Asymmetric Synthesis of Lignans of the Dibenzylbutanediol and Tetrahydrodibenzocyclooctene Series

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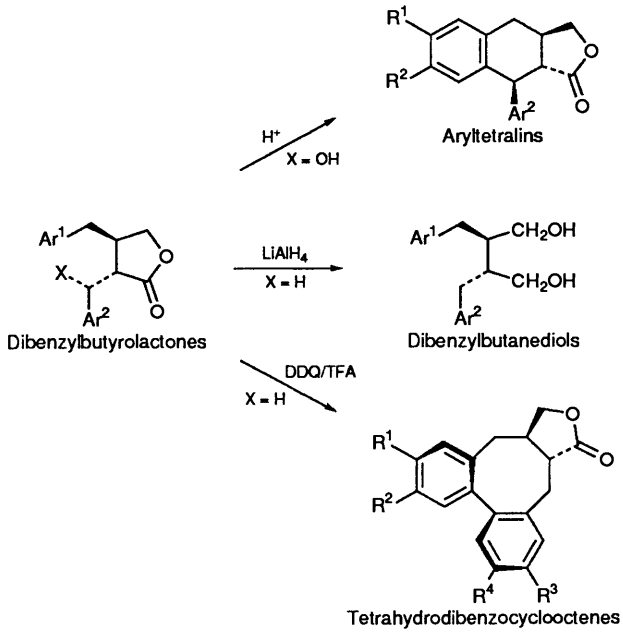
Enolate anions obtained by conjugate addition to (−)-5-(1-menthyloxy)furan-2(5*H*)-one are quenched with benzyl bromides or iodides to yield homochiral dibenzylbutyrolactones. Desulfurisation followed by lithium aluminium hydride reduction affords homochiral 2,3-dibenzylbutane-1,4-diols, including (−)-dimethylsecoisolariciresinol and (−)-dihydroclusin. Desulfurisation followed by reduction with $NaBH_4$/KOH gives the homochiral 2,3-dibenzylbutyrolactones (−)-dimethylmatairesinol, (−)-kusunokinin and (−)-yatein, which undergo stereoselective oxidative coupling with DDQ in trifluoroacetic acid to give homochiral tetrahydrodibenzocyclooctene lignans belonging to the isostegane series.

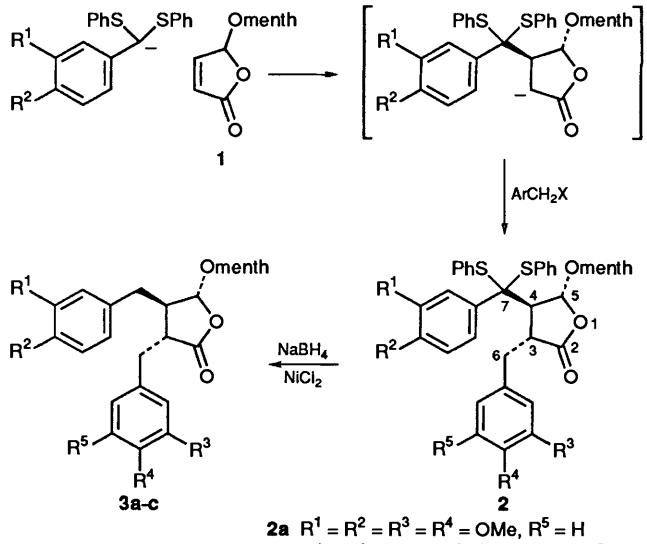
The wide ranging biological activities of lignans makes them prime synthetic targets.[1–4] In particular, there is increasing interest in the asymmetric synthesis of these compounds.[5,6] In the preceding paper we have described the use of (−)-5-(1-menthyloxy)furan-2(5*H*)-one **1** as a chiral synthon for the asymmetric synthesis of lignans belonging to the dibenzylbutyrolactone and aryltetralin series.[7,8] In this paper we report the extension of this strategy in combination with appropriate reduction and oxidative coupling steps, as a route for the asymmetric synthesis of dibenzylbutanediol and tetrahydrodibenzocyclooctene† lignans (Scheme 1).



Scheme 1

Reaction of the anion derived from 3,4-dimethoxybenzaldehyde diphenyl thioacetal or 3,4-methylenedioxybenzaldehyde diphenyl thioacetal with **1**, followed by reaction of the initially formed enolate anions with appropriate benzyl bromides or iodides in the presence of DMI gave the 2,3-dibenzylbutyrolactones **2a–c** in 92, 81 and 100% yields, respectively (Scheme 2).

† Although in earlier work tetrahydrodibenzocyclooctenes have been referred to as dibenzocyclooctadienes, the former name is now preferred, being in accord with the IUPAC rules of nomenclature.



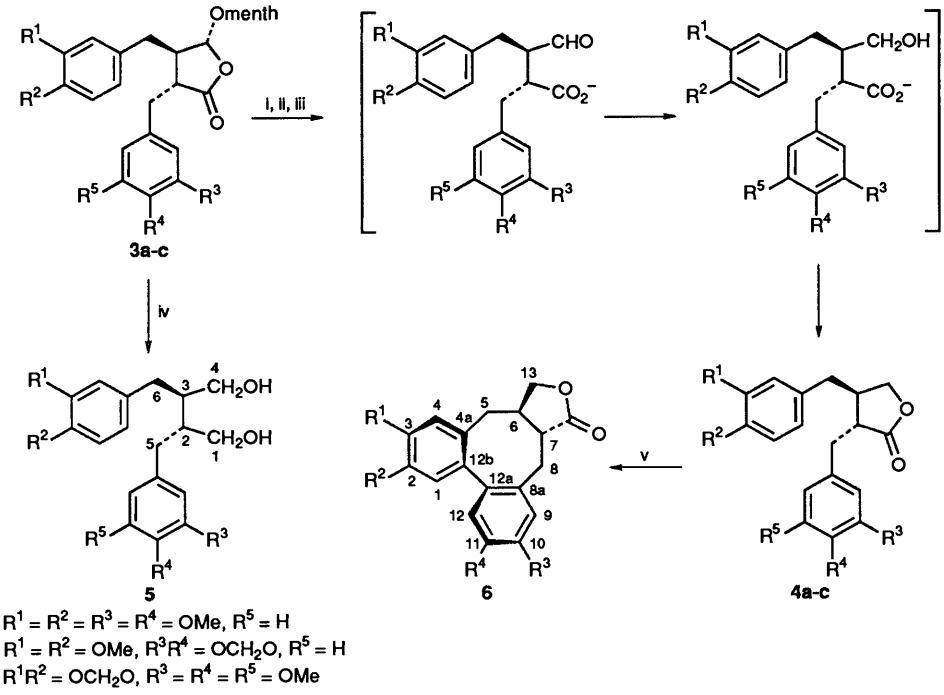
2a $R^1 = R^2 = R^3 = R^4 = OMe$, $R^5 = H$
2b $R^1 = R^2 = OMe$, $R^3R^4 = OCH_2O$, $R^5 = H$
2c $R^1R^2 = OCH_2O$, $R^3 = R^4 = R^5 = OMe$

