Decagram-Scale Synthesis of the Neocarzinostatin Carboxylic Acid

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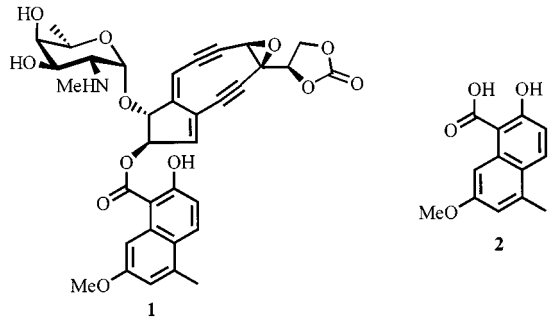
Keywords: Aromatization / Cyclizations / Heck coupling / Natural products / Antibiotics / Neocarzinostatin

Neocarzinostatin carboxylic acid (**2**) was synthesized on a 10-g scale in 9 steps and 43% overall yield from 3,5-dimethylanisol (**9**) (Schemes 5, 7). The hindered bromoarene **23**, reached after 3 steps, underwent a high-temperature Heck coupling with ethyl acrylate, generating cinnamic ester **24**. The C=C bond was reduced and the C≡N group methanolized to obtain diester **30**. This underwent a regioselective Dieckmann cyclization, furnishing the dihydronaphthalene **13**, that was then aromatized. The resulting ester **31** was carefully hydrolyzed such that the target acid **2** arose free from decarboxylation product **32**.

Introduction

Neocarzinostatin[1] is a highly potent antitumor chromoprotein. Its biological activity[2] resides in a noncovalently bound chromophore **1** (Scheme 1). It is the longest-known member of a growing class of antitumor antibiotics collectively called the "enediyne antibiotics".[3] In order for one of these enediyne antibiotics to be able to destroy a tumor cell, it must first bind to the DNA duplex. Secondly, it must be activated by a chemical reaction whereupon it is transformed into a highly reactive biradical. Finally, this biradical must attack the DNA, such that a double-strand scission is caused. The ability of an enediyne antibiotic to bind to DNA is mediated, inter alia, by the intercalation of its aromatic moiety into DNA. Analogous binding should be provided for in synthetic analogs of these compounds. Given this, and our long-standing interest in the chemistry of analogs of the neocarzinostatin chromophore,[4] we desired to gain access to the neocarzinostatin carboxylic acid **2** (Scheme 1) through a high-yielding and easy-to-perform synthesis.[5]



Scheme 1

So far, compound **2** has been synthesized in four different ways[6–10] (Scheme 2). Shibuya et al. achieved the first synthesis of **2** in 15 steps from acetoacetate and crotonaldehyde.[6] Fukumoto et al. needed four steps more in their synthesis of the methyl ester of **2** from isophorone (silylation → **3**) and methyl propiolate.[7] Rewardingly, it displayed a greatly improved overall yield of 26% [the missing hydrolysis step methyl-**2** (≡ **31**) → **2** could have been realized in 91% yield according to ref.[8] and in 89% yield according to the present study (cf. Scheme 7)]. Hirama and co-workers started towards the neocarzinostatin carboxylic acid **2** from the fairly expensive methylcyclohexanedione **4**, but they obtained **2** in only 6 steps and with a 20% total yield.[9] Myers' group accessed **2** from the cheap bromoanisole **8**, also in no more than six steps, albeit with distinctly higher yields (31–37%).[8] Our own synthesis of **2** starts from the equally inexpensive dimethylanisol **9**. Our overall yield of 43% surpasses that of Myers et al. although we need three steps more than they did. The other advantages of our synthesis are that it is amenable to the decagram scale and is experimentally easy.

Our initial intention was to synthesize Hirama's naphthol **7** from a cheaper starting material than from the expensive diketone **4** which they had used. One option was to begin with the dimethylated anisol **9** and to proceed from there either via the trisubstituted anisol **10** ("strategy 1" in

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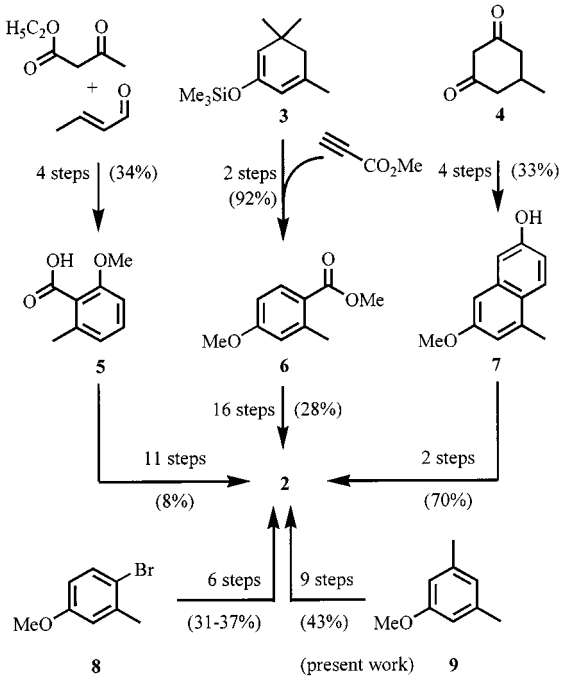
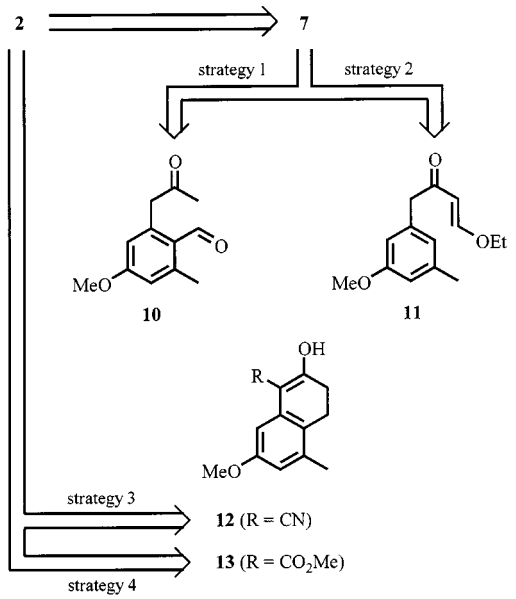


