Application of organolithium and related reagents in synthesis. Part 21.[1] Synthetic strategies based on *ortho*-aromatic metallation. A concise regiospecific synthesis of arylnaphthalanes as precursors of naphthylisoquinoline alkaloids

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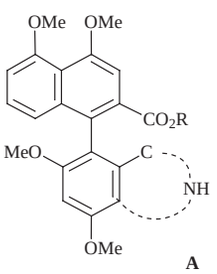
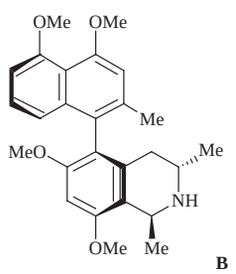
A novel procedure is described for synthesising regioselectively substituted biaryls such as 12. It involves converting phthalides 4, *via* cycloaddition of dimethyl acetylenedicarboxylate to 1-arylisobenzofurans 6, into dimethyl 1-arylnaphthalene-2,3-dicarboxylates 8, which upon hydrolytic decarboxylation give lactones 11 and then esters 12.

Introduction

In recent years a lot of attention has been paid to the synthesis of biaryls that exhibit interesting biological activity.[2,3] In particular, our attention has been focused on developing a synthetic methodology for biaryls of type **A** with this specific pattern of substituents, which are perfect starting materials for the preparation of naphthylisoquinoline alkaloids[4–12] isolated from plant families *Dinocophyllaceae* and *Ancistrocladaceae*



A

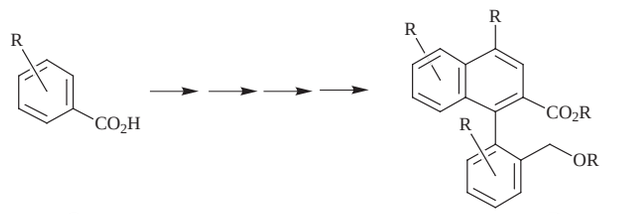


B

represented, for example, by *o*-methylancistrocladine **B**. The extracts of these plants have been used in the traditional medicine for the treatment of malaria and dysentery.[13] Furthermore, it has been observed that dimeric alkaloid michellamine inhibits the cytopathic effects of the AIDS virus *in vitro*.[10–12] The most frequently travelled synthetic routes toward the systems **A** have been used upon intra- and inter-molecular approaches to constructing the biaryl linkage.[2,3] The intramolecular aryl-coupling version in most cases is based upon the classical Ullmann reaction or palladium-catalysis procedure applied to the ester, ether or polymethylene type of aromatic precursor.[3,8,9–11] For the intermolecular procedure the substitution of an aromatic methoxy group by an aryl Grignard reagent following Meyers synthesis has generally been involved.[4–6,14–19] In turn, for the construction of the biaryls Diels–Alder reaction of 1-arylisobenzofurans with appropriate dienophiles is often applied as well.[20–25] However, in most cases labour-intensive starting materials are required or the applied processes are related only to specific instances.

Results and discussion

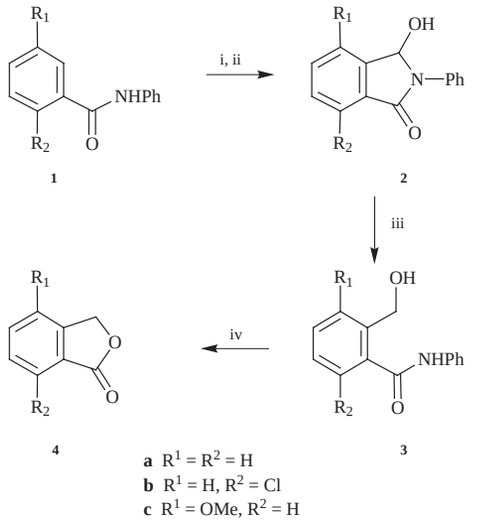
Herein we wish to report a novel efficient and regiospecific synthetic sequence as a general strategy for the transformation of aromatic carboxylic acid **C** into corresponding biaryls **D** starting from benzoic acids anilides as depicted in the outline scheme **C**→**D**.



