These acids were also examined in the chronic adjuvant-induced rat arthritis model.[25] Adjuvant arthritis was induced in male Lewis rats (125–150 g) by the intradermal injection of 0.05 mL of a 0.65% suspension of *Mycobacterium tuberculosis* in Freund's adjuvant into the plantar surface of the right hind foot (day 0). Negative control groups received only mineral oil. Test compounds were administered once daily, by gavage, at a dose of 0.2 mmol/kg to groups of six rats from day 0 to 21. The change in right and left hind foot volumes over the period from days 0 to 21 was determined plethysmographically for both the injected and uninjected foot of each rat. The significance of differences between treated and untreated control groups was assessed using Dunnet's test.[26]

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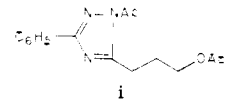

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4-(6-Methoxy-2-naphthyl)butan-2-one and Related Analogues, a Novel Structural Class of Antiinflammatory Compounds[1]

Alexander C. Goudie,* Laramie M. Gaster, Antony W. Lake, Carl J. Rose, Patricia C. Freeman, Bryn O. Hughes, and David Miller

Beecham Pharmaceuticals, Research Division, Medicinal Research Centre, Coldharbour Road, The Pinnacles, Harlow, Essex, CM19 5AD, England.

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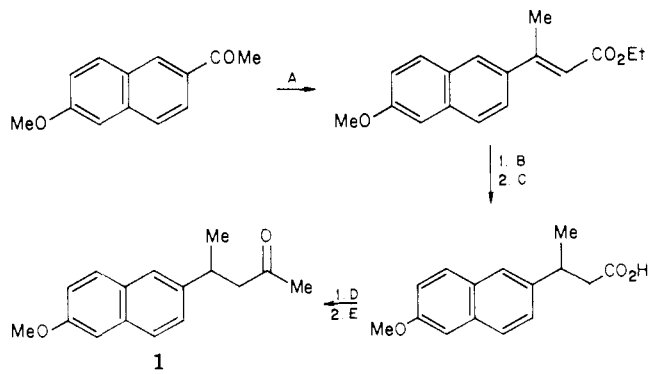
A series of compounds related to 4-(6-methoxy-2-naphthyl)butan-2-one has been prepared and tested for antiinflammatory activity by the cotton pellet granuloma method. Compounds possessing a small lipophilic group such as methoxyl, methyl, or chloro in the 6 position in conjunction with a butan-2-one side chain in the 2 position of the naphthalene ring were most active. The introduction of a methyl group along the side chain was invariably deleterious. Good activity was generally retained by forming esters of a butan-2-ol side chain.

Numerous arylacetic and arylpropionic acids have been synthesized in the search for nonsteroidal antiinflammatory agents. Although many of these acids have been shown to possess good activity, they invariably cause harmful irritation to the gastrointestinal tract. It is thought that this property could be related to the acidic nature of such compounds. In order to overcome this important drawback we decided to screen a variety of compounds lacking a carboxyl group, and from this investigation we have now prepared a structurally novel class of antiinflammatory compounds. This class consists of 2,6-disubstituted naphthylalkanones and derivatives thereof. We hoped that such compounds, when given orally, would be absorbed without causing gastric damage.

Chemistry. The initial lead compound, **1**, was prepared from 2-acetyl-6-methoxynaphthalene[2] according to Scheme I. The majority of compounds which were subsequently synthesized are shown in Scheme II. The reaction of 6-methoxy-2-naphthaldehyde[3] or 6-methyl-2-naphthaldehyde[4] with acetone and dilute NaOH gave the enones **2** and **18**, respectively, and these underwent catalytic hydrogenation to their corresponding butanones **3** and **19**. The preparation of **3** using an alternative route involving 6-methoxy-2-naphthylacetic acid has previously been

Scheme I[a]



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[a] Reagents: method A, NaH-triethyl phosphonoacetate; B, 10% Pd/C-H_2; C, 10% NaOH; D, $SOCl_2$; E, $(Me)_2CuLi$.