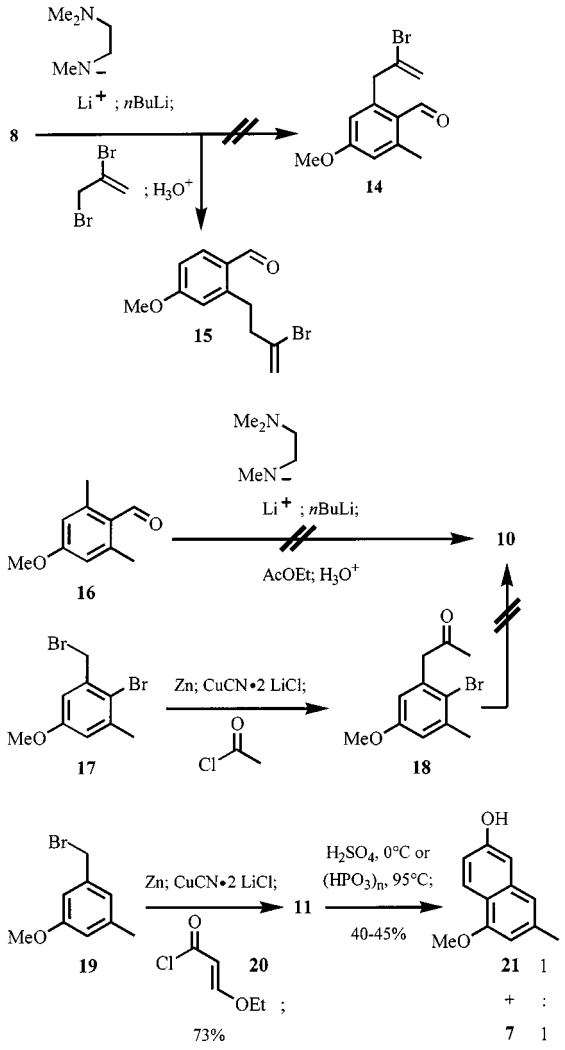
Scheme 2



Scheme 3

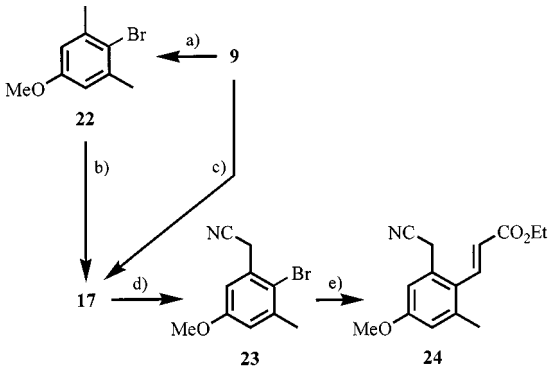
Scheme 3) or via the disubstituted anisol **11** ("strategy 2"). As alternative routes to the NCS carboxylic acid **2** we would do without Hirama's naphthol **7**, and consider the more highly functionalized dihydronaphthols **12** ("strategy 3") or **13** ("strategy 4") as key intermediates.

The top three equations of Scheme 4 summarize our futile efforts to synthesize naphthol **7** by "strategy 1" via the anisols **14** (a masked form of anisol **10**) or **10**; the latter is an oxo aldehyde and was thus expected to be amenable to an intramolecular aldol reaction providing an enone that would enolize spontaneously to give compound **7**. First, we subjected the aromatic aldehyde **8** to Comins' half-aminal formation/directed lithiation protocol by successive treatment with Li^+ $MeN^--CH_2-CH_2-NMe_2$ and *n*BuLi.[10] However, this led to a benzylic lithiation rather than the expected *ortho* lithiation so that allylation with 2,3-dibromopropene produced compound **15** rather than the required compound **14**. Subjecting the aromatic aldehyde **16** to the identical half-aminal formation/directed lithiation protocol did not give the (now desired) benzyllithium, since quenching with ethyl acetate followed by aqueous work up did not provide the acetylation product **10**. More promising was that we could convert the dibromoaromatic **17** (preparation: Scheme 5) into a zinc cuprate,[11] which was then acetylated to provide the bromo ketone **18**. However, in spite of extensive experimentation, a Li/Br exchange reaction with *n*BuLi followed by formylation with DMF was impossible with the enolate obtained from this ketone and LiHMDS. This prevented us from advancing in this way to our target **10**.



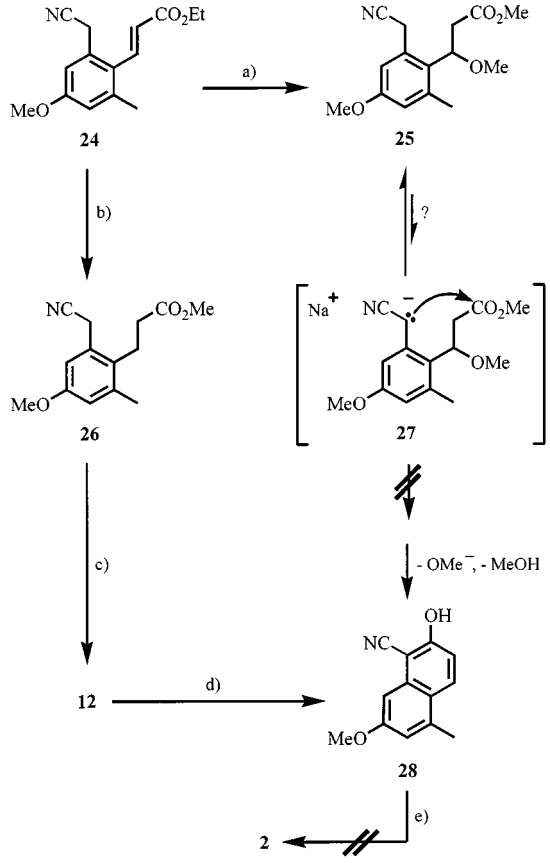
Scheme 4

The fourth equation in Scheme 4 illustrates that synthesizing Hirama's naphthol **7** by "strategy 2" of Scheme 3, via the disubstituted anisol **11**, was at least partly a success. The CuCN-modified organozinc bromide, obtained from benzyl

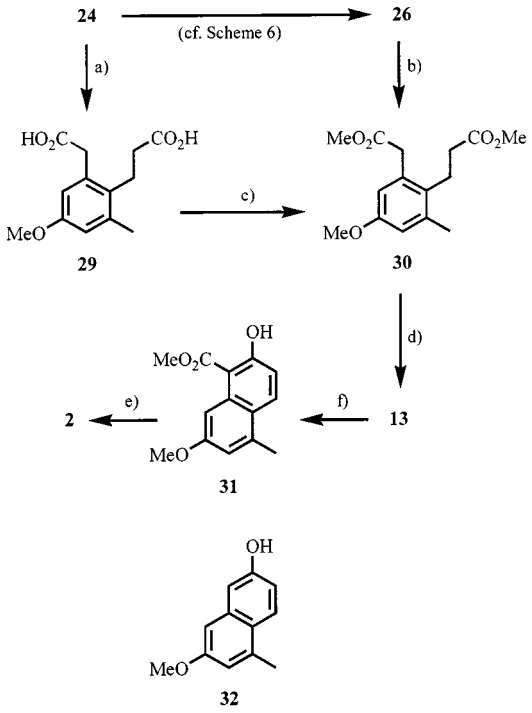


Scheme 5. a) NBS (0.95 equiv.), acetonitrile, 0 °C, → room temp., ca. 12 h; 100%; b) NBS (1.0 equiv.), AIBN (0.05 equiv.), CCl_4, 70 °C → reflux, 2 h; 87%; c) Br_2 (1.0 equiv.), CCl_4, 0 °C, instantaneous reaction; NBS (1.0 equiv.), AIBN (0.05 equiv.), reflux; up to 46%; d) NaCN (1.8 equiv.), DMF, 90 °C, 2 h; 92%; e) ethyl acrylate (1.5 equiv.), $[Pd(PPh_3)_2]Cl_2$ (0.05 equiv.), P(*o*-tolyl)$_3$ (0.15 equiv.), NEt_3 (1.0 equiv.), toluene, sealed tube, 165 °C, 16 h; 91% of a 94:6 *E*:*Z* mixture.

