A concise total synthesis of brasiliquinones B and C and 3-deoxyrabelomycin

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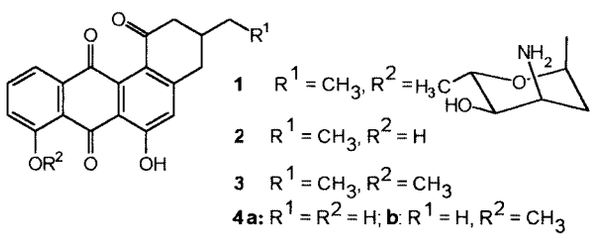
Synthesis of brasiliquinones B and C, **2** and **3** and 3-deoxyrabelomycin **4a** has been accomplished in 6–7 steps from the common precursor **18b**. The key naphthalenones **6** were prepared in 5 steps from tetralone **17** in a regioselective manner. Anionic annulation of cyanophthalide **7c** with **6** readily provided tetracyclic precursors **5** in excellent yields, sunlight-promoted photooxidation of which led to the synthesis of the title compounds.

Brasiliquinones A–C, **1**–**3** have recently been isolated from the actinomycete *Nocardia brasiliensis* IFM 0089 and their structures elucidated by chemical and spectroscopic means. All three members have been shown to possess both antibacterial and antitumour activities.[1] They belong to a large group of microbial secondary metabolites called angucyclines,[2] which have varied chemical structures and a wide range of biological activities. The members of this group of antibiotics share a benz[*a*]anthraquinone moiety as the basic skeleton, differing widely in level of oxidation states and location of oxygen functionalities. The commonly known angucyclines have a C_1 unit at C-3. In contrast, brasiliquinones, **1**–**3** have an ethyl group at C-3. The stereochemistry of the only chiral center, C-3, of brasiliquinones was determined to be *S* by comparison of the optical rotations with that of rubiginone B_2.



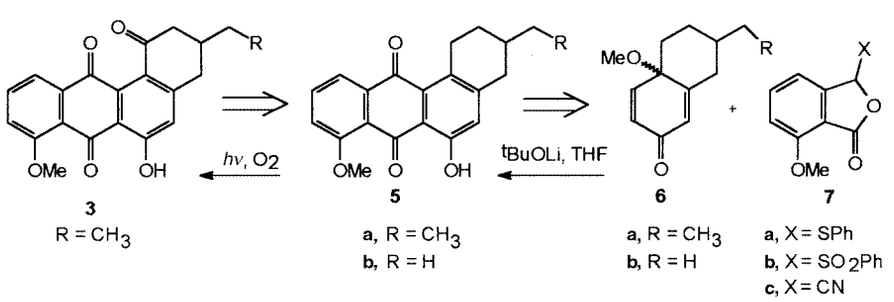
Beginning in 1976, synthetic activity in the field of angucyclines has become significantly intense. The synthetic approaches to the angucyclines reported so far have centered around (i) elaboration[3] of a prefabricated naphthaquinone or anthraquinone by nucleophilic or electrophilic reactions, (ii) Diels–Alder reaction[4] of a substituted naphthaquinone with a functionalized diene, (iii) biomimetic cyclization[5] of keto precursors and (iv) transition metal-mediated ring-forming reactions.[6] Among these, the Diels–Alder approach has proved very useful in the total synthesis of a few angucyclines. Our approach to the synthesis of brasiliquinones emanated from the model study[7] on the preparation of hydroxylated benz[*a*]-anthraquinones, involving phthalide annulation and photooxygenation as the key steps. It was conjectured that this approach would be a better alternative by virtue of its unambiguous regiochemical outcome and mild reaction conditions. In this paper, we describe an application of this strategy to the first total synthesis[8] of brasiliquinones B and C **2** and **3** as well as the synthesis of 3-deoxyrabelomycin **4a** from a readily available starting material.

Our retrosynthetic analysis of brasiliquinone **3** (Scheme 1), involving Krohn's photooxidation[9] as the first disconnection, reveals a requirement for the tetracyclic precursor **5a**. This, in turn, is conceived to be formed by anionic condensation of phthalide derivatives **7**[10] with naphthalenone **6a**, which is derivable from tetrahydronaphthol **20a** by hypervalent iodine oxidation.