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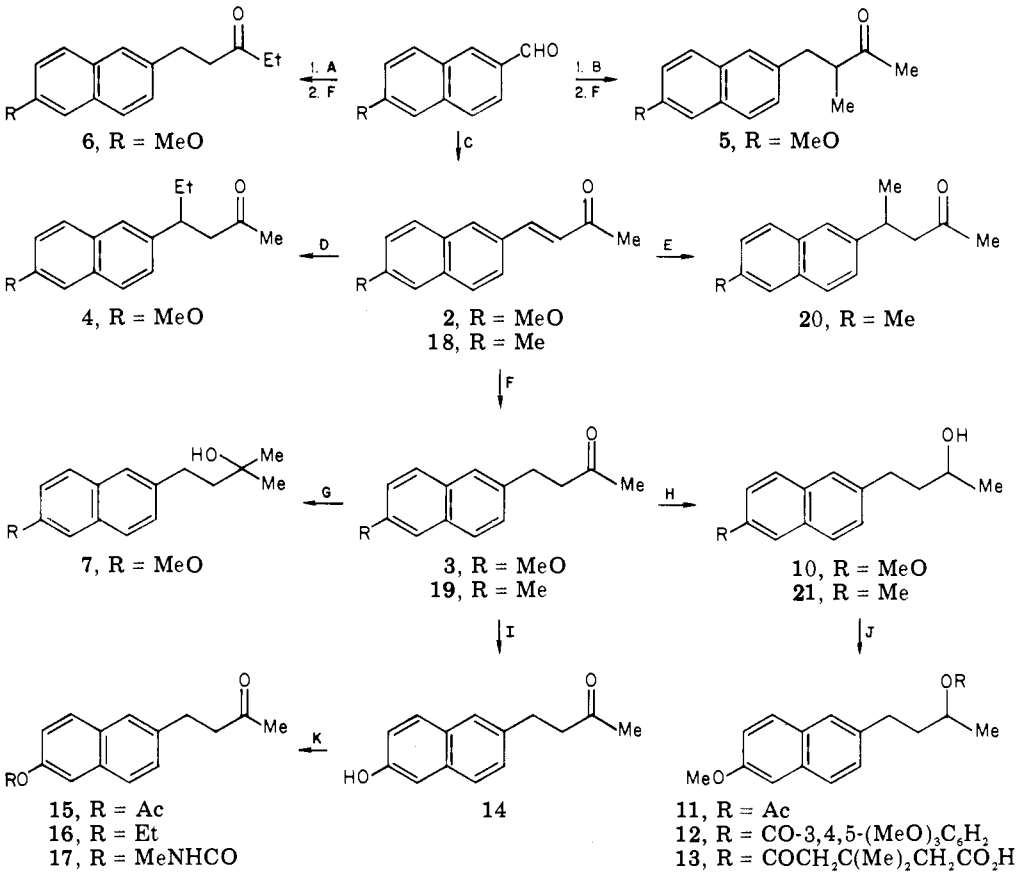
Scheme II[a]



[a] Reagents: method A, NaOH-ethyl methyl ketone; B, HCl-ethyl methyl ketone; C, NaOH-acetone; D, $(Et)_2CuLi$; E, $(Me)_2CuLi$; F, 10% Pd/C-H_2; G, MeMgI; H, $NaBH_4$-EtOH; I, concentrated HCl-AcOH; J, AcCl-pyridine (11), 3,4,5-$(MeO)_3C_6H_2COCl$-pyridine (12), 3,3-dimethylglutaric anhydride-pyridine (13); K, AcCl-pyridine (15), $NaOH/Et_2SO_4$ (16), Et_3N-MeNCO (17).

alleged.[5] However, investigation of the intermediates showed a number of discrepancies in the melting points and its seems probable that the compound actually prepared by these authors was a derivative of 6-hydroxy-2-naphthylacetic acid.[6]

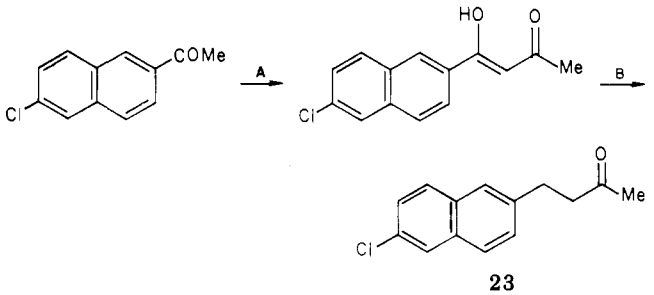
Condensation of 6-methoxy-2-naphthaldehyde with ethyl methyl ketone under acid conditions led to compound **5**, whereas a base-catalyzed reaction gave the ethyl ketone **6**[7] after catalytic hydrogenation of intermediate enones. Treatment of the enones **2** and **18** with dialkylcopper lithium reagents afforded the methyl ketones **4** and **20** while MeMgI and compound **3** gave the tertiary alcohol **7**.

