Asymmetric syntheses of isostegane derivatives using trivalent iodine reagents

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Two asymmetric syntheses of the isostegane derivative (+)-3 are reported, both involving oxidation of a homochiral 2,3-dibenzylbutyrolactone with phenyliodonium bis(trifluoroacetate). Of particular interest is the fact that the oxidative step can be carried out directly on a precursor containing a hemiacetal functional group and leads to the same configuration of the biaryl unit.

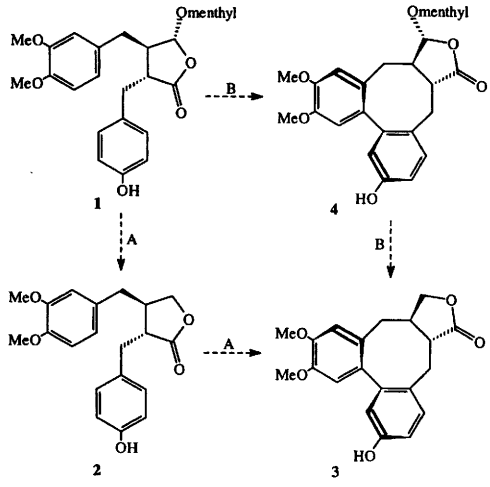
We have previously shown that phenyliodonium diacetate (PIDA) and phenyliodonium bis(trifluoroacetate) (PIFA) can be used to bring about two-electron oxidation of phenols leading to quinone-monoketals and cyclohexa-2,5-dienones.[1,2] We have also shown that in the absence of an external nucleophile these reagents can be used to bring about intramolecular oxidative coupling leading, in the case of 2,3-dibenzylbutyrolactones, to spirodienones and dibenzocyclooctadiene lignans.[3,4] We have now adapted these reactions to provide an asymmetric synthesis of such compounds by starting with the homochiral 2,3-dibenzylbutyrolactone (−)-**1**.[5]

We envisaged two possible routes from **1** to compounds of the dibenzocyclooctadiene series (Scheme 1). The first (route A) would involve removing the menthyloxy group from **1** to give the homochiral 2,3-dibenzylbutyrolactone **2**. We have previously shown that treatment of racemic **2** with PIFA gives the isostegane derivative **3**.[3,4] The second route (route B) would involve treating **1** directly with PIFA which would be expected to give the menthyloxy substituted dibenzocyclooctadiene **4**. Removal of the menthyloxy substituent from **4** would then give the parent dibenzocyclooctadiene **3** (or a stereoisomer).

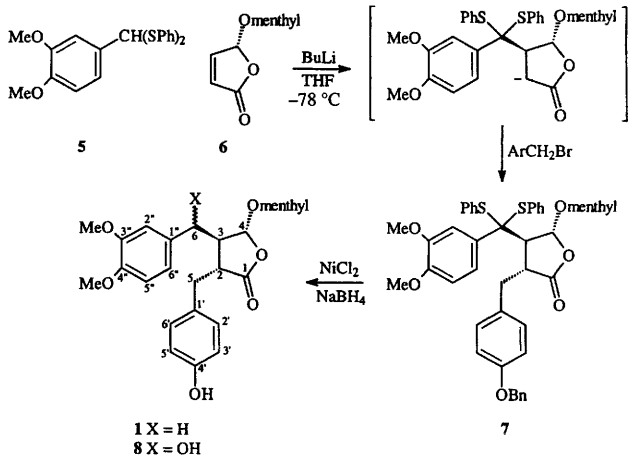
The 2,3-dibenzylbutyrolactone (−)-**1** was prepared using the tandem conjugate addition methodology developed in these and other laboratories.[4–8] Thus, conjugate addition of the lithio derivative of 3,4-dimethoxybenzaldehyde diphenyl dithioacetal **5** to (−)-(4*R*)-4-menthyloxybut-2-enolide **6**,[9–11] followed by *in situ* trapping with 4-benzyloxybenzyl bromide, gave a single adduct (−)-**7** in 61% yield (Scheme 2). The relative stereochemistry at C-2 and C-3 was assigned by analogy with other tandem conjugate addition products,[3–6] and from the lack of coupling between H-2, H-3 and H-4 in the ^{1}H NMR spectrum. Treatment of (−)-**7** with nickel boride[4,6,12,13] gave (−)-**1** in 60% yield, along with 9% of the benzylic alcohol (−)-**8**, which was obtained as a mixture of two epimers. The ^{1}H and ^{13}C NMR spectra of (−)-**7**, (−)-**1** and (−)-**8** are listed in Tables 1 and 2, respectively.

