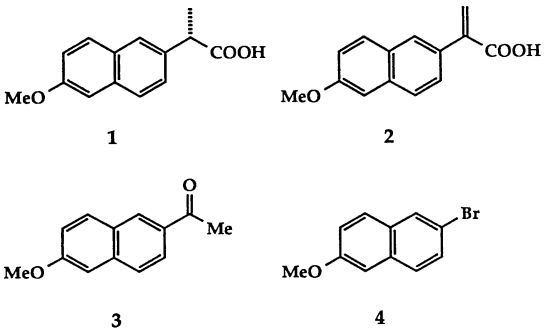
# A Facile, Practical Synthesis of 2-(6-Methoxy-2-naphthyl)propenoic Acid

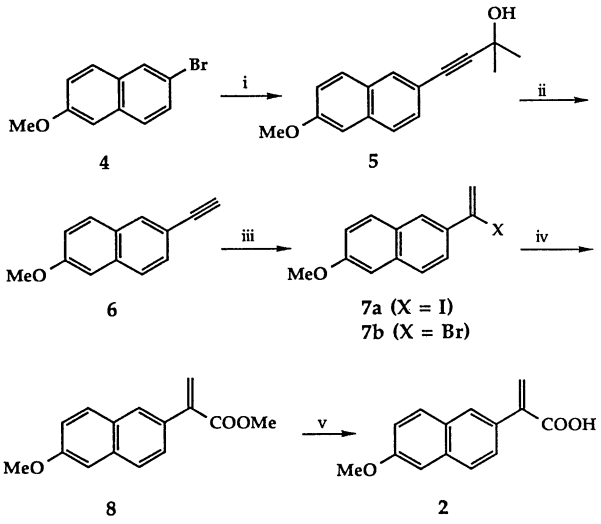
Tamejiro HIYAMA,* Noriko WAKASA, Tomoko UEDA, and Tetsuo KUSUMOTO
Sagami Chemical Research Center, 4-4-1 Nishiohnuma, Sagamihara, Kanagawa 229
(Received October 12, 1989)

**Synopsis.** A facile and practical method for the synthesis of 2-(6-methoxy-2-naphthyl)propenoic acid, a precursor of anti-inflammatory agent naproxen, is described. The method involves (1) Pd-catalyzed ethynylation of 2-bromo-6-methoxynaphthalene, (2) regioselective addition of HX to the triple bond, and (3) Pd-catalyzed carbonylation of the resulting vinyl halide followed by (4) alkaline hydrolysis.

Nonsteroidal anti-inflammatory agents, 2-arylpropanoic acids, have recently grown to be used widely for chemotherapy.[1] Of these, (*S*)-2-(6-methoxy-2-naphthyl)propanoic acid,[2] so called naproxen (**1**), is becoming more common due to its high potency. Thus, practical asymmetric synthesis of this agent in particular has been studied extensively.[3] A promising route should be the one which involves asymmetric hydrogenation of 2-(6-methoxy-2-naphthyl)-propenoic acid (**2**) using a chiral transition metal catalyst.[4] However, the unsaturated acid **2** is not readily accessible by the procedures[4,5] reported so far: all employ 1-(6-methoxy-2-naphthyl)ethanone (**3**) as the starting material which is prepared by the Friedel-Crafts acetylation of 2-methoxynaphthalene in nitrobenzene or polyphosphoric acid.[6] This particular step is pointed out to be incompatible to industrial production. We report a highly efficient procedure for the synthesis of **2** starting with readily accessible 2-bromo-6-methoxynaphthalene (**4**).