Derivatization of **3** with ethylene glycol and *p*-toluenesulfonic acid or with NH_2OH furnished the corresponding dioxolane **8** and the oxime **9**. Metal hydride reduction of **3** or **19** gave the alcohols **10** and **21**, respectively, and **10** was then esterified by conventional means to the esters **11**–**13**.

Demethylation of **3** using concentrated HCl and AcOH gave the naphthol **14** which was then converted to **15**, **16**, and **17** with AcCl, Et_2SO_4, and MeNCO, respectively. 4-(2-Naphthyl)butan-2-one (**22**) was prepared by condensation of 2-(bromomethyl)naphthalene with acetylacetone, followed by hydrolysis.

The chloro analogue **23** was prepared by a novel method as shown in Scheme III. Conversion of 2-acetyl-6-chloronaphthalene[8] to the intermediate enone was accomplished using NaH and EtOAc, and selective catalytic hydrogenation of the aryl ketone function then gave the butanone **23**.

Scheme III[a]



[a] Reagents: method A, NaH-EtOAc; B, 10% Pd/C-H_2 in AcOH.

The positional isomers of compound **3**, namely, 4-(2-methoxy-1-naphthyl)butan-2-one (**24**) and 4-(4-methoxy-1-naphthyl)butan-2-one (**25**), were prepared by condensation of their corresponding aldehydes with ethyl acetoacetate, followed by hydrogenation and hydrolytic decarboxylation of the intermediate β-keto esters with dilute HCl.

Pharmacology. The antiinflammatory activity of some of the compounds was initially discovered using an acute model of inflammation, namely, the carrageenan-induced edema test of the rat paw.[9] Cotton pellet induced granuloma formation in the rat[10] served as a chronic model of inflammation for further evaluation of the series. The method we used for this test is as follows.

Groups of 10 female Wistar rats (OLAC, 150–170-g body weight) were anesthetized with either Halothane (ICI) or Hypnorm (Janssen) plus Valium (Roche). Using an aseptic

Table I. Cotton Pellet Granuloma Results

compd	% inhibn of granuloma[c]	compd	% inhibn of granuloma[c]
1	24[a]	15	2[a]
2	18[a]	16	12[a]
3	39	17	21[a]
4	20[a]	18	29
5	7[a]	19	34
6	7[a]	20	11[a]
7	3[a]	21	35
8	22	22	20[a]
9	15[a]	23	53
10	32	24	10[a]
11	38	25	0[a]
12	41	naproxen	46 (30)[b]
13	26	aspirin	5[a] (100)
14	5[a]	hydrocortisone	30-40 (10)

[a] Result not significant on Student's t test at $p > 0.02$. [b] 4/10 deaths. No significant inhibition at 3 mg/kg. [c] 50 mg/kg po unless stated otherwise in parentheses (values in mg/kg po).

Table II. Carrageenan Edema Results

compd	% inhibn of edema[a]
1	36
2	50
3	37 (15)
naproxen	30 (6)
aspirin	31 (300)

[a] 100 mg/kg po unless stated otherwise in parentheses (values in mg/kg po).

technique, preweighed, sterile, cotton wool pellets cut from dental roll were implanted subcutaneously, two per rat, one on each side of a ventral midline incision. The wound was closed with a Michel clip and the animals were allowed to recover. Test compounds, suspended in 0.7% methylcellulose (BDH), were administered orally daily from days 0 to 5, commencing 2-3 h prior to pellet implantation. Control rats received suspending vehicle (10 mL/kg) only. On day 6 the rats were killed by excess intraperitoneal sodium pentabarbitone solution (Abbott Labs) and the pellets dissected out.

After drying to constant weight at 80 °C the pellets were weighed. The mean granuloma formed per rat was calculated from the final and the known original pellet weights. The means and standard errors for test and control granulomas were calculated and compared using Student's t test. Significances are shown in Table I, which also contains values for percentage inhibition of granuloma formation for test groups compared with the appropriate controls.

Results and Discussion

Antiinflammatory data are summmarized in Tables I and II. The initial lead compound, **1**, showed promising antiinflammatory activity in the rat carrageenan test but was unfortunately inactive in our chronic model of inflammation. The unsaturated ketone **2** was also inactive in the cotton pellet test, but very good activity was observed in both models when the methyl group of compound **1** was removed to give 4-(6-methoxy-2-naphthyl)butan-2-one (**3**). We therefore commenced a chemical program around compound **3** in order to optimize activity.

