CHEMISTRY LETTERS, pp. 1471-1472, 1986.

Asymmetric Synthesis of (*S*)-2-(6-Methoxy-2-naphthyl)propanoic Acid

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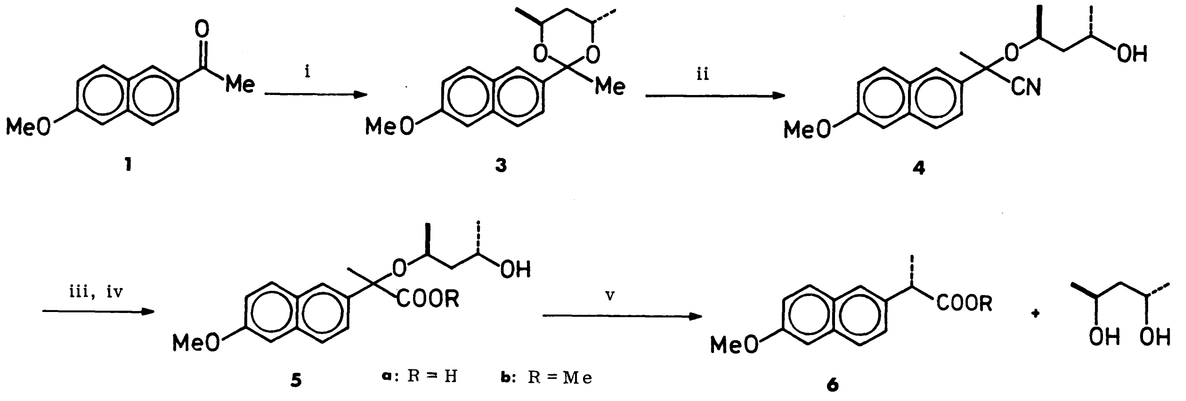
For the synthesis of the title compound of 60% ee, a new method is established which involves cyanation of an acetal derived from 1-(6-methoxy-2-naphthyl)ethanone and (*S*,*S*)-2,4-pentanediol, alkaline hydrolysis, and finally hydrogenolysis with palladium catalyst.

Synthesis of 2-arylpropanoic acids has been a hot synthetic problem in view of anti-inflammatory activity of these compounds.[1] Particularly, asymmetric synthesis of a highly potent enantiomer[2] of the title acid has been the goal of extensive studies.[3] We herein report a new strategy which involves asymmetric cyanation[4] of a chiral acetal of aryl methyl ketone followed by hydrolysis and stereospecific hydrogenolysis.[5]

The starting material, 1-(6-methoxy-2-naphthyl)ethanone (**1**),[6] was converted into an acetal **3** [mp 57-59 °C, $[\alpha]^{20}_{D}$ -1.6° (c 0.98, MeOH)] by the reaction with (*S*,*S*)-2,4-bis(trimethylsiloxy)pentane (**2**)[7] in the presence of trimethysilyl triflate catalyst.[8] A dichloromethane solution (4.5 ml) of tin(IV) chloride (4.5 mmol)[9] was added over 1 h to **3** (3.5 mmol) and trimethylsilyl cyanide (9.3 mmol) dissolved in dichloromethane (10 ml) at -78 °C. After the addition of the catalyst was completed, the reaction was quenched by addition of methanol (1 ml) at -78 °C. Workup gave an 87 : 13 (74% de) diastereomeric mixture of a nitrile **4** in 89% yield. Alkaline hydrolysis (50% KOH-EtOH, reflux, 15 h) of **4** gave a carboxylic acid **5a** (80%) which was submitted to hydrogenolysis (10% Pd/C (400 wt%), Na_2HPO_4 (1 mol),[10] MeOH, H_2 (1 atm), 100 °C, 2 h) to give (*S*)-2-(6-methoxy-



i: **2**, $Me_3SiOSO_2CF_3$, CH_2Cl_2, -30 °C, 85%, ii: Me_3SiCN, $SnCl_4$, CH_2Cl_2, -78 °C, 89%, iii: KOH, EtOH, reflux, 80%
iv: CH_2N_2, v: H_2, Pd/C

2-naphthyl)propanoic acid **(6a)** in 54% yield. The optical purity of the acid was estimated to be 60% ee by derivatization to the methyl ester **6b** and by ^{1}H NMR (400MHz) measurement with Eu(tfc)$_3$. On the basis of the optical purity (84-85%)[7) of the employed chiral diol, the stereospecificity[11) of the hydrogenolysis reaction is estimated to be (60/84) x (1/0.74) x 100 = 97%.

Hydrogenolysis (10% Pd/C, EtOAc, H_2 (2 atm), 60 °C, 45 min)[12) of the methyl ester **5b** (82% ds) proceeded equally well to give (*S*)-**6b** ($[\alpha]^{20}_{D}$ +47°, 61% ee by ^{1}H NMR with Eu(tfc)$_3$) in 42% yield along with the recovered **5b** (38%).

The advantage of the process reported here is that the chiral auxiliary diol is recovered after hydrogenolysis.[13)

References

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7) Prepared by trimethylsilylation of (*S*,*S*)-2,4-pentanediol. The optical purity of the commercially available chiral diol (both from Aldrich and Wako) was proved to be 84-85% ee by derivatization to a bis MTPA ester followed by ^{1}H NMR (400 MHz) measurement as compared with the bis MTPA ester of (*R*,*R*)-2,4-pentanediol.
8) R. Noyori, S. Murata, and M. Suzuki, Tetrahedron, 37, 3899 (1981).
9) Lewis acid such as $BF_3 \cdot OEt_2$ or $TiCl_4$ turned out to be less effective or to inverse the ratio.
10) Without the buffer, reduction of the naphthalene ring took place remarkably to give rise to tetralins.
11) Based on the expected stereochemical course[5) of the reaction, we tentatively assign (*S*) configuration to the stereochemistry of the carbon attached to CN of **4** in accord with the predicted configuration.[4)
12) Raney nickel of any grade was proved to be useless for the desired hydrogenolysis.
13) Financial support by Syntex (USA), Inc., is highly acknowledged.

(Received June 18, 1986)