Scheme 2

In each case only one diastereoisomer of the product was detected.

Desulfurisation of the dibenzylbutyrolactones **2a–c** using $NaBH_4/NiCl_2$[7–9] gave **3a–c** in almost quantitative yield. The ^1H and ^{13}C NMR spectra of **2a–c** and **3a–c** are listed in Tables 1 and 2. The very small coupling constants observed between 4-H and 5-H and between 4-H and 3-H confirm, as expected, that the three substituents are *trans* to one another on the five-membered ring. This is in line with the X-ray analysis of a closely related compound reported in the accompanying paper.[7]

Removal of the menthyloxy group from **3a–c** was again achieved using a combination of $NaBH_4$ and KOH (Scheme 3).[10] However, when this procedure was carried out by first adding KOH in EtOH and then $NaBH_4$ an approximately 1:1 mixture of two diastereoisomeric products was obtained. These were the *cis* and *trans* isomers of **4a–c**, the *cis* isomers being formed by base-catalysed epimerisation of the intermediate aldehydes (Scheme 3). This is in contrast to our previous results with the 6-OH compounds,[7,8] which did not epimerise under the same conditions. Presumably, the 6-OH group was ionised in the basic solution and hence discouraged production of the dianion necessary for epimerisation. When the order of addition



Scheme 3 *Reagents:* i, $NaBH_4$; ii, KOH; iii, H^+, iv, $LiAlH_4$; v, DDQ/TFA

of the reagents was reversed and an excess of $NaBH_4$ was added to **3a–c** followed by dropwise addition of KOH/EtOH, a single diastereoisomer **4a–c** was obtained in each case in 60, 55 and 45% yields, respectively (Scheme 3). The ^1H and ^{13}C NMR spectra of (−)-dimethylmataresinol **4a**,[11] (−)kusunokinin **4b**[12,13] and (−)-yatein **4c**[14] are listed in Tables 1 and 2.

Reduction of **3a–c** with lithium aluminium hydride gave the *threo*-2,3-dibenzylbutane-1,4-diols **5a–c**. The ^1H and ^{13}C NMR spectra of (−)-dimethylsecoisolariciresinol **5a**,[12] **5b**, and (−)-dihydroclusin **5c**[15] are listed in Tables 3 and 4.

We have previously shown that 3,4-dibenzylbutane derivatives undergo oxidative coupling to yield tetrahydrodibenzocyclooctenes on treatment with DDQ in trifluoroacetic acid.[16] Application of this reaction to homochiral **4a** and **4b** gave homochiral dibenzocyclooctene lactones **6a** and **6b** in 56 and 34% yield respectively (Scheme 3). In this case the rigidity of the homochiral *trans*-lactone system has imposed a single chirality on the newly formed diphenyl unit. The ^1H and ^{13}C NMR spectra of **6a** and **6b** are listed in Tables 5 and 6. The zero couplings observed for one of the methylene protons at both C-5 and C-8 to their vicinal neighbours and the positions of C-6 and C-7 in the ^{13}C NMR spectra indicated that the compounds belong to the isostegane series.[17–19] Attempts to carry out the same reaction on **4c** in order to prepare **6c** were unsuccessful.

Experimental

IR spectra were recorded on a Pye Unicam SP1050 spectrometer. UV spectra were recorded on a Philips PU8720 scanning spectrometer. ^1H NMR spectra were recorded on a Bruker 250WM spectrometer at 250 MHz and, where indicated, a Hitachi Perkin-Elmer R24B spectrometer at 60 MHz. The highfield spectra were recorded using Bruker spectrometers at 300, 360 and 400 MHz. ^{13}C NMR spectra were recorded on a Bruker 250WM spectrometer at 62.5 MHz. All 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 quadrupole mass spectrometer, whilst accurate mass measurements were obtained from a ZAB-E high-resolution, double focusing mass spectrometer. M.p.s were recorded on an Electrothermal digital melting point apparatus, and are uncorrected. Optical rotation values, $[\alpha]_D$, were obtained from a Perkin-Elmer 141 polarimeter, using a sodium lamp at 589 nm and are recorded in units of 10^{-1} deg cm^2 g^{-1}.

The analytical HPLC work was carried out on a Milton Roy 3100 Spectromonitor, 3000 constaMetric pump, CI-4100 integrator, and used an Apex II ODS 5 μm column. Preparative HPLC work was carried out on a Gilson 806 manometric module, 305 pump, 115 UV detector, and used a L. Chrosorb BP18 10 μm Knauer preparative column. Thin layer chromatography 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). Small-scale purifications were conducted on a Chromatotron 7924 using 1, 2 or 4 mm plates prepared from silica gel (Merck 7749, Kieselgel 50 F_{254} gipshaltig).