Initially we decided to study the effect of modifying the butanone side chain. The introduction of a methyl or ethyl group, as in compounds **4-7**, greatly reduced antiinflammatory activity. Derivatization of the ketone function was then investigated, and the dioxolane **8** was found to retain good activity, whereas the oxime **9** was not significantly active at the same dose. The alcohol **10** and its corresponding esters **11-13** were all active.

The importance of the ring substituents was investigated next. Removal of the 6-methoxyl group to give **22** resulted in reduced activity, but when this was replaced by a methyl or chloro substituent, as in compounds **19** and **23**, antiinflammatory activity was largely retained. The naphthol **14**, its derivatives **15-17**, and the positional isomers **24** and **25** were all much less active.

The compounds in the series also have a remarkably low propensity for causing ulcers in starved rats and this property, together with the detailed pharmacology of compound **3**, will be discussed in a pending publication.[11]

Preliminary metabolism studies using compound **3** have shown that 6-methoxy-2-naphthaleneacetic acid is one of the metabolites[12] and we have shown that this acid does have antiinflammatory activity. The complete metabolic picture is still under investigation.

Experimental Section

Where microanalyses have been carried out as indicated by the symbols of the elements, the results are within 0.4% of the theoretical values. The melting points are uncorrected. IR and NMR spectra of all new compounds are consistent with their structures.

4-(6-Methoxy-2-naphthyl)pentan-2-one (1). A mixture of triethyl phosphonoacetate (54 g, 0.24 mol) and NaH (6.48 g, 0.27 mol) was stirred at room temperature in 1,2-dimethoxyethane (150 mL) under N_2. A solution of 2-acetyl-6-methoxynaphthalene[2] (30 g, 0.15 mol) in 1,2-dimethoxyethane (300 mL) was added dropwise and the mixture then refluxed overnight. The reaction mixture was diluted with H_2O (500 mL), acidified with concentrated HCl, and extracted with Et_2O. The ethereal extracts were washed with 1 N Na_2CO_3 solution and with H_2O, dried (Na_2SO_4), and concentrated to give ethyl 3-(6-methoxy-2-naphthyl)but-2-enoate as a yellow oil which solidified on standing (40.5 g, 100%): IR (film) 1708 cm^{-1} (C=O).

The crude product (24 g, 0.089 mol) in EtOAc was hydrogenated at atmospheric pressure and room temperature using 10% Pd/C (2.4 g) as the catalyst. The catalyst was removed by filtration and the filtrate concentrated to yield ethyl 3-(6-methoxy-2-naphthyl)butanoate as a colorless oil which solidified on standing (24.2 g, 100%): IR (film) 1730 cm^{-1} (C=O).

A mixture of the saturated ester (14.4 g, 0.053 mol), 10% NaOH solution (150 mL, 0.37 mol of NaOH), and MeOH (300 mL) was refluxed for 2 h before being diluted with H_2O (500 mL) and extracted with EtOAc. The aqueous layer was acidified with concentrated HCl and extracted with EtOAc. The acid extract was washed with H_2O, dried ($MgSO_4$), and concentrated to give 3-(6-methoxy-2-naphthyl)butanoic acid as a colorless solid (11.9 g, 92%): mp 126-129 °C; IR (Nujol) 1700 cm^{-1}.

The above acid (19.0 g, 0.078 mol) in benzene (200 mL) was treated dropwise with $SOCl_2$ (8.15 mL, 0.11 mol) and the resulting mixture was gently refluxed overnight. The solvent was removed in vacuo to give the crude acid chloride as a brown oil. A solution of the latter in Et_2O (250 mL) was added dropwise to a stirred suspension of Me_2CuLi, prepared from MeLi (233 mL of a 2.18 M solution in Et_2O, 0.51 mol) and CuI (48.6 g, 0.26 mol), at -70 °C under N_2. The mixture was stirred at -70 °C for 15 min, treated with MeOH (35 mL), diluted with H_2O (500 mL), and acidified with concentrated HCl. After filtration through a pad of Kieselguhr, the Et_2O layer was washed with 1 N Na_2CO_3 solution and with H_2O, dried ($MgSO_4$), and concentrated. The product was purified by chromatography on alumina using benzene as eluant, followed by recrystallization from pentane to afford pure **1** (10.7 g, 57%): mp 48-49 °C; IR (film) 1705 cm^{-1}. Anal. ($C_{16}H_{18}O_2$) C, H.

4-(6-Methoxy-2-naphthyl)but-3-en-2-one (2). A mixture of 6-methoxy-2-naphthaldehyde (30 g, 0.16 mol), acetone (500 mL), and 10% aqueous NaOH (10 mL) was stirred for 3 h before being acidified with concentrated HCl and extracted with Et_2O. The Et_2O extract was dried ($MgSO_4$) and evaporated to yield a solid (30 g) which was purified on a silica gel column using benzene

as eluant to give **2** as a pale-yellow solid (15 g, 41%): mp 120 °C. Anal. ($C_{15}H_{14}O_2$) C, H.

