Pergamon

Tetrahedron, Vol. 52, No. 39, pp. 12799-12814, 1996

0040-4020/96 $15.00 + 0.00

PII: S0040-4020(96)00761-2

Asymmetric Synthesis of a Lignan Lactone from a *Meso* Anhydride

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Abstract: The synthesis of a *meso*-2,3-dibenzylbutanedioic acid anhydride is given. Reaction of this with (+)-α-methylbenzylamine proceeds diastereoselectively to give a butanedioic acid monoamide which is converted into an enantiomerically enriched *cis*-2,3-dibenzylbutyrolactone lignan. Copyright © 1996 Elsevier Science Ltd

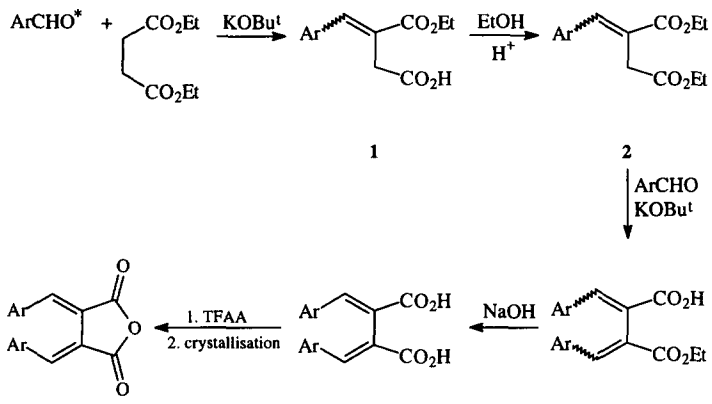
INTRODUCTION

Meso bifunctional compounds are of interest as substrates for asymmetric synthesis since they can be converted stereoselectively into compounds containing at least two chiral centres in 50-100% yield.[1] Such reactions can be brought about using chemical or enzymatic methods,[1,2] and cyclic anhydrides derived from dicarboxylic acids are valuable substrates.[3-13]

We now report the use of this methodology to synthesise a lignan lactone of the *cis*-dibenzylbutyrolactone type.[14] These compounds represent potential precursors for the synthesis of a wide variety of *cis* (and *trans*) disubstituted lignan lactones. Homochiral *trans*-lignan lactones are well known natural products with diverse and important physiological activities.[15,16] However the corresponding homochiral *cis*-lactones have remained unexplored both chemically and physiologically. While several methods for the asymmetric synthesis of *trans*-dibenzylbutyrolactones have been developed,[17,18] *no* methods for the asymmetric synthesis of the *cis*-lactones have been previously reported.

RESULTS

The required *meso*-2,3-dibenzylbutanedioic acid anhydride was prepared from a doubly unsaturated anhydride (**5**) which was prepared by a route involving two consecutive Stobbe condensations starting from diethyl succinate (Scheme 1). Thus, reaction of veratraldehyde with diethyl succinate gave the αβ-unsaturated ester **1** in 98% yield as a 3:1 mixture of the (*E*) and (*Z*) isomers. Esterification of the crude product gave the corresponding diesters **2** in 79% yield. The second Stobbe condensation proceeded in 48% yield to give mainly the (*E,E*) isomer **3**. Saponification of **3** gave the diacid **4** as a yellow crystalline solid in 82% yield, which was converted into the anhydride **5** by refluxing with excess trifluoroacetic anhydride. Compound **5** was obtained as deep red crystals and its structure was confirmed by X-ray crystallography.[19]

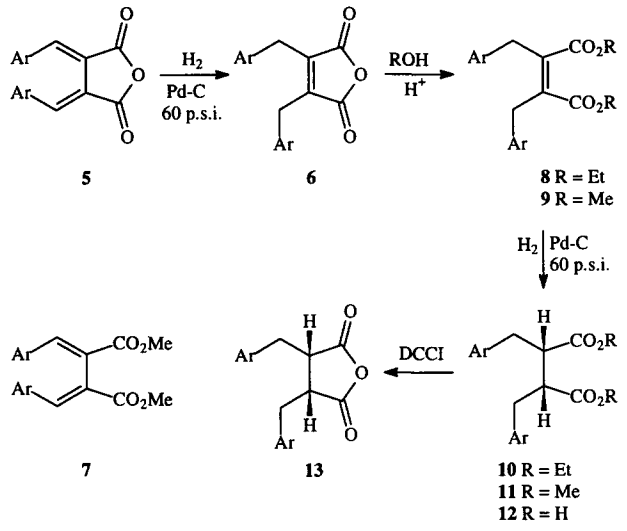


*(Ar = 3,4-dimethoxyphenyl in this and subsequent schemes)

Scheme 1

Hydrogenation of **5** using a 10% palladium on charcoal catalyst at 60 p.s.i. gave the dibenzylmaleic anhydride **6** in 86% yield (Scheme 2). However attempted further hydrogenation of **6** using a wide variety of catalysts and conditions was unsuccessful. Furthermore hydrogenation of the doubly unsaturated diester **7** or the corresponding diacid **4** gave the required 2,3-dibenzylsuccinate **10** and the diacid **12** respectively, but as a mixture with the *d/l* and *meso* isomers in each case. We therefore converted the maleic anhydride **6** into the corresponding diesters **8** and **9** which underwent hydrogenation to give the *meso* diesters **10** and **11** respectively in 90 and 92% yield respectively. The structure of the diester **11** was confirmed by X-ray crystallography.[19] Hydrolysis of **10** required relatively harsh conditions which also induced epimerisation.