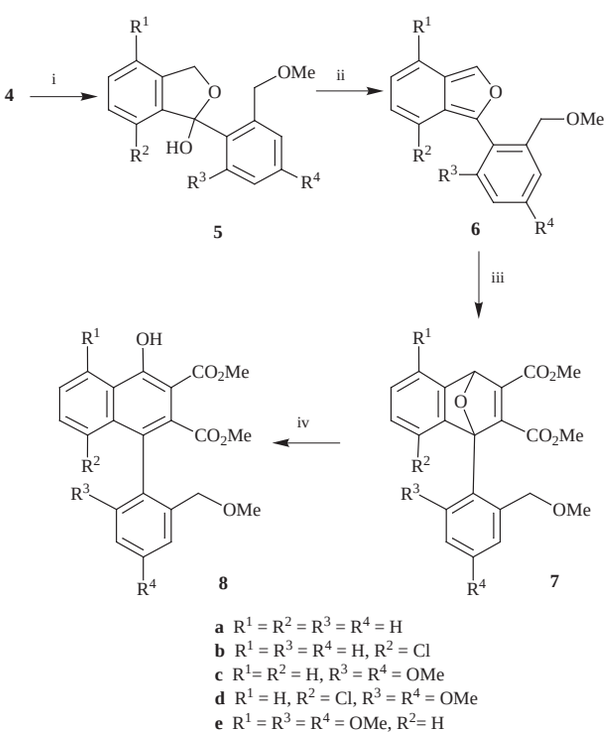
C **D**

The following key steps are essential for the synthesis of the required biaryls **12** as outlined in Schemes 2 and 3. First, the regioselective formation of isobenzofurans **6** that are readily converted, *via* Diels–Alder addition of dimethyl acetylenedicarboxylate (DMAD) and aromatization of the adducts, into the corresponding biaryls **8**. In the next step the biaryls **8** upon hydrolytic decarboxylation (retro Kolbe–Schmitt reaction)[26–29] gave the desired 5,7-dihydro-9-methoxybenzo[*c*]naphtho[1,2-*e*]-oxepin-7-one **11** and, subsequently, methyl 1-(2-hydroxymethylphenyl)-4-methoxynaphthalene-2-carboxylate **12**.

To this end, anilides **1** were reacted in tetrahydrofuran (THF) with BuLi (2.1 mol equiv.) and converted into the bis (*N*- and *C*-*ortho*)lithiated anilides. The treatment of the solution of the lithiated species with dimethylformamide (DMF) afforded the corresponding *ortho*-formylated anilides, which upon work-up spontaneously cyclized into 3-hydroxyisoindolin-1-ones **2** (masked *ortho*-formylated anilides). Afterwards isoindolin-1-ones **2** were reductively converted into phthalides **4**. Therefore, **2b** was treated with potassium borohydride (KBH_4) in MeOH and then by acid driven cyclization it gave phthalide **4b**, but **4c** was prepared upon the treatment of **2c** with zinc dust in water in the presence of lithium hydroxide (LiOH) (Scheme 1). Phthalides **4** reacted in THF with 1 mol equiv. *o*-methoxymethylphenyllithiums (prepared *via* reaction of *o*-bromomethoxymethylbenzenes with BuLi[30]) and were converted into corresponding phthalans **5**. The obtained phthalans **5**, without purification, on exposure to acid catalysis by trifluoroacetic acid (CF_3COOH) in methylene dichloride (CH_2Cl_2) generated isobenzofurans **6**, which subsequently were trapped with DMAD and gave adduct **7**. The resulting adducts **7** upon treatment with toluene-*p*-sulfonic acid (TsOH) in boiling toluene gave the required 1-aryl-4-hydroxynaphthalenes **8** in overall good yields (Scheme 2). In the course of an attempt to prove the high rigidity of the obtained biaryls **8**, following Sternhell[31] methodology, dynamic ^1H NMR spectroscopy techniques were used to study the rotational barriers. For this study the least (**8a**) and the most (**8d**) overcrowded compounds were selected. In both cases, at up to 180 °C in [$^2H_5$]nitrobenzene as solvent, the methylene groups give rise to AB patterns (chemical shifts and coupling constants for **8a** and **8d**