Results and discussion

Our initial investigations were directed towards the synthesis of tetracyclic framework **11** (Scheme 2), since it contains all the important structural attributes of brasiliquinones, except the alkyl side chain at C-3, and the corresponding AB ring precursor methoxynaphthalenone **8**[7] is readily accessible by phenyliodonium diacetate (PIDA) oxidation of commercially available 5,6,7,8-tetrahydro-β-naphthol. Accordingly, CD ring precursor **7c**[10] was prepared from *N*,*N*-diethyl-3-methoxybenzamide through directed orthometallation as described by Swenton and co-workers. Reaction between **7c** and **8** under typical conditions (^{t}BuOLi, THF, −60 °C to rt) of annulation,[7] followed by acidification afforded, the annulated product **10** in 85% yield.

When the reaction was carried out with **7a**[11] in the place of **7c**, the product **10** was obtained in a lower yield (52%). On the other hand, the sulfone **7b** resisted reaction with the naphthalenone **8**, apparently due to a steric effect between the

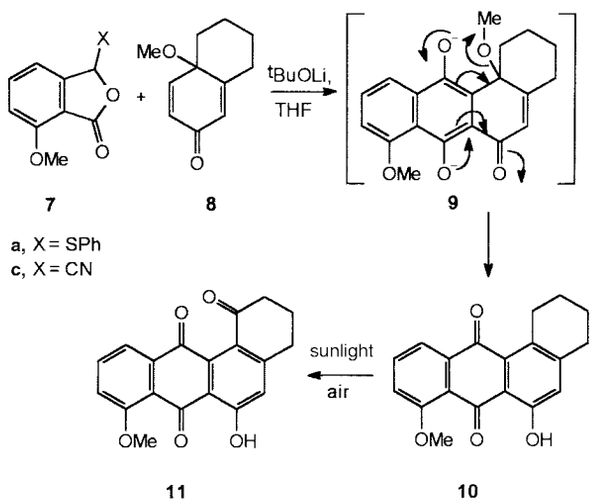


Scheme 1 Synthetic and retrosynthetic analysis of brasiliquinone C **3**.

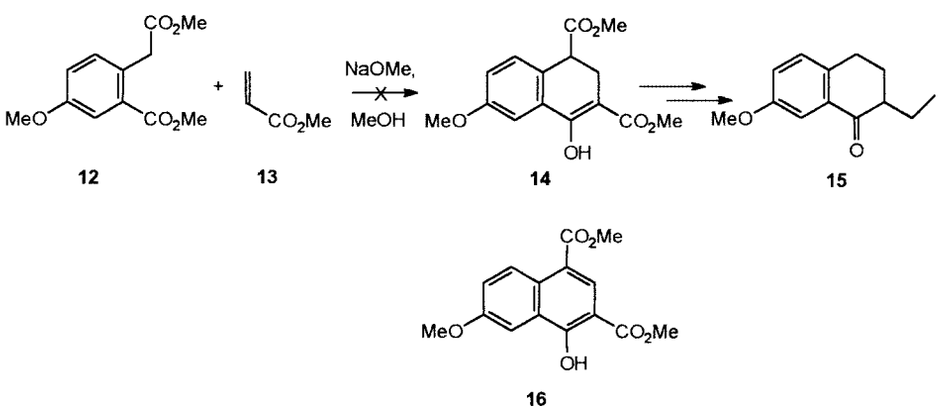
SO_2Ph group of **7b** and the methoxy group of **8**. The desired disposition of the C-6 hydroxy group and the C-8 methoxy group in the tetracycle **10** was dictated by regiospecific formation of intermediate **9** through initial Michael addition of the C-3 anion of **7c** to **8**. Sunlight-mediated photochemical oxidation of **10** in $CHCl_3$ in the presence of aerial oxygen furnished 1-ketoangucycline analog **11** in 93% yield.