Our procedure is summarized in Scheme 1. Though a similar route is previously claimed in a patent,[5b] it employs **3** as the starting material and toxic nickel carbonyl for a carbonylating reagent. We started with 2-bromo-6-methoxynaphthalene **4** which is now commercially available. The bromide was coupled with 2-methyl-3-butyn-2-ol, an oily acetylene equivalent, under the Hagihara's conditions[7a] to give **5** which upon treatment with alkali[7b] was converted into 2-ethynyl-6-methoxynaphthalene (**6**) in almost quantitative yield. Carbonylation of **6** carried out using palladium black and hydriodic acid[8] afforded in 56% yield methyl ester **8** accompained by the ketone **3** (6%). To improve the yield, we first treated **6** with hydriodic acid to produce in situ the




i: $HC{\equiv}CC(Me)_2OH$, $PdCl_2(PPh_3)_2$, CuI, $Et_2NH$, reflux
ii: NaOH, $H_2O$-PhMe, reflux
iii: HX
iv: CO (20 atm), Pd cat, MeOH, $Et_3N$, 65-70°C
v: KOH, $Me_2CO$-$H_2O$, r.t.

Scheme 1.

intermediary vinyl iodide **7a** which was then successfully transformed to the methyl ester **8** (82% yield based on the consumed acetylene). All attempts to isolate the vinyl iodide **7a** in an analyticaly pure form failed due to its instability to light and air. In contrast, the corresponding vinyl bromide **7b** was proved to be relatively stable and was produced by treatment of **6** with hydrobromic acid (90% yield) or preferably with anhydrous hydrogen bromide (97% yield). Though isolated and characterized spectrometrically, the bromide **7b** became colored soon after a couple of days but underwent the carbonylation reaction using $Pd(PPh_3)_4$ catalyst to give the methyl ester **8** in 90% yield (or 96% yield based on the conversion). The ester was found to polymerize upon exposure to air. However, immediate hydrolysis afforded the desired acid **2**. The acid was shown to be relatively stable. The total yield from **4** to **2** through the vinyl bromide **7b** is 86% or 91% on the basis of conversion. Asymmetric hydrogenation of **2** to give (*S*)-naproxen (**1**) of high optical purity is achieved by means of a chiral ruthenium catalyst.[4]

The procedure reported herein should find wide application to the synthesis of various types of 2-arylpropenoic acids and chiral 2-arylpropanoic acids as well in combination with the asymmetric hydrogenation process.

## Experimental

**4-(6-Methoxy-2-naphthyl)-2-methyl-3-butyn-2-ol (5).** In

a 200 ml-flask were placed 6-methoxy-2-bromonaphthalene (**4**, 14.23 g, 60 mmol), bis(triphenylphosphine)palladium dichloride (0.42 g, 0.60 mmol), and copper(I) iodide (0.114 g, 0.60 mmol) under an argon atmosphere. To this mixture were added diethylamine (120 ml) and 2-methyl-3-butyn-2-ol (7.57 g, 8.72 ml, 90 mmol), and the resulting mixture was heated to reflux for 17 h. Excess diethylamine was evaporated under reduced pressure, and the residue was dissolved in ether (ca. 300 ml), and the insoluble material was filtered off. The ethereal solution was washed successively with sat sodium chloride aq solution, 10% citric acid aq solution (3 times), sat sodium chloride aq solution, 5% sodium hydrogencarbonate aq solution, and finally with sat sodium chloride aq solution, dried over anhydrous magnesium sulfate, and then concentrated in vacuo to give pale yellow solid (16.3 g). Recrystallization from hexane-ethyl acetate afforded **5** as colorless needles (10.7 g, 75% yield). The mother liquor was concentrated, and the residue was purified by medium-pressure column chromatography (silica gel, hexane-ethyl acetate 3:1) to give additional product **5** (3.8 g, 25% yield). Total yield was quantitative. Mp 119—121 °C. $^1$H NMR ($CDCl_3$) $\delta$=1.62 (s, 6H), 2.30 (br s, 1H), 3.81 (s, 3H), 7.02—7.83 (m, 6H); IR (KBr) 3450 (br), 2230, 1627, 1605, 1500, 1490, 1385, 1253, 1167, 1158, 1027, 937, 895, 858, 818, 474 cm$^{-1}$; MS *m/z* (rel intensity) 240 ($M^+$, 47), 225 (70), 182 (10), 139 (15), 43 (100). Found: C, 80.09; H, 6.79%. Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71%.