bromide **19** by Knochel's method,[11] was readily acylated by treatment with the vinylogous ethyl chloroformate **20**.[12] The resulting enone **11** was ring-closed by a Friedel–Crafts-type alkylation in the presence of sulfuric acid or polyphosphoric acid. One molecule of ethanol was eliminated, and the keto group enolized. This led to the



Scheme 6. a) NaOMe in MeOH; 40%; b) iodine-activated Mg turnings (10 equiv.), nondried MeOH, sealed tube, 0 °C → room temp., 3 h; 96%; c) LiHMDS (1.2 equiv.), THF, −78 °C, 30 min; 92%; d) cat. Pd (10% on carbon), in 1-methylnaphthalene, 130 °C, 6 h; 36%; e) various conditions (cf. text)



Scheme 7. a) Iodine-activated Mg turnings (4.0 equiv.), nondried MeOH, sealed tube, 0 °C, 6 h; addition of KOH (ca. 4.4 equiv.) and H_2O; 130 °C, 24 h; 96%; b) conc. H_2SO_4, MeOH, 140 °C, ca. 12 h; 98%; c) H_2SO_4 (cat.), MeOH, 65 °C, 5 h; 98%; d) LiHMDS (1.2 equiv.), THF, −78 °C, 30 min; 89%; e) KOH pellets (50 equiv.), portionwise addition to MeOH/H_2O (3:1) at room temp., heat of solution → ca. 70 °C, → room temp. ca. 12 h; 89%; f) $BrCCl_3$ (1.5 equiv.), DBU (2.0 equiv.), 0 °C → room temp., ca. 12 h; 79%

naphthol **7** after a total of only 3 steps. However, **7** was only one constituent of an approximately 1:1 mixture with the isomeric naphthol **21**. When we effected the same Friedel–Crafts cylization using Lewis acids (such as BF_3–diethyl ether or $TiCl_4$) as catalysts, no regiocontrol was again achieved.

Our successful route towards **5** begins with the reaction sequence shown in Scheme 5. As the continuation of this route in Schemes 6 and 7 shows, it adheres to the strategies 3 and 4 of Scheme 3, that is, it no longer aims at the elusive naphthol **7** as a key intermediate, but at its derivatives **12**/**28** (Scheme 6) or **13**/**31** (Scheme 7), respectively. The dimethylanisole **9** was a reasonably cheap starting material (Scheme 5). Using NBS, it can be brominated faster on the aromatic ring than at the benzylic position.[13] We confirmed this by performing the aromatic bromination[14] **9** → **22** first (100% yield), and a benzylic bromination **22** → **17**[13] (87%) thereafter. In spite of having sought intensely, the combination of these brominations in a one-pot operation never worked well:[15] The overall yield was cut back by one half. The opposite order of the brominations, i.e., first in the side-chain (→ **19**) and then in the ring (→ **17**) also gave inferior results, because of the formation of more side-products. An S_N2 substitution with sodium cyanide[16] converted dibromide **17** into nitrile **23**. As was true for its precursors **22** and **17**, compound **23** was readily purified by distillation. A high-temperature Heck coupling (165 °C in toluene)[17] between this bromoarene and ethyl

acrylate followed. It afforded the cinnamic ester **24** in a very good yield − considering how hindered the bromoarene **23** is − of 91%, and in up to 50-g quantities from a single experiment. Ester **24** formed as a 94:6 mixture of the *E* and the *Z* isomers. It is the only intermediate on our way to the neocarzinostatin carboxylic acid **2**, which was purified by chromatography, although isomer separation was neither accomplished, nor required for the remainder of the synthesis.

Having assembled the carbon atoms of the target acid **2** in the correct oxidation states, we tried to link and refunctionalize them as required. We hoped that this would occur in a single step by treating cinnamate **24** with NaOMe in methanol: The nucleophile MeO^- was supposed to form the Michael adduct **25** (Scheme 6). The isolation of this adduct in 40% yield shows that this first step did take place. In addition to that, the base MeO^- was supposed to reversibly deprotonate the nitrile moiety of this Michael adduct, thereby forming the nitrile-substituted "carbanion" **27**. This would allow for a kind of Dieckmann condensation to occur, which, if followed by a β-elimination of the added methoxy group and an enolization of the initially obtained ketone, would produce the desired naphthalene **28**. Disappointingly, the reaction of NaOMe with cinnamate **24** did not proceed further than to the Michael adduct **25**. Treatment of cinnamate **24** with other nucleophiles such as piperidine (100 °C), hydrazine (23 or 78 °C), DABCO (65 °C), thiophenol/$Bu_4N^+F^-$ (23 °C), or lithium piperidide (−78 °C) also failed to give any conversion.

From the foregoing we concluded that the C=C bond of cinnamate **24** would have to be removed in an *irreversible* reaction before a Dieckmann-type ring closure/dehydration/enolization akin to **27** → **28** could have any success (unfortunately, this also meant adding steps to our synthesis). In compliance with these considerations, the olefinic C=C bond of the Heck product **24** was reduced by magnesium turnings dissolving in methanol.[18] Gratifyingly, this did not affect the C≡N group. At the same time, the COOEt group underwent a transesterification with the solvent (MeOH). Thus, after acidification, extraction, and concentration, we obtained the saturated analog **26** of the unsaturated cyano ester **24** in 96% yield. Incidentally, the crude product was pure enough to make any purification of the saturated cyano ester **26** superfluous. When **26** was treated at −78 °C with LDA in THF, the desired Dieckmann-type cyclization occurred in 57% yield. This could be improved to 92% by using LiHMDS instead of LDA. The bicyclic material produced was 100% enolized, i.e., it possessed structure **12** of a β-hydroxylated α,β-unsaturated nitrile. Since this compound also represents a dihydronaphthalene, it could be aromatized at 130 °C by a catalytic dehydrogenation in the presence of Pd/C.[19] We did not attempt to optimize the yield of this reaction (36%) since we had arrived at a cul-de-sac: The cyano-substituted naphthol **28** now obtained resisted all attempts to hydrolyze the C≡N group. We attempted this in the presence of base (25% NaOH in MeOH, 65 °C, 1 d or 25% NaOH and H_2O_2 in THF, 65 °C, 12 h), acid (concentrated H_2SO_4, 90 °C, 14 h), or under Pinner conditions (treatment with gaseous HCl in EtOH at 0 °C, 4 h), but all to no avail. This inertness of substrate **28** is likely to reflect a considerable amount of full conjugation in either its HO−C=C−C≡N or $^-$O−C=C−C≡N substructure, depending on the pH value. In line with this interpretation, none of these hydrolysis conditions altered the dihydroaromatic precursor **12** of compound **28**, either − it contains the same stabilized substructures HO−C=C−C≡N or $^-$O−C=C−C≡N. These thwarts meant that the C≡N group had to be destroyed at an even earlier stage of our synthesis. That this view turned out to be correct is documented in Scheme 7.