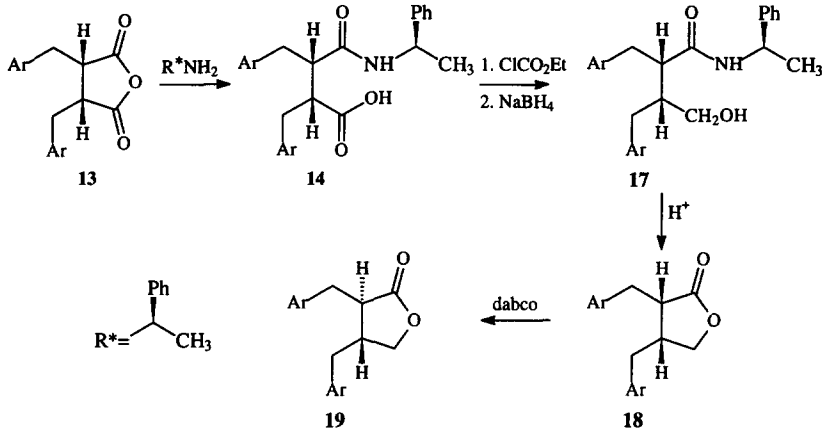
However hydrolysis of **11** using 5M HCl in diglyme gave the required diacid **12**, which was converted into the *meso* anhydride **13** in 62% yield, using DCCI.



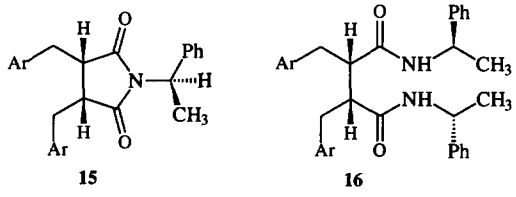
Scheme 2

Reaction of the anhydride **13** with (+)-α-methylbenzylamine gave the acid-amide **(+)-14**, having 86% d.e. (hplc, ^{1}H nmr) , in 62% yield (Scheme 3). In one reaction, in which *ca.*10% DCCI was present, two minor products were obtained, which were identified as the succinimide **(+)-15**(10%) and the diamide **(-)-16**(6%). Reaction of the acid-amide **(+)-14** with ethyl chloroformate followed by reduction with sodium borohydride gave the hydroxy-amide **(+)-17**, having 86% d.e. in 50% yield, which on treatment with hydrochloric acid in glyme gave the *cis*-lactone **(+)-18**, $[\alpha]_D^{21}$ +32.3 (c 1.434 in CH_2Cl_2), in 69% yield.

The absolute configuration of **(+)-18** was established by correlation with (-)-*trans-(2R,3R)*-2,3-dibenzylbutyrolactone **(-)-(19)**, $[\alpha]_D^{21}$ -28.2 (c 1.620 in $CHCl_3$).[17] Thus epimerisation of (+)-**18** with DABCO gave a mixture of **18** and **19** in a 1:1 ratio. The mixture was not separated, but in the ^{13}C nmr subtraction of the peaks due to **18** (Table 2) left a spectrum corresponding exactly to that of our sample of **19**.[17] The 1:1 ratio of the two isomers was established by hplc and fully supported by ^{13}C nmr. The optical rotation of the mixture was *ca.* zero, as would be expected for a 1:1 mixture of (+)-**18** and (-)-**19**, the absolute configuration of which we have previously established.[17] Epimerisation must have occurred α to the lactone carbonyl and therefore the absolute configuration of (+)-**18** is as shown, leading back to structure **14** for the major ring opened product.



Scheme 3



EXPERIMENTAL

^{1}H Nmr spectra were recorded on a Bruker AC 400 spectrometer at 400 MHz or a Bruker 250 WM spectrometer at 250 MHz. ^{13}C Nmr spectra were recorded at 100 MHz or 62.5 MHz respectively. All spectra used tetramethylsilane as the internal standard, and were run in deuterated chloroform, unless otherwise stated. The mass spectra were recorded on a VG-12-250 low resolution quadrupole mass spectrometer, while a ZAB-E, high resolution, double focusing mass spectrometer was used for accurate mass measurements. Optical rotation values were obtained from a Perkin-Elmer 141 polarimeter, using a sodium lamp at 589 nm and values are recorded in units of 10^{-1} deg cm^2g^{-1}. Infra-red spectra were recorded on a Perkin-Elmer Fourier transform 1725X spectrometer and ultra-violet spectra were recorded on a Philips PU8720 scanning spectrometer. Melting points were recorded on an Electrothermal 9100 melting point apparatus, and are uncorrected.

Thin layer chromatography was carried out on Merck 5785 Kieselgel $60F_{254}$ fluorescent plates. Analytical hplc was carried out on a Milton Roy system using a 3100 SpectroMonitor, 3000 ConstaMetric pump and CI-4100 integrator. Reverse phase analysis was performed using a Hichrom 15 cm column with

Table 1. ^1H N.m.r. spectra of unsaturated dicarboxylic acid derivatives[a]

	3	4[b]	5	6	8[b]	9
H-5	7.96 s	7.78 s	7.83 s	3.57 s	3.79 s	3.78 s
H-6	8.00 s					
H-2'/2"		7.22d (1.73)				6.66 d (1.72)
H-5'/5"	6.78-7.18 m	6.93 d (8.47)	6.64-6.46 m	6.66-6.79 m	6.84 - 6.69 m	6.77 d (8.25)
H-6'/6"		7.17 dd (1.73, 8.47)				6.68 dd (1.72, 8.25)
OCH_2CH_3	4.22q (7.05)	------	------	------	4.09 m - 4.01 m	------
OCH_2CH_3	1.14t (7.05)	------	------	------	1.01 t (7.09)	------
OMe	3.74 s					
	3.75 s	3.65 s	3.85 s	3.85 s	3.71 s	3.84 s
	3.85 s	3.74 s	3.54 s	3.78 s	3.69 s	3.81 s
	3.86 s					
CO_2H	9.85 br s	12.49 br s	------	------	------	------

[a] Samples dissolved in $CDCl_3$ unless otherwise indicated
[b] Sample dissolved in d_6-DMSO

Table 2. ^{13}C N.m.r. spectra[a,b]