The reactions carried out under an inert atmosphere refer to the use of argon and 'white spot' nitrogen used directly from the cylinder. Tetrahydrofuran was dried by being stirred overnight over calcium hydride, passed down a dry alumina column, and then distilled from sodium wire and benzophenone. Diethyl ether and dichloromethane were dried by passage down a dry alumina column and then distillation from calcium hydride. Dimethylformamide was distilled from calcium hydride, whilst dry toluene and benzene were prepared by distillation from calcium hydride and stored over sodium wire. Solutions of butyllithium in hexane were obtained from Aldrich and were regularly estimated.[20,21] Lithium aluminium hydride was used as a solid, or a solution in dry tetrahydrofuran, estimated as described by Brown.[22]

Preparation of (−)-(3R,4R,5R)-3-(3′,4′-*Dimethoxybenzyl*)-4-[3″,4″-*dimethoxy*-α,α-*bis*(*phenylthio*)*benzyl*]-5-(1-*menthyloxy*)-*butyrolactone* **2a**.—A solution of 3,4-dimethoxybenzaldehyde diphenyl thioacetal (5.06 g, 13.8 mmol) in dry THF (70 cm^3), under argon, was cooled to −78 °C and stirred. To this was added, *via* a syringe, BuLi (2.30 mol dm^{-3}; 6.90 cm^3, 15.9 mmol, 1.15 mol equiv.), and stirring was then continued at −78 °C for 3 h. After this time, pre-cooled (−78 °C) (−)-5-(1-menthyloxy-

Table 1 ^{1}H NMR spectra of dibenzylbutyrolactone derivatives*

	2a	2b	2c	3a	3b
3-H	3.36m	3.32m	3.40m	2.57m	2.53m
4-H	3.06br s	3.04br s	2.87br s	2.37m	2.31m
5-H_A	5.75br s	5.73br s	6.03br s	5.37s	5.38s
5-H_B	—	—	—	—	—
6-H_A	2.95–3.03m (2 H)	2.96–3.01m (2 H)	3.31d (13.6)	2.99dd (4.9, 13.7)	2.96dd (4.1, 13.5)
6-H_B			3.00dd (10.0, 13.6)	2.80dd (9.8, 13.7)	2.70dd (9.6, 13.5)
7-H_A	—	—	—	2.73 dd (4.45, 9.1)	2.72m
7-H_B	—	—	—	2.38d (9.1)	2.32d (9.9)
1-H†	3.41dt (4.0, 10.6)	3.41dt (3.4, 9.8)	3.56dt (3.7, 10.0)	3.49dt (3.9, 10.0)	3.49dt (3.4, 10.0)
OMe	3.85s	3.85s	3.83s	3.85s	3.84s
OMe	3.85s	3.66s	3.83s	3.85s	3.74s
OMe	3.80s	—	3.74s	3.77s	—
OMe	3.68s	—	—	3.77s	—
OCH_2O	—	5.90s (2 H)	5.95d (1.4)	—	5.92s
	—		5.90d (1.4)	—	5.89s
Me	0.90d (6.6)	0.90d (6.5)	0.96d (6.5)	0.90d (7.2)	0.90d (6.6)
Me	0.88d (7.2)	0.89d (7.0)	0.92d (7.1)	0.89m	0.89m
Me	0.71d (6.9)	0.71d (6.9)	0.79d (6.9)	0.79d (6.8)	0.78d (7.0)
				6.61d (8.5)	6.70d (8.0)
				6.59d (7.95)	6.61d (7.7)
Arom	6.6–7.3m	6.5–7.3m	6.4–7.3m	6.43s	6.50d (8.0)
				6.42d (8.0)	6.43d (7.9)
				6.36d (8.35)	6.34s
				6.33s	6.31s

	3c	4a	4b	4c
3-H	2.70m	2.5–2.65m (2 H)	2.45–2.65m (2 H)	2.68m
4-H	2.42m			2.59m
5-H_A	5.39d (1.1)	4.13dd (6.35, 8.8)	4.15dd (6.6, 9.1)	4.23dd (7.2, 8.9)
5-H_B	—	3.89m	3.88m	3.92d (7.2)
6-H_A	3.24dd (5.2, 13.6)	2.95m (2 H)	2.95dd (4.9, 14.05)	3.29dd (5.0, 13.8)
6-H_B	3.05dd (10.0, 13.6)		2.83dd (6.6, 14.05)	3.07dd (8.15, 13.8)
7-H_A	2.70m	2.5–2.65m (2 H)	2.45–2.65m (2 H)	2.68dd (5.0, 12.6)
7-H_B	2.39d (8.0)			2.44dd (8.2, 12.6)
1-H†	3.50dt (4.0, 10.6)	—	—	—
OMe	3.87s	3.86s	3.85s	3.91s
OMe	3.87s	3.86s	3.82s	3.88s
OMe	3.77s	3.84s	—	3.81s
OMe	—	3.82s	—	
OCH_2O	5.92d (1.5)	—	5.92d (1.4)	5.93d (0.75)
	5.90d (1.5)	—	5.91d (1.4)	5.92d (0.75)
Me	0.92d (5.05)	—	—	—
Me	0.89d (5.8)	—	—	—
Me	0.79d (6.9)	—	—	—
	6.59d (7.8)	6.78d (7.9)	6.77d (8.1)	6.66d (8.15)
	6.57s	6.76d (8.05)	6.71d (8.45)	6.64s
Arom	6.44s	6.68s	6.60s	6.64
	6.39dd (1.5, 7.9)	6.66d (8.05)	6.58d (8.8)	6.44d (9.6)
	6.30d (1.5)	6.56dd (1.65, 8.15)	6.57dd (3.4, 8.7)	6.42s
		6.49d (1.5)	6.48d (1.8)	

* All spectra recorded in $CDCl_3$ solution. † 1-H of menthyloxy group.