The Heck product **24** was reduced as before − with magnesium turnings dissolving in methanol[18] − such that the C≡N group was left intact. However, prior to the workup we added aqueous KOH to the reaction mixture and heated it. This ensured that the C≡N group as well as the CO_2Me group (obtained by the in-situ transesterification mentioned earlier) were hydrolyzed. Thus, after acidification and crystallization, we obtained the dicarboxylic acid **29** in 96% yield. Esterification with methanol delivered the corresponding diester **30** in 98% yield, without the need of purification arising. A slightly different sequence, which led to the same diester with the same yield, and that was selected for decagram-scale preparations was the following: The Heck product **24** was reduced to the saturated cyano ester **26** as shown in Scheme 6. This was methanolyzed in 5:1 methanol/conc. H_2SO_4 at 140 °C − i.e., in a sealed tube (Scheme 7). Attempted Dieckmann cyclizations of diester **30** in the presence of NaOMe failed at various temperatures. However, such cyclizations could be executed by exposing a THF solution of the substrate at −78 °C to 1.2 equivalents of lithium hexamethyldisilazide. The desired cyclized compound, β-oxo ester **13**, arose as a single regioisomer and completely enolized. It was isolated in 89% yield and not separable from 9% of the unchanged precursor **30**.

Being an acidic dihydronaphthalene, compound **13** was best aromatized by treatment with DBU and $BrCCl_3$ in CH_2Cl_2 at 0 °C. These reagents were used by Williams et al. for aromatizing heterocyclic C−H-acidic dihydroaromatics.[20] The aromatization product of Scheme 7 is the known methyl ester **31**.[8,9] We isolated it in 79% yield by passing the crude reaction mixture through a pad of silica gel and removing the solvent from the filtrate.

The synthesis of neocarzinostatin carboxylic acid **2** was completed by saponifying the ester **31** (89% yield; ref.[8] 91%) in aqueous methanol. This was done by adding KOH pellets to the aqueous methanol, whereupon the heat of dissolution caused the reaction mixture to reflux gently. Such an elevated temperature was essential for a complete hydrolysis, however, resulted in decomposition of the desired carboxylic acid **2** when it was maintained longer, i.e., through external heating. In the latter case, the material proceeded to the decarboxylation product **32**. This partial decomposition was complete after 6 h of reflux in 87% yield.

Experimental Section

All reactions were performed in oven-dried (80 °C) glassware under N_2. THF was freshly distilled from K, and CH_2Cl_2 from CaH_2. Products were purified by flash chromatography[21] on Merck silica gel 60 (eluents given in brackets). Yields refer to analytically pure samples.– ^1H [$CHCl_3$ (δ = 7.26) as internal standard in $CDCl_3$] and ^{13}C NMR [$CDCl_3$ (δ = 77.00) as internal standard in $CDCl_3$]: Varian VXR 200 and Bruker AMX 300; integrals in agreement with assignments; coupling constants in Hz; APT ^{13}C NMR spectra: "+" for CH or CH_3, "−" for CH_2 or C_{quat}. The assignments of ^1H and ^{13}C NMR resonances refer to the IUPAC nomenclature; primed numbers belong to side-chain(s) in the order of their appearance IUPAC in the name. – Combustion analyses: M. Beller and F. Hambloch, Institute of Organic Chemistry, University of Göttingen. – MS: G. Remberg, Institute of Organic Chemistry, University of Göttingen. – IR spectra: Perkin–Elmer 1600 Series FTIR in KBr, as a film or as $CDCl_3$ solution in a NaCl cuvette.

2-Hydroxy-7-methoxy-5-methylnaphthalene-1-carboxylic Acid (2): Ester **31** (8.38 g, 34.0 mmol) was dissolved in MeOH/H_2O [3:1 (v:v), 180 ml]. Solid KOH (95.5 g, 1.70 mol, 50.0 equiv.) was added portionwise under stirring. The temperature rose such that gentle reflux occurred. The mixture was allowed to cool to room temp. for about 12 h. It was diluted with H_2O (500 mL), extracted with ethyl acetate (3 × 150 mL), and the organic phase discarded. The aqueous phase was acidified (pH = 2) with HCl (5 M) and then extracted with ethyl acetate (3 × 150 mL). After evaporation of the solvent in vacuo, the title compound was obtained as a white solid (7.04 g, 89%; ref.[8] 91%; m.p. 135 °C; ref.[8] 136–138 °C). – ^1H NMR (300 MHz, $CHCl_3$ as internal standard in $CDCl_3/CD_3OD$): δ = 2.58 (s, 5-CH_3), 3.87 (s, 7-OCH_3), 6.84 (br. d, $^4J_{6,8}$ = 1.9 Hz, 6-H), 6.98 (d, $J_{3,4}$ = 8.6 Hz, 3-H), 7.99 (d, $J_{4,3}$ = 9.0 Hz, 4-H), 8.27 (d, $^4J_{8,6}$ = 2.7 Hz, 8-H). – ^{13}C NMR (75 MHz, $CDCl_3$ as internal standard in $CDCl_3/CD_3OD$): δ = 19.8 (5-CH_3), 54.9 (OCH_3), 104.1, 115.8, 116.0 and 132.2 (C-3, C-4, C-6, C-8), 104.5, 122.9, 134.2, and 136.6 (each of these signals considerably less intensive than the four previously listed signals; C-1, C-4a, C-5, C-8a), 159.1 and 164.4 (C-2, C-7), 174.4 (COOH). – IR (KBr): $\tilde{\nu}$ = 2925, 1615, 1445, 1285, 1220, 850 cm^{-1}. – $C_{13}H_{12}O_4$ (232.2): calcd. C 67.23, H 5.20; found C 67.41, H 5.11.