	3	4[c]	5	6	8[c]	9	10	11	12[c]	13	14[d]	15[d]	16[d]	17[d]	18
C-1	167.1	167.9	166.6	166.0	167.7	168.8	174.4	174.0	174.2	171.9	176.5	178.3	172.1	174.3	178.0
C-2	125.2	127.3	117.6	142.8	129.7	137.5	50.1	50.1	34.8	45.8	48.9	45.5	48.3	48.5	45.4
C-3											49.4		48.6	44.1	40.1
C-4	172.4	167.9	166.6	166.0	167.7	168.8	174.4	174.0	174.2	171.9	173.5	178.3	172.1	62.6	69.5
C-5	142.5	140.3	138.3	29.9	60.6	35.0	36.2	36.2	49.2	31.5	35.5	35.0	36.7	35.3	32.6
C-6	144.1										36.0		36.9	33.7	30.5
C-1'/1"	127.5	126.0	127.0	127.3	137.0	129.4	130.9	130.7	131.3	128.7	131.4	129.4	131.9	132.2	131.1
	127.4										131.1		131.6	132.1	130.9
C-2'/2"	112.0	126.6	112.6	111.9	112.3	111.2	112.0	111.9	120.6	111.6	112.2	112.4	112.1	112.3	112.0
	148.8										112.3		112.2	112.0	111.7
C-3'/3"	150.6	148.2	147.7	148.4	147.7	147.8	147.6	147.7	147.2		147.7		147.8	147.3	147.6
C-4'/4"	150.9	150.0	152.2	149.3	148.8	148.9	148.7	148.7	148.4	148.2	149.0	147.9	147.6	147.5	147.8
										149.1	149.9	148.9	149.0	149.1	149.1
C-5'/5"	110.9	111.5	109.6	111.4	116.6	111.7	111.0	111.0	111.6				148.9	148.9	
	111.0									111.2	111.2	111.1	111.4	111.2	111.4
													111.1	111.3	111.3
C-6'/6"	125.0	126.6	126.3	122.0	120.4	120.5	120.6	120.8	120.6	120.5	120.7	121.3	121.1	121.0	120.8
	124.5										120.9		120.9	120.6	120.4
OCH_2CH_3	61.2	------	------	------	60.4	------	60.5	------	------	------	------	------	------	------	------
OCH_2CH_3	14.1	------	------	------	14.0	------	14.1	------	------	------	------	------	------	------	------
	56.2														
OMe	55.8	55.4	56.0	55.8	55.3	55.8	55.8	51.7	55.4	55.9	55.9		56.1	55.9	
	55.7	55.1	55.4	55.9	55.2	55.7	55.8	55.3			55.8	55.8	56.7	55.8	55.9
											55.7	55.7	56.0	55.7	55.8
CO_2Me	------	------	------	------	------	52.2	------	51.7	------				55.8		
NCH										------	------	------	------	------	------
										------	50.7	49.9	52.8	50.7	------
													52.6		
α-CH										------	21.6	16.5	21.9	21.7	------
													21.4		

[a]Samples dissolved in $CDCl_3$ unless otherwise indicated
[b]All assignments supported by DEPT spectra
[c]Sample dissolved in d_6-DMSO
[d]Ph signals omitted

Table 3. ^1H N.m.r. spectra of butanedioic acid derivatives[a]

	10	11	12[b]	13	14[c]	15[c]	16[c]	17[c]	18
H-2	)				2.52 - 2.49 m	) 2.64 - 2.80 m	2.17 - 2.83	2.59 - 2.52 m	3.01 ddd (4.80, 10.53, 7.07)
H-3	) 3.04 - 2.79 m	3.01 - 3.07 m	2.69 - 2.77 m	3.50 - 3.46 m	2.81 - 2.92 m	)		2.27 - 2.29 m	2.54 - 2.65 m
H-4	----------	----------	----------	----------	----------	----------	----------	3.86 m	3.76 - 3.79 m
H-5	)				) 3.23 - 3.13 m	)		(2.84 dd (13.32,4.07)	3.19 dd (14.90, 4.80)
	) 3.04 - 2.79 m	2.85 dd (9.67, 13.63)	2.69 - 2.77 m	3.07 d (6.62)	)	) 2.64 - 2.80 m	2.17 - 2.83 m	(2.95 dd (13.32, 11.29)	2.72 dd (14.90, 10.53)
H-6	)	2.76 dd (4.08, 13.63)			) 2.80 - 2.70 m	)		2.66 m	(2.89 dd (13.68, 3.69)
									(2.26 dd (13.68, 12.43)
H-2'/2"	)	6.65 d (1.90)	6.71 d (1.73)	6.64 d (1.98)	)			)	
H-5'/5"	) 6.78 - 6.67 m	6.77 d (8.18)	6.83 d (8.18)	6.81 d (8.16)	) 6.79 - 6.62 m	6.37 - 6.64 m	6.54 - 6.83 m	) 6.57 - 6.83 m	6.40 - 6.80 m
H-6'/6"	)	6.67 dd (1.90, 8.18)	6.67 dd (1.73, 8.18)	6.70 dd (1.98, 8.16)	)			)	
OCH_2CH_3	4.03 q (7.11)	----------	----------	----------	----------	----------	----------	----------	----------
OCH_2CH_3	1.12 t (7.11)	----------	----------	----------	----------	----------	----------	----------	----------
OMe	(				(3.84 s		3.90 s	(3.67 s	3.75 s
	(3.85 s	3.84s	3.71 s	3.84 s	(3.81 s	3.77 s	3.88 s	(3.84 s	3.78 s
	(3.84 s	3.85 s	3.70	3.86 s	(3.79 s	3.64 s	3.83 s	(3.87 s	3.81 s
					(3.64 s		3.67 s	(3.88 s	3.82 s
CO_2H	----------	----------	12.39 s	----------		----------	----------	----------	----------
CO_2Me	----------	3.57 s	----------	----------	----------	----------	----------	----------	----------
NCH					4.95 qu (7.31)	5.27 q (7.30)	(5.04 qu (7.34)	4.99 qu (7.38)	----------
							(4.96 qu (7.28)		
NH					5.63 d (7.34)	----------	(5.79 d (8.08)	5.57 d (7.92)	----------
							(5.65 d (8.05)		
α-CH_3					1.34 d (6.91)	1.63 (7.30)	(1.40 d (6.92)	1.36 d (6.92)	----------
							(1.11 d (6.89)		
OH								3.61 s	----------

nucleosil 120-5c18 packing and normal phase analysis was carried out with a 20 cm Hypersil 5μ column. Preparative hplc was carried out on a Gilson instrument comprising a 806 manometric module, 305 pump and 115 UV detector with a Rainin axial compression column packed with Microsorb C18 5μ. Flash chromatography was performed with silica gel (Merck 9385, Kieselgel 60, 230-400 mesh) and reverse phase flash chromatography with Lichroprep (Merck S160RP). Small scale purifications were conducted on a Chromatotron 7924 using 1 mm and 2 mm plates prepared from silica gel (Merck 7749, Kieselgel 50F254 gipshaltig).