Having established the viability of the proposed route (Scheme 1) to brasiliquinone **3** by the synthesis of model compound **11**, we focussed our attention on preparation of the tetrahydronaphthol **20b** required for brasiliquinones. This was thought to be capable of preparation from **14** through tetralone **15b** by selective alkylation followed by demethoxycarbonylation. As a possible route to **14**, Michael-initiated ring closure of homophthalate **12** with methyl acrylate **13** was considered. Although such a reaction[12] was known in the literature, in the case of reaction between **12** and **13** in the presence of NaOMe in MeOH the cyclocondensed product **14** was not produced. Instead, the corresponding aromatized compound **16** was obtained in 20% yield as the sole isolable product. The presumed susceptibility of **14** to oxidative aromatization discouraged us from any further study of Scheme 3.

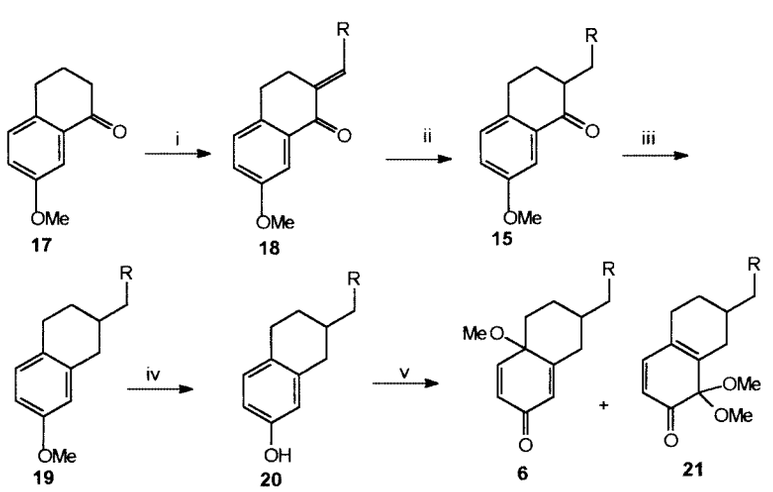
Following this failure we decided to elaborate commercially available methoxytetralone **17** to naphthalenones **6**. The preparation of naphthalenones **6** was achieved in five steps starting from **17** (Scheme 4). Treatment of **17** with paraformaldehyde in the presence of *N*-methylanilinium trifluoroacetate[13] in THF furnished **18b** in 72% yield. This reaction is quite erratic as far as the yield is concerned. Quite often, it does not undergo completion and the starting tetralone is recovered in appreciable amounts (20–40%). All attempts at standardizing the reaction by changing the conditions failed. Conjugate addition of CH_3MgI to **18b** in the presence of cuprous [copper(I)] iodide provided **15a** (66%). An attempt at direct introduction of an ethylidene group at C-2 of **17** by treatment with paraldehyde in the presence of *N*-methylanilinium trifluoroacetate failed to provide **18a**. Similarly, direct alkylation of **17** under various conditions was complicated by formation of significant amount of the corresponding dialkylated product. The tetralone **15a**,



Scheme 2 Synthesis of tetracycle **11**.



Scheme 3 Attempted synthesis of tetralones **15**.



Scheme 4 *Reagents and conditions*: (i) $(HCHO)_n$, $PhN\overset{+}{H}_2CH_3$ $CF_3CO_2^-$; (ii) **a** CH_3MgI, CuI; **b** Zn, AcOH, EtOH; (iii) NH_2NH_2, KOH, diethylene glycol; (iv) BBr_3, CH_2Cl_2; (v) PIDA, MeOH.