Treatment of (−)-**1** with PIFA in trifluoroethanol (TFE) for 24 hours gave a mixture of products which were purified by chromatography to give the isostegane derivatives (+)-**4** and (+)-**9** in 44% combined yield, along with minor amounts (5 and 2% respectively) of the stegane isomer (−)-**10** and the trifluoroethoxy derivative **11** (Scheme 3). The intermediate spirodienone **12** was not isolated but HPLC analysis indicated that after 0.5 h an intermediate, for which this is the most likely structure, was the major product present. Such compounds have been isolated and fully characterised in related reactions.[3,4]

The structures of (+)-**4**, (+)-**9** and (−)-**10** were based on an analysis of their ^{1}H and ^{13}C NMR spectra (Tables 3 and 4) and, in particular, upon comparison with the spectra of similar racemic compounds lacking only the menthyloxy substituent.[3,4,6] Thus, the isostegane derivatives (+)-**4** and (+)-**9**



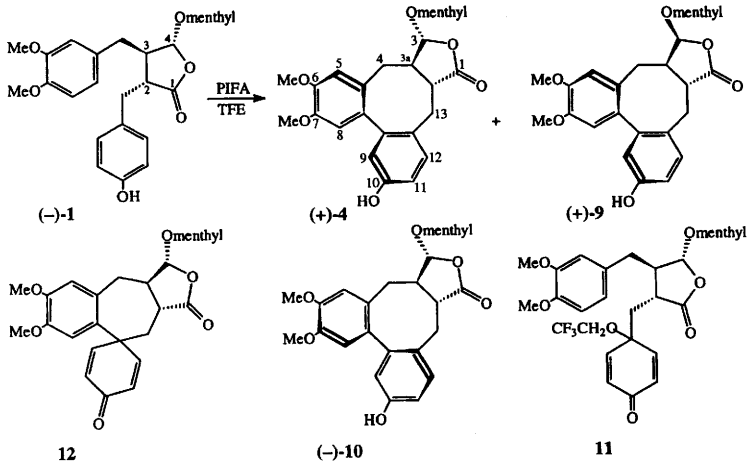
Scheme 1



Scheme 2

showed characteristic signals in their ^{13}C NMR spectra at δ 46.6 and 50.6, and 47.6 and 50.8, respectively, due to C-6 and C-7, while (−)-**10** had corresponding signals at δ 41.9 and 47.5, characteristic of the stegane series.[3,4,14,15] That **4** and **9** only differed in their configuration at C-3 was evident from their ^{1}H NMR spectra, which differed only in that they contained doublets at δ 5.51 (J 4.70 Hz) and 5.23 (J 8.15 Hz) respectively.

It is assumed that epimerisation at C-3 is brought about by trifluoroacetic acid formed during the reaction. It is of interest to note that both (+)-**4** and (+)-**9** arise from an aryl migration from the spirodienone **12**, in line with our previous experience using related compounds.[3,4]



Scheme 3

Table 1 ^{1}H NMR spectra of dibenzylbutyrolactones **7**, **1**, **8**, **11**, **2** and diol **15**[a,b]

	Peak position, multiplicity (*J* values/Hz)[c]					
Proton	**7**	**1**	**8**[d]	**11**	**2**	**15**
H-1	—	—	—	—	—	3.46–3.75m
H-2	3.34m	2.56m	2.41m	2.59m	2.47–2.62m	1.89br s
H-3	3.07br s	2.31m	2.33m	2.32m		
H-4	5.73br s	5.39d (1.4)	5.87s	4.50s	4.11dd (6.5, 9.1)	3.46–3.75m
					3.88m	
H-5	2.94–3.03m	3.01dd (4.8, 13.5)	2.94dd (4.5, 13.5)	2.02m	2.91m	2.63–2.76m
		2.75dd (10.2, 13.5)	2.68dd (11.0, 13.5)	2.19m		
H-6	—	2.71m	4.27d (9.2)	2.67m	2.47–2.62m	
		2.40d (9.5)		2.40d (10.4)		
H-2″	7.11–7.44m	6.32d (1.8)	6.43d (1.5)	6.72–6.84m	6.47d (1.8)	6.63d (1.8)
H-5″	6.80d (8.8)	6.71d (8.1)			6.76d (8.2)	6.76d (8.0)
H-6″	7.06dd (1.9, 8.8)	6.50dd (1.8, 8.1)	6.27–6.29m		6.57dd (1.8, 8.2)	6.68dd (1.8, 8.0)
H-2′/6′	6.96d (8.5)	6.79d (8.5)		6.34dd (1.6, 10.6)	6.97d (8.5)	6.95d (8.4)
H-3′/5′	6.67d (8.5)	6.66d (8.5)		6.28dd (1.6, 10.6)	6.77d (8.5)	6.70d (8.4)
OMe	3.67s	3.73s	3.67s	3.88s	3.79s	3.79s
	3.84s	3.86s	3.85s	3.88s	3.83s	3.83s
OCH_2Ph	5.02s	—	—	—	—	—
OCH_2Ph	7.11–7.44m	—	—	—	—	—
OH	—	6.25s	6.20s	—	6.75s	—
OCH_2CF_3	—	—	—	3.62m	—	—

[a] Samples dissolved in $CDCl_3$. [b] Omenthyl and SPh groups not included. [c] Multiplicities: s = singlet, d = doublet, dd = doublet of doublets, m = multiplet, br = broad. [d] Only major isomer listed.