Reactions carried out under nitrogen refer to the use of 'white spot' nitrogen which was dried by bubbling through concentrated sulphuric acid and passing through calcium chloride granules. Low temperature baths were prepared by making a slurry of solid carbon dioxide with acetone (-78°C). Diethyl ether and dichloromethane were dried by passing down an alumina column and distilling from calcium hydride. Diethyl ether was stored over sodium wire and shielded from light. *Tert*-butanol was dried by distilling from a small quantity of freshly cut potassium metal. Methanol and ethanol were dried by distillation from the corresponding alcoxide. Toluene was obtained dry by use of a Dean and Stark apparatus to remove water prior to distillation. Ethyl acetate was dried over potassium carbonate and distilled from calcium hydride Tetrahydrofuran was passed down a dry alumina column and distilled from sodium metal and benzophenone. Diethylene glycol dimethyl ether (diglyme) was shaken with Amberlite 1R-120 resin and distilled under reduced pressure using calcium hydride as drying agent. Ethylene glycol dimethyl ether (monoglyme) was distilled at atmospheric pressure from freshly cut sodium metal. Trifluoroacetic anhydride was freshly distilled from phosphorus pentoxide. *N,N*-Dicyclohexylcarbodiimide (DCCI) was purified by vacuum distillation using a Buchi GKR-50 Kugelrohr distillation apparatus.

*Preparation of 2-(3,4-dimethoxybenzylidene)butanedioic acid monoethyl ester(***1***)*

A solution of potassium *t*-butoxide was prepared by adding freshly cut potassium (29.3 g, 0.75 moles) to dry distilled *t*-butanol (436 ml) under a nitrogen atmosphere. The mixture was stirred and heated under reflux until all of the potassium had dissolved (*ca.* 0.5 h). A solution of 3,4-dimethoxybenzaldehyde (83.09 g, 0.5 moles) and diethyl succinate (92 ml, 0.55 moles) in *t*-butanol (250 ml) was slowly added to the refluxing potassium *t*-butoxide solution over 1.5 h and the entire mixture then refluxed for a further 3 h. The crude reaction mixture was treated with aq.HCl until pH2 and the *t*-butanol removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (500 ml) and extracted with aq.$NaHCO_3$ (3 x 500 ml). Acidification of the $NaHCO_3$ extracts using aq.HCl and extraction with CH_2Cl_2 (3 x 200 ml) followed by

evaporation of the dried organic extracts gave the product (**1**) as a yellow/brown solid (144 g, 98%). ν_{max} (CH_2Cl_2) : 3060 cm^{-1} (OH), 1704 cm^{-1} (C = O); λ_{max} (EtOH) : 323 and 237 nm; δ_H ($CDCl_3$) : 1.34t (3H, J = 7.11, OCH_2CH_3), 3.65s (2H, H-3), 3.87s, 3.90s (6H, OMe), 4.29 q (2H, J = 7.11, OCH_2CH_3), 6.84 - 7.02 m (3H, aromatic), 7.87 s (1H, H-5), 10.90 s (1H, CO_2H); δc ($CDCl_3$) : 14.2 (OCH_2CH_3), 33.8 (C-3), 55.9 (OMe), 61.3 (OCH_2CH_3), 111.2 (C-5'), 112.3 (C-2'), 122.7 (C-6'), 123.7 (C-2), 127.5 (C-1'), 142.3 (C-5), 149.0 (C-3'), 150.0 (C-4'), 167.8 (C-1), 177.0 (C-4); *m/z* (e.i.) 294 (M^+, 95%), 250 (M-CO_2, 75%), 176 (Ar CH = CH CH_2^+, 100%); Found : M^+ 294.1103. $C_{15}H_{18}O_6$ requires M^+ 294.1103.

*Preparation of diethyl 2-(3,4-dimethoxybenzylidene)butanedioate(**2**)*

The monoethyl ester **1** (144 g, 0.49) moles) dissolved in a mixture of ethanol (250 ml) and toluene (150 ml) containing conc. H_2SO_4 (12.5 ml) was heated under reflux for 16 h. The azeotrope (*ca.* 30 ml) was removed using a Dean and Stark apparatus, dry toluene (50 ml) was added and heating under reflux continued for a further 18 h. Aq.$NaHCO_3$ (250 ml) was then added and the toluene and ethanol removed under reduced pressure. The residual solution was extracted with CH_2Cl_2 (3 x 150 ml) and the combined extracts dried ($MgSO_4$), filtered and evaporated to give the product as a brown oil (124.9 g, 79%). ν_{max} (neat) : 1728 cm^{-1} (C = O); λ_{max} (EtOAc) 280 and 232 nm; δ_H ($CDCl_3$) : 1.20 t (3H, J = 7.13), 1.27 t (3H, J = 7.13) (OCH_2CH_3), 3.56 s (2H, H-3), 3.78s, 3.81s (6H, OMe), 4.12 q (2H, J = 7.13), 4.21 q (2H, J = 7.13) (OCH_2CH_3), 7.02 m, 7.05 m (3H, aromatic); δc ($CDCl_3$) 13.9 (OCH_2CH_3), 33.3 (C-3), 55.3, 55.4 (OMe), 60.3 (OCH_2CH_3), 111.6 (C-5'), 112.6 (C-2'), 122.3 (C-6'), 123.7 (C-2), 126.8 (C-2'), 140.9 (C-5), 148.5 (C-3'), 149.7 (C-4'), 166.7 (C-1), 170.5 (C-4); *m/z* (e.i.) 322 (M^+, 100%), 277 (M-OEt, 18%), 276 (M-EtOH, 20%), 249 (M-CO_2Et, 25%), 248 (20%), 175 (75%); *m/z* (c.i.) 323 ($M+H^+$, 100%), 277 (M-OEt, 70%); Found : M^+ 322.1416. $C_{17}H_{22}O_6$ requires M^+ 322.1416.