4-(6-Methoxy-2-naphthyl)butan-2-one (3). A solution of **2** (32 g, 0.14 mol) in EtOAc (500 mL) was hydrogenated at atmospheric pressure and room temperature over 10% Pd/C (3 g) until no further uptake of H_2 occurred. The solution was filtered and the solvent removed in vacuo. Recrystallization of the product from Et_2O gave pure **3** (22.5 g, 70%): mp 80–81 °C. Anal. ($C_{15}H_{16}O_2$) C, H.

Alternative Preparation of 3. A mixture of methyl 6-methoxy-2-naphthylacetate[6] (18.9 g, 0.082 mol) and $LiAlH_4$ (9.5 g, 0.25 mol) in Et_2O (500 mL) was refluxed for 5 h. After cooling and acidification with 2 N H_2SO_4, the Et_2O layer was separated and the aqueous layer further extracted with Et_2O. The combined organic extracts were washed with H_2O, dried (Na_2SO_4), and concentrated to give a colorless solid. Recrystallization of this product from benzene gave pure 2-(6-methoxy-2-naphthyl)ethanol (10.9 g, 65%): mp 115–116 °C (lit.[5] mp 133–134 °C). Anal. ($C_{13}H_{14}O_2$) C, H.

The above alcohol (1 g, 0.005 mol), PBr_3 (1 mL, 0.011 mol), and benzene (25 mL) were refluxed for 4 h, cooled, and then poured into H_2O (150 mL). The benzene layer was separated and the aqueous layer extracted with benzene (25 mL). The combined benzene layers were washed with H_2O, dried (Na_2SO_4), and concentrated to give an oil which solidified on standing. Recrystallization of the crude product from bp 80–100 °C petroleum ether gave pure 2-(6-methoxy-2-naphthyl)bromoethane (0.6 g, 46%): mp 60 °C (lit.[5] mp 95–96 °C). Anal. ($C_{13}H_{13}BrO$) C, H, Br.

The above bromide (4.2 g, 0.016 mol), KCN (3.3 g, 0.05 mol), H_2O (50 mL), and EtOH (90 mL) were refluxed for 4 h. The resulting mixture was diluted with H_2O (100 mL) and extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with H_2O, dried (Na_2SO_4), and concentrated to give an oil which was chromatographed on silica using benzene as eluant to give pure 3-(6-methoxy-2-naphthyl)propionitrile (2 g, 60%): mp 103 °C (lit.[5] mp 84–85 °C). Anal. ($C_{14}H_{13}NO$) C, H, N.

The above nitrile (1 g, 0.005 mol) in Et_2O (100 mL) was added to MeMgI, prepared from MeI (1.4 g, 0.01 mol) and Mg (0.24 g, 0.01 mol), in Et_2O (100 mL). The mixture was refluxed for 1 h, allowed to stand overnight at room temperature, and acidified with 5 N HCl (100 mL). The Et_2O layer was separated, washed with H_2O, dried (Na_2SO_4), and concentrated. Recrystallization of the crude product from EtOH gave pure **3** (0.52 g, 48%): mp 80 °C (lit.[5] no melting point given; thick, pale-yellow oil).

4-(6-Methoxy-2-naphthyl)hexan-2-one (4). EtLi (75.5 mL of a 1.06 M solution in benzene, 0.08 mol) was added over 30 min to a suspension of CuI (7.6 g, 0.04 mol) in dry Et_2O (25 mL) at −10 °C under an atmosphere of N_2. A solution of **2** (4.52 g, 0.2 mol) in dry Et_2O (25 mL) was then added over 20 min and, after a further 30 min at −10 °C, the black reaction mixture was poured into a cold, saturated, aqueous solution of NH_4Cl (100 mL). The resulting mixture was filtered, the organic layer separated, and the aqueous layer further extracted with Et_2O. The combined organic extracts were washed with H_2O, dried (Na_2SO_4), and concentrated to give a dark-brown gum which was chromatographed on silica gel using a mixture of Et_2O and bp 60–80 °C petroleum ether. The residue from the fraction eluted with bp 60–80 °C petroleum ether containing 6% Et_2O was recrystallized from bp 60–80 °C petroleum ether to give **4** (1.36 g, 27%): mp 64–65 °C. Anal. ($C_{17}H_{20}O_2$) C, H.