Table 2 ^{13}C NMR spectra of dibenzylbutyrolactones **7**, **1**, **8**, **2** and diol **15**[a,b,c]

Carbon	**7**	**1**	**8**[d]	**2**	**15**
C-1	177.4	178.4	178.8/178.7	179.6	60.2
C-2	47.9	46.9	47.7	46.5	44.0
C-3	45.6	46.4	42.2/ 44.8	41.1	44.0
C-4	100.1	103.7	101.9/101.9	71.6	60.4
C-5	37.2	35.9	35.9/ 35.1	34.0	35.2
C-6	71.2	37.4	72.7/ 74.3	38.0	35.7
C-1″	130.4	129.6	133.6/133.4	130.5	133.2
C-2″	110.1	111.0	108.5	111.3	111.2
C-3″	148.6	148.8	149.0/149.2	148.9	148.8
C-4″	148.2	147.6	148.5/148.8	147.6	147.2
C-5″	112.7	111.7	110.9/110.4	111.7	112.1
C-6″	120.7	121.2	117.6/119.2	120.7	121.1
C-1′	130.7	129.9	129.4	129.0	131.9
C-2′/6′	130.7	130.0	130.2/130.0	130.4	130.0
C-3′/5′	114.7	115.4	115.2/115.4	115.5	115.3
C-4′	157.6	154.5	154.4/154.5	155.1	154.4
OMe	55.7	55.5	55.6/ 55.5	55.8	55.8
OMe	55.7	55.9	56.0	55.9	55.9

[a] Samples dissolved in $CDCl_3$. [b] OCH_2Ph, Omenthyl and SPh groups not included. [c] Assignments supported by DEPT spectra. [d] Both isomers included.

Treatment of a mixture of (+)-**4** and (+)-**9** with $NaBH_4$ and KOH[4,6] gave as a major product (+)-**3** (37%) in which the menthyloxy group had been removed, along with smaller amounts of the diol (+)-**13** (28%) and the hydroxy acid **14** (22%) (Scheme 4). When compound **14** was left in a desiccator over P_2O_5 it was slowly and quantitatively transformed into the lactone (+)-**3**. Thus the overall yield of (+)-**3** from **4** and **9** was 59%. The structure of (+)-**3** was firmly established by comparison of its ^{1}H and ^{13}C NMR spectra (Tables 3 and 4) with those of the corresponding racemic compound.[3,4]

Finally, treatment of the 2,3-dibenzylbutyrolactone (−)-**1** with $NaBH_4$ and KOH gave as the major product (−)-**2** (43%) along with the diol (+)-**15** (11%). The ^{1}H and ^{13}C NMR spectra of (−)-**2** and (+)-**15** are listed in Tables 1 and 2. Treatment of (−)-**2** with PIFA in TFE gave once again the isostegane (+)-**3**, identified by HPLC comparison with the sample prepared from (+)-**4** and (+)-**9** (Scheme 5).

The methodology described in this paper therefore provides an alternative to the known methods for the synthesis of dibenzocyclooctadienes by oxidative aromatic coupling,[7,8,16,17] and illustrates the application of this methodology to two alternative approaches to the asymmetric synthesis of such compounds.

Table 3 ^{1}H NMR spectra of dibenzocyclooctadiene derivatives[a,b]

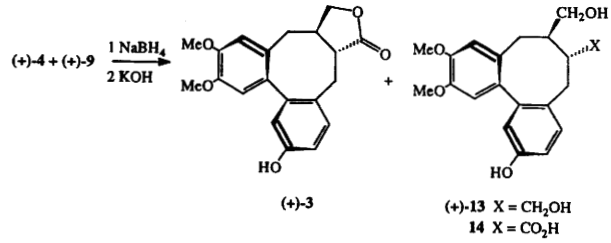
Proton	Peak position, multiplicity (*J* values/Hz)[c]					
	4	**9**	**10**	**3**	**13**[d]	**14**[d]
H-4	2.69d (13.3)	2.77d (12.9)	2.93m	2.64d (13.2)	2.82d (13.3)	2.72d (13.5)
	2.60dd (9.7, 13.3)	2.35dd (9.7, 12.9)	2.83m	2.38dd (9.8, 13.2)	2.04–2.11m	2.15–2.42m
H-3a, H-13a	2.16–2.26m	2.15–2.26m	2.18–2.27m, 2.33–2.41m	2.20m, 2.10dd (9.4, 13.2)	1.53br s	1.96–2.07m
H-13	2.49dd (9.9, 13.6)	2.30m	2.76m	2.26dd (9.4, 13.6)	2.04–2.11m	2.15–2.42m
	3.21d (13.6)	3.23d (12.5)	3.02dd (2.6, 10.9)	3.17d (13.6)	2.83d (13.2)	2.78d (13.4)
H-3	5.51d (4.7)	5.23d (8.1)	5.27d (5.1)	4.39dd (6.7, 8.4)	3.74–3.78m	2.63dd (2.6, 10.2)
				3.77dd (11.2, 8.4)	3.33–3.40m	3.25–3.37m
H-8	6.67s	6.67s	6.70s	6.66s	6.78s	6.76s
H-5	6.68s	6.68s	6.58s	6.66s	6.89s	6.92s
H-12	7.18d (8.3)	7.14d (8.4)	6.73d (6.4)	7.13d (8.3)	7.13d (7.9)	7.18d (8.2)
H-11	6.86dd (2.7, 8.3)	6.83dd (2.8, 8.4)	6.98dd (2.4, 6.4)	6.81dd (2.7, 8.3)	6.73m	6.80dd (2.5, 8.2)
H-9	6.70d (2.7)	6.67d (2.8)	6.74d (2.4)	6.68d (2.7)		6.73d (2.5)
OMe	3.84s	3.84s	3.84s	3.90s	3.82s	3.82s
	3.95s	3.94s	3.94s	3.81s	3.82s	3.85s
OH	5.92s	5.99s	4.99s	6.06br s	3.04s	5.57s
H-1	—	—	—	—	3.74–3.78m	—
					3.33–3.40m	