*Preparation of 2,3-*bis*(3,4-dimethoxybenzylidene)butanedioic acid monoethyl ester(**3**)*

A solution of potassium *t*-butoxide was prepared by adding freshly cut potassium (23.5 g, 0.6 moles) to dry distilled *t*-butanol (350 ml). The solution was stirred and heated under reflux until all of the potassium had dissolved. A solution of the diester (**2**) (124.9 g, 0.39 moles) and 3,4-dimethoxybenzaldehyde (74.35 g, 0.43 moles) in *t*-butanol (1060 ml) was added to the refluxing potassium *t*-butoxide solution over a period of 1.5 h, and the entire mixture then heated under reflux for a further 3 h. The crude mixture was acidified to pH2 using aq.HCl and the *t*-butanol removed under reduced pressure. The remaining emulsion was extracted with CH_2Cl_2 (3 x 300 ml). The combined extracts were extracted with aq.$NaHCO_3$ (3 x 250 ml),

the bicarbonate extracts acidified to pH1 using aq.HCl, and the latter aqueous solution then extracted with CH_2Cl_2 (3 x 200 ml). The combined CH_2Cl_2 extracts were washed with brine, dried ($MgSO_4$), filtered and evaporated to yield the product as a brown oil (82.3 g, 48%). ν_{max} (neat) : 1733cm^{-1} (C = O); λ_{max} (EtOH) : 233.9 nm; see Tables 1 and 2 for ^1H and ^{13}C n.m.r. spectral data; *m/z* (e.i.) 442 (M^+, 21%), 151 ($ArCH_2^+$, 100%), 138 (ArH^+, 52%); Found : M^+ 442.1628. $C_{24}H_{26}O_8$ requires M^+442.1628.

*Preparation of 2,3-*bis*(3,4-dimethoxybenzylidene)butanedioic acid(**4**)*

2 M NaOH (200 ml) was added to the monoester (**3**) (82.9 g, 0.19 moles) and the solution heated under reflux for 12 h. The solution was then acidified to pH2 using aq.HCl and the resulting emulsion extracted with CH_2Cl_2 (5 x 100 ml). The combined extracts were dried ($MgSO_4$), filtered and evaporated to give the crude product (76.4 g). Trituration with EtOAc gave a yellow solid which after recrystallisation from CH_2Cl_2 gave the product as a yellow crystalline powder (63.7 g, 82%) m.p. 222-4°C (lit.[20] 217-9°C). ν_{max} ($CHCl_3$) : 3340 cm^{-1} (OH), 1740 cm^{-1} (C = O); for ^1H and ^{13}C n.m.r. spectra see Tables 1 and 2; *m/z* (e.i.) 414 (M^+, 88%), 396 (M-18, 100%) 151 (Ar CH_2^+, 49%), 138 (ArH^+, 75%).

*Preparation of 2,3-*bis*(3,4-dimethoxybenzylidene)butanedioic acid anhydride(**5**)*

TFAA (189 g, 126 ml, 10 equiv.) was added dropwise with stirring to the diacid (**4**) (37.8 g, 0.09 moles) at -78°C under a nitrogen atmosphere. The flask and contents were then allowed to warm to room temperature over 1 h before being heated under reflux for 3 h. Excess TFAA and TFA were removed by distillation, and the crude product recrystallised from EtOAc to give deep red crystals (23.9 g, 67%), m.p. 176 - 7°C (lit.[20] 172-3°C). ν_{max} (KBr): 1840 and 1764 cm^{-1} (C = O); λ_{max} (CH_2Cl_2): 443.4 nm (ε = 18 425); 326 nm (ε = 15 092), 230 nm (ε = 14 138). Found: C, 66.61; H, 5.22. $C_{22}H_{20}O_7$ requires C, 66.67; H, 5.05; see Tables 1 and 2 for ^1H and ^{13}C n.m.r. data; *m/z* (e.i.) 396 (M^+, 28%), 151 ($ArCH_2^+$, 28%), 138 (ArH^+, 100%); Found: M^+ 396.1209. $C_{22}H_{20}O_7$ requires M^+ 396.1209.

*Preparation of 2,3-*bis*(3,4-dimethoxybenzyl)maleic anhydride(**6**)*

The anhydride **5** (10.48 g, 26.5 mmoles) was dissolved in EtOAc (80 ml) and 10% palladium on carbon (1.05 g) was added. The mixture was placed under 60 psi pressure of hydrogen in a Parr hydrogenator and rocked for 32 h. The crude mixture was filtered through celite and the residue washed with EtOAc (2 x 40 ml). The solvent was evaporated to give the crude product (10.11 g) as a yellow semi solid which on recrystallisation from EtOAc yielded fine yellow crystals (9.05 g, 86%), m.p. 112-3°C. ν_{max} (KBr): 1766

cm^{-1} (C = O); λ_{max} (CH_2Cl_2): 233 nm (ε = 17 024); Found: C, 66.37; H, 5.83. $C_{22}H_{22}O_7$ requires C, 66.32; H, 5.57; see Tables 1 and 2 for ^1H and ^{13}C n.m.r. data; *m/z* (e.i.) 398 (M^+, 23%), 151 ($ArCH_2^+$, 75%), 138 (ArH^+, 100%); Found: M^+ 398.1366. $C_{22}H_{22}O_7$ requires M^+ 398.1368.