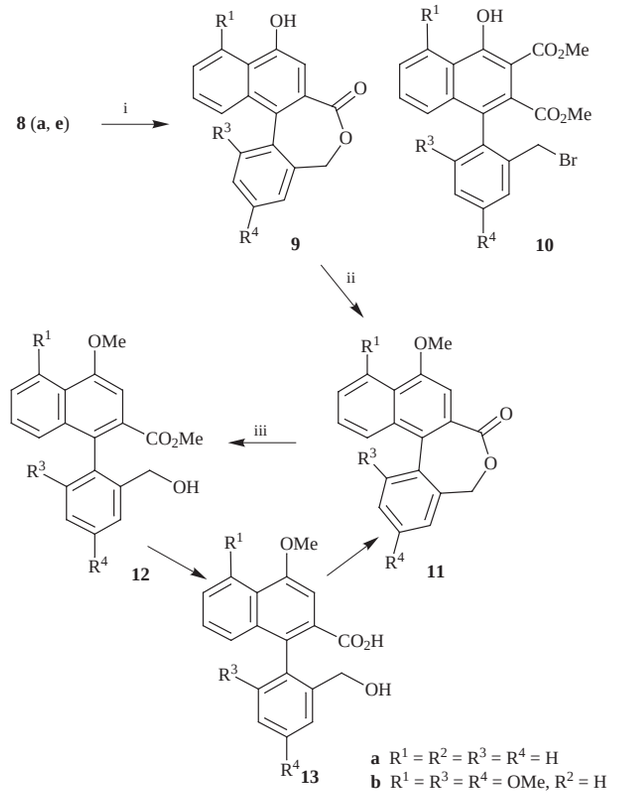


Scheme 1 *Reagents and conditions*: i, BuLi in THF, −78 °C (0.5 h) → 0 °C (0.1 h); ii, DMF, −78 °C (1 h)→20 °C (1 h), hydrolytic workup; iii, KBH_4 in MeOH (**2b**) or Zn–LiOH (**2c**); iv, H^+



Scheme 2 *Reagents and conditions*: i, 2-methoxymethylphenyllithium (for **a**, **b**) or 4,6-dimethoxy-2-methoxymethylphenyllithium (for **c**–**e**) in THF, −78 °C; ii, CF_3CO_2H (cat.) in CH_2Cl_2, 20 °C; iii, $MeO_2CC{\equiv}CCO_2Me$ in CH_2Cl_2, 20 °C; iv, TsOH (cat.) in boiling toluene

are δ_H 4.07 and 4.25, *J* 12.09 Hz and δ_H 4.19 and 4.30, *J* 13.4 Hz, respectively) rather than singlets, since the two protons are diastereotopic when rotation around the bond under discussion is slow. In the final step, biaryls **8** were subjected to reaction with hydrogen bromide in acetic acid–water solution in the presence of hypophosphorous acid (H_3PO_2) and gave decarboxylated systems **9**. The addition of H_3PO_2 appeared to be crucial for this hydrolytic decarboxylation. An attempted reaction without the reductor yielded only an unidentifiable mixture. It was observed that transformation of **8** into **9** was accompanied by the formation of bromides **10**. It can be inferred (see Experimental section) that the quantity of the bromides formed depends upon the rigidity of the biaryls **8**.



Scheme 3 *Reagents and conditions*: i, HBr and H_3PO_2 in acetic acid; ii, K_2CO_3, MeI in acetone; iii, MeOH, DOWEX (cat.)

Thus, following the transformation of **8a** into **9a** (less rigid case) a separable amount of **10a** was formed. In the case of the hydrolytic decarboxylation of **8e** the formed **9b** was accompanied only by traces of bromide **10b**, as was indicated in the ^1H NMR spectrum of the crude product.

The compounds **9** were first converted with methyl iodide in dry acetone in the presence of anhydrous potassium carbonate into the corresponding derivatives **11**, which gave the esters **12** after treatment with methanol (Scheme 3). An attempted conversion of ester **12** into acid **13** failed in practice. The acid **13** formed *via* alkaline hydrolysis (KOH in mixed solvent THF–water) spontaneously converted into lactones **11** upon an acidic workup.

In summary, we have shown a regiospecific synthetic method for the preparation of biaryls such as **11** or **12** with an economy of steps which involves: (i) successive conversion of benzanilides **1** into phthalides **4**, and then (ii) direct formation of dimethyl 1-arylnaphthalene-2,3-dicarboxylates **8**, as precursors of **11** and subsequently **12** *via* hydrolytic decarboxylation.

Experimental

Melting points were determined using a Boetius hot-stage apparatus and they are uncorrected. IR spectra were recorded on a Zeiss-Jena Specord 71-IR. The ^1H NMR spectra were determined on a Varian-Gemini-200 (200 MHz), Bruker AC-200 (200 MHz) or Bruker AM 400-WB (400 MHz) spectrometer using TMS as an internal standard. Mass spectra were recorded on a LKB 2091 instrument at an ionization energy of 15 eV. The ascending thin layer chromatography was performed on precoated silica gel 60 F 254 (Merck) and the spots were visualized using UV lamp or iodine vapour. Macherey Nagel & Co. silica gel (100–200 mesh ATSM) was used for column chromatography. All reagents, commercially available materials, were used without purification unless otherwise stated. Tetrahydrofuran was dried over calcium hydride and used directly after distillation.