**2-Ethynyl-6-methoxynaphthalene (6).** A mixture of **5** (8.28 g, 34.5 mmol), powdered sodium hydroxide (1.38 g, 34.5 mmol) and toluene (250 ml) was heated to reflux for 17 h under an argon atmosphere. The reaction mixture was diluted with ether, washed successively with aq sodium chloride solution, 10% citric acid aq solution, sat sodium chloride aq solution, 5% sodium hydrogencarbonate aq solution, and finally with sodium chloride aq solution, and dried over anhydrous magnesium sulfate. Concentration followed by medium-pressure column chromatography (silica gel, hexane-ethyl acetate 8:1) afforded **6** as colorless solid (6.23 g, 99% yield). Mp 109—109.5 °C; $^1$H NMR ($CDCl_3$) $\delta$=3.07 (s, 1H), 3.89 (s, 3H), 7.07(s, 1H), 7.10—7.78 (m, 4H), 7.91 (s, 1H); IR (KBr) 3280, 2110, 1627, 1600, 1500, 1485, 1390, 1270, 1230, 1170, 1030, 903, 857, 818, 480 cm$^{-1}$; MS *m/z* (rel intensity) 183 ($M^+$+1, 15), 182 ($M^+$, 100), 167 (14), 140 (10), 139 (79). Found: C, 85.49; H, 5.55%. Calcd for $C_{13}H_{10}O$: C, 85.69; H, 5.53%.

**Methyl 2-(6-Methoxy-2-naphthyl)propenoate (8).** A mixture of **6** (1.82 g, 10.0 mmol), tetrahydrofuran (THF, 15 ml), and hydriodic acid (55—58%, 1.48 ml, 11.1 mmol) was heated under an argon atmosphere to reflux for 2 h to prepare the vinyl iodide **7a**. The reaction mixture, methanol (12 ml), triethylamine (0.70 ml, 5.0 mmol), and palladium black (0.106 g, 1.00 mmol) were placed in an autoclave, and the atmosphere was replaced by 20 atm of carbon monoxide. The autoclave was heated at 65 °C for 17 h under vigorous stirring. The excess gas was purged, and the reaction mixture diluted with ether was washed with sat sodium chloride aq solution, 10% citric acid aq solution, and then with sat sodium chloride aq solution. Concentration followed by medium-pressure column chromatography (silica gel, hexane-ethyl acetate 6:1) gave **8** as colorless solid (1.69 g, 70% yield, 82% yield based on the conversion) along with **3** (0.19 g, 9%) and the starting material **6** (0.27 g, 15%). The ester **8** showed following physical data. Mp 65—68 °C. $^1$H NMR ($CDCl_3$) $\delta$=3.80 (s, 3H), 3.88 (s, 3H), 5.93 (d, *J*=1.2 Hz, 1H), 6.34 (d, *J*=1.2 Hz, 1H), 7.06—7.98 (m, 6H); IR (KBr) 3020, 2960, 1725, 1620, 1605, 1494, 1435, 1430, 1386, 1295, 1260, 1220, 1200, 1178, 1165, 1027, 992, 952, 930, 900, 860, 820, 755, 715, 665, 480 cm$^{-1}$; MS *m/z* (rel intensity) 243 ($M^+$+1, 17), 242 ($M^+$, 100), 199 (10), 185 (16), 184 (15), 183 (72), 168 (13), 140 (20), 139 (32). Found: C, 74.28; H, 5.75%. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82%.

**One-pot Synthesis of 8.** In an autoclave were placed **6** (91 mg, 0.50 mmol); palladium black (5.3 mg, 0.05 mmol), 55—58% hydriodic acid (25 mg, 0.11 mmol), THF (1 ml), and methanol (1 ml), and the atmosphere was repalced by 20 atm carbon monoxide. The whole was heated at 65 °C for 2 h. Workup as before followed by purification gave **8** (68 mg, 56% yield), **3** (6 mg, 6% yield) and a product tentatively assigned as dimethyl 2-(6-methoxy-2-naphthyl)-2-butenedioate (7 mg, 5%), mp 109—112 °C; $^1$H NMR ($CDCl_3$) $\delta$=3.80 (s, 3H), 3.93 (s, 3H), 4.00 (s, 3H), 6.41 (s, 1H), 7.1—7.7 (m, 6H); MS *m/z* (rel intensity) 301 ($M^+$+1, 19), 300 ($M^+$, 100), 242 (18), 243 (47), 182 (25), 139 (47), 59 (16).