*Preparation of diethyl 2,3-*bis*(3,4-dimethoxybenzyl)maleate(***8***)*

The maleic anhydride **6** (2.17 g, 5.45 mmoles) was dissolved in ethanol (50 ml) and toluene (30 ml) containing conc.H_2SO_4 (2 ml), and the mixture heated under reflux for 16 h. The azeotrope (*ca.* 30 ml) was removed using a Dean and Stark apparatus and ethanol (30 ml) and toluene (10 ml) added. After a further 16 h under reflux the solution was neutralised with aq.Na_2CO_3 and evaporated to remove most of the organic solvents. The residual material was extracted with CH_2Cl_2 (3 x 50 ml) and the combined organic extracts were re-extracted with aq.$NaHCO_3$ (2 x 50 ml), and brine (50 ml) before being dried ($MgSO_4$), filtered and evaporated to give a red oil (2.27 g, 88%). Recrystallisation from EtOAc/petroleum spirit (30 - 40°C) gave white crystals, m.p. 122 - 3°C. ν_{max} ($CHCl_3$): 1769 cm^{-1} (C = O): λ_{max} ($CHCl_3$): 234.2 nm (ε = 15 796); for ^1H and ^{13}C n.m.r. spectra see Tables 1 and 2; *m/z* (e.i.) 472 (M^+, 21%), 151 ($ArCH_2^+$, 42%); Found: M^+ 472.2097. $C_{26}H_{32}O_8$ requires M^+ 472.2097.

*Preparation of dimethyl 2,3-*bis*(3,4-dimethoxybenzyl)maleate(***9***)*

The maleic anhydride **6** (7.43 g, 18.7 mmoles) was dissolved in methanol (100 ml) and toluene (60 ml) containing conc. H_2SO_4 (5 ml), and the mixture heated under reflux for 16 h. Further methanol (25 ml) and dry toluene (15 ml) were added and the heating continued for a further 16 h. After cooling to room temperature aq.NH_4Cl (40 ml) was added and the mixture extracted with EtOAc (4 x 50 ml). The organic extracts were evaporated to remove methanol and redissolved in EtOAc (40 ml). This solution was washed with aq.$NaHCO_3$ (2 x 50 ml) and brine (50 ml), before being dried ($MgSO_4$), filtered and evaporated to give the product as a white semi-solid which on crystallisation afforded white crystals (6.47 g, 78%),, m.p. 75 - 6°C. ν_{max} (KBr): 1722 cm^{-1} (C = O); λ_{max} (MeOH): 208.9 nm; for ^1H and ^{13}C n.m.r. data see Tables 1 and 2; *m/z* (e.i.) 444 (M^+, 22%), 151 ($ArCH_2^+$, 100%); *m/z* (c.i.) 462 ($M+NH_4^+$, 100%); Found: M^+ 444.1784. $C_{24}H_{28}O_8$ requires M^+ 444.1784.

Preparation of meso*-diethyl 2,3-*bis*(3,4-dimethoxybenzyl)butanedioate(***10***)*

The unsaturated diester **8** (1.46 g, 3.10 mmoles) was dissolved in EtOAc (50 ml) and 10% palladium on carbon (0.14 g) added. The mixture was placed under 60 psi pressure of hydrogen on a Parr hydrogenator

and rocked for 32 h. The resulting mixture was filtered through celite and the residue washed with EtOAc (2 x 40 ml). Evaporation of the combined EtOAc fractions gave the crude product as a white semi solid (1.33 g, 90%) and crystallisation from EtOAc and petroleum spirit (30 - 40°C) (8:2) gave white crystals (0.8 g, 57.5%), m.p. 116 - 7°C. λ_{max} (EtOH): 322 nm (ε 26 272); for ^{1}H and ^{13}C nmr data see Tables 2 and 3; *m/z* (e.i.) 474 (M^+, 59%), 151 ($ArCH_2^+$, 100%); *m/z* (c.i.) 475 (M+1, 100%), 151 ($ArCH_2^+$, 65%); Found: M^+ 474.2254. $C_{26}H_{34}O_8$ requires M^+ 474.2254.

Preparation of meso-*dimethyl 2,3*-bis*(3,4-dimethoxybenzyl)butanedioate*(**11**)

The unsaturated diester **9** (2.31 g, 5.2 mmoles) was dissolved in EtOAc (100 ml) and 10% palladium on carbon (0.23 g) added. The mixture was placed under 60 psi pressure of hydrogen in a Parr hydrogenator and rocked for 18 h. The mixture was then filtered through Celite and the residue washed with EtOAc (2 x 50 ml). The combined filtrate and washings were evaporated to give the crude product as a white crystalline solid which was recrystallised from methanol to give fine white crystals (1.9 g, 92%), m.p. 138-9°C (lit.[20] 143.2-143.7°C). ν_{max} (KBr): 1726 cm^{-1} (C = O); λ_{max} (MeOH): 233.3 nm (ε = 17 938); for ^{1}H and ^{13}C n.m.r. spectra see Tables 2 and 3; *m/z* (e.i.) 446 (M^+, 10%), 151 ($ArCH_2^+$, 100%), 138 (ArH^+, 28%); *m/z* (c.i.) 464 ($M+NH_4^+$, 55%), 447 ($M+H^+$, 65%), 415 (100%); Found: M^+446.1941. $C_{24}H_{30}O_8$ requires M^+ 446.1941.

Preparation of meso-*2,3*-bis*(3,4-dimethoxybenzyl)butanedioic acid*(**12**)

The diester **11** (1.95 g, 4.4 mmoles) was dissolved in diethylene ether glycol dimethyl ether (26 ml) and 5 M HCl (5 ml) added. The solution was heated under reflux for 21 h, when aq.NH_4Cl (10 ml) was added and the mixture extracted with EtOAc (3 x 40 ml). The combined extracts were then extracted with aq.$NaHCO_3$ (3 x 50 ml) and the bicarbonate extracts acidifed to pH2 using aq.HCl. Re-extraction into EtOAc (3 x 50 ml) followed by washing of the extracts with brine, drying ($MgSO_4$), filtration and evaporation gave the crude product which was recrystallised from CH_2Cl_2 to give white crystals (1.13 g, 62%), m.p. 197-8°C (lit.[20] 222-3°C). ν_{max} (KBr): 2962 cm^{-1} (OH), 1700 cm^{-1} (C = O); for ^{1}H and ^{13}C n.m.r. data see Tables 2 and 3; *m/z* (e.i.) 400 (M-18, 50%), 151 ($ArCH_2^+$, 100%); *m/z* (c.i.) 418 ($M-H_2O+NH_4^+$, 100%), 401 ($M+H-H_2O$, 53%); Found: $M-H_2O+NH_4$ 418.1870. $C_{22}H_{28}O_7N$ requires 418.1866.

