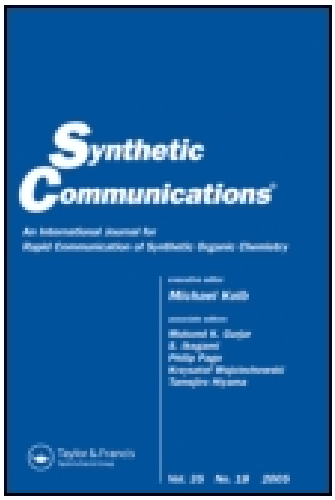

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CHIRAL MANNITOL AS AUXILIARY IN SYNTHESIS OF OPTICAL ACTIVE 2-ARYLPROPANOIC ACIDS BY 1,2-ARYL ENANTIOSELECTIVE MIGRATIONS

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ABSTRACT

(S)-(+)-2-(6′-methoxy-2-naphthyl) propanoic acid has been prepared from (6-methoxy-2-naphthyl)-1-propanone and D-mannitol with $ZnCl_2$ catalysis by 1,2-aryl enantioselective migration in high yields.

Key Words: Naproxen; D-mannitol; Catalysis; Migration

S-2-(6′-methoxyl-α-naphthyl) propionic acid (Naproxen) is an important class of non-steroidal antiflammatory agents,[1,2] which is formed by many different strategies,[3,4] such as symmetric hydrogenation of 2-arylpropenoic acid,[5] asymmetric methylation of 2-arylacetic acid,[6] asymmetric hydroformylation[7]/hydrocarboxylation[8] of the appropriate styrene derivative, asymmetric aryl alkyl coupling reaction[9] or asymmetric alkylation[10] of appropriate aromatic compounds and stereospecific 1,2-aryl migration in chiral α-substituted acetals of propiophenones.[11] The last

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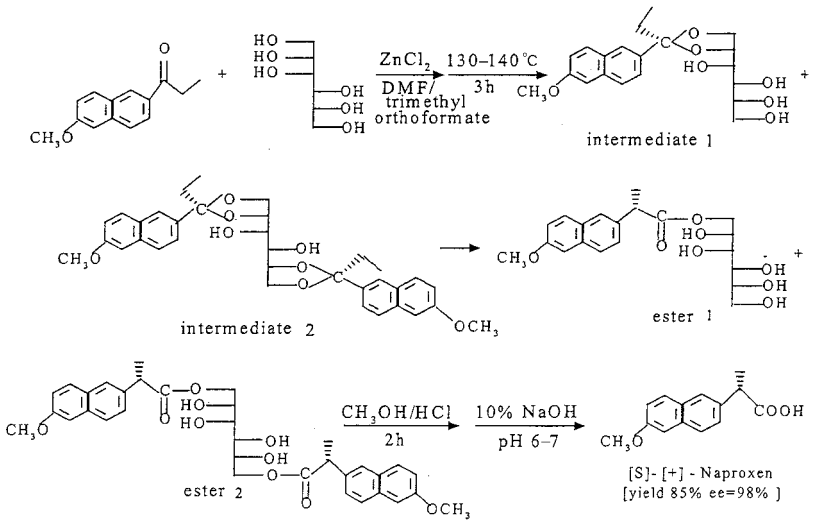

Scheme 1.

method is the most practical method, which thrust great interest upon us. We have found that (S)-(+)-2-(6′-methoxy-2-naphthyl)propanoic acid could be easily synthesized in high yields, through reactions of (6-methoxy-2-naphthyl)-1-propanone with chiral auxiliary D-mannitol with $ZnCl_2$ catalysis. The method can be depicted in Scheme 1.

Compared with the traditional methods, the procedure has been more simplified and the yield of (S)-(+)-Naproxen is high, up to 85% with ee up to 98% without the protection of hydroxyl groups, and the procedure can be easily industrialized.

Preparation of esters (1) and (2) was accomplished in two steps from commercially available (6-methoxy-2-naphthyl)-1-propanone: ketalation of (6-methoxy-2-naphthyl)-1-propanone by D-mannitol with $ZnCl_2$ catalysis in DMF/trimethyl orthoformate (TMOF) (1/3, v/v) produced the acetals—intermediates 1 and 2—which subsequently underwent esterization to produce the mixture of esters (1) and (2) by 1,2-aryl enantioselective migration in 91% yield.

