Oxidative rearrangement of pentaalkoxychalcones with phenyliodine(III) bis(trifluoroacetate) (PIFA): synthesis of (±)-10-bromopterocarpin and (±)-pterocarpin

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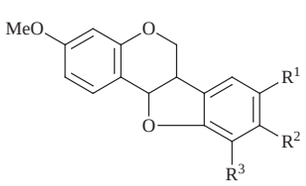
The oxidative rearrangement of pentaalkoxychalcones using the hypervalent iodine compound, phenyliodine(III) bis(trifluoroacetate) (PIFA), has been examined. Treatment of 2,2′-bis(benzyloxy)-4′-methoxy-4,5-methylenedioxychalcone with PIFA gives a rearrangement product in low yield, but 2,2′-bis(benzyloxy)-3-bromo-4′-methoxy-4,5-methylenedioxychalcone yields the rearrangement product, which leads to (±)-bromopterocarpin and (±)-pterocarpin.

Pterocarpans **1**,[1] (±)-homopterocarpin **1a** and (±)-pterocarpin **1c**, are known as phytoalexins which are produced when plants are attacked biologically. Moreover, Engler *et al.* have shown that several pterocarpans inhibit HIV-1 reverse transcriptase and the cytopathic effect of HIV-1 in cell culture.[2] Pterocarpans have been synthesized by several methods,[2–5] but the most efficient method for their synthesis is the rearrangement of chalcones by thallium nitrate,[3,4] which is a highly toxic compound. Moriarty *et al.*[6] have reported that treatment of 4-methoxy- or 4,4′-dimethoxy-chalcones with [hydroxy(tosyloxy)iodo]-benzene gives rearrangement products which could not be converted to pterocarpans because the chalcones had no 2,2′-dihydroxy substituent on the benzene ring. Recently, we have developed a synthesis of (±)-homopterocarpin **1a** by the rearrangement of 2,2′-bis(benzyloxy)-4,4′-dimethoxychalcone with phenyliodine(III) bis(trifluoroacetate) (PIFA).[7] In this paper we report the application of PIFA to the rearrangement of pentaalkoxychalcones, and the conversion of the rearrangement product to (±)-10-bromopterocarpin **1b** and (±)-pterocarpin **1c**.



1a; $R^1 = R^3 = H$, $R^2 = OMe$
1b: R^1, $R^2 = OCH_2O$, $R^3 = Br$
1c; R^1, $R^2 = OCH_2O$, $R^3 = H$

Results and discussion

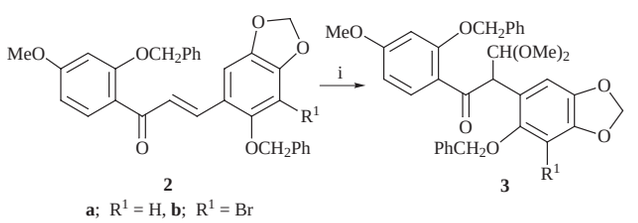
An initial attempt to obtain the rearrangement product **3a** from the chalcone **2a**[3] with PIFA in $CH(OMe)_3$ in the presence of trifluoroacetic acid[7] was unsuccessful. However, treatment of **2a** with PIFA in MeOH for two weeks gave **3a** in 7% yield and the starting material **2a** was recovered in 42% yield. Many attempts to attain **3a** under various conditions were less than satisfactory. The ease of rearrangement of 2,2′,4,4′,5-pentaalkoxychalcone **3a** is dependent on the electron density of the benzene ring compared with 2,2′,4,4′-tetraalkoxychalcone[7] and 2,2′-bis(benzyloxy)-4,4′-dimethoxychalcone. Consequently, we introduced an electron-withdrawing bromo group on the benzene ring of **2a**, which could be easily converted to many other functional groups.[8]