[a] Samples dissolved in $CDCl_3$, except where indicated. [b] Omenthyl signals not listed. [c] For multiplicities, see Table 1 footnote (*c*). [d] Sample dissolved in [$^2H_6$]acetone.

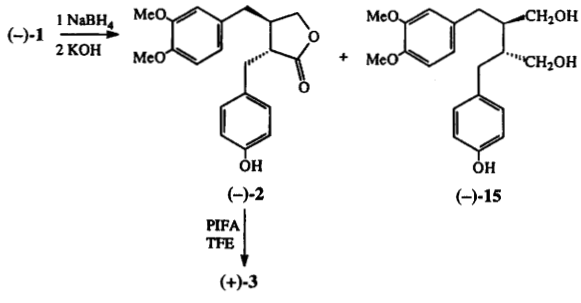
Table 4 ^{13}C NMR spectra of dibenzocyclooctadiene derivatives[a,b,c]

Carbon	**4**	**9**	**10**	**3**	**13**[d]	**14**[d]
C-1	177.2	174.3	178.7	177.2	66.6	177.4
C-3	104.8	103.1	104.3	70.2	66.6	66.2
C-3a	46.6	46.5	41.9	46.7	45.2	45.8
C-4	34.1	34.2	32.3	34.1	35.6	35.1
C-4a	132.5	132.4	132.6	131.8	133.8	133.2
C-5	114.1	113.9	114.0	114.0	113.7	113.5
C-6	148.7	148.7	147.8	148.7	149.8	149.9
C-7	147.1	147.1	147.1	147.1	148.2	148.2
C-8	112.2	112.4	113.8	112.0	112.6	112.7
C-8a	131.9	131.7	129.2	132.4	134.5	133.9
C-8b	131.0	130.5	129.1	130.5	133.5	131.1
C-9	115.3	115.3	114.4	115.4	115.2	115.4
C-10	154.3	154.3	154.5	154.3	155.9	156.3
C-11	117.5	117.6	117.0	117.7	115.5	115.7
C-12	130.5	130.3	130.4	130.4	131.0	131.0
C-12a	141.8	141.8	144.1	141.8	142.4	142.5
C-13	33.4	32.8	34.2	31.4	35.2	33.7
C-13a	50.6	50.8	42.5	50.5	45.8	49.7
OMe	56.0	56.0	55.9	56.0	56.1	56.0
	56.1	55.1	55.9	56.0	56.2	56.0

[a] Samples dissolved in $CDCl_3$ unless otherwise indicated. [b] Omenthyl signals not listed. [c] All assignments are consistent with DEPT spectra. [d] Samples dissolved in [$^2H_6$]acetone.



Scheme 4



Scheme 5

Experimental

IR spectra were recorded on a Pye Unicam SP1050 spectrometer. UV spectra were recorded on a Philips PU8720 scanning spectrometer. ^{1}H NMR spectra were recorded on a Bruker 250WM spectrometer at 250 MHz. The high field spectra were recorded using a Bruker AC 400 spectrometer at 400 MHz. ^{13}C NMR spectra were recorded on a Bruker 250WM spectrometer at 62.9 MHz. All NMR spectra used tetramethylsilane as the internal standard, and were run in deuteriated chloroform, unless otherwise stated. The mass spectra were recorded on a VG-12-250 low resolution quadruple mass spectrometer, whilst accurate mass measurements were obtained from a ZAB-E, high resolution, double focussing mass spectrometer. Melting points were recorded on an Electrothermal digital melting point apparatus, and are uncorrected.

Analytical HPLC work was carried out on a Milton Roy instrument, consisting of a 3100 SpectroMonitor, 3000 ConstaMetric pump, and CI-4100 integrator, and used an Apex II ODS 5 μm column. Thin layer chromatography (TLC) was carried out on Merck 5735 Kieselgel 60 F_{254} fluorescent plates. Flash chromatography was performed with silica gel (Merck 9385, Kieselgel 60, 230–400 mesh) or neutral alumina. Small scale purifications were conducted on a Chromatotron 7924 using 1 mm, 2 mm or 4 mm plates prepared from silica gel (Merck 7749, Kieselgel 50 F_{254} gipshaltig).