**Alternative Synthesis of 8. Preparation of 1-Bromo-1-(6-methoxy-2-naphthyl)ethene (7b).** A mixture of **6** (3.64 g, 20.0 mmol), THF (60 ml), and 47% hydrobromic acid (10 ml, 86.5 mmol) was heated to reflux for 3 h. The reaction mixture was extracted with ether (ca. 400 ml), and the ethereal extract was washed three times with sat sodium chloride aq solution and dried over magnesium sulfate. Concentration and medium-pressure column chromatography (hexane-ethyl acetate 10:1) gave, in addition to **3** (0.35 g, 9% yield), **7b** (4.74 g, 90% yield) as colorless solid which became colored after a couple of days. Mp 104—105.5 °C [lit[5b] 78—80 °C]. $^1$H NMR ($CDCl_3$) $\delta$=3.92 (s, 3H), 5.82 (d, *J*=2.0 Hz, 1H), 6.19 (d, *J*=2.0 Hz, 1H), 7.10 (s, 1H), 7.14—7.27 (m, 1H), 7.63—7.86 (m, 3H), 8.00 (br s, 1H); IR (KBr) 2970, 2950, 1627, 1610, 1595, 1485, 1270, 1200, 1185, 1170, 1030, 880, 860 cm$^{-1}$; MS (50 eV) *m/z* (rel intensity) 264 ($M^+$+2, 17), 262 ($M^+$, 18), 184 (15), 183 (100), 168 (18), 152 (9), 140 (22), 139 (28). Found: C, 59.50; H, 4.13%. Calcd for $C_{13}H_{11}BrO$: C, 59.34; H, 4.21%.

**Alternative Preparation of 7b.** Anhydrous hydrogen bromide gas was bubbled into a dichloromethane (60 ml) solution of **6** (1.82 g, 10 mmol) at room temperature for 6 h. The solvent was evaporated under reduced pressure, and the residue was chromatographed as above to give **7b** (2.54 g, 97% yield) as colorless solid.

**Carbonylation of 7b.** In a 100 ml-stainless steel autoclave were placed the bromide **7b** (1.32 g, 5.0 mmol), tetrakis(triphenylphosphine)palladium (0.29 g, 0.25 mmol), triethylamine (0.51 g, 5.0 mmol), THF (10 ml), and methanol (10 ml), and the mixture was stirred at 70 °C for 21 h under an atmosphere of 20 atm of carbon monoxide. After cooling and releasing the excess CO, the reaction mixture was diluted with diethyl ether (ca. 150 ml) and washed twice with sat sodium chloride aq solution. The organic layer was dried over anhydrous sodium sulfate and concentrated to give a yellow oil which was purified by medium-pressure column chromatography (hexane-ethyl acetate 6:1). The desired ester **8** (1.09 g, 90% yield) was obtained as colorless solid. The bromide **7b** (0.08 g, 6%) was recovered unchanged. Thus, the yield of **8** based on the consumed bromide was 96%.

**2-(6-Methoxy-2-naphthyl)propenoic Acid (2).** A mixture of **8** (0.86 g, 3.6 mmol), potassium hydroxide aq solution (2 mol dm$^{-3}$, 2.66 ml, 5.3 mmol), and acetone (7 ml) was stirred at room temperature for 16 h. The reaction mixture was extracted with ether. The aqueous layer was then acidified with dil hydrochloric acid and extracted with ether. The ethereal extract was washed with sodium chloride aq solution and dried over anhydrous sodium sulfate. Concentration gave practically pure acid **2** (0.80 g, 99% yield) as colorless solid. Mp 173.5—175.5 °C ($CHCl_3$) [lit[5e] 175 °C]. $^1$H NMR ($CDCl_3$ and $CD_3OD$) $\delta$=3.91 (s, 3 H), 6.01 (d, *J*=1.3 Hz, 1H), 6.41 (d, *J*=1.3 Hz, 1H), 7.05—7.86 (m, 6H); IR (KBr) 3200—2200 (br), 1710, 1682, 1601, 1422, 1288, 1260, 1232, 1200, 1162, 1028, 901, 854, 814 cm$^{-1}$; MS *m/z* (rel

