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Synthesis of Optical Active 2-Arylpropionic Acids

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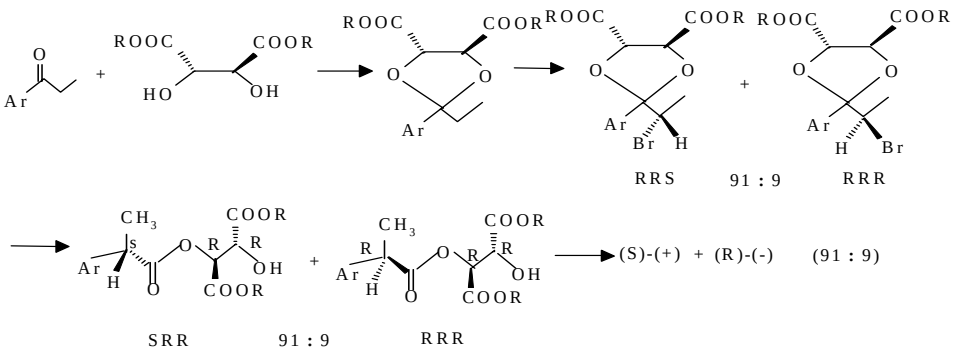
Abstract: (S)-2-(6′-methoxyl-α-naphthyl) propionic acid ((S)-Naproxen, ee 99%) has been prepared starting from (6-methoxyl-α-naphthyl)propan-1-one and D-sorbitol under $SmCl_3$ catalysis.

Keywords: Propionic acid, (S)-naproxen, D-sorbitol, catalysis.

2-Arylpropionic acid and its derivatives are pharmaceutically and agriculturally useful products[1,2], especially, the optical isomer possesses extra higher biological or pharmaceutical activity, for example the antiflammatory agent[3] of S-2-(6′-methoxyl-α-naphthyl) propionic acid (Naproxen), the effect of (S)-isomer is 28 times as actives as its R isomer. For the preparation of optically active 2-arylalkanoic acids many different synthetic strategies have been reported, such as, the resolution of racemates, asymmetric hydrogenation of prochiral unsaturated 2-aryl carboxylic acids, asymmetric carboalkoxy -lation of aryl alketones, asymmetric carbonylation of benzyl halides, asymmetric cross-coupling reactions of organometallic regents either with aryl and vinyl halides or with allylic derivatives[3,4]. Among these the method used by Castaldi *et al*[5] is more practical. The key step of this method is the stereospecific rearrangement of optically active acetals to esters as shown in **Scheme 1**.

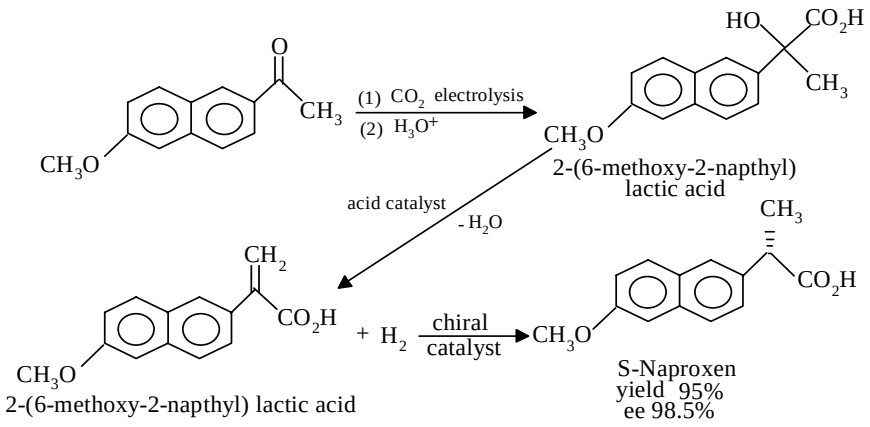
Scheme 1



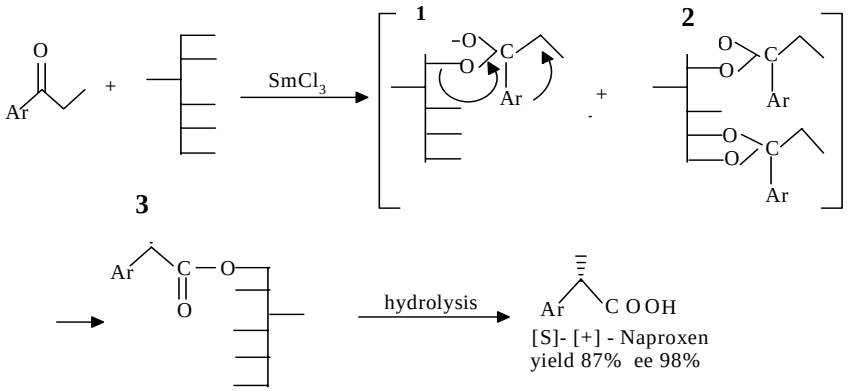
Depending on the nature of X group, basic or acidic catalysts are used to catalyze this rearrangement. This method has been applied to prepare (S)-(+)-naproxen by Zambon company in Italy, but the yield is relatively low (80%), and the chiral auxiliary is expensive.

Another industrial method is Monsanto procedure (**Scheme 2**)[6], which give high yield product (95%) with ee value 98.5%, but the catalyst turnover number is only 215 and the reaction must be performed under 13.5 Mpa, which lead to more difficult in continue procedure.