Reactions carried out under an inert atmosphere refer to the use of argon or 'white spot' nitrogen used directly from the cylinder. Tetrahydrofuran (THF) was dried by being stirred overnight over calcium hydride, passed down a dry alumina column, and then distilled from sodium wire and benzophenone. Dichloromethane was dried by passing down a dry alumina column and then distilled from calcium hydride. Methanol and ethanol were dried by treatment with magnesium activated with iodine followed by heating under reflux and distillation. Solutions of butyllithium in hexane were obtained from Aldrich and were regularly estimated.[18,19] Low temperature baths were prepared by making a slurry of solid carbon dioxide with acetone (−78 °C) or using a mixture of solid carbon dioxide with acetone monitored using a digital temperature probe (−25

to −30 °C). All other reagents were purified by distillation under nitrogen prior to use, the pressure being reduced if the boiling point of the compound was > 110 °C at atmospheric pressure.

Preparation of (−)-(2*R*,3*R*,4*R*)-2-(4′-benzyloxybenzyl)-3-{3″,4″-dimethoxyphenyl[bis(phenylsulfanyl)]methyl}-4-(menthyloxy)butyrolactone 7

The diphenyldithioacetal **5**[20] (3.00 g, 8.15 mmol) was dissolved in dry THF (50 ml), under an argon atmosphere, and cooled to −78 °C. To this stirred solution was added, *via* syringe, BuLi (2.94 mol l^{-1}; 3 ml, 8.8 mmol, 1.08 mol equiv.) and stirring was continued at −78 °C for 2.5 h. After this time, pre-cooled (−)-4-menthyloxybut-2-enolide **6**[6] (2.6 g, 10.92 mmol, 1.34 mol equiv.), dissolved in dry THF (16 ml), was added *via* a double-ended needle. Stirring was continued at −78 °C for 2.5 h before pre-cooled 1,3-dimethylimidazolidin-2-one (DMI) (1 ml, 1.04 g, 9.11 mmol, 1.12 mol equiv.) was added *via* syringe, immediately followed by pre-cooled 4-benzyloxybenzyl bromide[21] (2.5 g, 9.03 mmol, 1.11 mol equiv.) dissolved in dry THF (11 ml), which was added *via* a double-ended needle. The mixture was stirred, and allowed to warm to room temperature overnight, before adding water (60 ml) and extracting with EtOAc (3 × 100 ml). The combined organic extracts were washed with aqueous NaCl (3 × 50 ml), dried ($MgSO_4$), filtered and evaporated, yielding a thick reddish oil. Purification by flash chromatography on silica and elution with light petroleum (bp 60–80 °C)–CH_2Cl_2 (85:15) afforded (−)-**7** as a white foam (3.97 g, 60.7%), mp 50–55 °C, $[\alpha]_D^{22}$ −103.38 (*c* 0.207, $CHCl_3$) (Found: C, 73.5; H, 7.3. $C_{49}H_{54}O_6S_2$ requires C, 73.32; H, 6.73%); ν_{max}(film)/cm^{-1} 1779 (γ-lactone); see Tables 1 and 2 for ^1H and ^{13}C NMR data; *m*/*z* (EI) 584 (M − 2SPh, 83%), 151 ($Ar^1CH_2^+$, 10%), 91 ($PhCH_2^+$, 100%); *m*/*z* (CI) 693 (M − SPh, 3%), 585 (M + H − 2SPh, 10%), 259 (Ar^1CHSPh^+, 100%) [Found (HRMS): $(M - 2SPh)^+$, 584.3138. $C_{37}H_{44}O_6$ requires $(M - 2SPh)^+$, 584.3138].

Preparation of (−)-(2*R*,3*R*,4*R*)-2-(4′-hydroxybenzyl)-3-(3″,4″-dimethoxybenzyl)-4-(menthyloxy)butyrolactone 1 and (−)-(2*R*,3*S*,4*R*)-2-(4′-hydroxybenzyl)-3-[3″,4″-dimethoxyphenyl(hydroxy)methyl]-4-(menthyloxy)butyrolactone 8

To (−)-**7** (1.14 g, 1.42 mmol), dissolved in MeOH (130 ml) and THF (44 ml) was added $NiCl_2 \cdot 6H_2O$ (96.77 g, 28.48 mmol, 20.06 mol equiv.). The stirred green solution was cooled to 0 °C and $NaBH_4$ (3.23 g, 85.36 mmol, 60.11 mol equiv.) was added carefully, in order to minimize the effervescence produced. The mixture was removed from the ice-bath and stirred for 1 h at room temperature. After this time, water (20 ml) was added and the reaction mixture passed through a short Celite column, in order to remove the nickel salts. Water (100 ml) was added and the resulting solution extracted with $CHCl_3$ (3 × 150 ml). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated to give a colourless gum. Purification by flash chromatography on silica and elution with light petroleum (bp 60–80 °C)–EtOAc (50:50) afforded (−)-**1** as a white crystalline foam (0.43 g, 60%), mp 50–55 °C. $[\alpha]_D^{22}$ −145.8 (*c* 0.402, $CHCl_3$) (Found: C, 72.5; H, 8.2. $C_{30}H_{40}O_6$ requires C, 72.58; H, 8.06%); ν_{max}(film)/cm^{-1} 3420 (OH), 1768 (γ-lactone); λ_{max}(MeOH)/nm 209.5 (ε/l mol^{-1} ml^{-1} 16 850), 227.2 (15 810), 280.3 (5014); see Tables 1 and 2 for ^1H and ^{13}C NMR data; *m*/*z* (EI) 496 (M^+, 4%), 357 (M − menthyl, 7), 251 (31), 151 ($Ar^1CH_2^+$, 92), 107 ($Ar^2CH_2^+$, 100); *m*/*z* (CI) 514 ($M + NH_4^+$, 14%) 497 ($M + H^+$, 13), 358 (M + H − menthyl, 6), 341 (M − Omenthyl, 100) (Found: M^+, 496.2825. $C_{30}H_{40}O_6$ requires *M*, 496.2825).