3,4-Dihydro-2-hydroxy-7-methoxy-5-methylnaphthalene-1-carbonitrile (12): At −78 °C, *n*BuLi (1.4 M in *n*-hexane, 3.5 mL, 4.9 mmol, 1.2 equiv.) was added dropwise to a solution of hexamethyldisilazane (1.1 mL, 0.85 g, 5.3 mmol, 1.3 equiv.) in THF (10 mL) under continued stirring. After another 30 min a solution of ester **26** (1.00 g, 4.04 mmol) in THF (5 mL) was added. Yet another 30 min later, quenching with HCl (30 mL), extraction with ethyl acetate (3 × 30 mL), evaporation of the solvent in the rotary evaporator, and flash-chromatography [4 cm, *tert*-butyl methyl ether/ethyl acetate (10:1)] of the residue provided the enol **12** (fractions 7–25, 801 mg, 92%) as a yellow solid (m.p. 168 °C). – ^1H NMR (300 MHz): δ = 2.25 (s, 5-CH_3), 2.58 (t, $J_{3,4}$ = 8.1 Hz, 3-H)*, 2.81 (t, $J_{4,3}$ = 8.1 Hz, 4-H)*, 3.80 (s, 7-OCH_3), 6.56 and 6.71 (2 d, both $^4J_{meta}$ = 2.6 Hz, 6-H, 8-H); *assignment interchangeable. – ^{13}C NMR (50 MHz/CD_3OD): δ = "+"19.6 (5-CH_3), "−" 22.6 and "−" 28.2 (C-3, C-4), "+" 55.1 (7-OCH_3), "−" 84.8 (C-1), "+" 106.3 and "+" 113.1 (C-6, C-8), "−" 116.9, "−" 120.6, "−" 131.6 and "−" 136.0 (C-1, C-2, C-5, CN), "−" 158.0 and "−" 171.4 (C-2, C-7). – IR ($CDCl_3$): $\tilde{\nu}$ = 3510, 3155, 2960, 2845, 2255, 2215, 1610, 1580, 1480, 1385, 1340, 1220, 1165, 1115, 1060, 915, 755, 725, 650 cm^{-1}.– $C_{13}H_{13}NO_2$ (215.3): calcd. C 72.54, H 6.09: found C 72.38, H 6.38.

Methyl 3,4-Dihydro-2-hydroxy-7-methoxy-5-methylnaphthalene-1-carboxylate (13): At −78 °C, *n*BuLi (1.87 M in hexane, 62.1 mL, 116 mmol, 1.2 equiv.) was added slowly to a solution of hexamethyldisilazane (30.3 mL, 23.4 g, 145 mmol, 1.5 equiv.) in THF (250 mL). Stirring was continued for 30 min whereupon a solution of ester **30** (27.1 g, 96.7 mmol) in THF (100 mL) was added dropwise after which the misture was stirred for another 30 min. The reaction was quenched with HCl (2 M, 400 mL) and the resulting mixture extracted with ethyl acetate (3 × 330 mL). After evaporating the solvent in a rotary evaporator, the title compound [23.5 g which constituted a 91:9 mixture (mol:mol) of **13** and **30**, i.e. 21.4 g pure **13**, 89%] remained as a yellow solid (m.p. 57 °C). – ^1H NMR (300 MHz, $CDCl_3$).[22] – ^{13}C NMR (75 MHz): δ = "+" 20.3 (5-CH_3), "−" 22.6 and "−" 29.5 (C-3, C-4), "+" 51.7 and "+" 55.2 (2 × OCH_3), "−" 100.0 (C-1), "+" 110.6 and "+" 111.9 (C-6, C-8), "−" 124.0, "−" 132.4 and "−" 135.2 (C-4a, C-5, C-8a), "−" 157.4 (C-7), "−" 172.4 and "−" 178.5 (C-2, *C*OOMe). – IR ($CDCl_3$): $\tilde{\nu}$ = 2955, 2840, 2360, 1740, 1645, 1615, 1480, 1445, 1375, 1335, 1250, 1215, 1165, 1095, 1065, 1010, 955, 935, 870, 810, 760 cm^{-1}.– $C_{14}H_{16}O_4$ (248.3): calcd. C 67.73, H 6.50; found C 67.89, H 6.44.

1-Bromo-2-(bromomethyl)-4-methoxy-6-methylbenzene (17): *N*-Bromosuccinimide (109 g, 0.610 mol, 1.0 equiv.) and AIBN (5.01 g, 30.5 mmol, 0.05 equiv.) were added to a solution of bromide **22** (131 g, 610 mmol) in warm (70 °C) CCl_4 (500 mL). After heating to reflux until no more precipitated brominating reagent remained (2 h), the resulting succinimide was removed by filtration and the CCl_4 evaporated in vacuo (for recycling). A fractionating distillation (b.p. 115°–120 °C/0.1 mbar) of the residue provided the title compound **17** (156 g, 87%) as a white solid (m.p. 92 °C). – ^1H NMR (300 MHz): δ = 2.40 (s, 6-CH_3), 3.79 (s, OCH_3), 4.60 (s, 1′-H_2), 6.76 and 6.84 (2 d, both $^4J_{meta}$ = 3.0 Hz, 3-H and 5-H). – ^{13}C NMR (50 MHz): δ = "+" 24.0 (6-CH_3), "−" 34.7 (C-1′), "+" 55.4 (OCH_3), "+" 113.9 and "+" 116.9 (C-3, C-5), "−" 117.5, "−" 137.9 and "−" 140.3 (C-1, C-2, C-6), "−" 158.3 (C-4). – IR ($CDCl_3$): $\tilde{\nu}$ = 3020, 2400, 2255, 1590, 1465, 1325, 1215, 1165, 920, 915, 775, 670 cm^{-1}. – $C_9H_{10}Br_2O$ (294.0): calcd. C 36.77, H 3.43; found C 36.90, H 3.49.

4-Bromo-3,5-dimethylanisol (22): At 0 °C, a solution of *N*-bromosuccinimide (203 g, 1.14 mol, 0.95 equiv.) in acetonitrile (1.6 L) was added slowly to 3,5-dimethylanisol (**9**; 163 g, 1.20 mol) in acetonitrile (200 mL). After allowing to warm to room temp. and stirring for about 12 h, we added H_2O (1 L) and extracted with *tert*-butyl methyl ether (3 × 500 mL). The combined organic phases were back-extracted with H_2O (500 mL) and dried with $MgSO_4$, and then liberated from the solvent in a rotary evaporator. The title compound (245 g; 100%) resulted as a white solid (m.p. 71–72 °C). – ^1H NMR (300 MHz): δ = 2.39 (s, 3-CH_3, 5-CH_3), 3.77 (s, OCH_3), 6.66 (s, 2-H, 6-H). – ^{13}C NMR (50 MHz): δ = "+" 24.0 (3-CH_3 and 5-CH_3), "+" 55.3 (OCH_3), "+" 113.8 (C-2 and C-6), "−" 118.2 (C-4), "−" 139.0 (C-3* and C-5*), "−" 158.0 (C-1); * distinguishable from C-4 by the greater signal intensity. – IR (Film): $\tilde{\nu}$ = 2955, 2835, 1695, 1590, 1470, 1410, 1380, 1315, 1280, 1235, 1195, 1160, 1075, 1035, 995, 935, 855, 835, 695, 615 cm^{-1}. – $C_9H_{11}BrO$ (215.1): calcd. C 50.26, H 5.16; found C 50.39, H 5.25.