Synthesis of phthalides 4b and 4c

(a) Preparation of 3-hydroxy-2-phenyl-2,3-dihydro-1*H*-isoindol-1-ones 2b and 2c. To the anilide **1b** (4.64 g, 0.02 mol) or **1c** (4.54 g, 0.02 mol) stirred in THF (50 cm^3) at −78 °C BuLi (0.042 mol) was added. The solution was held at −78 °C for 0.5 h, then allowed to warm to 0 °C and kept at 0 °C for 0.1 h. The whole lot was cooled to −78 °C and DMF (2.92 g, 0.04 mol) was added. The reaction after 1 h at −78 °C was warmed up to room temperature, and kept for 1 h, and then water (25 cm^3) was added. The mixture was adjusted to pH ≈ 2 with hydrochloric acid and the organic layer was separated. The water layer was extracted with mixture $CHCl_3$:THF (1:1) (3 × 30 cm^3). The combined organic solutions were dried with magnesium sulfate and evaporated to give the crude products. The products were purified by crystallization.

The solvents for crystallization, the isolated yields and the physical characteristics of the isoindolinones **2** are given below.

7-*Chloro*-3-*hydroxy*-2-*phenyl*-2,3-*dihydro*-1H-*isoindol*-1-*one* **2b**.—(4.26 g, 82%) mp 152–155 °C (benzene) (lit.,[32] mp 152–156 °C.

3-*Hydroxy*-4-*methoxy*-2-*phenyl*-2,3-*dihydro*-1H-*isoindol*-1-*one* **2c**.—(3.83 g, 75%) mp 168–170 °C (methanol) (lit.,[25] 167–169 °C).

(b) Conversion of isoindolinone 2b into 7-chlorophthalide 4b. To the solution of isoindolinone **2b** (7.79 g, 0.03 mol) in methanol (250 cm^3) potassium borohydride (3.24 g, 0.06 mol) was added, and the mixture was refluxed for 1 h. After cooling the next part KBH_4 (3.24 g, 0.06 mol) was added and refluxing continued for 2 h. Then the solvent was evaporated and water (70 cm^3) was added. The precipitated solid was collected. The solid was suspended in 15% hydrochloric acid, and heated till boiling for 1 h, and left overnight. The solid was separated and purified by crystallization.

7-*Chlorophthalide* **4b**.—(3.64 g, 72%), mp 141–144 °C (lit.,[32] mp 142–144 °C).

(c) Reductive cleavage of isoindolinone 2c with zinc–lithium hydroxide system into 4-methoxyphthalide 4c. The suspension of freshly prepared zinc–copper couple [prepared from commercial Zn dust (3.00 g) and copper(II) sulfate (0.10 g) in water (10 cm^3)], lithium hydroxide monohydrate (4.20 g, 0.1 mol) and the isoindolinone **2c** (2.55 g, 0.01 mol) in water (30 cm^3) were heated till boiling for 1 h. The aniline formed was removed by steam distillation and water (50 cm^3) was added, and then the excess of zinc was filtered off. The filtrate was adjusted to pH ≈ 1 with hydrochloric acid, and the precipitated product **4c** was filtered, and purified by crystallization.

4-*Methoxyphthalide* **4c**.—(1.23 g, yield 75%), mp 126–128 °C (ethanol) (lit.,[33] mp 127 °C).

Synthesis of 1-bromo-2-methoxymethylbenzenes

The mixture of sodium hydride (0.53 g, 0.022 mol), 2-bromobenzyl alcohol (3.74 g, 0.02 mol, Aldrich) or 2-bromo-3,5-dimethoxybenzyl alcohol (4.90 g, 0.02 mol, obtained according to a known procedure[34]) and THF (50 cm^3) was stirred at room temperature for 1 h. Then iodomethane (5.68 g, 0.04 mol) was added and after 1 h the solvent was evaporated under reduced pressure. To the residue water (20 cm^3) was added and the whole lot was extracted with CH_2Cl_2 (3 × 30 cm^3). The combined organic solutions were dried and after evaporation of the solvent, the residue was purified differently in each case. 1-*Bromo*-2-*methoxymethylbenzene* was distilled, bp 80–82 °C at 1.5 mmHg (lit.,[35] 111–112 °C at 17 mmHg), 2.94 g, yield 73%. 1-*Bromo*-3,5-*dimethoxy*-2-*methoxymethylbenzene* was purified by crystallization, 3.90 g, yield 75%, mp 61–62 °C (from MeOH) (Found: C, 46.0; H, 4.9; Br, 30.3. Calc. for $C_{10}H_{13}BrO_3$: C, 45.98; H, 5.02; Br, 30.63%); δ_H(200 MHz, $CDCl_3$) 3.47 (3H, s, OMe), 3.80 (3H, s, OMe), 3.85 (3H, s, OMe), 4.50 (2H, s, CH_2), 6.41 (1H, d, *J* 2.7, 5ArH), 6.67 (1H, d, *J* 2.8, 3ArH).