Further elution with light petroleum (60–80 °C)–EtOAc (65:35) gave (−)-**8** as a white gum (0.66 g, 9%), $[\alpha]_D^{22}$ −115.57 (*c* 0.244, $CHCl_3$); ν_{max}(film)/cm^{-1} 3446 (OH), 1747 (γ-lactone); see Tables 1 and 2 for ^1H and ^{13}C NMR data; *m*/*z* (EI) 512 (M^+, 13%), 356 (M − menthol, 15), 250 (4), 167 (Ar^1CHOH^+, 45), 107 ($Ar^2CH_2^+$, 100); *m*/*z* (CI) 530 ($M + NH_4^+$, 4%), 374 (M + H − menthyl, 25), 357 (M − Omenthyl, 44), 167 (Ar^1CHOH^+, 100) (Found: M^+, 512.2770. $C_{30}H_{40}O_7$ requires *M*, 512.2774).

Preparation of (+)-(3*R*,3a*R*,8a/8b*S*,13a*R*)-10-hydroxy-3-(menthyloxy)-6,7-dimethoxy-3a,4,13,13a-tetrahydro-1*H*,3*H*-dibenzo[4,5:6,7]cycloocta[1,2-*c*]furan-1-one 4 and (+)-(3*S*,3a*R*,8a/8b*S*,13a*R*)-10-hydroxy-3-(menthyloxy)-6,7-dimethoxy-3a,4,13,13a-tetrahydro-1*H*,3*H*-dibenzo[4,5:6,7]-cycloocta[1,2-*c*]furan-1-one 9

To (−)-**1** (0.11 g, 0.22 mmol) dissolved in dry trifluoroethanol (TFE) (2 ml), under an argon atmosphere, was added, phenyliodonium bis(trifluoroacetate) (PIFA) (0.11 g, 0.256 mmol, 1.16 mol equiv.) dissolved in dry TFE (2 ml) *via* syringe. Stirring was continued at room temperature for 24 h, after which time, the reaction mixture was neutralized by addition of powdered $NaHCO_3$, the mixture concentrated *in vacuo*, and the residue dissolved in EtOAc and filtered. The filtrate was evaporated and the residue purified by flash chromatography on silica using light petroleum (bp 60–80 °C)–EtOAc (80:20) which yielded (+)-**4** together with (+)-**9** (0.048 g, 44%) as a white gum. Some (+)-**4** was separated by a second column; $[\alpha]_D^{22}$ +186.9 (*c* 0.312, $CHCl_3$); ν_{max}(film)/cm^{-1} 3436 (OH), 1774 (γ-lactone); λ_{max}(MeOH)/nm 215.6 (ε/l mol^{-1} ml^{-1} 24 790), 280.4 (13 395); see Tables 3 and 4 for ^1H and ^{13}C NMR data; *m*/*z* (EI) 494 (M^+, 29%), 354 (M − H − menthyl, 3), 339 (M − Omenthyl, 3), 312 (17), 282 (6); *m*/*z* (CI) 512 ($M + NH_4^+$, 1%), 495 ($M + H^+$, 14), 374 ($M + NH_4$ + H − menthyl, 100), 311 (3), 283 (4), 156 (7) [Found (HRMS): M^+, 494.2668. $C_{30}H_{38}O_6$ requires *M*, 494.2668]. One fraction contained mainly isomer (+)-**9**; $[\alpha]_D^{22}$ +84.3 (*c* 0.325, $CHCl_3$); ν_{max}(film)/cm^{-1} 3440 (OH), 1768 (γ-lactone), see Tables 3 and 4 for ^1H and ^{13}C NMR data; *m*/*z* (EI) 494 (M^+, 57%), 354 (M − H − menthyl, 5), 339 (M − Omenthyl, 4), 312 (37), 282 (11); *m*/*z* (CI) 512 ($M + NH_4^+$, 1%), 495 ($M + H^+$, 14), 374 ($M + NH_4$ + H − menthyl, 100), 311 (9), 283 (5), 156 (7) [Found (HRMS): M^+, 494.2668. $C_{30}H_{38}O_6$ requires *M*, 494.2668].