when subjected to Huang-Minlon reduction, gave **19a** (46%). The decision of proceeding through intermediates **15** and **18** was taken with an eye towards enantioselective synthesis of the target molecules and 3-heteromethyl analogs of angucyclines. Demethylation of **19a** was performed by treatment with a 1 M solution of BBr_3 in CH_2Cl_2 to give **20a** (91%). Action[7] of PIDA on **20a** in dry methanol provided naphthalenone **6a** (52%) as a 1 : 1 mixture of two diastereoisomers along with a small amount (8%) of monoketal **21a**. Both **6a** and **21a** were sufficiently stable to be purified by silica gel chromatography. The formation of the diastereoisomers of **6** was ascertained by the appearance of two triplets at δ 0.85 and 0.93, two singlets at δ 3.05 and 3.04, and the complexities of signals of the olefinic hydrogens. Since the stereochemical outcome of the reaction is of no consequence in the context of synthesis of **1**–**3**, the mixture of naphthalenones **6a** was submitted to annulation with cyanophthalide **7c**. Treatment of cyanophthalide **7c** with lithium *tert*-butoxide in THF at −60 °C, followed by addition of a THF solution of **6a** gave, after usual acidic work-up, the expected tetracyclic intermediate **5a** (92%) with two different oxygen functionalities. Photooxidation of **5a** to brasiliquinone B **3** was then accomplished in 76% yield, by exposing its $CHCl_3$ solution to sunlight for about 6 h. The reaction was performed according to the procedure described for compound **11**. The physical data (IR, NMR, MS) of the synthetic material are in good agreement with those[1] reported for the natural product. Further, demethylation[14] of **3** with $AlCl_3$ in CH_2Cl_2 at room temperature produced brasiliquinone C **2** (87%).

Our next goal was the synthesis of 3-deoxyrabelomycin **4a**,[15] which is also a natural product. The synthesis of **4a** thus proceeded as follows: Reduction of **18b** with Zn–AcOH yielded the 2-methyltetralone **15b** in 57% yield. The tetralone **15b** was then subjected to Huang–Minlon reduction to give the tetrahydronaphthol **19b** in 68% yield. Demethylation of **19b** with BBr_3 in CH_2Cl_2, followed by PIDA oxidation of **20b** in methanol, provided methoxynaphthalenone **6b** in overall 40% yield. The corresponding monoketal product **21b** could not be isolated, presumably because of its presence in only insignificant amounts. This was followed by annulation of **6b** with **7c** in the presence of ′BuOLi, giving **5b**. Though this product could not be purified to our satisfaction due to the presence of an inseparable and unidentifiable impurity, the completion of the synthesis of **4a** from **5b** proved to be somewhat uneventful. Photooxidation of **5b** in the presence of sunlight furnished **4b** (70%). Finally, $AlCl_3$-promoted demethylation[14] of **4b** afforded 3-deoxyrabelomycin **4a** in 65% yield. The physical data of this material matched those of the natural product.

In conclusion, the applicability and brevity of our phthalide annulation–photooxidation strategy in the synthesis of an angucycline has been established by the first, yet concise, total synthesis of brasiliquinones B and C, **2** and **3**. It is hoped that this methodology will find more applications in angucycline synthesis. Further utilization of this protocol in enantioselective synthesis of an angucycline using tetralones **15** is underway.

Experimental

Mps were measured on a Toshniwal hot-coil apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 883 spectrometer for samples as KBr pellets or neat and the characteristic bands are presented in cm^{-1}. ^1H NMR and ^{13}C NMR spectra were recorded on a Brucker-200 for solutions in [^2H] chloroform with tetramethylsilane as the internal standard. Chemical shifts are reported as δ-values and ^1H–^1H coupling constants (J) are in Hz. All necessary solvents were purified prior to use. THF was distilled from sodium–benzophenone under an Ar atmosphere. Column chromatography was performed with silica gel (60–120 mesh, S.D. Fine Chemicals, Mumbai). Petroleum ether (60–80 °C) containing 1–10% ethyl acetate was used as an eluent for the chromatographic separations. TLC was performed on GF_{254} silica gel (S.D. Fine Chemicals). Preparation of lithium *tert*-butoxide was carried out by addition of *n*-butyllithium (Fluka) to a stirred solution of *tert*-butyl alcohol in THF under an Ar atmosphere at 0 °C.