The bromo-substituted chalcone **2b** was obtained by reaction of 1-(2-benzyloxy-4-methoxyphenyl)ethanone[9] and 2-benzyloxy-3-bromo-4,5-methylenedioxybenzaldehyde in the presence of NaOEt. Treatment of **2b** with PIFA in $CH(OMe)_3$ gave a complex mixture, but in hot MeOH afforded the rearrangement product **3b** in 35% yield (Table 1, entries 1 and 2). A better result was obtained by treating **2b** in hot MeOH in the presence of trifluoroacetic acid and **3b** was isolated in 56% yield (entry 3) (Scheme 1 and Table 1).[10]

Table 1 Rearrangement reactions of chalcone **2b** with PIFA in MeOH

Entry	R^1	PIFA (Equiv.)	CF_3COOH (Equiv.)	*t*/h	Yield of **3b** (%)
1	Br	1.2	5.0	24[a]	—[b]
2	Br	6.0	—	9	35
3	Br	4.8	5.0	7	56

[a] Rt in $CH(OMe)_3$. [b] Many compounds seen by TLC.



2
a; $R^1 = H$, **b**; $R^1 = Br$

3

Scheme 1 *Reagents and conditions*: i, PIFA, MeOH, reflux

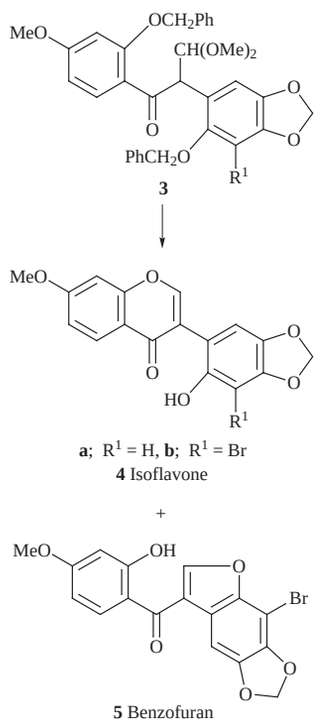
Compound **3a** was converted into the isoflavone **4a** by treatment with $BF_3{\cdot}Et_2O$ (20 equiv.) and Me_2S (55 equiv.) in 58% yield, but **3b** gave a mixture of the 3′-bromoisoflavone **4b** and 7-bromobenzofuran **5** in 52 and 19% yields, respectively (Table 2, entries 1 and 2). However, **4b** was obtained in 61% yield as the sole product by using $BF_3{\cdot}Et_2O$ (3 equiv.) and Me_2S (3 equiv.) (entry 4) (Scheme 2 and Table 2).

The isoflavone **4b** could be converted to anhydropisatin **7**[11] by catalytic hydrogenation with PtO_2, followed by acid cyclization and reduction with 10% Pd–C and ammonium formate in 52% overall yield. However, reduction of the double bond of **7** to give (±)-pterocarpin **1c** under several catalytic reduction conditions[7] could not be achieved (Scheme 3).

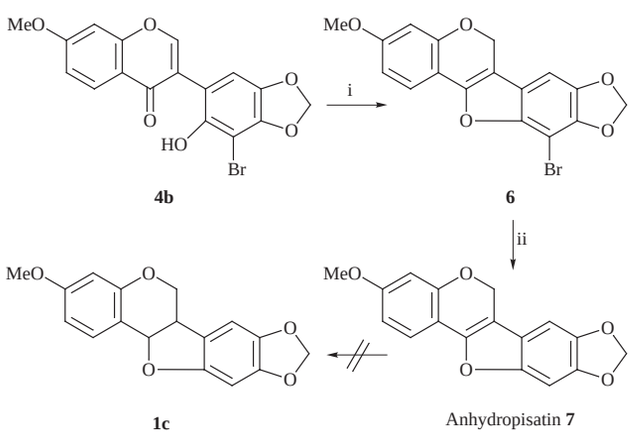
Next, we attempted to obtain (±)-pterocarpin by using Mori's method.[12] Sodium borohydride reduction of **4b** afforded the diol **8**, which was treated with $BF_3{\cdot}Et_2O$ to give (±)-10-bromopterocarpin **1b** in 40% yield. Reduction of the bromo group of **1b** was performed by using 10% Pd–C and ammonium formate to yield (±)-pterocarpin **1c**[13] in 81% yield (Scheme 4).