Continued elution with light petroleum (60–80 °C)–EtOAc (80:20) gave (−)-(3R,3*a*R,8*a*/8*b*R,13*a*R)-10-*hydroxy*-3-(*menthyloxy*)-6,7-*dimethoxy*-3*a*,4,13,13*a*-*tetrahydro*-1H,3H-*dibenzo*[4,5:6,7]*cycloocta*[1,2-c]*furan*-1-*one* **10** as a white gum (5.5 mg, 5%), $[\alpha]_D^{22}$ −136.1 (*c* 1.00, $CHCl_3$); ν_{max}(film)/cm^{-1} 3440 (OH), 1775 (γ-lactone); see Tables 3 and 4 for ^1H and ^{13}C NMR data; *m*/*z* (EI) 494 (M^+, 100%), 354 (M − H − menthyl, 12), 338 (M − menthol, 10), 282 (18), 255 (84), 242 (77); *m*/*z* (CI) 495 ($M + H^+$, 3%), 374 ($M + NH_4$ + H − menthyl, 100), 357 (M + 2H − menthyl, 73), 339 (M − Omenthyl, 27), 283 (13) [Found (HRMS): M^+, 494.2668. $C_{30}H_{38}O_6$ requires *M*, 494.2668] and 2-{[1′-(2,2,2-*trifluoroethoxy*)-4-*oxocyclohexa*-2′,5′-*dienyl*]*methyl*}-3-(3″,4″-*dimethoxybenzyl*)-4-(*menthyloxy*)*butyrolactone* **11** as a white gum (2.65 mg, 2%); see Table 1 for ^1H NMR data; *m*/*z* (EI) 594 (M^+, 7%), 496 (M − CF_3CHO, 11), 438 (M − menthol, 6), 357 (M − menthyl − CF_3CHO, 6), 339 (M − menthol − CF_3CH_2O, 17), 151 ($Ar^1CH_2^+$, 100); *m*/*z* (CI) 514 ($M + NH_4$ − CF_3CHO, 8%), 497 (M + H − CF_3CHO, 3), 341 (M + H − Omenthyl − CF_3CH_2O, 31), 313 (4), 107 (8) [Found (HRMS): M^+, 594.2804. $C_{32}H_{41}O_7F_3$ requires *M*, 594.2804].

Preparation of (+)-10-hydroxy-6,7-dimethoxy-3a,4,13,13a-tetrahydro-1*H*,3*H*-dibenzo[4,5:6,7]cycloocta[1,2-*c*]furan-1-one 3, (+)-(6*R*,7*R*,1a/12a*S*)-6,7-bishydroxymethyl-11-hydroxy-2,3-dimethoxy-5,6,7,8-tetrahydrodibenzo[*a*,*c*]cyclooctene 13 and (6*R*,7*R*,1a/12a*S*)-6-hydroxymethyl-11-hydroxy-2,3-dimethoxy-5,6,7,8-tetrahydrodibenzo[*a*,*c*]cyclooctene-7-carboxylic acid 14

To a mixture of (+)-**4** and (+)-**9** (0.15 g, 0.30 mmol) dissolved in dry EtOH (5 ml), under an argon atmosphere, was added $NaBH_4$

(0.115 g, 3.04 mmol, 10.13 mol equiv.). KOH in EtOH (0.043 g, 1 ml of 0.75 mol l^{-1}, 0.77 mmol, 2.57 mol equiv.) was then added, *via* a syringe, and stirring continued at room temperature for 5 h. The reaction was quenched by the addition of aqueous HCl until pH = 3.0. An equal volume of water (6 ml) was then added and the mixture extracted with CH_2Cl_2 (3 × 30 ml). The organic extracts were combined and the product was allowed to lactonise. This process was monitored by HPLC and typically took 24 h to reach completion. The reaction mixture was then thoroughly washed with water (3 × 20 ml), dried ($MgSO_4$), and filtered. Purification by flash chromatography on silica using light petroleum (bp 60–80 °C)–EtOAc (60:40) afforded (+)-**3** as a white solid (0.038 g, 37%); $[\alpha]_D^{22}$ +108.8 (*c* 0.25, $CHCl_3$); mp 190–191 °C (lit.,[4] 190–192 °C); ν_{max}(film)/cm^{-1} 3434 (OH), 1752 (γ-lactone); λ_{max}(MeOH)/nm 216.2 nm (ε/l mol^{-1} ml^{-1} 13 520), 230.9 (13 620), 281.1 (6908); see Tables 3 and 4 for ^1H and ^{13}C NMR data; *m/z* (EI) 340 (M^+, 100%), 325 (3), 279 (10), 255 (38); *m/z* (CI) 358 (M + NH_4^+, 100%), 341 (M + H^+, 20%) [Found (HRMS): M^+, 340.1311. $C_{20}H_{20}O_5$ requires *M*, 340.1311].