Scheme 2



Here we report a very practical method of (S)-(+)-naproxen preparation. We use cheap chiral auxiliary, D-sorbitol and $SmCl_3$ as catalyst. The synthesis of optically **Scheme 3** active acetals and stereospecific rearrangement can be achieved by one step, the route can be summarized as **Scheme 3**. Comparing with the **Scheme 1**, the procedure is more simple and the yield is high (87%), ee value 99%. This method can be easily industrialized.



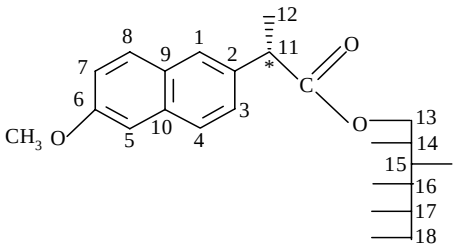
Theoretically D-sorbitol can react with (6-methoxyl-α-naphthyl) propan-1-one with $SmCl_3$ as catalyst to form 1,2-(S)-O-(6-methoxyl-naphthyl)propylidene-D-sorbitol **1** and 1,2,5,6-O-diketal **2** (**Scheme 3**). This reaction is kinetically and thermal controlled. However, the rearrangement of acetal is difficult in polar solvent (DMF), the mixture of DMF and trimethoxyl orthoformate was used as the solvent and the periodate oxidation test indicate that 1,2-(S)-O-(6-methoxyl-α-naphthyl) propylidene-D-sorbitol is the main intermediate.

Experimental

All ^{1}HNMR spectra were recorded at 400MHz, all ^{13}C-NMR spectra were recorded at 100 MHz in $\mathbf{D_7}$-DMF. MS, IR (KBr pellets) and mp were also measured.

Synthesis of **3**

A mixture of 1.82g D-sorbitol (10 mmol), 2.2 g (6-methoxyl-α-naphthyl) propan-1-one (10 mmol) and 0.26 g $SmCl_3$ (1 mmol) in 10 mL DMF and 30 mL trimethoxyl orthoformate were heated to 130-140°C for 3 h. Then the solvent was evaporated under reduced pressure. The residue was extracted by methanol (20 mL × 3) and chromatographed on silica column (CH_2Cl_2 : MeOH=70 : 30), a pale yellow product was obtained. mp 84-86°C. $[\alpha]_D^{20}$ +126 (c 1.8, $CHCl_3$), yield 90%, ee 92%. Elemental analysis: Calcd. C 60.4%, H 7.4%; Found C 60.4%, H 7.4%; MS (*m/z*): 397 ($M\text{-}1^+$, 20), 398 (M^+, 14), 105 (15); IR (KBr): 3450 br, 2900, 1726, 1604, 1540, 1445, 1320, 1225, 1110, 1030, 985, 780, 685cm^{-1}.



^{1}HNMR (δ, ppm, DMF-d_7): 7.4 (m, 6H, naphthyl), 4.0 (s, 3H, OMe), 1.2 (d, 3H, J=7.8Hz, CH_3-12), 3.5 (q, 1H, J=6.5Hz, CH-11), 4.7 (d, 2H, J=3.2Hz,CH-13), 4.5 (dd, 1H, J=5.0, 2.6Hz, CH-14), 3.9 (dd, 1H, J=4.8, 2.5Hz, CH-15), 3.7 (dd, 1H, J=5.6, 2.3Hz, CH-16), 4.1 (dd, 1H, J=5.2, 2.4 Hz, CH-17), 4.3 (dd, 2H, J=4.8, 2.3Hz, CH-18), 5.1 (d, 5H, J=2.8Hz, -OH).

^{13}C-NMR (δ, ppm, DMF-d_7): 170 (CO), 129 (C-1), 127 (C-2), 124 (C-3), 128 (C-4), 129 (C-5), 126 (C-6), 125 (C-7), 130 (C-8), 131 (C-9), 132 (C-10), 39.5 (C-11), 21 (C-12), 81 (C-13), 78 (C-14), 76 (C-15), 74 (C-16), 76 (C-17), 78 (C-18), 55 (s, OMe).

Hydrolysis of **3**

The solid was dissolved in 40 mL methanol and 10 mL hydrochloric acid was added. The mixture was refluxed for 2 h, then the solvent was evaporated under reduced pressure. The residue was dissolved in 1mol/L NaOH solution (50mL), and extracted by $CHCl_3$ and chromatographed on silica column (CH_2Cl_2: MeOH=70: 30), a white powder obtained (2g, yield 87%). mp 154-156℃. $[\alpha]_D^{20}$ +63.2 (c 1.8. $CHCl_3$), ee 99%; mp 154-156°C. In the reference, $[\alpha]_D^{20}$ +63.5 (c 1.8. $CHCl_3$)[3].

References

1. T. Y. Shen. *Angew. Chem, Int. Ed. Engl.* **1972**, *11*, 460.
2. D. Artl, M. Jautelat, R. Lantzsch. *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 703.
3. H. Alper, H. Hamel. *J. Am. Chem. Soc.*, **1990**, *112*, 2803.
4. R. S. Harikisan, S.B. Nanjundiah, R. Jaimala, G. K. Dilip. *Tetrahedron: Asymmetry*, **1992**, *3*(2), 163.
5. G. Castaldi, S. Cavicchioli, C. Giordano, F. Uggeri. *J. Org. Chem.* **1987**, *60*, 1027.
6. R. J. Noyori, *Chemtech.*, **1992**, 360.

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