intensity) 229 ($M^+$+1,32), 228 ($M^+$, 100), 185 (33), 184 (16), 183 (64), 168 (14), 152 (11), 140 (28), 139 (41), 129 (10), 115 (10), 114 (10), 63 (13). Found: *m/z* 228.0792. Calcd for $C_{14}H_{12}O_3$: M, 228.0785.

We thank Syntex (USA), Inc., for financial support and generous gift of 2-bromo-6-methoxynaphthalene.

**References**

1) J.-P. Rieu, A. Boucherle, H. Cousse, and G. Mouzin, *Tetrahedron*, **41**, 4095 (1985).

2) I. T. Harrison, B. Lewis, P. Nelson, W. Rooks, A. Roszkowski, A. Tomolonis, and J. H. Fried, *J. Med. Chem.*, **13**, 203 (1970).

3) T. Hiyama, K. Saito, K. Sato, N. Wakasa, and M. Inoue, *Chem. Lett.*, **1986**, 1471 and references cited therein.

4) T. Ohta, H. Takaya, M. Kitamura, K. Nagai, and R. Noyori, *J. Org. Chem.*, **52**, 3174 (1987); H. Takaya, T. Ohta, R. Noyori, N. Sayo, H. Kumobayashi, and S. Akutagawa, Japan Kokai Tokkyo Koho, 63-239245 [*Chem. Abstr.*, **110**, 114447w (1989)]; N. Sayo, T. Taketomi, H. Kumobayashi, and S. Akutagawa, European Patent Appl. EP 271311 A2 [*Chem. Abstr.*, **110**, 39189h (1989)].

5) a) S. Kudo, T. Naraoka, and H. Nishino, Japan Kokai Tokkyo Koho, 55-07225 [*Chem. Abstr.*, **93**, 95001h (1980)]; b) Montedison S.p.A., Japan Kokai Tokkyo Koho, 55-154937 [*Chem. Abstr.*, **94**, 192004q (1981)]; S. Campolmi, M. G. Felicioli, V. Carletti, and R. Santi, German Patent 2919919 [*Chem. Abstr.*, **92**, 146491g (1980)]; c) K. Maehara, M. Tsuda, and S. Shishido, Japan Kokai Tokkyo Koho, 63-203631 [*Chem. Abstr.*, **110**, 172885y (1989)]; d) K. Arai and Y. Ohara, Japan Kokai Tokkyo Koho, 57-118554; e) J. D. Andre, Japan Kokai Tokkyo Koho, 61-191649; f) US Patent 3960957 [*Chem. Abstr.*, **85**, 123663f (1976)]; g) F. S. Alvarez, U. S. Patent 3994968 [*Chem. Abstr.*, **87**, 5718w (1977)]; h) Syntex Corp., British Patent 1274273 [*Chem. Abstr.*, **77**, 88157e (1972)].

6) L. Arsenijevic, V. Arsenijevic, A. Horeau, and J. Jacuques, *Org. Synth.* Coll. Vol. VI, 34 (1988); B. P. Gupta and C. N. Haksar, *Agra Univ. J. Res. (Sci.)* **11**, Pt. 2, 165 (1962) [*Chem. Abstr.*, **59**, 1546f (1963)].

7) a) S. Takahashi, Y. Kuroyama, K. Sonogashira, and N. Hagihara, *Synthesis*, **1980**, 627; b) D. E. Ames, D. Bull, and C. Takundwa, *Synthesis*, **1981**, 364.

8) K. Mori, T. Mizoroki, and A. Ozaki, *Chem. Lett.*, **1975**, 39.