Further elution with light petroleum (bp 60–80 °C)–EtOAc (10:90) gave (+)-**13** as a white gum (0.029 g, 28%); $[\alpha]_D^{22}$ +63.2 (*c* 0.25, EtOH); ν_{max}(KBr)/cm^{-1} 3441 (OH); λ_{max}(MeOH)/nm 214.4 (ε/l mol^{-1} ml^{-1} 37 460), 283.2 (8504); see Tables 3 and 4 for ^1H and ^{13}C NMR data; *m/z* (EI) 344 (M^+, 100%), 326 (M − H_2O, 6), 314 (M − CH_2O, 2), 295 (M − CH_2OH − H_2O, 12), 268 (10); *m/z* (CI) 362 (M + NH_4^+, 83), 345 (M + H^+, 64), 327 (M + H − H_2O, 100), 283 (3), 269 (6) [Found (HRMS): M^+, 344.1624. $C_{20}H_{24}O_5$ requires *M*, 344.1624] and **14** as a white foam (0.02 g, 22%); see Tables 3 and 4 for ^1H and ^{13}C NMR data.

Preparation of (−)-(2*R*,3*R*)-2-(4′-hydroxybenzyl)-3-(3″,4″-dimethoxybenzyl)butyrolactone 2 and (−)-(2*R*,3*R*)-2-(4′-hydroxybenzyl)-3-(3″,4″-dimethoxybenzyl)butane-1,4-diol 15

To (−)-**1** (0.27 g, 0.544 mmol) dissolved in dry EtOH (10 ml), under an argon atmosphere, was added $NaBH_4$ (0.226 g, 5.97 mmol, 10.97 mol equiv.), *via* a solid addition side arm. KOH in EtOH (2 ml of 0.75 mol l^{-1}, 1.51 mmol, 2.78 mol equiv.) was then added *via* a syringe, and stirring continued at room temperature for 4.5 h. The reaction was quenched by the addition of aqueous HCl until pH = 3.0. An equal volume of water (12 ml) was then added and the solution extracted with CH_2Cl_2 (3 × 40 ml). The organic extracts were combined and the product was allowed to lactonise. This process was monitored by HPLC and typically took 12–24 h to reach completion. The reaction mixture was then thoroughly washed with water (3 × 30 ml), dried ($MgSO_4$), and filtered. Purification by Chromatotron on silica using light petroleum (bp 60–80 °C)–EtOAc (50:50) afforded (−)-**2** as a white solid (0.08 g, 43%); $[\alpha]_D^{22}$ −29.5 (*c* 0.27, $CHCl_3$); mp 148–149 °C (lit.,[4] 148.4–148.8 °C; ν_{max}(film)/cm^{-1} 3422 (OH), 1767 (γ-lactone); λ_{max}(MeOH)/nm 207.4 (ε/l mol^{-1} ml^{-1} 17 970), 227.2 (13 630), 279.7 (4 416); see Tables 1 and 2 for ^1H and ^{13}C NMR data; *m/z* (EI) 342 (M^+, 36%), 178 (10), 151 ($Ar^1CH_2^+$, 100), 107 ($Ar^2CH_2^+$, 73); *m/z* (CI) 360 (M + NH_4^+, 91%), 343 (M + H^+, 100) [Found (HRMS): M^+, 342.1467. $C_{20}H_{22}O_5$ requires *M*, 342.1467). Further elution with light petroleum (bp 60–80 °C)–EtOAc (45:55) gave (−)-**15** as a colourless gum (0.021 g, 11%); $[\alpha]_D^{22}$ −32.14 (*c* 0.14, $CHCl_3$); ν_{max}(film)/cm^{-1} 3281 (OH); see Tables 1 and 2 for ^1H and ^{13}C NMR data; *m/z* (EI) 346 (M^+, 24%), 328 (M − H_2O, 10), 300 (M − CO_2, 1), 151 ($Ar^1CH_2^+$, 100), 137 (Ar^{1+}, 8), 107 ($Ar^2CH_2^+$, 57); *m/z* (CI) 464 (M + NH_4^+, 36%), 347 (M + H^+, 45), 346 (100), 329 (M + H − H_2O, 47), 311 (M + H − $2H_2O$, 31), 297 (M − CH_2OH − H_2O, 3) (Found (HRMS): M^+, 346.1780. $C_{20}H_{26}O_5$ requires *M*, 346.1780).

Preparation of (+)-10-hydroxy-6,7-dimethoxy-3a,4,13,13a-tetrahydro-1*H*,3*H*-dibenzo[4,5:6,7]cycloocta[1,2-*c*]furan-1-one 3

The phenolic dibenzylbutyrolactone (−)-**2** (0.064 g, 0.187 mmol) was dissolved in dry TFE (2 ml) under nitrogen and the solution was stirred. PIFA (0.096 g, 0.22 mmol) dissolved in dry TFE (1 ml) was then added *via* syringe and stirring was continued at room temperature for 24 h. After this time the reaction mixture was neutralised by addition of powdered $NaHCO_3$, the mixture concentrated *in vacuo* and the residue dissolved in EtOAc and filtered. The filtrate was examined by HPLC and shown to contain a single product which by coinjection was identical with (+)-**3** prepared earlier by route B.

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Paper 5/08210B
Received 18*th December* 1995
Accepted 6*th February* 1996