Table 2 Conversion of **3** into isoflavones **4** and benzofuran **5**

Entry	R^1	$BF_3{\cdot}Et_2O$ (Equiv.)	Me_2S (Equiv.)	Yield (%) **4**	**5**
1	H	20	55	58	—
2	Br	20	55	52	19
3	Br	3	7.5	35	4
4	Br	3	3	61	—



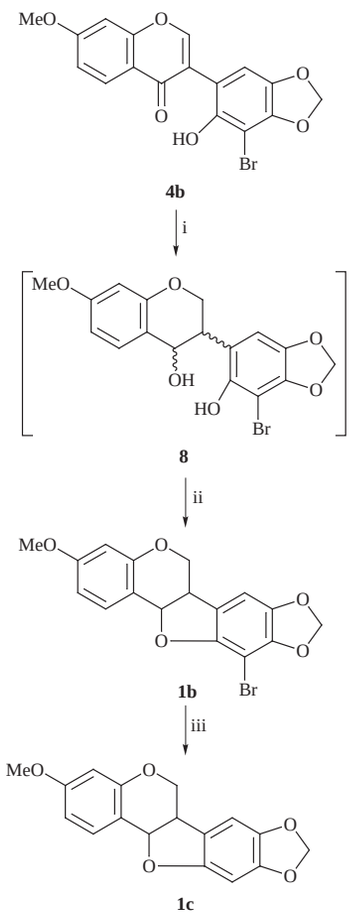
Scheme 2 *Reagents and conditions*: i, $BF_3{\cdot}Et_2O$, Me_2S in CH_2Cl_2, rt



Scheme 3 *Reagents and conditions*: i, 1) PtO_2, H_2, acetone, 2) conc. HCl, MeOH, 68%; ii, 10% Pd–C, $HCOONH_4$, MeOH, reflux, 10 h, 76%

Experimental

Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. The ^1H NMR spectra were determined on a JEOL JNM-GSX 270 spectrometer using tetramethylsilane as an internal standard and $CDCl_3$ as solvent. The IR spectra were recorded with a JASCO FT/IR-7000 spectrophotometer. The high-resolution MS were recorded on a JEOL JMS-HX100 spectrometer. Column chromatography was performed on E. Merck silica gel 60 (70–230 mesh or 230–400 mesh). Tetrahydrofuran (THF) was distilled from sodium and benzophenone prior to use. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride prior to use.



Scheme 4 *Reagents and conditions*: i, $NaBH_4$, EtOH–THF; ii, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 40%; iii, 10% Pd–C, $HCOONH_4$, MeOH, reflux, 10 h, 81%

2-Benzyloxy-3-bromo-4,5-methylenedioxybenzaldehyde

To a mixture of 2-benzoyl-4,5-methylenedioxybenzaldehyde[14] (2.05 g, 8 mmol) and pyridinium hydrobromide perbromide (5.12 g, 16 mmol) in CH_2Cl_2 (20 cm^3) was added trifluoroacetic acid (3.1 cm^3, 40 mmol) and the mixture was stirred for 1 day at room temperature. The reaction mixture was diluted with CH_2Cl_2 (120 cm^3), washed with water, and dried over Na_2SO_4, then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane–AcOEt = 10 : 1) to yield 3-bromo-2-hydroxy-4,5-methylenedioxybenzaldehyde (1.44 g, 74%).