4-(6-Methoxy-2-naphthyl)-3-methylbutan-2-one (5). A slurry of 6-methoxy-2-naphthaldehyde (9.3 g, 0.05 mol) in ethyl methyl ketone (8 g, 0.1 mol) was treated at 5 °C with 5 mL of ethereal HCl and then stirred at room temperature for 3 days. The ethyl methyl ketone was removed in vacuo and the resulting oil triturated with Et_2O to remove 2.5 g (26.9%) of the initial aldehyde. A solution of the residual dark oil in EtOAc (100 mL) was hydrogenated at atmospheric pressure and room temperature over 10% Pd/C (0.45 g) for 1 h. The solution was filtered, concentrated, and chromatographed on silica gel using 10% Et_2O in bp 60–80 °C petroleum ether to give **5** as a colorless oil (2.55 g, 29%). Anal. ($C_{16}H_{18}O_2$) C, H.

5-(6-Methoxy-2-naphthyl)pentan-3-one (6). Preparation analogous to methods employed for compounds **2** and **3** using ethyl methyl ketone instead of acetone afforded **6** after recrystallization from MeOH: mp 76 °C (lit.[7] mp 74 °C).

4-(6-Methoxy-2-naphthyl)-2-methylbutan-2-ol (7). A solution of MeMgI in Et_2O (10 mL), made from MeI (3 g, 0.021 mol) and magnesium (0.6 g, 0.025 mol), was treated dropwise with stirring with a solution of **3** (4.4 g, 0.019 mol) in Et_2O (50 mL). After a further 1 h at room temperature, the solution was poured into cold, aqueous NH_4Cl solution and the organic layer separated. The aqueous layer was extracted with Et_2O and the combined extracts were washed with H_2O, dried (Na_2SO_4), and concentrated. The product was recrystallized from bp 60–80 °C petroleum ether to afford pure **7** (3.6 g, 90%): mp 103–105 °C. Anal. ($C_{16}H_{20}O_2$) C, H.

2-[2-(6-Methoxy-2-naphthyl)ethyl]-2-methyl-1,3-dioxolane (8). A solution of **3** (5 g, 0.022 mol), ethylene glycol (30 mL, 0.54 mol), and *p*-toluenesulfonic acid (0.2 g, 1.2 mmol) in benzene (250 mL) was refluxed for 20 h with constant separation of H_2O by means of a Dean-Stark trap. The mixture was cooled to room temperature, basified with 1 N $NaHCO_3$ solution (60 mL), and extracted with Et_2O. The organic extract was washed with H_2O, dried (Na_2SO_4), and concentrated. Recrystallization of the resulting solid from bp 40–60 °C petroleum ether gave pure **8** as colorless needles (4.5 g, 75%): mp 69 °C. Anal. ($C_{17}H_{20}O_3$) C, H.

4-(6-Methoxy-2-naphthyl)butan-2-one Oxime (9). A mixture of **3** (5 g, 0.022 mol), hydroxylamine hydrochloride (5 g, 0.072 mol), pyridine (5 mL, 0.062 mol), and EtOH (50 mL) was heated at 90 °C for 1 h. The solvent was then removed in vacuo, and the product was added to H_2O (50 mL) and then filtered. Recrystallization from EtOH gave **9** (4.6 g, 86%): mp 125–127 °C. Anal. ($C_{15}H_{17}NO_2$) C, H, N.

4-(6-Methoxy-2-naphthyl)butan-2-ol (10). To a stirred solution of **3** (5 g, 0.22 mol) in EtOH (500 mL) at 5 °C was added $NaBH_4$ (1 g, 0.26 mol) portionwise. After a further 3 h at room temperature the mixture was treated with aqueous NH_4Cl, concentrated, and extracted several times with Et_2O. The organic extract was washed with H_2O, dried (Na_2SO_4), and concentrated to give **10** (4.7 g, 93%): mp 94–95 °C. Anal. ($C_{15}H_{18}O_2$) C, H.

4-(6-Methoxy-2-naphthyl)but-2-yl Acetate (11). To a solution of **10** (1.15 g, 5 mmol) in dry pyridine (10 mL) was added AcCl (1.4 g, 0.02 mol) dropwise at 0 °C. After a further 1 h at room temperature the solution was poured into H_2O and extracted with Et_2O, and the ethereal solution was dried (Na_2SO_4) and concentrated. The product was chromatographed on alumina using 10% Et_2O in bp 60–80 °C petroleum ether to afford **11** as a colorless oil (1.16 g, 85%). Anal. ($C_{17}H_{20}O_3$) C, H.