Esters 1 and 2 were treated with concentrated hydrochloric acid (4/1, v/v) in methanol and refluxed for 2 h, cooled, then neutralized by 10% NaOH solution to pH = 6–7; the mixture was extracted with CH_2Cl_2 and washed with water, concentrated, and finally chromatographed on silica column, obtaining (S)-(+)-Naproxen in high yield (93%).

When the ketallization of (6-methoxy-2-naphthyl)-1-propanone by D-mannitol with $ZnCl_2$ catalysis was conducted by reflux in a single solvent such as DMF or TMOF, the corresponding product was produced in less than 30% yield (Table 1). Esters (1) and (2) crystallized from the reaction medium as the mixture was allowed to cool to room temperature. The yield of ester (1) was decreased with longer reflux time when the target product was obtained in relative lower yield and ee value. It can be found that the asymmetric induction of the D-mannitol in the presence of $ZnCl_2$ allows the enantioselective synthesis of optically active (S)-(+)-naproxen in one-pot.

In theory, three types of ketals can be produced in the reaction of D-mannitol with (6-methoxy-2-naphthyl)-1-propanone under $ZnCl_2$ catalysis, however, only two kinds of optically active intermediates—(1) and (2)—were tested, maybe due to the "space effect". The chirality of the intermediate and the formation mechanism were easily detected by measurement of CD spectra in Nujol mulls as shown in Figure 1. It is found that the reaction was consisted by two steps of ketallization and esterization. Furthermore, the ketallization is a transition process for esterization and the two steps may be completed in the same time or in a fast way as the CD-time relation curve shows that absorption at *ca.* 320 and 420 nm attributed to naphthyl ring and carbonyl, respectively. As the reaction proceeds, the intensity of the band at about 320 nm becomes stronger and the bands arise from carbonyl at 420 nm, showing no adsorption for ketal formation to the band, becoming stronger as the ester formed. The two esters possess the same symmetrical property and the whole procedure of strong CD spectra

Table 1. Result of Synthesis of (S)-(+)-2-(6′-Methoxy-2-naphthyl)-propanoic Acid*

Time (h)	Temp. (°C)	Solvent (v/v)	S/C	Yield of Esters (%) 1	2	(S)-(+)-Naproxen (%) Yield	Ee
3	90–100	DMF	100	63	45	29	87
3		DMF/TMOF, 1/3	300	80	58	63	91
1	120–130	DMF/TMOF, 1/3	100	72	0	65	86
Overnight		DMF/TMOF, 1/3	300	34	65	80	85
3	130–140	DMF/TMOF, 1/3	100	80	47	72	93
3		DMF/TMOF, 1/3	300	88	56	85	98
3	140–150	DMF/TMOF, 1/3	300	82	66	73	95
3		TMOF	300	70	22	65	90

*S-(+)-Ibrofen[(S)-(+)-2-(4-i-butylbenzenyl-)propanoic acid] has also been synthesized with D-mannitol and $ZnCl_2$ catalysis in one-pot.

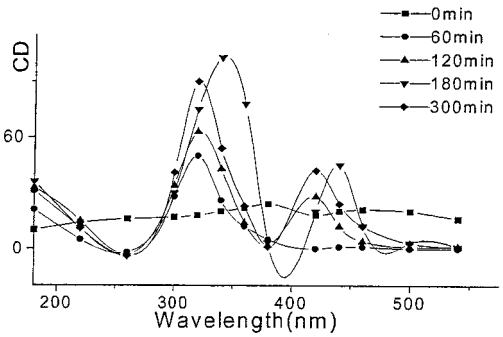

Figure 1. CD spectra of D-mannitol with (6-methoxy-2-naphthyl)-1-propanone.

shows a (+)-Cotton effect of the two absorptions, indicating that the transition of ketals to esters in a chiral deserve model and the chiral center originated from the chiral ketal formation.

In conclusion, we have developed a straightforward, simple and high yielding route to (S)-(+)-Naproxen using commercially available (6-methoxy-2-naphthyl)-1-propanone and chiral auxiliary D-mannitol with $ZnCl_2$ catalysis. This methodology is also useful for synthesis of S-(+)-Ibrofen and should be widely applicable to the preparation of other optically active 2-aryl carboxylic acids. Further investigations on the synthesis of optically active 2-aryl carboxylic acids by natural compounds with the most asymmetric centers per molecule are currently in progress.