A mixture of 3-bromo-2-hydroxy-4,5-methylenedioxybenzaldehyde (0.98 g, 4 mmol), benzyl chloride (0.25 cm^3, 4.4 mmol), Adgen 464 (Aldrich®) (0.3 cm^3) in 10% KOH (6.4 cm^3) and CH_2Cl_2 (4 cm^3) was stirred for 1 day at room temperature. The mixture was diluted with CH_2Cl_2 (80 cm^3), washed with water, and dried over Na_2SO_4, then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane–AcOEt = 10 : 1) to yield 2-benzyloxy-3-bromo-4,5-methylenedioxybenzaldehyde (1.20 g, 90%), mp 120–123 °C (from EtOH) (Found: C, 53.52; H, 3.42. $C_{15}H_{11}O_4Br$ requires C, 53.76; H, 3.31%); ν_{max}(Nujol)/cm^{-1} 1681; δ_H 5.08 (2H, s, CH_2Ph), 6.14 (2H, s, OCH_2O), 7.19 (1H, s, 6-H), 7.34–7.46 (5H, m, ArH), 9.96 (1H, s, CHO).

2,2′-Bis(benzyloxy)-3-bromo-4′-methoxy-4,5-methylenedioxychalcone 2b

A solution of 1-(2-benzyloxy-4-methoxyphenyl)ethanone[9] (1.51 g, 4.5 mmol), 2-benzyloxy-3-bromo-4,5-methylenedioxybenzaldehyde (1.51 g, 4.5 mmol), and sodium (207 mg, 9 mmol) in EtOH (27 cm^3) was refluxed for 1 h. The mixture was acidified with 2 M HCl and extracted with CH_2Cl_2. The organic extracts were washed with water, dried over Na_2SO_4 and con-

centrated. The residue was purified by column chromatography (*n*-hexane–AcOEt = 10 : 1) to afford 2,2′-bis(benzyloxy)-3-bromo-4′-methoxy-4,5-methylenedioxychalcone **2b** (2.15 g, 83%), mp 129–130 °C (from EtOH) (Found: C, 64.70; H, 4.47. $C_{31}H_{25}O_6Br$ requires C, 64.93; H, 4.39%); ν_{max}(Nujol)/cm^{-1} 1643; δ_H 3.87 (3H, s, OMe), 4.83 (2H, s, CH_2), 5.08 (2H, s, CH_2), 6.08 (2H, s, OCH_2O), 6.56 (1H, d, *J* 2, 3′-H), 6.59 (1H, dd, *J* 9 and 2, 5′-H), 6.63 (1H, s, 6-H), 7.28–7.50 (11H, m, COC*H*=CH and ArH), 7.81 (1H, d, *J* 9, 6′-H), 7.91 (1H, d, *J* 16, COCH=C*H*).

1-(2-Benzyloxy-4-methoxyphenyl)-2-(2-benzyloxy-4,5-methylenedioxyphenyl)-3,3-dimethoxypropan-1-one 3a

A suspension of 2,2′-bis(benzyloxy)-4′-methoxy-4,5-methylenedioxychalcone **2a**[3] (45 mg, 0.1 mmol), PIFA (52 mg, 0.12 mmol), and zinc chloride in THF solution (2 M; 40 μl, 0.02 mmol) in MeOH (6 cm^3) was stirred for 2 weeks at room temperature. The reaction mixture was neutralized with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined extracts were washed with water and dried over Na_2SO_4, then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (CH_2Cl_2–AcOEt = 200 : 1) to give **2a** (21 mg, 42%) and 1-(2-benzyloxy-4-methoxyphenyl)-2-(2-benzyloxy-4,5-methylenedioxyphenyl)-3,3-dimethoxypropan-1-one **3a**[3] (4 mg, 7%) as an oil; ν_{max}(Nujol)/cm^{-1} 1670; δ_H 3.13 (1H, s, OMe), 3.38 (1H, s, OMe), 3.74 (3H, s, OMe), 4.80 (1H, d, *J* 12, PhC*H*H), 4.88 (1H, d, *J* 12, PhC*H*H), 4.92 (1H, d, *J* 12, PhCH*H*), 4.96 (1H, d, *J* 12, PhCH*H*), 5.13 (1H, d, *J* 8, COCH), 5.63 [1H, d, *J* 8, C*H*(OMe)$_2$], 5.85 (1H, d, *J* 1.5, OC*H*HO), 5.87 (1H, d, *J* 1.5, OCH*H*O), 6.31–6.38 (2H, m, 3″-H and 5″-H), 6.44 (1H, s, 3′-H), 6.99 (1H, s, 6′-H), 7.22–7.33 (10H, m, ArH), 7.60 (1H, d, *J* 8, 6″-H).