3,4-Dihydro-6-hydroxy-8-methoxy-3-methylbenz[*a*]anthracene-1,7,12(2*H*)-trione 4b

The cyanophthalide **7c** was annulated with **6b** in accordance with the procedure for the preparation of **10** as given below to give **5b** which was, without purification, subjected to photooxidation as described for **10**, to give **4b** in 70% yield. Solid (orange red), mp 218–220 °C, ν_{max}(KBr) 1680, 1635, 1220, 1174, 1024; δ_H 13.04 (s, 1 H), 7.77–7.68 (m, 2 H), 7.35–7.26 (m, 1 H), 6.96 (s, 1 H), 4.06 (s, 3 H), 2.97–2.80 (m, 2 H), 2.67–2.37 (m, 3 H), 1.18 (d, J 6.0, 3 H); m/z; 336 (M^+).

3-Ethyl-1,2,3,4-tetrahydro-6-hydroxy-8-methoxybenz[*a*]-anthracene-7,12-dione 5a

This compound was prepared in 92% yield from **7c** and **6a** according to the procedure described for the preparation of **10** as given below; Solid; mp 177 °C; ν_{max}(KBr) 3438, 1631, 1585, 1456, 1279, 1240, 1039; δ_H 13.25 (s, 1 H), 7.88–7.84 (m, 1 H), 7.71 (t, J 8.2, 1 H), 7.31–7.26 (m, 2 H), 7.02 (s, 1 H), 4.06 (s, 3 H), 3.45–3.34 (m, 1 H), 3.18–2.88 (m, 2 H), 2.54–2.40 (m, 1 H), 2.06–1.99 (m, 1 H), 1.65–1.47 (m, 1 H), 1.43–1.27 (m, 2 H), 0.99 (t, J 7.2, 3 H); m/z 336 (M^+) (Found: C, 75.0; H, 5.9. Calc. for $C_{21}H_{20}O_4$: C, 75.0; H, 6.0%).

7-Ethyl-5,6,7,8-tetrahydro-4a-methoxynaphthalen-2(4a*H*)-one 6a

To a stirred solution of naphthol **20a** (see below) (100 mg, 0.57 mmol) in methanol (7 cm^3) at 0 °C under an Ar atmosphere was added PIDA (200 mg, 0.62 mmol). After about 30 min at 0 °C, the reaction mixture was allowed to come to ambient temperature. The bulk of methanol was removed under reduced pressure and the resulting residue was quickly chromatographed to give **6a** (61 mg, 52%) and **21a** (10 mg, 8%).

Data for 6a. Oil, ν_{max}(Neat) 1671; δ_H 6.70–6.66 (m, 1 H), 6.34–6.28 (m, 1 H), 6.20 (br s, 1 H), 3.04 (br s, 3 H), 2.59–2.06 (m, 3 H), 1.67–1.22 (m, 6 H), 0.97–0.81 (m, 3 H).

Data for 21a. Oil, ν_{max}(Neat) 1673; δ_H 6.69 (d, J 10, 1 H), 5.96 (d, J 10, 1 H), 3.22 (s, 3 H), 3.05 (s, 3 H), 2.73–2.43 (m, 1 H), 2.35–2.28 (m, 2 H), 1.92–1.82 (m, 2 H), 1.52–1.36 (m, 4 H), 0.96 (t, J 7, 3 H).

Compound 6b

Oil, Yield 59%; This was prepared from compound **20b** (see below), following the procedure described for the preparation of **6a** from **20a**, and had ν_{max}(Neat) 1660; δ_H 6.68 (d, J 10, 1 H), 6.32 (dd, J 1.6 and 10, 1 H), 6.19 (br s, 1 H), 3.04 (s, 3 H), 2.32–1.89 (m, 4 H), 1.63–1.52 (m, 1 H), 1.40–1.32 (m, 2 H), 1.05 (d, J 6.2, 3 H).