(2-Bromo-5-methoxy-3-methylphenyl)acetonitrile (23): At 90 °C, dibromide **17** (86.4 g, 294 mmol) was added gradually to a solution of NaCN (28.0 g, 530 mmol, 1.8 equiv.) in DMF (400 mL). After 2 h, H_2O (500 mL) was added. Extraction with *tert*-butyl methyl ether (3 × 100 mL), back-extraction of the organic phase with H_2O (2 × 200 mL), drying with $MgSO_4$, evaporation of the solvent in vacuo, and fractionating distillation (b.p. 91 °C/0.1 mbar) led to

nitrile **23** (64.9 g, 92%) as a white solid (m.p. 57 °C). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.40 (s, 3′-CH_3), 3.81 (s, OCH_3), 3.83 (s, 2-H_2), 6.79 and 6.92 (2 d, $^4J_{meta}$ = 2.6 Hz bzw. $^4J_{meta}$ = 2.7 Hz, 4′-H and 6′-H). – ^{13}C NMR (50 MHz): δ = "+" 23.9 (3′-CH_3), "–" 25.7 (C-2), "+" 55.5 (OCH_3), "+" 112.7 and "+" 116.2 (C-4′ and C-6′), "–" 116.4, "–" 117.1, "–" 130.8 and "–" 140.2 (C-1′, C-2′, C-3′ and CN), "–" 158.6 (C-5′). – IR ($CDCl_3$): ṽ = 3155, 2960, 2840, 2255, 1815, 1795, 1590, 1465, 1440, 1380, 1325, 1290, 1250, 1195, 1165, 1095, 1075, 1030, 920, 865, 760, 650 cm^{-1}. – $C_{10}H_{10}BrNO$ (240.1): calcd. C 50.03, H 4.20; found C 50.07, H 4.17.

Ethyl 3-[2-(Cyanomethyl)-4-methoxy-6-methylphenyl]acrylate (24, 94:6 *E*/*Z* Mixture): [$Pd(PPh_3)_2$]Cl_2 (9.09 g, 11.0 mmol, 0.05 equiv.) and tri-*o*-tolylphosphane (10.1 g, 33.0 mmol, 0.15 equiv.) were heated in toluene (200 mL) until a yellow suspension was formed. Nitrile **23** (52.8 g, 0.220 mol), ethyl acrylate (35.8 mL, 33.0 g, 0.330 mol, 1.5 equiv.) and triethylamine (30.7 mL, 22.3 g, 0.220 mol, 1.0 equiv.) were added, whereupon the resulting mixture was heated for 16 h in a sealed bottle in an oil-bath (165 °C). Quenching with brine (300 mL), extraction with *tert*-butyl methyl ether (3 × 150 mL), concentration in vacuo, and flash chromatography [7 cm, *tert*-butyl methyl ether/petroleum ether (1:5 → 1:1)] provided the coupling product **24** (fractions 25–40; 51.9 g, 91%) as a yellow solid (m.p. 57 °C). The isomer ratio was determined by the integrals over the signals of 2-H and 3-H. – ^{1}H NMR (300 MHz): δ = 1.13, $J_{2''',1'''}$ = 7.2 Hz, *Z*-2′′′-H_3), 1.34 (t, $J_{2''',1'''}$ = 7.2 Hz, *E*-2′′′-H_3), 2.18 (s, *Z*-6′-CH_3), 2.33 (s, *E*-6′-CH_3), 3.64 (s, *Z*-1′′-H_2), 3.74 (s, *E*-1′′-H_2), 3.81 (s, *Z*-OCH_3), 3.83 (s, *E*-OCH_3), 4.05 (q, $J_{1''',2'''}$ = 7.2 Hz, *Z*-1′′′-H_2), 4.28 (q, $J_{1''',2'''}$ = 7.2 Hz, *E*-1′′′-H_2), 6.01 (d, J_E = 16.2 Hz, *E*-2-H), 6.21 (d, $J_{Z\,=}$ 11.7 Hz, *Z*-2-H), 6.72 and 6.82 (2 d, both $^4J_{meta}$ = 2.3 Hz, *Z*-3′-H, *Z*-5′-H), 6.75 and 6.89 (2 d, both $^4J_{meta}$ = 2.3, *E*-3′-H, *E*-5′-H), 7.02 (d, $J_{Z\,=}$ 11.7, *Z*-3-H). 7.71 (d, J_E = 16.2 Hz, *E*-3-H). – ^{13}C NMR (50 MHz): δ = "+" 14.2 and "+" 21.2 (C-2′′′ and 6′-CH_3), "–" 22.6 (C-1′′), "+" 55.3 (OCH_3), "–" 60.7 (C-1′′′), "+" 112.3, "+" 115.9, "+" 124.5 and "+" 141.0 (C-2, C-3, C-3′ and C-5′), "–" 117.6, "–" 126.1, "–" 129.8 and "–" 139.5 (C-1′, C-2′, C-6′ and CN), "+" 159.6 and "+" 166.1 (C-1 and C-4′). – IR ($CDCl_3$): ṽ = 3155, 2985, 2360, 2255, 1710, 1640, 1605, 1485, 1385, 1310, 1290, 1275, 1215, 1180, 1145, 1095, 1060, 1035, 990, 920, 890, 760, 705, 650 cm^{-1}. – $C_{15}H_{17}NO_3$ (259.3): calcd. C 69.48, H 6.61; found C 69.59, H 6.67.