*Preparation of 2,3-*bis*(3,4-dimethoxybenzyl)butanedioic anhydride(***13***)*

2,3-*Bis*(3,4-dimethoxybenzyl)butanedioic acid (**12**) (1.994 g, 4.8 mmoles) was suspended at -78°C in dry diethyl ether (40 ml) and a solution of DCCI (1.5 g, 7.2 mmoles) in dry diethyl ether (15 ml) was added in a dropwise manner using a double ended needle. The mixture was allowed to attain room temperature (~1.5 h) and then left stirring for a further two hours after which time no starting material remained by hplc. The crude product was worked up by filtering the urea from the solution after cooling to 5°C and the residue extracted with diethyl ether at 5°C (2 x 10 ml). Evaporation under vacuum gave the crude product as a clear oil (2.016g). Recrystallisation from dry diethyl ether furnished meso-*2,3*-bis(*3,4-dimethoxybenzyl)butanedioic anhydride* (**13**) (1.133 g, 59.4%) as opaque white crystals (m.p. 177 - 8°C). ν_{max} (KBr): 1788 cm^{-1} (C = O); Found: C, 65.87; H, 5.89; $C_{22}H_{24}O_7$ requires C, 65.99; H, 6.04; for ^1H and ^{13}C n.m.r. data see Tables 2 and 3; *m/z* (e.i.) 400 (M^+, 49%), 151 ($ArCH_2^+$, 100%); *m/z* (c.i.) 418 ($M+NH_4^+$, 100%), 401 ($M+H^+$, 12%).

*Preparation of (2S,3R,*α*R)-N-(*α*-phenylethyl)-2,3-*bis*(3,4-dimethoxybenzyl)butanedioic acid monoamide(**14**)*

2,3-*Bis*(3,4-dimethoxybenzyl)butanedioic anhydride (**13**) (50 mg, 0.13 mmoles) was dissolved in CH_2Cl_2 (1 ml) and cooled to -78°C. To this was added in a dropwise manner (+)-α-methylbenzylamine (16 μl, 0.015g 0.13 mmoles) in CH_2Cl_2 (1 ml). The reaction was allowed to attain room temperature over 2 h and after 12 h no starting material remained by hplc. The product was acidified to pH2 with aq. HCl and extracted in CH_2Cl_2 (3 x 5 ml). The CH_2Cl_2 extracts were dried ($MgSO_4$) and evaporated to give the crude product as a white solid, recrystallisation of which from CH_2Cl_2 gave the amide product (**14**) (40 mg, 62%, d.e. = 86%) as white crystals (m.p. 184 - 186°C). ν_{max} (KBr): 3339 cm^{-1} (NH str), 1642 cm^{-1} (NH bend), 1731 cm^{-1} (C = O); λ_{max} (CH_2Cl_2) : 242 nm; for ^1H and ^{13}C nmr spectra see Tables 2 and 3; $[\alpha]_{Na}^{21}$ = +56.7° (c 0.48 in CH_2Cl_2); *m/z* (e.i.) 503 (M-18, 2%), 151 ($ArCH_2^+$, 100%), *m/z* (c.i.) 522 ($M+H^+$, 21%), 504 (M-17, 14%). Found: $M+H^+$, 522.2490. $C_{30}H_{36}O_7N$ requires $M+H^+$, 522.2492; Increasing the scale of reaction to 0.58 mmole or 1.35 mmole required the use of semi preparative hplc using a reverse phase system with 60% MeOH/40% H_2O in conjunction with a Rainin Microsorb C18 5 μ column, prior to crystallisation. The product was obtained as a single peak at 4.12 min, collection of which gave in both cases a 48% isolated yield.

*Preparation of (2S,3R,αR)-N-(α-phenylethyl)-2,3-*bis*(3,4-dimethoxybenzyl)succinimide* (**15**) *and (2S,3R,αR,α'R)-N,N'-*bis*(α-phenylethyl)-2,3-*bis*(3,4-dimethoxybenzyl)butanedioic acid diamide* (**16**)

An identical procedure to that described in the previous experiment was carried out on *meso*-2,3-*bis*(3,4-dimethoxybenzyl)butanedioic anhydride (**13**) (1.46 mmol, 0.584 g) containing 10% DCCI with (+)-α-methylbenzylamine (1.6 mmoles, 1.1 eq). The crude product obtained was a mixture of starting material and three products which were separated by preparative hplc (60% MeOH, 40% H_2O) to give 2,3-*bis*(3,4-dimethoxybenzyl)butanedioic acid (**9**), and the three products. *(2S,2R,αR)-N-(α-phenylethyl)-2,3-*bis*(3,4-dimethoxybenzyl)butanedioic acid monoamide* (**14**) (0.103g, 13.5%), had identical spectral results to those given previously. *(2S,3R,αR)-N-(α-phenylethyl)-2,3-*bis*(3,4-dimethoxybenzyl) succinimide* (**15**) (76 mg, 10.4%) was also obtained which on recrystallisation from CH_2Cl_2 gave a white crystalline product (68 mg, 9%), m.p. 169-171°C. ν_{max} (KBr): 1620 cm^{-1} (C = O); for ^1H and ^{13}C nmr see Tables 2 and 3), *m/z* (e.i.) 503 (M^+, 22%), 151 ($ArCH_2^+$, 100%); *m/z* (c.i.) 521 ($M+NH_4^+$, 100%), 504 ($M+H^+$, 78%), 151 ($ArCH_2^+$, 76%). Found: M^+, 503.2310, $C_{30}H_{33}O_6N$ requires M^+, 503.2310), $[\alpha]_{Na}^{18}$= +20.46°. *(2S,3R,αR)-N,N'-*bis*(α-phenylethyl)-2,3-*bis*(3,4-dimethoxybenzyl) butanedioic acid diamide* (**16**) (56 mg, 6.1%), was isolated as a white solid. ν_{max} (KBr): 1632cm^{-1} (NH bend), 3293 cm^{-1} (NH stretch); λ_{max} (CH_2Cl_2) : 235.3 nm; for ^1H and ^{13}C nmr spectra see Tables 2 and 3; *m/z* (FAB) 648 (M+Na, 12%), 626 (M+1, 41%), 625 (M^+, 30%), 151 ($ArCH_2^+$, 52%); $[\alpha]_{Na}^{18}$ = -142.1°.