EXPERIMENTAL

General methods and materials. ^{1}H and ^{13}C NMR 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. 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. HPLC analysis was recorded in Varian 5060. The chiral properties of the reaction mediate were investigated by circular dichroism (CD) spectra at 20°C on Cary Model 60 spectropolarimeter with a CD model 6001 accessory. The sample cell was 1 cm and the slit was programmed for a spectral bandwidth of 1.5 nm. Cut-off was indicated when the dynode voltage reached 400 V. Spectral measurements began at 200 nm, and the molecular ellipticity ($[\theta]$)

values were adjusted to enantiomeric excesses of 100%. All reagents and solvents were purified and dried as required.

Synthesis of the esters (1) and (2): A mixture of (6-methoxy-2-naphthyl) 1-propanone (2.2 g, 10 mmol) and $ZnCl_2$ (1.36 g, 1 mmol) was dissolved in 40 ml DMF/trimethyl orthoformate, followed by the addition of D-mannitol (1.82 g, 10 mmol). The reaction mixture was stirred and heated to 130–140°C for 3 h. The resulting solution was evaporated in reduced pressure, the residue was extracted with methanol (20 ml) three times and chromatographed on silica column ($CH_2Cl_2 : CH_3OH = 70 : 30$, v/v); two components were obtained.

Esters (1): M.p. 82–84°C, $[\alpha]_D^{20} + 98^\circ$ (c1.8. $CHCl_3$). MS (*m/z*): 397 ($(M-1)^+$, 20), 398 (M^+, 14), 105(15). ^{1}H-NMR (δ, ppm, DMF-d_7): 7.4 (m, naphthyl, 8H), 4.0 (s, 3H), 1.2 (d, 3H), 3.5 (q, 1H), 3.9–4.7 (m, 6H), 5.1 (s, 1H). ^{13}C-NMR (δ, ppm, DMF-d_7): 170, 129, 127, 124, 128, 129, 126, 125, 130, 131, 132, 39.5, 21, 81, 78, 76, 74, 76, 78, 55. IR (KBr, cm^{-1}): 3450 br, 2900, 1726, 1604, 1540, 1445, 1320, 1225, 1110, 1030, 985, 780, 685. Anal. calcd for $C_{20}H_{26}O_8$: C, 60.9; H, 6.6. Found C, 60.7; H, 6.7.

Esters (2): M.p. 82–84°C, $[\alpha]_D^{20} + 156^\circ$ (c 1.8. $CHCl_3$). MS (*m/z*): 598 (M^+, 14), 597 ($(M-1)^+$, 20), 105 (10). ^{1}H-NMR (δ, ppm, DMF-d_7): 7.4 (m, naphthyl, 16H), 4.0 (s, 3H), 1.2 (d, 2H), 3.5 (q, 2H), 3.7–4.7 (m, 6H), 5.1 (s, 1H). ^{13}C-NMR (δ, ppm, DMF-d_7): 170, 129, 127, 124, 128, 129, 126, 125, 130, 131, 132, 39.5, 21, 81, 78, 76, 74, 76, 81, 55. IR (KBr, cm^{-1}): 3450 br, 2900, 1726, 1604, 1540, 1445, 1320, 1225, 1110, 1030, 985, 780, 685. Anal. calcd for $C_{34}H_{38}O_{10}$: C, 67.3; H, 6.3. Found C, 67.2; H, 6.1.

Hydrolysis of the esters (1) and (2): The residue was dissolved directly in 40 ml methanol and 10 ml concentrated hydrochloric acid was added and refluxed for 2 h. After being cooled to room temperature, the mixture was neutralized by 10% NaOH solution to pH = 6–7; the mixture was extracted with CH_2Cl_2 (20 ml) three times and washed with water, concentrated, and finally chromatographed on silica column ($CH_2Cl_2 : CH_3OH = 70 : 30$, v/v). A white product was obtained (1.96 g, yield: 85%). M.p. 153–155°C, $[\alpha]_D^{20} + 63.2^\circ$ (c 1.8. $CHCl_3$), ee 98%; m.p. 154–156°C, $[\alpha]_D^{20} + 63.5^\circ$ (c 1.8. $CHCl_3$).[5]

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