Synthesis of 4-hydroxy-1-(2-methoxymethylphenyl)naphthalene-2,3-dicarboxylates 8

To the stirred solution of 1-bromo-2-methoxymethylbenzene (2.00 g, 0.01 mol) or 1-bromo-3,5-dimethoxy-2-methoxymethylbenzene (2.61 g, 0.01 mol) in THF (40 cm^3), BuLi (0.01 mol) at −78 °C was added. The reaction mixture was held at −78 °C for 0.25 h and then phthalide **4a** (1.34 g, 0.01 mol), **4b** (1.68 g, 0.01 mol) or **4c** (1.64 g, 0.01 mol) in THF (20 cm^3) was added. The whole lot after 0.5 h was warmed up to −30 °C and kept at −30 °C for 0.5 h. Then methanol (20 cm^3) was added and the solvents were evaporated under reduced pressure. To the residue water (30 cm^3) was added and the whole lot was extracted with $CHCl_3$ (3 × 40 cm^3).

The combined organic solutions were dried ($MgSO_4$) and evaporated to give the residue, which was dissolved in CH_2Cl_2 (20 cm^3). To the obtained solution, dimethyl acetylenedicarboxylate (5.68 g, 0.04 mol) and a catalytic amount of trifluoroacetic acid (two drops) were added and the reaction mixture was kept at room temperature overnight. The solvent was evaporated and the residue was aromatized by reflux (2 h) with a catalytic amount of toluene-*p*-sulfonic acid in dry toluene. Then toluene was removed and product **8** was separated by column chromatography [eluent chloroform, then chloroform:ethyl acetate (95:5)] and purified by crystallization. The solvents for crystallization, the isolated yields and the physical and spectral characteristics of arylnaphthalenes **8** are given below.

Dimethyl 4-hydroxy-1-(2-methoxymethylphenyl)naphthalene-2,3-dicarboxylate 8a. (1.14 g, yield 30%), mp 133–135 °C (from MeOH); R_f = 0.33 (chloroform–ethyl acetate, 95:5) (Found: C, 69.3; H, 5.5. Calc. for $C_{22}H_{20}O_6$: C, 69.45; H, 5.30%); ν_{max}(KBr)/cm^{-1} 1720 and 1660 (CO); δ_H(400 MHz; $CDCl_3$) 3.17 (3H, s, OMe), 3.49 (3H, s, OMe), 3.95 (3H, s, OMe), 4.07 (1H, d, *J* 12.9, CH_2), 4.25 (1H, d, *J* 12.9, CH_2), 7.17 (1H, d, *J* 7.5, 3ArH), 7.25 (1H, d, *J* 8.2, 6ArH), 7.34 (1H, dd, *J* 7.4 and 7.5, 4ArH), 7.44–7.63 (4H, m, 6, 7, 8NapH and 5ArH), 8.51 (1H, d, *J* 8.1, 5NapH), 12.42 (1H, s, OH).

Dimethyl 8-chloro-4-hydroxy-1-(2-methoxymethylphenyl)-naphthalene-2,3-dicarboxylate 8b. (1.45 g, yield 35%), mp 182–184 °C (from MeOH); R_f = 0.30 (chloroform–ethyl acetate, 95:5) (Found: C, 63.7; H, 4.7; Cl, 8.5. Calc. for $C_{22}H_{19}ClO_6$: C, 63.69; H, 4.61; Cl, 8.56%); ν_{max}(KBr)/cm^{-1} 1730 and 1660 (CO); δ_H(400 MHz, $CDCl_3$) 3.25 (3H, s, OMe), 3.38 (3H, s, OMe), 3.93 (3H, s, OMe), 4.08 (1H, d, *J* 13.2, CH_2), 4.24 (1H, d, *J* 13.3, CH_2), 7.11–7.49 (5H, m, 6NapH and ArH), 7.64 (1H, dd, *J* 7.5 and 1.1, 7NapH), 8.55 (1H, dd, *J* 8.3 and 1.1, 5NapH), 12.55 (1H, s, OH).