4-(6-Methoxy-2-naphthyl)but-2-yl 3,4,5-Trimethoxybenzoate (12). Preparation analogous to **11** using 3,4,5-trimethoxybenzoyl chloride gave **12** as a pale-yellow oil (65%). Anal. ($C_{25}H_{28}O_6$) C, H.

4-(6-Methoxy-2-naphthyl)but-2-yl Hydrogen 3,3-Dimethylglutarate (13). A mixture of **10** (2.3 g, 0.01 mol), 3,3-dimethylglutaric anhydride (1.56 g, 0.011 mol), pyridine (3 mL), and toluene (50 mL) was refluxed for 48 h. The resulting solution was concentrated and partitioned between Et_2O and H_2O, and the organic layer was separated and extracted with 1 N NaOH solution. These basic extracts were washed with Et_2O and acidified with 5 N HCl. The solid which precipitated was recrystallized from hexane to afford **13** (2 g, 54%): mp 85–86 °C. Anal. ($C_{22}H_{28}O_5$) C, H.

4-(6-Hydroxy-2-naphthyl)butan-2-one (14). A solution of **3** (7.5 g, 0.033 mol) in AcOH (300 mL) and concentrated HCl (150 mL) was refluxed overnight and then concentrated in vacuo. The dark-green oil obtained was diluted with 1 N $NaHCO_3$ solution and extracted into Et_2O. The organic extract was washed with H_2O, dried (Na_2SO_4), and concentrated. Recrystallization of the crude product from bp 100–120 °C petroleum ether gave pure **14** (6.1 g, 82%): mp 122–124 °C. Anal. ($C_{14}H_{14}O_2$) C, H.

6-(3-Oxobutyl)-2-naphthyl Acetate (15). This was prepared from **14** using the same procedure as was used for compound **11**. Recrystallization of the crude product from bp 60–80 °C petroleum ether gave pure **15** (42%): mp 94–95 °C. Anal. ($C_{18}H_{18}O_3$) C, H.

4-(6-Ethoxy-2-naphthyl)butan-2-one (16). A solution of **14** (5 g, 0.023 mol) in 40% aqueous NaOH (30 mL) and EtOH (50 mL) was refluxed while being treated with Et_2SO_4 (20 mL, 0.15 mol) in four equal portions. After a further 2 h the mixture was

cooled and extracted with Et_2O. The organic extract was washed with 10% aqueous NaOH and with H_2O, dried (Na_2SO_4), and concentrated. The crude product was crystallized twice from aqueous EtOH to give pure **15** (3.6 g, 65%): mp 78 °C. Anal. ($C_{16}H_{18}O_2$) C, H.

6-(3-Oxobutyl)-2-naphthyl *N*-Methylcarbamate (17). A solution of **14** (3.5 g, 0.016 mol) in dioxane (10 mL) containing Et_3N (0.7 mL, 4.8 mmol) was treated at 0 °C with MeNCO (0.82 g, 0.014 mol) and then stirred at 0 °C for a further 2 h. The mixture was poured into H_2O (25 mL) and extracted with Et_2O. The organic extract was washed with H_2O, dried (Na_2SO_4), and concentrated. The crude product was chromatographed on silica using chloroform as eluant and then recrystallized from Et_2O to give pure **17** (0.86 g, 23%): mp 110–112 °C. Anal. ($C_{16}H_{17}NO_3$) C, H, N.

4-(6-Methyl-2-naphthyl)but-3-en-2-one (18). This compound was prepared from 6-methyl-2-naphthaldehyde[5] and acetone by the method described for compound **2**. The product was recrystallized from benzene to give **18** (26%): mp 128–129 °C. Anal. ($C_{15}H_{14}O$) C, H.

4-(6-Methyl-2-naphthyl)butan-2-one (19). This was prepared from **18** using the method described for compound **3**. Recrystallization from pentane gave pure **19** (65%): mp 60 °C. Anal. ($C_{15}H_{16}O$) C, H.

4-(6-Methyl-2-naphthyl)pentan-2-one (20). MeLi (40 mL of a 2 M solution in Et_2O, 0.08 mol) was added dropwise to a stirred suspension of CuI (7.6 g, 0.04 mol) in Et_2O (25 mL) at −10 °C under N_2. After 30 min the mixture was treated dropwise with a solution of **18** (2.1 g, 0.01 mol) in Et_2O (50 mL) and then left a further 1 h before being poured into a saturated solution of NH_4Cl (100 mL). The reaction mixture was extracted with $CHCl_3$, washed with H_2O, dried (Na_2SO_4), and concentrated. The crude product was purified on a silica gel column using 10% ether in bp 60–80 °C petroleum ether as eluant to give **20** (2 g, 88%) as a low-melting solid. Anal. ($C_{16}H_{18}O$) C, H.