*Preparation of (2S,2R,αR)-N-(α-phenylethyl)-2,3-*bis*(3,4-dimethoxybenzyl)-4-hydroxybutanamide* (**17**)

(2S,3R,αR)-N-(α-Phenylethyl)-2,3-*bis*(3,4-dimethoxybenzyl)butanedioic acid monoamide (**14**) (41 mg, 0.079 mmoles) was dissolved in dry THF (1 ml) and cooled to -78°C. A solution of Et_3N(8.3 mg, 0.086 mmoles) and $ClCO_2Et$ (9.3 mg. 0.086 mmoles) in THF (1 ml) was injected into the stirring soluton at -78°C. The reaction mixture was warmed to 0°C over 1 h and left stirring at 0°C for a further 1 h. The resultant precipitate was filtered off under vacuum and $NaBH_4$ (6.29 mg) then added and the mixture stirred for 1.5 h. at room temperture. The reaction was quenched with 10% aq. HCl (2 ml) and extracted with EtOAc (3 x 10 ml). The combined EtOAc extracts were evaporated to give the crude product (38 mg, 95%) as a clear oil which was purified by reverse phase flash chromatography using MeOH (60%)/H_2O (40%) and crystallised from CH_2Cl_2 to give a white crystalline solid (19.8 mg, 50%) d.e. = 86% (m.p. 109-110.5°C). ν_{max} (KBr): 3307 cm^{-1} (OH), 1645 cm^{-1} (CO); for ^1H and ^{13}C nmr spectra see Tables 2 and 3; *m/z* (e.i.) 508 (M^+, 10%), 386 (4%), 151 ($ArCH_2^+$, 100%). Found: C, 68.86; H, 7.68; N, 2.61. $C_{30}H_{37}O_6N$ requires C, 70.98; H, 7.35; N, 2.76); $[\alpha]_{Na}^{20}$ = +19.6° (c 0.50 in CH_2Cl_2).

*Preparation of (2S,3R)-2,3-*bis*(3,4-dimethoxybenzyl)butyrolactone (***18***)*

(2S,3R,αR)-N-(α-Phenylethyl)-2,3-*bis*(3,4-dimethoxybenzyl)-4-hydroxybutanamide (**17**) (63.4 mg, 0.126 mmoles) was dissolved in ethylene glycol dimethyl ether (10 ml) to which was added 5 M aq. HCl (7.5 ml). The solution was refluxed for 2 h and extracted with CH_2Cl_2 (3 x 10 ml). The combined CH_2Cl_2 extracts were evaporated to remove ethylene glycol dimethyl ether and CH_2Cl_2. The crude product, a clear oil, was purified on a chromatotron using a 1 mm silica plate (Merck 7749, Kieselgel 50 F254 gipshaltig) and neat CH_2Cl_2 as a eluent giving the purified product (33 mg, 69%) as a clear oil. ν_{max} ($CHCl_3$,NaCl plates): 1769 cm^{-1} (γ-lactone); λ_{max} ($CHCl_3$) : 238 nm; for ^1H and ^{13}C nmr data see Tables 2 and 3; *m/z* (c.i.) 404 ($M+NH_4^+$, 100%), 386 (M^+, 12%), 151 ($ArCH_2^+$, 21%). (Found: $M+NH_4^+$, 404.2073. $C_{22}H_{30}O_6N$ requires $M+NH_4^+$, 404.2073), $[\alpha]_{Na}^{21}$ = +32.3° (c 1.434 in CH_2Cl_2).

*Preparation of (2R,3R)-2,3-*bis*(3,4-dimethoxybenzyl)butyrolactone (***19***) by epimerisation of (2S,3R)-2,3-*bis*(3,4-dimethoxybenzyl)butyrolactone (***18***)*

*(2S,3R)-*2,3-*Bis*(3,4-dimethoxybenzyl)butyrolactone (**18**) (17 mg, 0.04 mmoles) was dissolved in CH_2Cl_2 (10 ml) and Dabco (9.9 mg, 0.088 mmoles) added at room temperature. The solution was stirred for 12 h at which point a 1:1 mixture (hplc) of starting material and product was observed and this remained constant even after a further 24 h. The product mixture was acidified with aq. HCl, the solid residue filtered off, and the filtrate shaken with aq. $NaHCO_3$. The aq. $NaHCO_3$ layer was washed with CH_2Cl_2 (2 x 5 ml) and the combined CH_2Cl_2 extracts washed with brine (5 ml), dried ($MgSO_4$), filtered and evaporated to give the product as a clear oil (13 mg, 76%). ν_{max} ($CHCl_3$,NaCl plates): 1769 cm^{-1} (γ- lactone); $[\alpha]_{Na}^{21}$ = 0°. δc($CDCl_3$): **178.74**, *178.00*(C-2), **46.54**, *45.44*(C-3), **41.04**, *40.07* (C-4), **71.25**, *69.55* (C-5), **34.46**, *32.55*(C-6), **38.16**, *30.47*(C-7), **130.41**, *131.12*(C-1'), **130.15**, *130.90*(C-1"), **111.26**, *111.97*(C-2'), **111.02**, *111.67*(C-2"), **147.77**, *147.82*, **147.89**, *148.97*, **149.00**, *149.06* (C-3', C-3", C-4', C-4"), **112.29**, *111.37*(C-5'), **111.77**, *111.32*(C-5"), **121.32**, *120.82*,(C-6'), **120.53**, *120.34*(C-6"), *55.91*, **55.83**, *55.80*, **55.72** (OMe). The italicised figures correspond to compound **18** (Table 2) and the bold to compound **19**.[17]

ACKNOWLEDGEMENT

Financial support from the SERC and Lilly Research is gratefully acknowledged. We are also grateful to Professor M. B. Hursthouse (SERC X-ray crystallography service, University of Wales Cardiff) for X-ray structures of compounds **5** and **11**.

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(*Received in UK* 25 *June* 1996; *revised* 16 *August* 1996; *accepted* 22 *August* 1996)