furan-2(5*H*)-one **1** (3.95 g, 16.6 mmol, 1.21 mol equiv.), dissolved in dry THF (40 cm^3), was added, *via* a double-ended needle, to the well stirred orange solution. Stirring was continued at −78 °C for 2 h and then pre-cooled DMI (5 cm^3) was added to it, *via* a syringe, immediately followed by pre-cooled 3,4-dimethoxybenzyl bromide (4.83 g, 20.9 mmol, 1.52 mol equiv.) dissolved in dry THF (40 cm^3), added *via* a double-ended needle. The reaction mixture was stirred, and allowed to warm to room temperature overnight, before it was diluted with water (100 cm^3) and extracted with EtOAc (3 × 100 cm^3). The combined extracts were washed with brine (3 × 50 cm^3), dried ($MgSO_4$), filtered and evaporated, to yield a yellow foam. Purification of this by flash chromatography on silica (light petroleum–CH_2Cl_2) afforded **2a** as a pale yellow foam (9.60 g, 92%); $[\alpha]_D^{24}$ −156.9 (*c* 0.362, $CHCl_3$) (Found: C, 69.9; H, 6.9. $C_{44}H_{52}O_7S_2$ requires C, 69.84; H, 6.8%); ν_{max}(neat)/cm^{-1} 1780 (γ-lactone); λ_{max}(MeOH)/nm 279.2 (ε 11 283); see Tables 1 and 2 for ^{1}H and ^{13}C NMR data; *m/z* 647 ($M - SPh^+$, 2%), 463 (8), 435 (31), 355 (9), 327 (18), 259 (Ar^1CHSPh^+, 100) and 151 ($Ar^2CH_2^+$, 100).

Preparation of (−)-(3R,4R,5R)-3-(3′,4′-*Methylenedioxybenzyl*)-4-[3″,4″-*dimethoxy*-α,α-*bis*(*phenylthio*)*benzyl*]-5-(1-*menthyloxy*)*butyrolactone* **2b**.—To a stirred and cooled (−78 °C) solution of 3,4-dimethoxybenzaldehyde diphenyl thioacetal (6.31 g, 17.1 mmol) in dry THF (100 cm^3), under an argon atmosphere, was added, *via* a syringe, BuLi (2.30 mol dm^{-3}; 8.57 cm^3, 19.7 mmol, 1.15 mol equiv.), and stirring was then continued at −78 °C for 3 h. A pre-cooled solution of (−)-5-(1-menthyloxy)furan-2(5*H*)-one **1** (4.74 g, 19.9 mmol, 1.16 mol equiv.) in dry THF (50 cm^3) was then added, *via* a double-ended needle, to the well stirred orange solution. Stirring was continued at −78 °C for 2 h before pre-cooled DMI (2.25 cm^3) was added to it, *via* a syringe, immediately followed by pre-cooled solution of 3,4-methylenedioxybenzyl iodide (8.39 g, 32.0 mmol, 1.87 mol equiv.) in dry THF (50 cm^3), added *via* a

Table 2 ^{13}C NMR spectra of dibenzylbutyrolactone derivatives*

Carbon Atom	2a	2b	2c	3a	3b	3c	4a	4b	4c
C-2	177.31s	177.35s	177.15s	177.88s	177.92s	177.79s	178.76s	178.56s	178.41s
C-3	47.81d	47.85d	48.11d	47.80d	47.67d	47.76d	46.49d	46.37d	45.58d
C-4	45.48d	45.60d	43.23d	47.11d	46.82d	46.76d	41.05d	41.20d	41.70d
C-5	99.97d	100.07d	100.54d	103.60d	103.54d	103.48d	71.25t	71.25t	71.40t
C-6	37.55t	37.74t	38.87t	36.29t	36.58t	37.12t	34.43t	34.70t	35.17t
C-7	71.04s	71.25s	70.31s	37.44t	37.49t	37.41t	38.11t	38.17t	38.35t
C-1′1″	132.55s	131.07s	132.68s	130.54s	131.56s	133.01s	130.50s	131.36s	133.07s
	130.58s	130.65s	131.12s	129.83s	129.71s	130.80s	130.19s	130.45s	131.53s
C-2′2″	110.82d	109.95d	107.60d	111.09d	108.89d	109.80d	111.25d	109.44d	109.77d
	109.96d	108.04d	109.16d	111.04d	107.73d	108.80d	111.02d	108.13d	108.60d
C-3′3″4′4″	148.69s	148.68s	152.21s	148.93s	148.88s	152.36s	148.95s	149.00s	152.71s
	148.58s	148.27s	152.21s	148.93s	147.74s	150.77s	148.21s	149.00s	150.80s
	148.10s	147.53s	147.86s	147.80s	147.68s	147.71s	147.85s	146.41s	147.82s
	147.69s	146.30s	147.86s	147.74s	146.15s	146.25s	147.77s	146.41s	146.27s
C-5′5″	112.88d	112.66d	147.36s	112.18d	111.54d	141.92d	112.30d	111.63d	142.08s
	112.73d	110.04d	110.72d	112.18d	110.80d	110.98d	111.78d	111.24d	111.07d
C-6′6″	121.67d	122.83d	122.53d	121.13d	121.98d	122.01d	121.34d	122.24d	121.51d
	120.67d	120.74d	109.16d	121.01d	121.12d	107.92d	120.56d	120.62d	108.13d
OMe	55.59q	55.69q	61.11q	55.84q	55.73q	61.02q	55.87q	55.87q	61.11q
OMe	55.59q	55.69q	60.90q	55.84q	55.49q	60.84q	55.87q	55.72q	60.99q
OMe	55.54q	—	55.99q	55.74q	—	53.93q	55.81q	—	56.05q
OMe	55.54q	—	—	55.67q	—	—	55.81q	—	—
OCH_2O	—	100.81t	101.46t	—	101.01t	101.07t	—	101.01t	101.04t

* All spectra recorded in $CDCl_3$ solution. O-Menthyl and SPh groups are not listed.