Methyl 3-[2-(Cyanomethyl)-4-methoxy-6-methylphenyl]propionate (26): Magnesium turnings (activated with I_2; 21.0 g, 864 mmol, 10 equiv.) were allowed to react with a solution of the acrylate **24** (22.6 g, 86.5 mmol) in nondried MeOH (300 mL), first while cooling in an ice bath, and subsequently for 3 h at room temp. Quenching with HCl (1 M, 1.0 L), extraction with *tert*-butyl methyl ether (3 × 300 mL) and removal of the solvent in vacuo furnished, as the residue, the title compound **26** (20.5 g, 96%) as a brownish liquid.– ^{1}H NMR (300 MHz): δ = 2.32 (s, 6′-CH_3), 2.44–2.52 and 2.86–2.94 (2 m, 2 H each ***((AUTHOR: Change ok?))***, 2-H_2 and 3-H_2), 3.68 and 3.78 (2 s, 4′-OCH_3 and 1′′′-H_3), 3.76 (s, 1′′-H_2), 6.70 and 6.79 (2 d, $^4J_{meta}$ = 2.2 Hz bzw. $^4J_{meta}$ = 2.6 Hz, 3′-H and 5′-H). – ^{13}C NMR (50 MHz): δ = "+" 19.9 (6′-CH_3), "–" 21.9, "–" 23.9 and "–" 33.5 (C-2, C-3 and C-1′′), "+" 51.7 and "+" 55.2 (C-1′′′ and 4′-OCH_3), "+" 112.3 and "+" 116.2 (C-3′ and C-5′), "–" 118.0, "–" 128.7, "–" 129.5 and "–" 138.7 (C-1′, C-2′, C-6′ and CN), "–" 158.0 and "–" 172.9 (C-1 and C-4′). – IR ($CDCl_3$): ṽ = 2955, 2840, 2255, 1735, 1610, 1485, 1440, 1365, 1290, 1200, 1140, 1065, 920, 890, 860, 745, 650 cm^{-1}. – $C_{14}H_{17}NO_3$ (247.1): calcd. C 68.00, H 6.93: found C 67.83, H 6.88.

2-Hydroxy-7-methoxy-5-methylnaphthalene-1-carbonitrile (28): A suspension of carbonitrile **12** (50 mg, 0.23 mmol) and Pd (10% on carbon; 12 mg) in 1-methylnaphthalene (2 g) was heated to 130 °C for 6 h. The reaction mixture was filtered through Celite, and the crude product purified by flash chromatography [2 cm, petroleum ether/*tert*-butyl methyl ether (1:2)]. The title compound was obtained (fractions 21–23, 18 mg, 36%) as a white solid whose m.p. was not determined due to the scarcity of this material. – ^{1}H NMR (300 MHz): δ = 2.53 (s, 5-CH_3), 3.51 (br. s, OH), 3.88 (s, OCH_3), 6.81 (br. d, $^4J_{meta}$ = 1.5 Hz, 6-H*), 6.92 (d, $^3J_{ortho}$ = 9.0 Hz, 3-H), 7.10 (d, $^4J_{meta}$ = 2.3 Hz, 8-H*), 7.87 (d, $^3J_{ortho}$ = 9.0 Hz, 4-H); * assignment interchangeable. – $C_{13}H_{15}NO_2$ [M^+]: calcd. 217.3 → two mol peaks 231.1 $[M + NH_4]^+$ and 248.2 $[M + NH_4 + NH_3]^+$ by DCI-MS (NH_3).

3-[2-(Carboxymethyl)-4-methoxy-6-methylphenyl]propionic Acid (29): In a sealed Pyrex tube (100 mL) the unsaturated ester **24** (1.04 g, 4.01 mmol), Mg turnings (activated with I_2; 390 mg, 160 mmol, 4.0 equiv.) and nondried MeOH (30 mL) were stirred at 0 °C for 6 h. After opening the tube carefully (H_2!), we added H_2O (40 mL) and KOH (ca. 1 g, ca. 18 mmol, ca. 4.4 equiv.), closed the tube again and heated it in an oil bath at 130 °C for 24 h. Quenching with H_2O (100 mL), extraction with *tert*-butyl methyl ether (100 mL), disposal of the organic phase, acidification (→ pH = 2) of the aqueous phase with dilute HCl, another extraction with ethyl acetate (3 × 50 mL), and removal of the solvent in vacuo led to dicarboxylic acid **29** (970 mg, 96%). – ^{1}H NMR (300 MHz, $CDCl_3$/CD_3OD): δ = 2.26 (s, 6′-CH_3), AA′BB′ signal centered at δ = 2.38 and δ = 2.87 (2-H_2, 3-H_2), 3.59 (s, 1′′-H_2), 3.70 (s, OCH_3), 6.57–6.66 (m, 3′-H, 5′-H). – ^{13}C NMR (50 MHz, $CDCl_3$/CD_3OD): δ = "+" 19.8 (6-CH_3), "–" 24.1, "–" 33.7 and "–" 38.8 (C-2, C-3, C-1′′), "+" 54.9 (OCH_3), "+" 113.6 and "+" 115.2 (C-3′, C-5′), "–" 129.7, "–" 133.7 and "–" 138.0 (C-1′, C-2′, C-6′), "–" 157.27 (C-4′), "–" 174.5 and "–" 175.9 (2 × COOH). – IR ($CDCl_3$): ṽ = 2975, 2840, 2610, 2250, 2090, 1720, 1605, 1485, 1440, 1415, 1365, 1295, 1205, 1140, 1065, 920, 845, 750, 710, 650 cm^{-1}. – $C_{13}H_{16}O_5$ (252.3): calcd. C 61.89, H 6.3; found C 61.74, H 6.52.

Methyl 3-{4-Methoxy-2-[(methoxycarbonyl)methyl]-6-methylphenyl}-propionate (30). – Procedure 1: The dicarboxylic acid **29** (400 mg, 1.59 mmol) and conc. H_2SO_4 (0.05 mL) were heated to reflux in MeOH solution (10 mL) for 5 h. Extraction with ethyl acetate (3 × 30 mL) followed by evaporation of the solvent furnished the title compound (437 mg, 98%) as a transparent liquid.

Procedure 2: Nitrile **26** (27.1 g, 110 mmol), conc. H_2SO_4 (20 mL) and MeOH (100 mL) were stirred in a sealed tube at 140 °C for about 12 h. Addition of H_2O (300 mL), extraction with ethyl acetate (3 × 250 mL) and evaporation of the solvent furnished ester **30** (30.1 g, 98%) as a dark liquid. – ^{1}H NMR (300 MHz).[23] – ^{13}C NMR (50 MHz): δ = "+" 20.1 (6′-CH_3), "–" 24.3, "–" 33.9 and "–" 38.9 (C-2, C-3, C-1′′), "+" 51.6, "+" 52.1 and "+" 55.1 (3 × OCH_3), "+" 113.7 and "+" 115.4 (C-3′, C-5′), "–" 129.6, "–" 133.7 and "–" 138.1 (C-1′, C-2′, C-6′), "–" 157.6 (C-4′), "–" 172.0 and "–" 173.3 (2 × *C*OOMe). – IR ($CDCl_3$): ṽ = 2955, 2840, 2255, 1730, 1605, 1485, 1465, 1435, 1295, 1200, 1175, 1140, 1065, 1015, 920, 845, 740, 650 cm^{-1}. – $C_{15}H_{20}O_5$ (280.3): calcd. C 64.27, H 7.19; found C 64.07, H 6.99.