1,2,3,4-Tetrahydro-6-hydroxy-8-methoxybenz[*a*]anthracene-7,12-dione 10

To a stirred solution of ′BuOLi (4.1 mmol) in THF (25 cm^3) under an Ar atmosphere at −60 °C ($CHCl_3$–liq. N_2-bath) was added 3-cyano-7-methoxyphthalide **7c** (500 mg, 1.8 mmol). A golden yellow colour developed at this point. After 10 min, a solution of 5,6,7,8-tetrahydro-4a-methoxynaphthalen-2(4a*H*)-one **8** in THF (10 cm^3) was introduced into the reaction mixture. The resulting deep green coloured mixture was further stirred at −60 °C for 2 h and then at ambient temperature for 4 h. It was quenched with 2 M HCl (7 cm^3) and concentrated to give a solid residue. This was filtered off, and washed with water several times. The filtrate was extracted with ethyl acetate

(3 × 25 cm^3). The combined extract was washed successively with brine (25 cm^3) and water (25 cm^3), dried (Na_2SO_4), and then concentrated to give a gummy solid which was combined with the first crop of the product and chromatographed to yield **10** (470 mg, 85%).

The same reaction when performed with **7a** furnished **10** in 52% yield; mp 205–207 °C; ν_{max}(KBr) 3424, 1641, 1447, 1261, 846; δ_H 13.24 (s, 1 H), 7.86 (dd, *J* 0.8 and 8.1, 1 H), 7.70 (t, *J* 8.1, 1 H), 7.37–7.27 (m, 1 H), 7.01 (s, 1 H), 4.05 (s, 3 H), 3.21–3.18 (m, 2 H), 2.87–2.84 (m, 2 H), 1.82–1.76 (m, 4 H); δ_C 190.2, 185.1, 160.3, 160.0, 148.6, 147.6, 137.4, 135.3, 133.9, 129.9, 124.6, 119.9, 118.2, 116.9, 56.6, 31.3, 28.8, 23.2, 21.8; *m/z* 308 (M^+) (Found: C, 74.2; H, 5.3. Calc. for $C_{19}H_{16}O_4$: C, 74.0; H, 5.2%).

3,4-Dihydro-6-hydroxy-8-methoxybenz[*a*]anthracene-1,7,12(2*H*)-trione 11

A solution of compound **10** (100 mg, 0.03 mmol) in $CHCl_3$ (10 cm^3), in a small conical flask covered with a watch glass, was directly exposed to sunlight. When the reaction was deemed complete (usually 5–6 h) by TLC (1:5 (v/v) ethyl acetate–petroleum ether), the solution was concentrated and chromatographed to furnish compound **11** as orange-red crystals in 93% yield; mp 212 °C; ν_{max}(KBr) 1695, 1648, 1600, 1251, 787; δ_H 13.06 (s, 1 H), 7.76–7.73 (m, 2 H), 7.35–7.29 (m, 2 H), 4.06 (s, 3 H), 2.88–2.78 (m, 4 H), 2.19–2.13 (m, 2 H); *m/z* 322 (M^+) (Found: C, 70.7; H, 4.5. Calc. for $C_{19}H_{14}O_5$: C, 70.8; H, 4.4%).

2-Ethyl-7-methoxy-α-tetralone 15a

Cuprous iodide (790 mg, 4.14 mmol) was added to a solution of CH_3MgI, prepared from magnesium turnings (170 mg, 6.99 mmol) and CH_3I (397 mg, 2.8 mmol), in dry diethyl ether (10 cm^3) at −5 °C. The resulting grey mixture was rapidly cooled to −70 °C and then a solution of enone **18b** (see below) (300 mg, 2.07 mmol) in dry diethyl ether (10 cm^3) was introduced into the mixture over a period of 5 min. The resulting mixture was then stirred for about 1 h at −70 °C, and then allowed to come to 0 °C and quenched with 2 M H_2SO_4 (8 cm^3). The organic layer was separated, extracted with diethyl ether (2 × 25 cm^3), dried (Na_2SO_4) and finally chromatographed to afford the pure product **15a** (180 mg, 66%). ν_{max}(Neat) 1677, 1609, 1246; δ_H 7.48 (d, *J* 2.7, 1 H), 7.06 (d, *J* 8.5, 1 H), 7.00 (dd, *J* 2.7 and 8.5, 1 H), 3.82 (s, 3 H), 2.95–2.85 (m, 2 H), 2.35–2.1 (m, 2 H), 2.05–1.8 (m, 2 H), 1.75–1.45 (m, 1 H), 0.99 (t, *J* 7.4, 3 H); δ_C 199.9, 158.5, 136.5, 133.5, 129.9, 121.6, 109.5, 55.5, 48.9, 28.9, 28.2, 27.7, 22.6, 11.6 (Found: C, 76.3; H, 7.7. Calc. for $C_{13}H_{16}O_2$: C, 76.4; 7.9%).