Table 3 ^1H NMR spectra of 2,3-dibenzylbutane-1,4-diols*

	5a	5b	5c
1-H	3.48–3.54m	3.57–3.61m	3.42–3.65m
4-H			
2-H	1.87br s	1.92m	1.94br s
3-H			
5-H	2.62–2.84m	2.59–2.68m	2.80–2.94m
6-H			
OMe	3.84s (6 H)	3.79s	3.88s
OMe	3.81s (6 H)	3.76s	3.86s
OMe	—	—	3.86s
OCH_2O	—	5.88d (1.2)	5.90s (2 H)
	—	5.87d (1.2)	
	6.76 d (7.9) (2 H)	6.80d (8.65)	6.69d (7.7) (2 H)
	6.74s	6.79d (1.8)	6.63d (3.0)
Arom	6.66dd (1.7, 8.65) (2 H)	6.77d (8.3) (2 H)	6.63s
	6.65s	6.69d (8.05)	6.60s
		6.68d (1.65)	

* All spectra recorded in $CDCl_3$ solution.

Table 4 ^{13}C NMR spectra of 2,3-dibenzylbutane-1,4-diols*

Carbon atom	5a	5b	5c
C-1	60.22t	60.90t	60.31t
C-2	43.82d	43.42d	44.82d
C-3	43.82d	43.59d	42.19d
C-4	60.22t	60.94t	59.41t
C-5	35.78t	35.22t	36.55t
C-6	35.78t	35.34t	35.85t
C-1′1″	133.15s	135.26s	135.62s
	133.15s	134.29s	134.27s
C-2′2″	110.04d	109.48d	109.27d
	111.04d	108.00d	109.27d
C-3′3″4′4″	148.74s	149.38s	152.26s
	148.74s	148.05s	150.77s
	147.18s	147.70s	147.53s
	147.18s	146.14s	145.68s
C-5′5″	112.12d	112.85d	145.68s
	112.12d	111.94d	110.10d
C-6′6″	121.00d	122.26d	121.86d
	121.00d	121.73d	108.07d
OMe	55.84q	55.71q	61.08q
OMe	55.84q	55.48q	60.93q
OMe	55.79q	—	56.11q
OMe	55.79q	—	—
OCH_2O	—	101.15t	100.78t

* All spectra recorded in $CDCl_3$ solution.

double-ended needle. The reaction mixture was stirred, and allowed to warm to room temperature overnight, before addition of water (100 cm^3) and extraction with EtOAc (3 × 100 cm^3). The combined extracts were washed with brine (3 × 50 cm^3), dried ($MgSO_4$), filtered and evaporated to yield a yellow gum. Purification of this by flash chromatography on silica (light petroleum–CH_2Cl_2) afforded **2b** as a colourless foam (12.69 g, 100%); $[\alpha]_D^{25}$ −162.9 (*c* 0.712, $CHCl_3$) (Found: C, 69.7; H, 6.7. $C_{43}H_{48}O_7S_2$ requires C, 69.73; H, 6.49%); ν_{max}(neat)/cm^{-1} 1785 (γ-lactone); λ_{max}(MeOH)/nm 280.8 (ε 10 250); see Tables 1 and 2 for ^1H and ^{13}C NMR data; *m/z* 631 (M − SPh^+, 10%), 495 (4), 447 (15), 419 (51), 339 (10), 331 (27), 259 (Ar^1CHSPh^+, 100%) and 135 ($Ar^2CH_2^+$, 100%).

Preparation of (−)-(3R,4R,5R)-3-(3′,4′,5′-*Trimethoxybenzyl*)-4-[3″,4″-*methylenedioxy-α,α-bis(phenylthio)benzyl*]-5-(1-*menthyloxy*)*butyrolactone* **2c**.—A solution of 3,4-methylenedioxybenzaldehyde diphenyl thioacetal (4.78 g, 13.6 mmol) in dry THF (70 cm^3), under an argon atmosphere, was cooled to −78 °C, and stirred. To this was added, *via* a syringe, BuLi (2.30 mol dm^{-3}; 6.80 cm^3, 15.6 mmol, 1.15 mol equiv.) and stirring was continued at −78 °C for 3 h. A pre-cooled solution of (−)-5-(1-menthyloxy)furan-5(2*H*)-one **1** (3.91 g, 16.4 mmol, 1.21 mol equiv.) in dry THF (40 cm^3) was added, *via* double-ended needle, to the well stirred orange solution. Stirring was continued at −78 °C for 2 h before pre-cooled DMI (5 cm^3) was added, *via* a syringe, to the mixture immediately followed by a pre-cooled solution of 3,4,5-trimethoxybenzyl bromide (5.67 g, 21.72 mmol, 1.60 mol equiv.), in dry THF (40 cm^3) added, *via* a double-ended needle. The reaction mixture was stirred, and allowed to warm to room temperature overnight, before it was diluted with water (100 cm^3) and extracted with EtOAc (3 × 100 cm^3). The combined extracts were washed with brine (3 × 50 cm^3), dried ($MgSO_4$), filtered and evaporated to yield a yellow foam. This was purified by flash chromatography on silica (light petroleum–CH_2Cl_2) to give **2c**

Table 5 ^{1}H NMR spectra of tetrahydrodibenzocyclooctene derivatives*

	6a	6b
5-H_A	2.42dd (9.4, 13.1)	2.40dd (9.0, 13.2)
5-H_B	2.68d (13.1)	2.65d (13.2)
6-H	2.25m	2.21m
7-H	2.15dd (9.1, 13.0)	2.11dd (9.3, 13.2)
8-H_A	3.18d (13.4)	3.12d (13.8)
8-H_B	2.33dd (9.2, 13.4)	2.28dd (9.3, 13.8)
13-H_A	4.41dd (6.4, 8.4)	4.38dd (6.6, 8.4)
13-H_B	3.80dd (8.4, 10.9)	3.77dd (8.4, 11.4)
OMe	3.94s	3.92s
OMe	3.93s	3.85s
OMe	3.87s	—
OMe	3.87s	—
OCH_2O	—	5.98d (1.2)
	—	5.97d (1.2)
Arom	6.81s	6.78s
	6.70s (2 H)	6.66s
	6.69s	6.66s
		6.65s

* All spectra recorded in $CDCl_3$ solution.