Dimethyl 4-hydroxy-1-(4,6-dimethoxy-2-methoxymethylphenyl)naphthalene-2,3-dicarboxylate 8c. (1.40 g, yield 32%), mp 131–133 °C (from MeOH); R_f = 0.17 (chloroform–ethyl acetate, 95:5) (Found: C, 65.2; H, 5.5. Calc. for $C_{24}H_{24}O_8$: C, 65.44; H, 5.50%); ν_{max}(KBr)/cm^{-1} 1730 and 1660 (CO); δ_H(400 MHz; $CDCl_3$) 3.15 (3H, s, OMe), 3.53 (3H, s, OMe), 3.61 (3H, s, OMe), 3.89 (3H, s, OMe), 3.92 (3H, s, OMe), 3.84 (1H, d, *J* 13.5, CH_2), 4.23 (1H, d, *J* 13.3, CH_2), 6.49 (1H, d, *J* 2.3, 3ArH), 6.79 (1H, d, *J* 2.2, 5ArH), 7.32 (1H, d, *J* 7.9, 8NapH), 7.50–7.58 (2H, m, 6 and 7NapH), 8.49 (1H, dd, *J* 7.9 and 1.3, 5NapH), 12.45 (1H, s, OH).

Dimethyl 8-chloro-4-hydroxy-1-(4,6-dimethoxy-2-methoxymethylphenyl)naphthalene-2,3-dicarboxylate 8d. (1.32 g, yield 28%), mp 152–154 °C (from MeOH); R_f = 0.43 (chloroform–ethyl acetate, 95:5) (Found: C, 60.6; H, 4.9; Cl, 7.6. Calc. for $C_{24}H_{23}ClO_8$: C, 60.69; H, 4.88; Cl, 7.47%); ν_{max}(KBr)/cm^{-1} 1730 and 1660 (CO); δ_H(400 MHz; $CDCl_3$) 3.22 (3H, s, OMe), 3.46 (3H, s, OMe), 3.66 (3H, s, OMe), 3.88–3.92 (7H, m, CH_2 and two OMe), 4.19 (1H, d, *J* 13.4, CH_2), 6.39 (1H, d, *J* 2.3, 5ArH), 6.69 (1H, d, *J* 2.3, 3ArH), 7.44 (1H, dd, *J* 8.2 and 7.9, 6NapH), 7.64 (1H, dd, *J* 7.5 and 1.3, 7NapH), 8.53 (1H, dd, *J* 8.4 and 1.1, 5NapH), 12.56 (1H, s, OH).

Dimethyl 4-hydroxy-5-methoxy-1-(4,6-dimethoxy-2-methoxymethylphenyl)naphthalene-2,3-dicarboxylate 8e. (1.13 g, yield

24%), mp 149–151 °C (from MeOH); R_f = 0.28 (chloroform–ethyl acetate, 95 : 5) (Found: C, 63.5; H, 5.3. Calc. for $C_{25}H_{26}O_9$: C, 63.82; H, 5.57%). ν_{max}(KBr)/cm^{-1} 1730 and 1660 (CO); δ_H(200 MHz, $CDCl_3$) 3.16 (3H, s, OMe), 3.52 (3H, s, OMe), 3.59 (3H, s, OMe), 3.80–3.90 (7H, m, CH_2 and two OMe), 4.04 (3H, s, OMe), 4.19 (1H, d, *J* 13.5, CH_2), 6.47 (1H, d, *J* 2.2, 5ArH), 6.78 (1H, d, *J* 2.1, 3ArH), 6.89–6.97 (2H, m, 6NapH and 8NapH), 7.31 (1H, d, *J* 8.2, 7NapH), 11.80 (1H, s, OH).

Preparation of 5,7-dihydro-9-hydroxybenzo[*c*]naphtho[1,2-*e*]-oxepin-7-ones 9

To the dimethyl 4-hydroxy-1-arylnaphthalenedicarboxylate **8a** (1.14 g, 0.003 mol) or **8e** (1.41 g, 0.003 mol) a mixture of glacial acetic acid (15 cm^3), hydrobromic acid (15 cm^3, 48 wt% in water) and hypophosphorous acid (two drops, 50 wt% solution in water) was added and the whole lot was refluxed for 2 h in the case of arylnaphthalene **8a** and 0.75 h in the case of **8e**. After cooling the solution was diluted with water (100 cm^3) and the precipitate obtained was separated, washed with water and column chromatographed [eluent chloroform : ethyl acetate (95 : 5)] to give the products **9a** and **10a** or **9b**, respectively. Compounds **9** and **10** were purified by crystallization.

