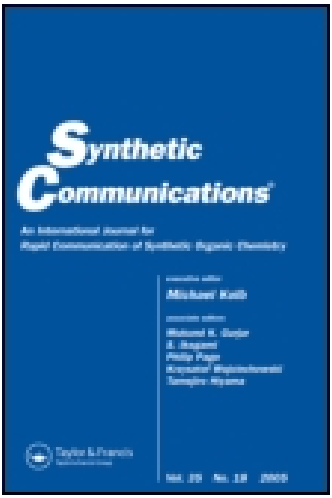

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SYNTHESIS OF OPTICAL ACTIVE 2-ARYLPROPIONIC ACIDS

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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)-Naprofen, ee% = 99) has been prepared by starting from (6-methoxyl-α-naphthyl)propan-1-one and D-sorbitol under $ZnCl_2$ catalysis.

2-Arylpropionic acid and its derivatives are pharmaceutically and agriculturally useful products,[1,2] specifically the optical isomer possesses an extra biological or pharmaceutical activity. A well-known example is 2-(6′-methoxyl-α-naphthyl) propionic acid, whose S isomer (Naproxen) is 28 times as active as the R isomer as an antiflammatory agent.[3,4] For the preparation of optically active 2-arylalkanoic acids, many different synthetic strategies have been reported: the use of racemates resolving by optically active bases; asymmetric hydrogenation of prochiral unsaturated 2-aryl carboxylic acids; asymmetric carboalkoxylation of aryl alkotones; asymmetric carbonylation of benzyl halides; and asymmetric cross-coupling reactions of organometallic reagents either with aryl and vinyl halides or with allylic derivatives.[3–5] Among these routes is the Castaldi et al.[6]

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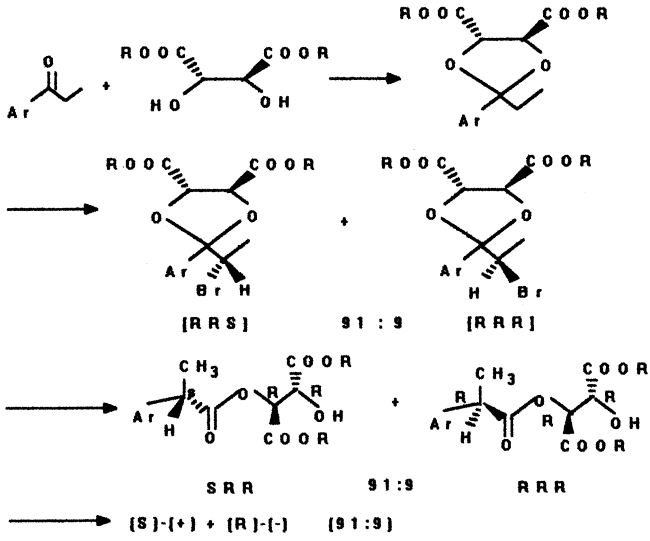
procedure, as shown in Scheme 1, where the stereospecific rearrangement of optically active acetals to esters is the key step, and depending on the nature of X group, basic or acidic catalysts are used to catalyze this step. This procedure has been applied to prepare (S)-(+)-Naproxen commercially by the Zambon Company of Italy, but the yield is relatively low (80%), the procedure is long, the chiral auxilliary is expensive and can be reused, which make production costly.

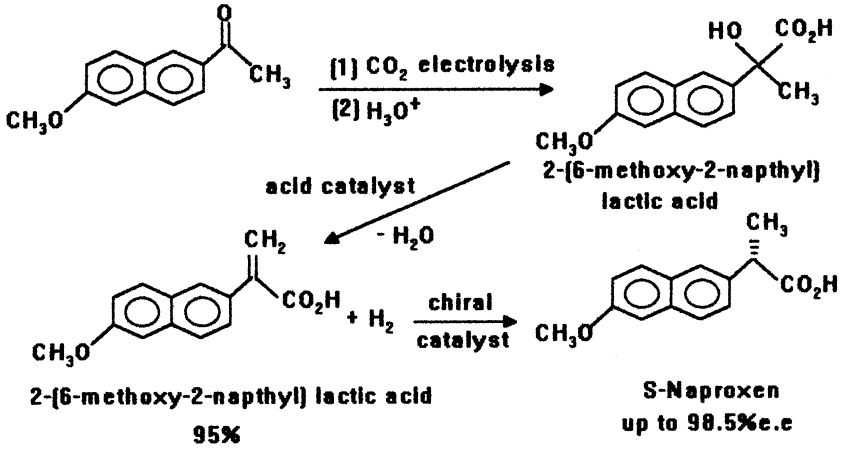


Scheme 1.

Another industrial method is the Monsanto procedure,[7] as shown in Scheme 2, which applies an electrochemical process that can get high-yield product (95%) with ee% = 98.5, but the catalyst turnover is only 215 and the reaction must be performed under 13.5 Mpa, which leads to difficult production.