Table 6 ^{13}C NMR spectra of tetrahydrodibenzocyclooctene derivatives*

Carbon atoms	6a	6b
C-1	113.68d	111.94d
C-2	148.38s	147.50s
C-3	148.50s	148.68s
C-4	113.89d	114.06d
C-4a	131.68s	132.21s
C-5	33.90t	34.15t
C-6	46.57d	46.73d
C-7	49.76d	50.05d
C-8	31.84t	32.05t
C-8a	132.09s	133.21s
C-9	111.47d	108.86d
C-10	146.86s	146.03s
C-11	146.94s	147.24s
C-12	111.78d	110.82d
C-12a	132.18s	133.60s
C-12b	130.65s	130.76s
C-13	69.80t	70.06t
C-14	176.46s	176.52s
OMe	55.76q	55.97q
OMe	55.76q	55.97q
OMe	55.76q	—
OMe	55.76q	—
OCH_2O	—	101.22t

* All spectra recorded in $CDCl_3$ solution.

as a white solid (8.43 g, 81%), m.p. 149–151 °C; $[\alpha]_D^{20}$ −179.9 (*c* 2.184, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1785 (γ-lactone); see Tables 1 and 2 for ^{1}H and ^{13}C NMR data; *m/z* 661 (M − SPh^+, 1%), 477 (5), 449 (13), 369 (5), 341 (18), 243 (Ar^1CHSPh^+, 100%) and 181 ($Ar^2CH_2^+$, 100%).

Preparation of (−)-(3R,4R,5R)-3,4-*Bis*(3′,4′-*dimethoxybenzyl*)-5-(1-*menthyloxy*)*butyrolactone* **3a**.—$NiCl_2$·$6H_2O$ (26.57 g, 112 mmol, 17.1 mol equiv.) was added to compound **2a** (4.93 g, 6.52 mmol) dissolved in MeOH (500 cm^3) and the stirred green solution was then cooled to 0 °C and $NaBH_4$ (12.78 g, 336 mmol, 51.6 mol equiv.) was added to it carefully, to minimise the effervescence produced. The black suspension was then removed from the ice-bath and thoroughly stirred at room temperature for 1 h before it was diluted with water (20 cm^3) and passed through a short Celite/silica column, in order to remove the nickel salts. Water (100 cm^3) was added to the resulting solution which was then extracted with diethyl ether (3 × 200 cm^3). The combined extracts were dried ($MgSO_4$), filtered and evaporated to afford **3a** as a colourless foam (3.42 g, 97%); $[\alpha]_D^{21}$ −117.2 (*c* 1.666, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1780 (γ-lactone); see Tables 1 and 2 for ^{1}H and ^{13}C NMR data; *m/z* 540 (M^+, 5%), 402 (10), 385 (16) and 151 ($ArCH_2^+$, 100%) (Found: M^+, 540.3090. $C_{32}H_{44}O_7$ requires M^+, 540.3087).

Preparation of (−)-3R,4R,5R)-3-(3′,4′-*Methylenedioxybenzyl*)-4-(3″,4″-*dimethoxybenzyl*-5-(1-*menthyloxy*)*butyrolactone* **3b**.—$NiCl_2$·$6H_2O$ (20.33 g, 854 mmol, 20.0 mol equiv.) was added to compound **2b** (3.16 g, 4.27 mmol) dissolved in MeOH (200 cm^3) and the stirred green solution was then cooled to 0 °C and $NaBH_4$ (9.74 g, 256 mmol, 60.0 mol equiv.) was added to it carefully, to minimise the effervescence produced. The black suspension was then removed from the ice-bath and thoroughly stirred for 1 h at room temperature before it was diluted with water (20 cm^3) and passed through a short Celite/silica column, in order to remove the nickel salts. Water (75 cm^3) was added to the resulting solution which was then extracted with diethyl ether (4 × 150 cm^3). The combined extracts were dried ($MgSO_4$), filtered and evaporated to afford **3b** as a colourless foam (2.14 g, 99%); $[\alpha]_D^{25}$ −124.2 (*c* 1.282, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1775 (γ-lactone); λ_{max}(MeOH)/nm 283.2; see Tables 1 and 2 for ^{1}H and ^{13}C NMR data; *m/z* 524 (M^+, 10%), 386 (4), 369 (32), 151 ($Ar^1CH_2^+$, 100%) and 135 ($Ar^2CH_2^+$, 51%) (Found: M^+, 524.2774. $C_{31}H_{40}O_7$ requires M^+, 524.2774).

Preparation of (−)-(3R,4R,5R)-3-(3′,4′,5′-*Trimethoxybenzyl*)-4-(3″,4″-*methylenedioxybenzyl*)-5-(1-*menthyloxy*)*butyro lactone* **3c**.—$NiCl_2$·$6H_2O$ (26.83 g, 113 mmol, 17.9 mol equiv.) was added to compound **2c** (4.86 g, 6.31 mmol) dissolved in MeOH/THF (500 cm^3/500 cm^3) and the stirred green solution was cooled to 0 °C and $NaBH_4$ (12.50 g, 319 mmol, 52.1 mol equiv.) was added to it carefully, to minimise the effervescence produced. The black suspension was then removed from the ice-bath, thoroughly stirred for 1 h at room temperature and filtered through a short Celite/silica column to remove nickel salts. The resulting filtrate was diluted with water (200 cm^3) and extracted with diethyl ether (4 × 300 cm^3). The combined extracts were dried ($MgSO_4$)$_4$, filtered and evaporated, to afford **3c** as a colourless foam (3.50 g, 100%); $[\alpha]_D^{20}$ −112.1 (*c* 4.400, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1780 (γ-lactone); see Tables 1 and 2 for ^{1}H and ^{13}C NMR data; *m/z* 554 (M^+, 3%), 415 (8), 399 (32), 355 (8), 181 ($Ar^2CH_2^+$, 34%) and 135 ($Ar^1CH_2^+$, 100%) (Found: M^+, 554.2880. $C_{32}H_{42}O_8$ requires M^+, 554.2880).