7-Methoxy-2-methyl-α-tetralone 15b

To a stirred solution of compound **18b** (see below) (500 mg, 2.7 mmol) in acetic acid (20 cm^3) was added Zn dust (3 equiv.) in portions over a period of 30 min. The resulting mixture was heated at reflux for 1.5 h, concentrated to about 10 cm^3, cooled, neutralized with aq. $NaHCO_3$, and extracted with diethyl ether (3 × 15 cm^3). The organic phase was then washed with water, dried (Na_2SO_4), and chromatographed to give product **15b** (293 mg, 57%), ν_{max}(KBr) 1682, 1610; δ_H 7.51 (d, *J* 2.8, 1 H), 7.13 (d, *J* 8.4, 1 H), 7.03 (dd, *J* 2.8 and 8.4, 1 H), 3.82 (s, 3 H), 2.97–2.89 (m, 2 H), 2.26–2.51 (m,1 H), 2.19–2.12 (m, 1 H), 1.80–1.79 (m, 1 H), 1.26 (d, *J* 8, 3 H); δ_C 200.0, 158.3, 136.5, 129.7, 121.3, 111.8, 109.3, 55.2, 42.4, 31.5, 26.9, 15.4.

Dimethyl 4-hydroxy-6-methoxynaphthalene-1,3-dicarboxylate 16

A solution of homophthalate **12** (200 mg, 0.84 mmol) in dry methanol (1.5 cm^3) was added to a stirred solution of NaOMe (2.5 equiv.) in dry methanol (5 cm^3) at room temperature. Methyl acrylate **13** (112 mg, 1.3 mmol) was then added to the mixture and the resulting mixture was heated on a steam-bath for 4 h. After cooling, the reaction mixture was poured into 1 M HCl (10 cm^3) and extracted with diethyl ether (3 × 20 cm^3). The combined extract was washed with brine (20 cm^3), dried (Na_2SO_4), evaporated and then chromatographed to produce **16** (50 mg, 20%), mp 187–189 °C; ν_{max}(KBr) 1705, 1667, 1217, 853; δ_H 12.33 (s, 1 H), 8.95 (d, *J* 9.2, 1 H), 8.50 (s, 1 H), 7.75 (d, *J* 2.8, 1 H), 7.39 (dd, *J* 2.8 and 9.2, 1 H), 4.03 (s, 3 H), 3.97 (s, 6 H); *m/z* 290 (M^+).

7-Methoxy-2-methylene-α-tetralone 18b

To a stirred solution of *N*-methylanilinium trifluoroacetate (937 mg, 3.40 mmol) in THF (30 cm^3) at room temperature was added paraformaldehyde (385 mg, 4.50 mmol), followed by a solution of 7-methoxy-α-tetralone **17** (500 mg, 2.8 mmol) in THF (10 cm^3) over a period of 0.5 h. The resulting solution was heated at reflux on an oil-bath for about 6–12 h. After the reaction reached the steady state as indicated by TLC (1:9 (v/v) ethyl acetate–petroleum ether as developer), the reaction mixture was cooled and diluted with diethyl ether (25 cm^3). The ether layer was decanted and the residue was titurated with CH_2Cl_2 (2 × 15 cm^3). The ether and dichloromethane phases were combined, washed successively with aq. $NaHCO_3$ and water, dried (Na_2SO_4), and chromatographed to pure product **18b** (385 mg, 72%, based on recovered starting material) as an oil, ν_{max}(Neat) 1682, 1600; δ_H 7.47 (d, *J* 2.7, 1 H), 7.04 (d, *J* 8.5, 1 H), 6.93 (dd, *J* 2.7 and 8.4, 1 H), 6.10 (m, 1 H), 5.33 (m, 1 H), 3.73 (s, 3 H), 2.9–2.6 (m, 4 H); δ_C 186.9, 158.3, 143.3, 135.3, 132.6, 129.6, 121.4, 121.2, 110.0, 55.3, 31.8, 27.7.