2-(2-Benzyloxy-3-bromo-4,5-methylenedioxyphenyl)-1-(2-benzyloxy-4-methoxyphenyl)-3,3-dimethoxypropan-1-one 3b

A suspension of 2,2′-bis(benzyloxy)-3-bromo-4′-methoxy-4,5-methylenedioxychalcone **2b** (688 mg, 1.2 mmol), PIFA (619 mg, 1.44 mmol), and trifluoroacetic acid (0.93 cm^3, 1.2 mmol) in MeOH (90 cm^3) was refluxed for 7 h. While the mixture was refluxed, PIFA (619 mg, 1.44 mmol) was added to the mixture at 2 h intervals. Finally, PIFA (619 mg, 1.44 mmol), and trifluoroacetic acid (0.93 cm^3, 1.2 mmol) were added, then the mixture was refluxed for 1 h. The reaction mixture was neutralized with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined extracts were washed with water and dried over Na_2SO_4, then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane–AcOEt = 1 : 2) to give 2-(2-benzyloxy-3-bromo-4,5-methylenedioxyphenyl)-1-(2-benzyloxy-4-methoxyphenyl)-3,3-dimethoxypropan-1-one **3b** (422 mg, 56%), mp 127 °C (from *n*-hexane–AcOEt) (Found: C, 62.37; H, 4.98. $C_{33}H_{31}O_8Br$ requires C, 62.37; H, 4.92%); ν_{max}(Nujol)/cm^{-1} 1669; δ_H 3.17 (1H, s, OMe), 3.36 (1H, s, OMe), 3.73 (3H, s, OMe), 4.69 (1H, d, *J* 11, PhC*H*H), 4.82 (1H, d, *J* 12.5, PhC*H*H), 4.91 (1H, d, *J* 12.5, PhCH*H*), 4.98 (1H, d, *J* 11, PhCH*H*), 5.06 (1H, d, *J* 8, COCH), 5.63 [1H, d, *J* 8, C*H*(OMe)$_2$], 5.99 (1H, d, *J* 1.5, OC*H*HO), 6.01 (1H, d, *J* 1.5, OCH*H*O), 6.31 (1H, d, *J* 2, 3″-H), 6.40 (1H, dd, *J* 9 and 2, 5″-H), 6.44 (1H, s, 3′-H), 6.97 (1H, s, 6′-H), 7.17–7.48 (10H, m, ArH), 7.63 (1H, d, *J* 9, 6″-H).

General procedure: preparation of isoflavones 4 and benzofuran 5

A solution of 3,3-dimethoxypropan-1-one **3**, Me_2S and BF_3·OEt_2 in CH_2Cl_2 was stirred for 1 day at room temperature. Water was added to the reaction mixture and the mixture was extracted with CH_2Cl_2. The combined extracts were washed with water and dried over Na_2SO_4, then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel ($CHCl_3$) to give isoflavones **4** and benzofuran **5**.

3-(2-Hydroxy-4,5-methylenedioxyphenyl)-7-methoxyisoflavone 4a. Compound **4a** was prepared in 58% yield according to the general procedure from compound **3a** (70 mg, 0.13 mmol), Me_2S (0.44 ml, 6.6 mmol) and BF_3·OEt_2 (0.30 ml, 2.4 mmol) in CH_2Cl_2 (1 cm^3), as a solid, mp 197–199 °C (from MeOH) (lit.,[3] mp 203–204 °C; lit.,[14] mp 197–198 °C), ν_{max}(Nujol)/cm^{-1} 1607; δ_H 3.94 (3H, s, OMe), 5.95 (2H, s, OCH_2O), 6.61 (1H, s, 3′-H or 6′-H), 6.64 (1H, s, 6′-H or 3′-H), 6.92 (1H, d, *J* 2.5, 8-H), 7.07 (1H, dd, *J* 9 and 2.5, 6-H), 8.04 (1H, s, 2-H), 8.26 (1H, d, *J* 9, 5-H), 8.76 (1H, s, OH).