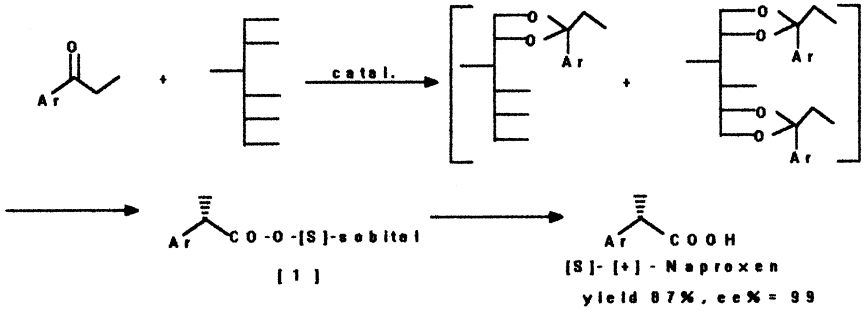
Here we report a very practical one-step method of (S)-(+)-Naproxen preparation involving the cheap chiral auxiliary, D-sorbitol, and $ZnCl_2$ catalyst, synthesis of optically active acetals, and stereospecific rearrangement. The route can be summarized as Scheme 3 shows. Compared with Scheme 1, the procedure has been simplified, the yield increased upto 87%, ee%=99, and it is easily industrialized.

In theory, D-sorbitol reaction with (6-methoxyl-α-naphthyl)propan-1-one under $ZnCl_2$ catalyst, two types of 1,2-(S)-O-(6-methyhoxyl-α-naphthyl)propylidene-D-sorbitol and 1,2,5,6-O-diketal (Scheme 3) formed in polar solvent (DMF), existing kinetically and thermal controlled



Scheme 2.

intermediate. But in polar solvent, the rearrangement of acetal is difficult, so the mixture solvent of DMF and trimethoxyl orthoformate was used. The periodate oxidation results indicate that 1 mol intermediate acetal produces 2.2 mmol formaldehyde (calc. 2 mmol) and 3.8 mmol (calc., 4 mmol) of formic acid. 1,2-(S)-O-(6-Methoxyl-α-naphthyl)propylidene-D-sorbitol is the main intermediate.



Scheme 3.

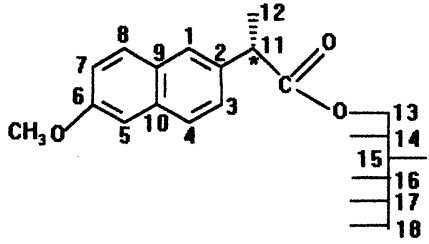
EXPERIMENTAL

All ^{1}H NMR spectra were recorded at 400 MHz, all ^{13}C NMR spectra at 100 MHz in D_4-methanol. MS, IR (KBr pellets) and m.p. tested.

Synthesis of 1

A mixture of 1 mmol D-sorbitol (1.82 g), 1 mmol (6-methoxyl-α-naphthyl)propan-1-one (2.2 g), and 0.01 mol, $ZnCl_2$ (1.3 g) in 10 cm^3 DMF and 30 cm^3 trimethoxyl orthoformate was heated 3 h to 130°–140°C in air. Then the solvent was evaporated by reduced pressure. The residue was crystallized in methanol (20 $cm^3 \times 3$) and chromatographed on silica column (CH_2Cl_2 : MeOH = 70 : 30). A pale yellow product was obtained and analyzed. M.p. 84°–86°C. $[\alpha]_D^{20} = +126°$ (cl.8, $CHCl_3$), yield 90%, ee% = 92.

Elemental analysis: Found: C 60.4%, H 7.4%; Calculated: C 60.4%, H 7.4%.



MS(m/e): 397(M-1$^+$, 20), 398(M$^+$, 14), 105(105).

IR (KBr): 3450br, 2900, 1726, 1604, 1540, 1445, 1320, 1225, 1110, 1030, 985, 780, 685 cm^{-1}.

^{1}H NMR (δ, ppm, DMF-d_7) 7.4(m, naphthyl, H_{1-8}), 4.0(s, OMe), 1.2(d, CH_3), 3.5(q, CH), 4.7(d, H_{13}), 4.5(dd, H_{14}), 3.9(dd, 3.7(dd, H_{16}), 4.1(dd, H_{17}), 4.3(dd, H_{18}), 5.1(-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 1

The solid was dissolved in 40 cm^3 methanol and 10 cm^3 hydroxyl chlorite was added and refluxed 2 h, then the solvent was evaporated by reduced pressure. The residue was dissolved in 1 M NaOH solution (50 cm^3), extracted by $CHCl_3$, and chromatographed on silica column (CH_2Cl_2: MeOH=70:30). A white product was obtained (2 g, yield 87%) and analyzed. M.p. 154°–156°C. $[\alpha]_D^{20} = +63.2°$ (cl.8. $CHCl_3$), ee% = 99, ref[3,4] m.p. 154°–156°C. $[\alpha]_D^{20} = +63.5°$ (cl.8. $CHCl_3$).

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