Preparation of (−)-*Di*-O-*methylmatairesinol* **4a**.[11]—$NaBH_4$ (0.54 g, 14.2 mmol, 6.28 equiv.) was added, *via* a solid addition side-arm, to a stirred solution of compound **3a** (1.22 g, 2.26 mmol) in EtOH (30 cm^3) under an argon atmosphere, at 0 °C. A solution of KOH in EtOH (0.75 mol dm^{-3}; 7.60 cm^3, 5.70 mmol, 2.52 mol equiv.) was then added to the reaction mixture, *via* a syringe, and the stirring continued for 1 h 40 min at 0 °C. The reaction was quenched by the addition of aqueous HCl to the mixture until pH 3.0; an equal volume of water (37 cm^3) was added to the resulting mixture which was then extracted with CH_2Cl_2 (4 × 30 cm^3). The combined extracts were stored for 24 h until lactonisation was complete (HPLC analysis). The solution was then thoroughly washed with water (3 × 30 cm^3), dried ($MgSO_4$), filtered and purified by chromatography on silica (light petroleum/CH_2Cl_2) using a Chromatotron. This gave **4a** as a colourless foam (0.52 g, 60%); $[\alpha]_D^{18}$ −28.2 (*c* 1.620, $CHCl_3$) (Found: C, 68.2; H, 6.7. $C_{22}H_{26}O_6$ requires C, 68.39; H, 6.74%); ν_{max}(neat)/cm^{-1} 1780 (γ-lactone); λ_{max}(MeOH)/nm 280.0 (ε 12 914); see Tables 1 and 2 for ^{1}H and ^{13}C NMR data; *m/z* 386 ($M^{\cdot+}$, 16%), 236 (100) and 151

($ArCH_2^+$, 100%) (Found: M^+, 386.1730. $C_{22}H_{26}O_6$ requires M^+, 386.1729).

Preparation of (−)-*Kusunokinin* **4b**.[12,13]—$NaBH_4$ (204 mg, 5.36 mmol, 10.31 mol equiv.) was added *via* a solid addition side-arm, to a stirred solution of compound **3b** (272 mg, 0.52 mmol) in EtOH (12.8 cm^3), under an argon atmosphere. A solution of KOH in EtOH (0.76 mol dm^{-3}; 1.52 cm^3, 1.16 mmol, 2.23 mol equiv.) was then added to the mixture, *via* a syringe, and the stirring continued for 30 min. The mixture was than treated with aqueous HCl until pH 3.0, diluted with water (14 cm^3) and extracted with CH_2Cl_2 (3 × 40 cm^3). The combined extracts were stored for 24 h until lactone formation was complete, and then thoroughly washed with water (3 × 30 cm^3), dried ($MgSO_4$), filtered and evaporated. Purification of the residue by chromatography on silica (light petroleum/CH_2Cl_2) using a Chromatotron afforded **4b** as a colourless foam (106 mg, 55%); $[\alpha]_D^{23}$ −36.5 (*c* 0.211, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1780 (γ-lactone); see Tables 1 and 2 for ^1H and ^{13}C NMR data; *m/z* 370 $M^{\cdot+}$, 26%, 151 ($Ar^1CH_2^+$, 69%) and 135 ($Ar^2CH_2^+$, 100%) (Found: M^+, 370.1416. $C_{21}H_{22}O_6$ requires M^+, 370.1416).

Preparation of (−)-*Yatein* **4c**.[14]—$NaBH_4$ (0.38 g, 10 mmol, 6.53 mol equiv.) was added, *via* a solid addition side-arm, to a stirred solution of compound **3c** (0.85 g, 1.53 mmol) in EtOH (20 cm^3), under argon at 0 °C. A solution of KOH in EtOH (0.78 mol dm^{-3}; 3.2 cm^3, 2.50 mmol, 1.63 mol equiv.) was then added to the mixture, *via* a syringe, and stirring continued for 2.3 h at 0 °C. The mixture was then treated with aqueous HCl until pH 3.0, diluted with water and extracted with CH_2Cl_2 (3 × 30 cm^3). The combined extracts were stirred for 24 h until lactone formation was complete and then thoroughly washed with water (3 × 40 cm^3), dried ($MgSO_4$), filtered and evaporated. The product was purified on silica (light petroleum–CH_2Cl_2) using a Chromatotron to give **4c** as a colourless foam (276 mg, 45%); $[\alpha]_D^{18}$ −44.2 (*c* 1.328, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1790 (γ-lactone); λ_{max}(MeOH)/nm 286.2 (ε 9115); see Tables 1 and 2 for ^1H and ^{13}C NMR data; *m/z* 399 ($M - H^+$, 20%), 181 ($Ar^1CH_2^+$, 34%) and 135 ($Ar^2CH_2^+$, 100%) (Found: M^+, 399.1420. $C_{22}H_{24}O_7$ requires M^+, 399.1444).

Preparation of (−)-*Di-O-methylsecoisolariciresinol* **5a**.[12]—$LiAlH_4$ (0.92 g, 24.2 mmol, 9.92 mol equiv.) was added, *via* a solid addition side-arm, to a stirred solution of compound **3a** (1.32 g, 2.44 mmol) in dry THF (40 cm^3), under an argon atmosphere. The reaction mixture was stirred for 3 days, after which it was cooled to 0 °C before careful quenching by the addition of wet THF, until no effervescence was observed. Water (30 cm^3) was added to the mixture which was then extracted with diethyl ether (3 × 50 cm^3). The combined extracts were dried ($MgSO_4$), filtered and evaporated, to yield a white foam, which was purified on silica (CH_2Cl_2/EtOAc) using a Chromatotron to give **5a** as a colourless gum (0.56 g, 59%); $[\alpha]_D^{18}$ −32.2 (*c* 2.350, $CHCl_3$) (Found: C, 67.55; H, 7.7. $C_{22}H_{30}O_6$ requires C, 67.79; H, 7.69%); ν_{max}(neat)/cm^{-1} 3400 (OH); λ_{max}(MeOH)/nm 316.9 (ε 6468); see Tables 3 and 4 for ^1H and ^{13}C NMR data; *m/z* 390 ($M^{\cdot+}$, 5%), 373 (32), 355 (17) and 151 ($ArCH_2^+$, 100%) (Found: M^+, 390.2040. $C_{22}H_{30}O_6$ requires M^+, 390.2042).