3-(3-Bromo-2-hydroxy-4,5-methylenedioxyphenyl)-7-methoxyisoflavone 4b and 7-bromo-3-(2-hydroxy-4-methoxyphenylcarbonyl)-5,6-methylenedioxybenzofuran 5. Compounds **4b** and **5** were prepared in 52 and 19% yields, respectively, according to the general procedure from compound **3b** (2.54 g, 4.0 mmol), Me_2S (16 ml, 220 mmol) and BF_3·OEt_2 (10 ml, 80 mmol) in CH_2Cl_2 (24 cm^3).

Compound **4b**, mp 216–219 °C (from AcOEt) (Found: C, 52.11; H, 3.00. $C_{17}H_{11}O_6Br$ requires C, 52.20; H, 2.83%); ν_{max}(Nujol)/cm^{-1} 1613; δ_H 3.95 (3H, s, OMe), 6.04 (2H, s, OCH_2O), 6.60 (1H, s, 6′-H), 6.93 (1H, d, *J* 2, 8-H), 7.08 (1H, dd, *J* 9 and 2, 6-H), 8.04 (1H, s, 2-H), 8.26 (1H, d, *J* 9, 5-H), 9.24 (1H, s, OH).

Compound **5**, mp 212–214 °C (from AcOEt) (Found: C, 52.02; H, 2.95. $C_{17}H_{11}O_6Br$ requires C, 52.20; H, 2.83%); ν_{max}(Nujol)/cm^{-1} 1622; δ_H 3.88 (3H, s, OMe), 6.12 (2H, s, OCH_2O), 6.50 (1H, dd, *J* 9 and 2.5, 5′-H), 6.53 (1H, d, *J* 2.5, 3′-H), 7.34 (1H, s, 7-H), 7.76 (1H, d, *J* 9, 6′-H), 8.05 (1H, s, 2-H), 12.50 (1H, s, OH).

10-Bromoanhydropisatin 6

A suspension of **4b** (391 mg, 1.0 mmol) and PtO_2 (60 mg) in acetone (30 cm^3) was stirred for 1 day under hydrogen. The catalyst was removed by filtration through Celite and the filtrate was evaporated off. A suspension of the residue and a few drops of conc. HCl in MeOH (15 cm^3) was refluxed for 2 h. Water was added to the reaction mixture and the mixture was extracted with CH_2Cl_2. The combined extracts were washed with water and dried over Na_2SO_4, then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (CH_2Cl_2–*n*-hexane = 1 : 2) to yield 10-bromo-3-methoxy-8,9-methylenedioxypterocarpene **6** (256 mg, 68%), mp 177–180 °C (from AcOEt) (Found: C, 54.29; H, 3.09. $C_{17}H_{11}O_5Br$ requires C, 54.43; H, 2.96%); δ_H 3.81 (3H, s, OMe), 5.50 (2H, s, 6-H), 6.07 (2H, s, OCH_2O), 6.50 (1H, d, *J* 2, 4-H), 6.55 (1H, dd, *J* 8 and 2, 2-H), 6.68 (1H, s, 7-H), 7.47 (1H, d, *J* 8, 1-H).