5,7-Dihydro-9-hydroxybenzo[*c*]naphtho[1,2-*e*]oxepin-7-one 9a. (0.45 g, yield 55%), mp 280–283 °C (from toluene); R_f = 0.21 (Found: C, 78.3; H, 4.4. Calc. for $C_{18}H_{12}O_3$: C, 78.25; H, 4.38%); ν_{max}(KBr)/cm^{-1} 1690 (CO); δ_H(200 MHz; [$^2H_6$]DMSO) 5.07 (1H, d, *J* 12.0, CH_2), 5.14 (1H, d, *J* 12.0, CH_2), 7.51–7.76 (6H, m, 1, 2, 3, 4, 11 and 12-H), 7.23 (1H, s, 8-H), 8.07–8.11 (1H, m, 13-H), 8.29–8.34 (1H, m, 10-H), 10.95 (1H, br s, OH) (HRMS calc. for $C_{18}H_{12}O_3$ 276.0786, found 276.081).

5,7-Dihydro-9-hydroxy-1,3,10-trimethoxybenzo[*c*]naphtho-[1,2-*e*]oxepin-7-one 9b. (0.36 g, yield 33%), mp 246–250 °C (from toluene); R_f = 0.46 (Found: C, 68.5; H, 4.6. Calc. for $C_{21}H_{18}O_6$: C, 68.85; H, 4.95%); ν_{max}(KBr)/cm^{-1} 1720 (CO); δ_H(200 MHz, [$^2H_6$]DMSO) 3.62 (3H, s, OMe), 3.88 (3H, s, OMe), 4.06 (3H, s, OMe), 4.87 (1H, d, *J* 11.8, CH_2), 4.99 (1H, d, *J* 11.7, CH_2), 6.80 (1H, d, *J* 2.4, 2-H), 6.95 (1H, d, *J* 2.4, 4-H), 6.97 (1H, s, 8-H), 7.08–7.15 (2H, m, 11 and 13-H), 7.40 (1H, dd, *J* 8.7 and 7.7, 12-H), 9.85 (1H, br s, OH).

Dimethyl 4-hydroxy-1-(2-bromomethylphenyl)naphthalene-2,3-dicarboxylate 10a. (0.42 g, yield 33%), mp 145–148 °C (from MeOH); R_f = 0.65 (Found: C, 58.8; H, 3.8; Br, 18.4. Calc. for $C_{21}H_{17}BrO_5$: C, 58.87; H, 4.00; Br, 18.44%); ν_{max}($CHCl_3$)/cm^{-1} 1730 and 1670 (CO); δ_H(200 MHz, $CDCl_3$) 3.47 (3H, s, OMe), 3.95 (3H, s, OMe), 4.23 (1H, d, *J* 10.6, CH_2), 4.31 (1H, d, *J* 10.7, CH_2), 7.11–7.69 (7H, m, NapH and ArH), 8.51 (1H, m, 5NapH), 12.44 (1H, s, OH).

Methylation of benzo[*c*]naphtho[1,2-*e*]oxepin-7-one system 9

The mixture of hydroxybenzo[*c*]naphtho[1,2-*e*]oxepin-7-one **9a** (0.83 g, 0.003 mol) or **9b** (1.10 g, 0.003 mol), acetone (50 cm^3), potassium carbonate (0.82 g, 0.006 mol) and methyl iodide (0.85 g, 0.006 mol) was refluxed for 5 h in the case of compound **9a** and for 48 h in the case of **9b**. After filtration the solution obtained was evaporated to give the solid residue. The product **11a** or **11b** was purified by crystallization.

5,7-Dihydro-9-methoxybenzo[*c*]naphtho[1,2-*e*]oxepin-7-one 11a. (0.54 g, yield 62%), mp 192–194 °C [from MeOH : toluene (9 : 1)]; R_f = 0.71 (Found: C, 78.9; H, 4.8. Calc. for $C_{19}H_{14}O_3$: C, 78.60; H, 4.86%); ν_{max}(KBr)/cm^{-1} 1710 (CO); δ_H(200 MHz, $CDCl_3$) 4.10 (3H, s, OMe), 4.98 (1H, d, *J* 12.0, CH_2), 5.14 (1H, d, *J* 12.0, CH_2), 7.27 (1H, s, 8-H), 7.40–7.67 (6H, m, 1,2,3,4,11,12-H), 8.15 (1H, dd, *J* 8.0 and 1.5, 13-H), 8.39 (1H, dd, *J* 7.5 and 1.5, 10-H).

