Chinese Chemical Letters Vol. 13, No. 6, pp 505 – 508, 2002
http://www.imm.ac.cn/journal/ccl/html

A Practical Synthesis of (S)-(+)-2-(6′-methoxyl-2-naphthyl) propionic Acid

Hong Zhu MA, Bo WANG*, Qi Zhen SHI

Department of Chemistry, Northwest University, ShaanXi Key Laboratory of Physico-Inorganic Chemistry, Xi'an 710068

Abstract: A simplified procedure for enantioselective synthesis of (S)-(+)-2-(6′-methoxyl-2-naphthyl) propionic acid ((S)-(+)-naproxen), starting from (6-methoxy-α-naphthyl) -1-propanone, with D-mannitol as auxiliary catalyzed by $SmCl_3$ in one–pot is described. The yield is 87.5 %(ee value 99 %).

Keywords: Auxiliary, D-mannitol, enantioselective synthesis, one–pot, (S)-(+)-naproxen.

α-Arylpropionic acids are an important class of non-steroidal anti-inflammatory agents[1,2]. The therapeutic efficacy of this class of drugs is well demonstrated by the introduction and extensive use of more than a dozen compounds exemplified by ibuprofen, naproxen, ketoprofen and flurbiprofen *etc*. However, in recent years the use of enantiomerical pure drugs in chemotherapy is becoming almost mandatory for enhancing specificity of drug action and reducing the toxicity. This awareness led to great efforts for obtaining optical pure isomer of this class of drugs. So far numerous asymmetric reactions have been reported[3-6]. Currently the practical method for optical pure compounds appears based on an entirely different strategy—stereospecific 1,2-aryl rearrangements[7,8].

Here we report a more simple strategy for synthesis of (S)-(+)-naproxen starting from (6-methoxy-α-naphthyl)-1-propanone, with D-mannitol as auxiliary catalyzed by $SmCl_3$. The reaction was carried out in one–pot, yield 87.5% ee value 99%. This method is suitable for industrial production. The synthesis of optically active acetals and stereospecific rearrangement are summarized as **Scheme 1**.

Theoretically three types of ketals can be produced by the reaction of D-mannitol and (6-methoxy-2-naphthyl)-1-propanone with $SmCl_3$ as catalyst, however only two kinds of optical active acetals **1** and **2** were obtained, maybe due to the "space effect".
The chirality of the acetals and the formation mechanism were easily detected by the measurement of CD spectra as shown in **Figure 1**. It was found that the reaction was consisted by two steps. The ketallization is first and then the esterification proceeded. These two steps might be completed in the same time or in a fast way as shown in the CD-time relation curve. As the reaction proceeded, the intensity of the band at about

*E-mail: wangbo@nwu.edu.cn

320 nm which attributed to naphthyl ring and the bands arised from carbonyl at 420 nm

Scheme 1

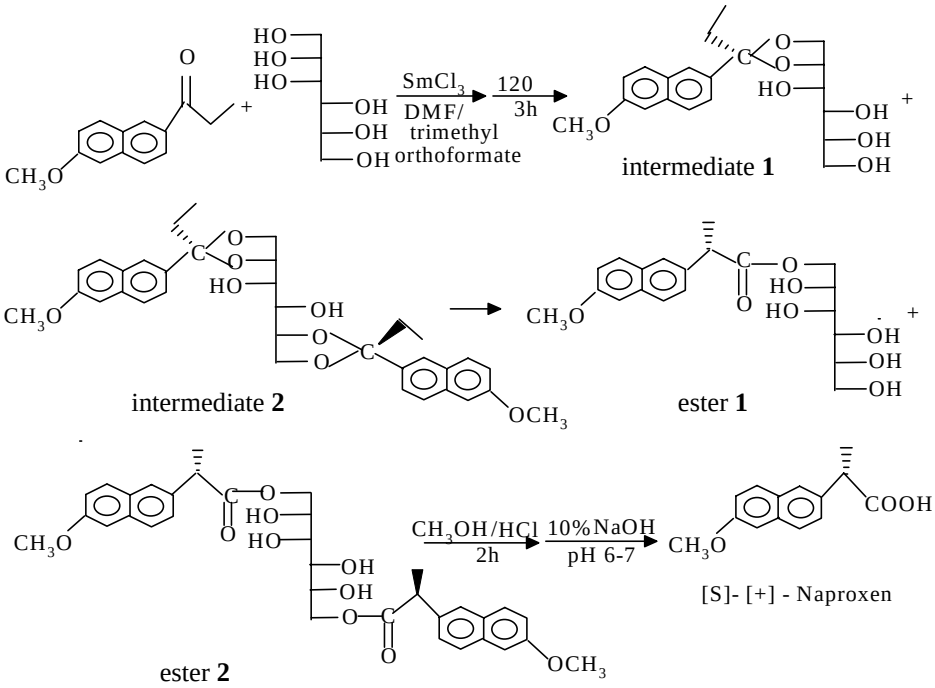
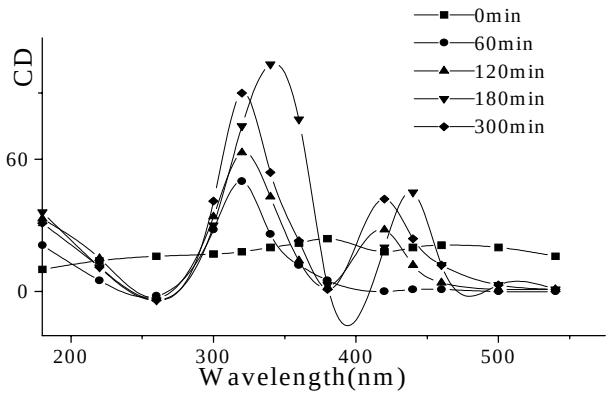


Figure 1



became stronger. It indicated that the ester formed. But adsorption for ketal in CD spectrum was not observed. The two esters possessed the same symmetrical property and showed a (+)-Cotton effect in CD spectrum.