Anhydropisatin 7

A suspension of **6** (38 mg, 0.1 mmol), $HCOONH_4$ (38 mg, 0.6 mmol) and 10% Pd–C (8 mg) in MeOH (2 cm^3) was refluxed for 6 h. The catalyst was removed by filtration through Celite and the filtrate was evaporated off. The residue was purified by PLC on silica gel (CH_2Cl_2–*n*-hexane = 1 : 2) to yield 3-methoxy-8,9-methylenedioxypterocarpene **7** (18 mg, 76%), mp 182–183 °C (from EtOH) (lit.,[11] mp 183–185 °C); δ_H 3.81 (3H, s, OMe), 5.52 (2H, s, 6-H), 5.99 (2H, s, OCH_2O), 6.50 (1H, d, *J* 2.5, 4-H), 6.53 (1H, dd, *J* 8 and 2.5, 2-H), 6.73 (1H, s, 7-H or 10-H), 7.02 (1H, s, 10-H or 7-H), 7.37 (1H, d, *J* 8, 1-H).

(±)-10-Bromopterocarpin 1b

A solution of $NaBH_4$ (113 mg, 3 mmol) in EtOH (16 cm^3) was added to a solution of **4b** (117 mg, 0.3 mmol) in THF (16 cm^3) and the mixture was stirred for 2 d. Saturated aqueous NH_4Cl was added to the reaction mixture, which was extracted with CH_2Cl_2. The extracts were washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over Na_2SO_4, and concentrated to give a residue. To the residue in CH_2Cl_2 (30 cm^3) was added BF_3·OEt_2 (0.03 cm^3) in CH_2Cl_2 (20 cm^3) at −78 °C and the mixture was stirred for 2 h. Saturated aqueous

$NaHCO_3$ was added to the reaction mixture, which was extracted with CH_2Cl_2. The extracts were washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over Na_2SO_4, and concentrated to give a residue, which was purified by column chromatography on silica gel (CH_2Cl_2–*n*-hexane = 2:1) to yield (±)-10-bromopterocarpin **1b** (45 mg, 40%), mp 190–191 °C (from $CHCl_3$–MeOH) (Found: C, 54.18; H, 3.67. $C_{17}H_{13}O_5Br$ requires C, 54.13; H, 3.47%); δ_H 3.58 (1H, ddd, *J* 11, 7 and 4.5, 6a-H), 3.71 (1H, t, *J* 11, 6-H), 3.79 (3H, s, OMe), 4.23 (1H, dd, *J* 11 and 4.5, 6-H), 5.59 (1H, d, *J* 7, 11a-H), 5.98 (1H, d, *J* 1.5, OC*H*HO), 6.01 (1H, d, *J* 1.5, OCH*H*O), 6.46 (1H, d, *J* 2.5, 4-H), 6.65 (1H, dd, *J* 8.5 and 2.5, 2-H), 6.67 (1H, s, 7-H), 7.47 (1H, d, *J* 8.5, 1-H) (Found: M, 375.9963. Calc. for $C_{17}H_{13}O_5Br$: *M*, 375.9947).

(±)-Pterocarpin 1c

A suspension of **1b** (33 mg, 0.09 mmol), $HCOONH_4$ (34 mg, 0.54 mmol) and 10% Pd–C (7 mg) in MeOH (2 cm^3) was refluxed for 6 h. The catalyst was removed by filtration through Celite and the filtrate was evaporated off. The residue was purified by recrystallization (EtOH) to yield (±)-pterocarpin **1c** (22 mg, 81%), mp 182–183 °C (from EtOH) (lit.,[13] mp 190–192 °C; lit.,[14] mp 184–185 °C); δ_H($CDCl_3$–CD_3OD = 10:1) 3.45–3.74 (2H, m, 6-H and 6a-H), 3.80 (3H, s, OMe), 4.25 (1H, dd, *J* 11 and 5, 6-H), 5.51 (1H, d, *J* 7, 11a-H), 5.90 (1H, d, *J* 1.5, OC*H*HO), 5.93 (1H, d, *J* 1.5, OCH*H*O), 6.43 (1H, s, 10-H), 6.47 (1H, d, *J* 2.5, 4-H), 6.64 (1H, dd, *J* 8.5 and 2.5, 2-H), 6.76 (1H, s, 7-H), 7.40 (1H, d, *J* 8.5, 1-H) (Found: M, 298.0817. Calc. for $C_{17}H_{14}O_5$: *M*, 298.0841).

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