5,7-Dihydro-1,3,9,10-tetramethoxybenzo[*c*]naphtho[1,2-*e*]-oxepin-7-one 11b. (0.68 g, yield 60%), mp 246–248 °C (from toluene); R_f = 0.46 (Found: C, 69.5; H, 5.3. Calc. for $C_{22}H_{20}O_6$: C, 69.46; H, 5.30%); ν_{max}(KBr)/cm^{-1} 1720 (CO); δ_H(200 MHz, $CDCl_3$) 3.95 (3H, s, OMe), 3.89 (3H, s, OMe), 3.99 (3H, s, OMe), 4.05 (3H, s, OMe), 4.84 (1H, d, *J* 11.6, CH_2), 5.00 (1H, d, *J* 11.6, CH_2), 6.62 (1H, d, *J* 2.4, 2-H), 6.69 (1H, d, *J* 2.4, 4-H), 6.95 (1H, d, *J* 6.6, 11-H), 7.20–7.37 (3H, m, 8, 12 and 13-H).

Transformation of benzo[*c*]naphtho[1,2-*e*]oxepin-7-one system 11 into esters 12

The mixture of methoxybenzo[*c*]naphtho[1,2-*e*]oxepin-7-one **11a** (0.58 g, 0.002 mol) or **11b** (0.76 g, 0.002 mol), methanol (50 cm^3) and a catalytic amount of cationite (DOWEX® 50WX4, mesh 100–200, ~0.5 g) was refluxed for 10 h. The cationite was separated and the obtained solution was evaporated to give a solid residue. The product **12a** or **12b** was separated by column chromatography [eluent chloroform : acetone (95 : 5)] and purified by crystallization.

Methyl 4-methoxy-1-(2-hydroxymethylphenyl)naphthalene-2-carboxylate 12a. (0.33 g, yield 52%), mp 147–150 °C (from MeOH); R_f = 0.36 (Found: C, 74.4; H, 5.6. Calc. for $C_{20}H_{18}O_4$: C, 74.52; H, 5.63%); ν_{max}(KBr)/cm^{-1} 1720 (CO); δ_H(200 MHz, $CDCl_3$) 2.62 (1H, br s, OH), 3.69 (3H, s, OMe), 4.08 (3H, s, OMe), 4.24 (2H, s, CH_2), 7.07 (1H, dd, *J* 6.0 and 1.2, ArH), 7.32–7.64 (7H, m, ArH and NapH), 8.33 (1H, d, *J* 8.0, 5NapH).

Methyl 1-(2-hydroxymethyl-4,6-dimethoxyphenyl)-4,5-dimethoxynaphthalene-2-carboxylate 12b. (0.45 g, yield 55%), mp 153–155 °C (from MeOH); R_f = 0.18 (Found: C, 66.8; H, 5.7. Calc. for $C_{23}H_{24}O_7$: C, 66.98; H, 5.87%); ν_{max}(KBr)/cm^{-1} 1700 (CO); δ_H(200 MHz, $CDCl_3$) 1.90–2.30 (1H, br s, OH), 3.57 (3H, s, OMe), 3.72 (3H, s, OMe), 3.91 (3H, s, OMe), 3.98 (3H, s, OMe), 4.05 (3H, s, OMe), 4.10 (2H, s, CH_2), 6.53 (1H, d, *J* 2.4, 3ArH), 6.79 (1H, d, *J* 2.4 Hz, 3ArH), 6.89–6.98 (2H, m, 6NapH and 8NapH), 7.21–7.32 (2H, m, 3NapH and 7NapH).

Hydrolysis of methyl ester 12a

A solution of methyl 4-methoxy-1-(2-hydroxymethylphenyl)-naphthalene-2-carboxylate **12a** (0.20 g, 0.000 62 mol) in a mixture of THF (15 cm^3), water (10 cm^3) and aqueous KOH (2.5 M, 2 cm^3) was heated at 55 °C for 3.5 h. The mixture was then cooled and THF was removed under reduced pressure. The aqueous residue was acidified using 10% HCl and extracted with CH_2Cl_2 (3 × 10 cm^3). The combined organic solutions were dried and after evaporation of the solvent the residue (0.15 g) was identified according to ^{1}H NMR data as lactone **11a**.

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