1**).

To a suspension of **6** (660 mg, 2.68 mmoles) in a mixture of *tert*-butyl alcohol and phosphate buffer (*p*H 7.0) (3:2 by volume, 0.1 *M* in substrate) was added aqueous sodium periodate solution (1.1 molar equivalent) at room temperature. The reaction mixture was then stirred at room temperature for 10 minutes. A white solid (the corresponding aldehyde) started to precipitate in about 5 minutes. Aqueous potassium permanganate (6 molar equivalents to the diol, 1 *M* solution) was then added portionwise (for large scale, cooling with an ice-bath is needed) under vigorous stirring. The resulting suspension was vigorously stirred for an additional few minutes at room temperature. The excess permanganate was destroyed with saturated aqueous sodium sulfite solution with cooling in an ice-bath. The *p*H of the mixture was adjusted to about 3 with cold dilute aqueous hydrochloric acid, then the product was extracted with ethyl acetate. Naproxen was obtained in 70% yield (435 mg) after purification by column chromatography (silica gel), mp 151-153° (acetone-hexane) (lit mp 152-154° [1b]); $[\alpha]_D$ +66.0° (*c* 1.0, chloroform) (lit $[\alpha]_D$ +68.5° (*c* 1, chloroform [1b]). The ^{1}H nmr, ms, ir and other spectral data are identical with those of the authentic sample.

Acknowledgements.

We express sincere thanks to the Korea Steel Chemical Co., Ltd. for the financial support of this work.

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