Experimental

^{1}HNMR spectra were recorded on a JOEL FX-60Q, Varian FT-80A spectrometer, with TMS as an internal standard. MS spectra were obtained on a JMS-D300 GC/MS spectrometer, while the enantiomeric excesses (ee%) were monitored by chiral gas chromatography (HP 5890 GC-FID, 30 m long Lipodex-A capillary column). The ee values were reproducible. IR (KBr pellets) spectra were recorded on a Shimadzu IR-1700 spectrophotometer. Melting points were recorded in open capillary tubes on Electrothermal Melting Point Apparatus and were uncorrected. CD spectra was measured at 20°C on Cary Model 60 spectropolarimeter. Spectral measurements began at 180 nm, and the molecular ellipticity ([θ]) values were adjusted to an enantiomeric excesses of 100%. All reagents and solvents were purified and dried as required.

*Synthesis of the ester **1** and **2***

2.2 g (6-methoxy-2-naphthyl) 1-propanone (10 mmol) and 0.26 g $SmCl_3$ (1 mmol) were dissolved in 40 mL DMF/trimethyl orthoformate(1/3, v/v), followed by the addition of 1.82 g D-mannitol (10 mmol). The reaction mixture was stirred and heated at 120°C for 3 hours. The resulting solution was evaporated under reduced pressure, the residue was extracted by methanol (20 mL) three times and the solvent was recovered, the residue was chromatographed on silica column (CH_2Cl_2 : CH_3OH =70 : 30), two components were obtained.

Ester **1** ($C_{20}H_{26}O_8$): mp 82-84°C, $[\alpha]_D^{20}$ +98 (c 1.8. $CHCl_3$). Elemental Analysis: Calcd.: C 60.9%, H 6.6%; Found C 60.7%, H 6.7%; MS (*m/z*): 398(M^+, 16), 397(M-1$^+$, 18), 105(14); ^{1}HNMR (δ ppm, DMF-d_7): 7.5(m, 6H, naphthyl), 4.2 (s, 3H, OCH_3), 1.3 (d, 3H, J=7.4Hz, CH_3), 3.5(q, 1H, J=7.5Hz, CH), 3.8-4.9(m, 8H), 5.1(s, 5H, -OH); IR (KBr): 3450, 2900, 1725, 1603, 1540, 1445, 1320, 1225, 1110, 1030, 985, 780, 680 cm^{-1}.

Ester **2** ($C_{34}H_{38}O_{10}$): mp 82-84°C, $[\alpha]_D^{20}$ +156 (c 1.8. $CHCl_3$). Elemental Analysis: Calcd.: C 67.3%, H 6.3%; Found C 67.2%, H 6.1%; MS (*m/z*): 598(M^+, 14), 597(M-1$^+$, 21), 105 (12); ^{1}HNMR(δ ppm, DMF-d_7): 7.5(m, naphthyl, 12H), 4.1(s, 6H, OCH_3), 1.4(d, 6H, J=7.6Hz, CH_3), 3.5(q, 2H, J=7.4Hz, CH), 3.7-4.9(m, 8H), 5.1(s, 4H, -OH); IR (KBr): 3450, 2900, 1725, 1605, 1540, 1445, 1320, 1225, 1110, 1030, 985, 780, 685 cm^{-1}.

*Hydrolysis of the ester **1** and **2***

The residue was dissolved directly in the mixture of 40 mL methanol and 10 mL concentrated hydrochloric acid and refluxed for 2 h. After cooled to room temperature the mixture was neutralized by 1 mol/L NaOH solution to pH=6-7, extracted by $CHCl_3$ (20 mL) three times and washed with water, concentrated, finally chromatographed on

silica column (CH_2Cl_2: CH_3OH=70: 30), a white product was obtained (1.96 g, yield 87.5%). mp 153-155°C, $[\alpha]_D^{20}$ +63.4 (c 1.8. $CHCl_3$), ee 99%. [mp 154-156°C, $[\alpha]_D^{20}$ +63.5 (c 1.8. $CHCl_3$)][9].

References

1. G. E Oosterom, R. J. van Haaren, J. N. H. Reek, P. C. J. Kamer, P. W. N. M. van Leeuwen, *Chem. Commun.*, **1999**, 1119.
2. P. Oreste, S. Franca, V. Giuseppina, *J. Org. Chem*., **1987**, *52*, 10.
3. R. S. Harikisan, S. B. Nanjundiah, R. Jaimala, G. K. Dilip, *Tetrahedron: Asymmetry*, **1992**, *3*, 163.
4. M. A. Hearshaw, J. R. Moss, *Chem. Commun.*, **1999,**1.
5. R. Noyori, *Chem. Soc. Rev.*, **1989**, *18*,187.
6. J. .M. Baird, J. R. Kern, G. R. Lee, D. J. Morgans, M. L. Sparacino, *J. Org. Chem.*, **1991,** *56*, 1928.
7. M. Saunders, J. Chandrasekhar, P. V. R. Schleyer, *Rearrangements in Ground and Excited States*, Academic Press, **1980**, 1.
8. V. G. Shubin, *Topic in Current Chemistry*, Springer-Verlag, **1984**, *116/117*, 267.
9. H. Alper, H. Hamel, *J. Am. Chem. Soc.*,**1990**, *112*, 2803.

Received 3 September, 2001