Preparation of (−)-(2R,3R)-2-(3′,4′-*Methylenedioxybenzyl*)-3-(3″,4″-*dimethoxybenzyl*)*butanediol* **5b**.—$LiAlH_4$ (0.41 g, 1.07 mmol, 10.0 mol equiv.) was added, *via* a solid addition side-arm, to a stirred solution of **3b** (0.56 g, 1.07 mmol) in dry THF (30 cm^3), under argon. The reaction mixture was stirred for 3 days, after which it was cooled to 0 °C before careful quenching by the addition of wet THF, until no effervescence was observed. Water (40 cm^3) was added to the mixture which was then extracted with diethyl ether (4 × 50 cm^3). The combined extracts were dried ($MgSO_4$), filtered and evaporated, to yield a white foam, which was purified by using a silica plate (CH_2Cl_2/EtOAc) on a Chromatotron to afford **5b** as a colourless gum (188 mg, 44%); $[\alpha]_D^{24}$ −37.0 (*c* 0.900, $CHCl_3$) (Found: C, 67.0; H, 6.75. $C_{21}H_{26}O_6$ requires C, 67.38; H, 6.95%); ν_{max}(neat)/cm^{-1} 3405 (OH); see Tables 3 and 4 for ^1H and ^{13}C NMR data; *m/z* 374 ($M^{\cdot+}$, 18%), 357 (100), 339 (59), 151 ($Ar^1CH_2^+$, 78%) and 135 ($Ar^2CH_2^+$, 48%) (Found: M^+, 374.1729, $C_{21}H_{26}O_6$ requires M^+, 374.1729).

Preparation of (−)-*Dihydroclusin* **9c**.[15]—$LiAlH_4$ (0.81 g, 21 mmol, 10.0 mol equiv.) was added, *via* a solid addition side-arm to a stirred solution of **3c** (1.18 g, 2.13 mmol) in dry THF (40 cm^3). The reaction mixture was stirred for 3 days, after which it was cooled to 0 °C before careful quenching by the addition of wet THF. Water (50 cm^3) was then added to the mixture which was then extracted with diethyl ether (3 × 50 cm^3). The combined extracts were dried ($MgSO_4$), filtered and evaporated, to yield a white foam, which was purified on a Chromatotron using a silica plate (CH_2Cl_2/EtOAc) to give **5c** as a colourless gum (0.53 g, 62%); $[\alpha]_D^{16}$ −30.6 (*c* 2.150, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3400 (OH); see Tables 3 and 4 for ^1H and ^{13}C NMR data; *m/z* 404 ($M^{\cdot+}$, 17%), 387 (21), 369 (3), 181 ($Ar^2CH_2^+$, 58%) and 135 ($Ar^1CH_2^+$, 100%) (Found: M^+, 404.1810. $C_{22}H_{28}O_7$ requires M^+, 404.1835).

Preparation of (+)-5-*Detigloyloxysteganolide C* **6a**.[23]—Freshly distilled TFA (8 cm^3) was added to a mixture of **4a** (241 mg, 0.625 mmol) and DDQ (286 mg, 1.26 mmol, 2.01 mol equiv.), and the purple mixture stirred at room temperature for 2 h. It was then poured onto crushed ice (50 g) and extracted with benzene (3 × 50 cm^3). The combined extracts were washed with aqueous $NaHSO_3$ (3 × 50 cm^3), water (3 × 50 cm^3), aqueous NaOH (3 × 50 cm^3) and brine (3 × 50 cm^3) and then dried ($MgSO_4$), filtered and evaporated, to yield a reddish brown residue (188 mg). This was purified using a Chromatotron with a silica plate (light petroleum–EtOAc) to give **6a**, which was crystallised from diethyl ether to give a white solid (134 mg, 56%), m.p. 211–212 °C (lit.,[24] 212–213 °C); $[\alpha]_D^{22}$ 188.2 (*c* 2.164, $CHCl_3$) (Found: C, 68.9; H, 6.28. $C_{22}H_{24}O_6$ requires C, 68.75; H, 6.25%); ν_{max}(neat)/cm^{-1} 1795 (γ-lactone); λ_{max}(MeOH)/nm 280.7 (ε 22 951); see Tables 5 and 6 for ^1H and ^{13}C NMR data; *m/z* (EI) 384 ($M^{\cdot+}$, 100%) (Found: M^+, 384.1570. $C_{22}H_{24}O_6$ requires M^+, 384.1567).

Preparation of (+)-(6R,7R,12b/12aS)-6-(*Hydroxymethyl*)-2,3-*dimethoxy*-10,11-*methylenedioxy*-5,6,7,8-*tetrahydrodibenzo*-[*a*,*c*]*cyclooctene*-7-*carboxylic Acid Lactone* **6b**.—Freshly distilled TFA (7 cm^3) was added to **4b** (197 mg, 0.521 mmol) and DDQ (242 mg, 1.07 mmol, 2.05 mol equiv.), and the purple mixture stirred at room temperature for 2 h. It was then poured onto crushed ice (50 g) and extracted with benzene (4 × 75 cm^3). The combined organic layers were washed with aqueous $NaHSO_3$ (3 × 30 cm^3), water (3 × 20 cm^3), aqueous NaOH (3 × 30 cm^3), and brine (3 × 30 cm^3), dried ($MgSO_4$), filtered and evaporated, to yield a reddish brown residue (137 mg). This was purified using a Chromatotron with a silica plate (EtOAc/hexane) to give **6b** as a colourless foam (67.1 mg, 34%); $[\alpha]_D^{22}$ 90.3 (*c* 0.824, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1785 (γ-lactone); see Tables 5 and 6 for ^1H and ^{13}C NMR data; *m/z* (EI) 368 ($M^{\cdot+}$, 100%) (Found: M^+, 368.1260. $C_{21}H_{20}O_6$ requires M^+, 368.1260).

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