Methyl 2-Hydroxy-7-methoxy-5-methylnaphthalene-1-carboxylate (31): Ester **13** (12.4 g, 49.8 mmol), $BrCCl_3$ (7.37 mL, 14.8 g, 74.8 mmol, 1.5 equiv.), and DBU (14.9 mL, 15.2 g, 99.7 mmol, 2.0 equiv.) were dissolved in CH_2Cl_2 (200 mL) at 0 °C. After allowing

to warm to room temperature and stirring for about 12 h, HCl (1 M, 250 mL) was added. After extraction with ethyl acetate (3 × 200 mL) and removal of the solvent in a rotary evaporator, the product was purified by passage through a pad of silica gel [5 cm high, 8 cm in diameter, ethyl acetate/cyclohexane (1:3)]. A yellow solid (m.p. 103 °C; ref.[8] 103−104 °C) was obtained (fractions 8−19; 9.69 g, 79%). − ^{1}H NMR (300 MHz): δ = 2.63 (s, 5-CH_3), 3.92 (s, 7-OCH_3), 4.11 (s, CO_2CH_3), 6.90 (incompletely resolved dq, $^4J_{6,8}$ = 2.5 Hz, $^4J_{6,6\text{-Me}}$ = 0.9 Hz, 6-H), 7.04 (d, $J_{3,4}$ = 9.0 Hz, 3-H), 8.03 (d, $J_{4,3}$ = 9.4 Hz, 4-H), 8.08 (d, $^4J_{8,6}$ = 2.3 Hz, 8-H), 12.14 (s, OH). − ^{13}C NMR (100.6 MHz): δ = "+" 19.9 (5-CH_3), "+" 52.2 (CO_2CH_3)*, "+" 54.9 (7-OCH_3)*, "+" 104.2 (C-8)**, "−" 104.6,"−" 123.0 and "−" 134.0 (C-1, C-4a, C-8a)***, "+" 115.9 and "+" 116.0 (C-3**, C-6**), "+" 132.4 (C-4)**, "−" 136.8 (C-5)***, "−" 159.3 (C-7)***, "−" 164.3 (C-2)***, "−" 172.7 (CO_2CH_3). *The O$^{13}CH_3$ resonances were distinguished in a 500 MHz/125.8 MHz HMQC spectrum ("short-range H,C COSY spectrum") by the following cross-peaks: δ_{CO2Me} = 52.3 ⇄ δ_{CO2Me} = 4.11, $\delta_{7\text{-OMe}}$ = 54.9 ⇄ $\delta_{7\text{-OMe}}$ = 3.92. **The aromatic $^{13}C(sp^2)$-H resonances were distinguished in a 500 MHz/125.8 MHz HMQC spectrum ("short-range H,C COSY spectrum") by the following cross-peaks: $\delta_{C\text{-}8}$ = 104.2 ⇄ $\delta_{8\text{-}H}$ = 8.08, $\delta_{C\text{-}3/C\text{-}6}$ = 115.9/116.0 ⇄ $\delta_{3\text{-}H}$ = 7.04/$\delta_{6\text{-}H}$ = 6.90, $\delta_{C\text{-}4}$ = 132.4 ⇄ $\delta_{4\text{-}H}$ = 8.03. ***Certain aromatic $^{13}C(sp^2$,quat) resonances were distinguished in a 300 MHz/75.5 MHz HMBC spectrum ("long-range H,C COSY spectrum") by the following cross-peaks: $\delta_{C\text{-}5}$ = 136.8 ⇄ $\delta_{5\text{-Me}}$ = 2.63 and $\delta_{4\text{-}H}$ = 8.03, $\delta_{C\text{-}7}$ = 159.3 ⇄ $\delta_{7\text{-OMe}}$ = 3.92, $\delta_{C\text{-}2}$ = 164.3 ⇄ $\delta_{2\text{-OH}}$ = 12.14. − IR (KBr): $\tilde{\nu}$ = 2955, 2360, 1645, 1615, 1455, 1435, 1415, 1375, 1320, 1250, 1210, 1170, 1035, 840, 815 cm^{-1}. − $C_{14}H_{14}O_4$ (246.2): calcd. C 68.28, H 5.73; found C 68.00, H 5.68.

7-Methoxy-5-methyl-2-naphthol (32): Ester **31** (199 mg, 0.81 mmol) and NaOH (145 mg, 4.04 mmol, 5.0 equiv.) were dissolved in MeOH/H_2O [3:1 (v:v), 8 ml] and heated at reflux for 6 h. Extraction with ethyl acetate (20 mL), disposal of the organic phase, acidification of the aqueous phase (→ pH = 2) with HCl (1 M), extraction with ethyl acetate (3 × 40 mL), and removal of the solvent furnished the title compound (133 mg, 87%) as a greyish solid (m.p. 126−127 °C). − ^{1}H NMR (300 MHz): δ = 2.60 (s, 5-CH_3), 3.88 (s, OCH_3), 5.15 (br. s, OH), 6.84 (br. s, 6-H, 8-H), 6.96 (dd, J_{ortho} = 8.9 Hz, $^4J_{meta}$ = 2.7 Hz, 3-H), 7.05 (d, $^4J_{meta}$ = 2.5 Hz, 1-H), 7.92 (d, J_{ortho} = 9.0 Hz, 4-H). − ^{13}C NMR (75.4 MHz): δ = 19.4 (5-CH_3), 55.2 (OCH_3), 102.9 and 117.0 (C-6, C-8)*, 109.4 (C-1)*, 114.6 (C-3)*, 125.9 (C-4)*, 123.7, 136.1 and 136.2 (C-5, C-4a, C-8a), 153.4 and 157.7 (C-2, C-7). *The aromatic $^{13}C(sp^2)$-H resonances were distinguished in a 300 MHz/75.5 MHz HMQC spectrum ("short-range H,C COSY spectrum") by the following cross-peaks: $\delta_{C\text{-}8}$ = 102.9/$\delta_{C\text{-}6}$ = 117.0 ⇄ $\delta_{8\text{-}H}$ = $\delta_{6\text{-}H}$ = 6.84, $\delta_{C\text{-}1}$ = 109.4 ⇄ $\delta_{1\text{-}H}$ = 7.05, $\delta_{C\text{-}3}$ = 114.6 ⇄ $\delta_{3\text{-}H}$ = 6.96, $\delta_{C\text{-}4}$ = 125.9 ⇄ $\delta_{4\text{-}H}$ = 7.92. − IR (film): $\tilde{\nu}$ = 3255, 1630, 1530, 1470, 1440, 1400, 1355, 1235, 1220, 1164, 1050, 980, 935, 859, 805, 790, 715 cm^{-1}. − $C_{12}H_{12}O_2$ (188.2): calcd. C 76.57, H 6.43; found C 76.53, H 6.34.

Acknowledgments

We thank Frank Hambloch (Universität Göttingen) for skillful technical assistance during a prolonged period of this study. Support of this work by a generous donation of $PdCl_2$ from DEGUSSA-HÜLS AG (Hanau) and of *n*BuLi by Metallgesellschaft GmbH (Langelsheim) are gratefully acknowledged.

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Received November 22, 1999
[O99640]