4-(6-Methyl-2-naphthyl)butan-2-ol (21). This compound was prepared from **19** using the same procedure as for compound **10**. Recrystallization of the product from bp 40–60 °C petroleum ether gave pure **21** (95%): mp 54–56 °C. Anal. ($C_{15}H_{18}O$) C, H.

4-(2-Naphthyl)butan-2-one (22). A mixture of 2-(bromomethyl)naphthalene (22.1 g, 0.1 mol), acetylacetone (10.0 g, 0.1 mol), and K_2CO_3 (13.0 g, 0.1 mol) in dry EtOH (500 mL) was refluxed for 16 h. The EtOH was evaporated in vacuo and the residue was partitioned between H_2O (400 mL) and Et_2O (400 mL). The Et_2O was dried ($MgSO_4$) and concentrated to leave a colorless oil which slowly solidified. Recrystallization from pentane gave pure **22** (12.9 g, 66%): mp 45–46 °C [lit.[13] bp 180–182 °C (8 mm)].

4-(6-Chloro-2-naphthyl)butan-2-one (23). A mixture of NaH (3.0 g of an 80% dispersion in oil, 0.1 mol) and EtOAc (8.8 g, 0.1 mol) in dry dimethoxyethane (50 mL) under N_2 was treated over 30 min at room temperature with a solution of 2-acetyl-6-chloronaphthalene[8] (10.22 g, 0.05 mol) in dry dimethoxyethane (50 mL). The reaction mixture was then stirred at 50 °C for 3.5 h. After cooling it was treated with H_2O (100 mL) and then 2.5 N HCl (50 mL). The precipitated yellow solid was collected by filtration and washed with water and with bp 60–80 °C petroleum ether. Recrystallization from Et_2O–MeOH gave 4-(6-chloro-2-naphthyl)-4-hydroxybut-3-en-2-one (6.69 g, 54%): mp 109–111 °C.

A solution of this compound (6.0 g, 0.024 mol) in AcOH (300 mL) was hydrogenated at atmospheric pressure and room temperature using 10% Pd/C (0.6 g). Hydrogen uptake ceased after 3 h and the catalyst was removed by filtration. The filtrate was evaporated to dryness, the product taken up in Et_2O, and the resulting solution washed with 10% aqueous $NaHCO_3$ solution and with H_2O and dried ($MgSO_4$). Evaporation of the solvent gave a yellow solid which was purified by column chromatography on silica gel using a 1:1 mixture of Et_2O–petroleum ether (bp 60–80 °C) as eluant. The product was recrystallized from Et_2O to give pure **23** (1.56 g, 28%): mp 65–67 °C. Anal. ($C_{14}H_{13}ClO$) C, H, Cl.

4-(2-Methoxy-1-naphthyl)butan-2-one (24). A mixture of 2-methoxy-1-naphthaldehyde (9.3 g, 0.05 mol), ethyl acetoacetate (7.15 g, 0.055 mol), piperidine (0.75 mL), and phenylacetic acid (0.23 g, 0.0017 mol) in dry benzene (150 mL) was heated under reflux for 15 h with constant separation of H_2O by means of a Dean-Stark trap. After cooling, the solvent was removed in vacuo, and the resulting red oil was dissolved in EtOH (150 mL) and hydrogenated at atmospheric pressure and room temperature using 10% Pd/C as the catalyst. The catalyst was removed by filtration and 5 N HCl (150 mL) was added to the filtrate. The resulting mixture was heated under reflux overnight. The EtOH was evaporated in vacuo and the residue extracted several times with Et_2O. The Et_2O layers were combined, washed with H_2O, dried ($MgSO_4$), and evaporated to dryness. The product was recrystallized from Et_2O–petroleum ether (bp 60–80 °C) to give **24** (5.01 g, 44%): mp 51–52 °C. Anal. ($C_{15}H_{16}O_2$) C, H.

4-(4-Methoxy-1-naphthyl)butan-2-one (25). This compound was prepared from 4-methoxy-1-naphthaldehyde by the same method as for **24**. Recrystallization from Et_2O–petroleum ether (bp 60–80 °C) gave pure **25** (75%): mp 67–69 °C. Anal. ($C_{15}H_{16}O_2$) C, H.

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