2-Ethyl-1,2,3,4-tetrahydro-7-methoxynaphthalene 19a

Ketone **15a** (250 mg, 1.23 mmol) and freshly distilled hydrazine hydrate (5 equiv.) were added to a stirred solution of powdered KOH (340 mg, 6 mmol) in diethylene glycol (15 cm^3). This mixture was heated at 110 °C for 3–5 h and then at 200 °C for 4–5 h. After cooling, the reaction mixture was extracted with $CHCl_3$ (5 × 25 cm^3). The combined extract was washed with water (20 cm^3), dried (Na_2SO_4), evaporated to dryness, and the resulting residue subjected to column chromatography to yield **19a** as an oil (108 mg, 46%), ν_{max}(Neat) 1611, 1588, 1500, 1256; δ_H 6.98 (d, *J* 8, 1 H), 6.69–6.59 (m, 2 H), 3.77 (s, 3 H), 2.79–2.69 (m, 2 H), 2.45–2.31 (m, 2 H), 1.97–1.87 (m, 2 H), 1.62–1.32 (m, 3 H), 0.98 (t, *J* 7.4, 3 H) (Found: C, 82.2; H, 9.7. Calc. for $C_{13}H_{18}O$: C, 82.0; H, 9.5%).

Compound 19b

This was prepared from **15b** according to the procedure described for the preparation of **19a** from **15a**. Clear liquid, 68%; yield; ν_{max}(Neat) 1606, 1549; δ_H 7.00 (d, *J* 8.4, 1 H), 6.70–6.60 (m, 2 H), 3.78 (s, 3 H), 2.84–2.74 (m, 2 H), 2.50–2.31 (m, 2 H), 1.94–1.78 (m, 2 H), 1.38–1.26 (m, 1 H), 1.06 (d, *J* 6.6, 3 H).

Compound 20a

To a stirred solution of **19a** (120 mg, 0.63 mmol) in dry CH_2Cl_2 (20 cm^3) under an argon atmosphere at 0 °C was introduced 1 M BBr_3 (1.2 equiv.). This mixture was stirred for 1 h at 0 °C and then at ambient temperature until completion of the reaction. It was then quenched with 1 M HCl (10 cm^3) and extracted with diethyl ether (2 × 20 cm^3); the extract was washed with water, dried (Na_2SO_4), and evaporated to give a light brown residue. This was then chromatographed to give **20a** (100 mg, 91%), ν_{max}(Neat) 3353, 1613, 1257; δ_H 6.91 (d, *J* 8, 1 H), 6.58–6.52 (m, 2 H), 4.50 (s, 1 H), 2.83–2.67 (m, 3 H), 2.40–2.28 (m, 1 H), 1.95–1.88 (m, 1 H), 1.7–1.2 (m, 4 H), 0.97 (t, *J* 7.2, 3 H); δ_C 153.2, 138.3, 129.4, 129.2, 115.3, 112.8, 36.0, 35.9, 29.0, 28.4, 11.4.

Compound 20b

This was prepared from **19b** according to the procedure described for **19a** ⟶ **20a**. Solid (low melting), 70% yield; ν_{max}(KBr) 3291, 1608, 1501; δ_H 6.94 (d, *J* 8, 1 H), 6,61–6.53 (m, 2 H), 4.55 (s, 1 H), 2.76–2.70 (m, 2 H), 2.48–2.35 (m, 2 H), 1.89–1.81 (m, 2 H), 1.44–1.24 (m, 1 H), 1.04 (d, *J* 6.4, 3 H); δ_C 153.2, 138.4, 129.8, 128.9, 115.1, 112.8, 38.2, 31.7, 29.2, 28.4, 21.9.

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