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The Asymmetric Synthesis of An Isomer of Podophyllotoxin

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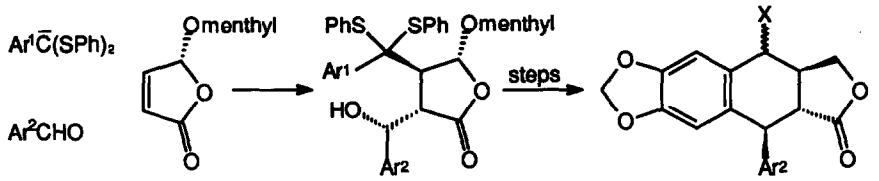
Abstract: Tandem conjugate addition by an O-silylcyanohydrin derived carbanion to 5-(1-menthyloxy)-2(5*H*)-furanone, followed by reaction with an aromatic aldehyde gives two diastereoisomeric adducts. These afford a single product on treatment with tetrabutylammonium fluoride. Reduction with concomitant removal of the menthyloxy group, followed by acid catalysed cyclisation gave a homochiral tetrahydronaphthalene retro-lactone which is an interesting structural isomer of podophyllotoxin.

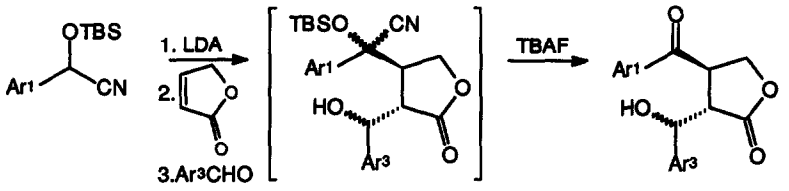
We have previously shown that tandem conjugate addition to (-)-5-(1-menthyloxy)-2(5*H*)-furanone (**1**) by sulphur stabilised carbanions occurs with a high degree of stereoselectivity and that the adducts produced can be converted into homochiral lignans including aryltetralin lactones (*e.g.* **2**).[1] However, this approach was of limited value for the preparation of compounds having a substituent at the 4-position (*e.g.* **3**) which would be more closely related to the physiologically active podophyllotoxin series.[2-5]



1 **2** X = H, **3** X = OH

Ar1 = piperonyl
Ar2 = 3,4,5-trimethoxyphenyl **Scheme 1**

We therefore decided to investigate the addition of the alternative acyl anion equivalent derived from the *tert*-butyldimethylsilylcyanohydrin (**4**).[6] This approach has been used previously by Iwasaki *et al.*[7] who showed that the anion undergoes tandem conjugate addition to butenolide to give adducts (**5**) which were used to prepare racemic furofuran lignans.

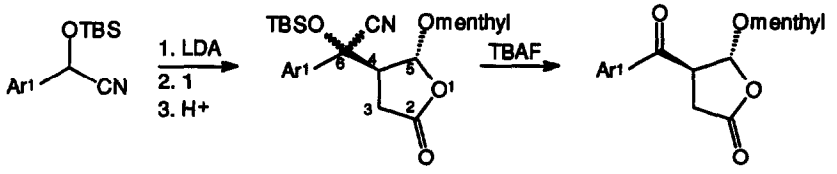


4 **5**

Ar^3 = veratryl

Scheme 2

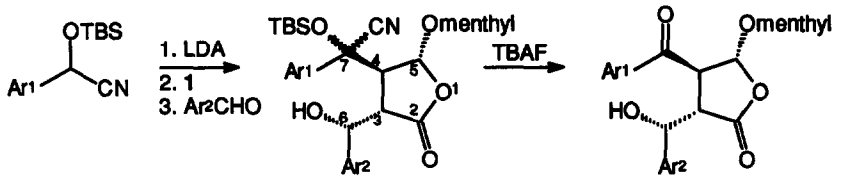
We first demonstrated that the anion derived from (**4**) reacted stereoselectively with the furanone (**1**) to give only the *trans*-disubstituted butyrolactone (**6**). This product consisted of only *one* diastereoisomer in which the absolute configuration at C-6 was not established. Treatment of (**6**) with tetrabutylammonium fluoride (TBAF) in THF afforded the ketone (**7**) ***as a single isomer in quantitative yield.***



4 **6** **7**

Scheme 3

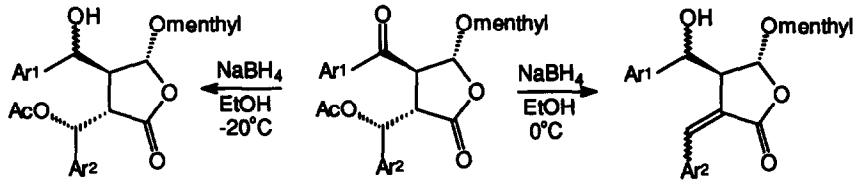
We therefore proceeded to carry out the tandem conjugate addition reaction shown in Scheme 4 which gave (**8**) in 84% yield. Compound (**8**) was obtained as a 1:1 mixture of diastereoisomers, both of which had the *trans, trans* configuration around the butyrolactone ring. In view of the fact that (**6**) had been obtained as only one isomer, we initially assumed that the two diastereoisomers of (**8**) differed in their configuration at C-6. However, treatment of (**8**) with TBAF in THF gave the ketone (**9**) *as a single isomer in 80% yield.* This may indicate that nucleophilic addition of the anion from (**4**) to the furanone (**1**) is slow and reversible, leading eventually to roughly equal amounts of two isomers differing in their configuration at C-7. Indeed this would be consistent with our earlier results (Scheme 1) in which we observed complete stereoselectivity in the reaction with the aromatic aldehyde leading to only the *anti*-configuration at C-6. An alternative explanation would be that TBAF is able to bring about epimerisation at C-6 leading to the more stable configuration. It is interesting to note that Iwasaki and coworkers obtained a 1:1 mixture of the C-6, C-3 *syn* and *anti* adducts (*5*) when the lithium enolate was employed (Scheme 2).



4 8 9

Ar1 = piperonyl
Ar2 = 3,4,5-trimethoxyphenyl **Scheme 4**

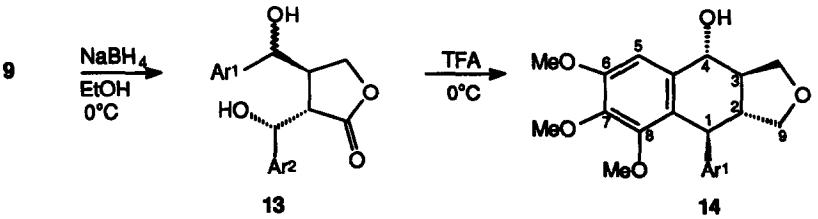
All attempts to directly cyclise (**9**) to an aryltetralin were unsuccessful. We therefore sought to differentiate between the two oxygen functionalities in (**9**). Acetylation of (**9**) gave the acetate (**10**). However, reduction of (**10**) using sodium borohydride at -20°C gave only a low yield of the alcohol (**11**) while carrying out the same reaction at 0°C gave the unsaturated lactone (**12**) in 50% yield. The configuration of the OH at C-7 in (**11**) and (**12**) and of the double bond in (**12**) were not determined.



11 10 12

Scheme 5

We therefore decided to investigate the direct reduction of (**9**). Reduction of (**9**) using sodium borohydride at 0°C gave the diol (**13**) as a ***single isomer in 50% isolated yield.*** This was interesting not only on account of the stereoselectivity of the reaction but also because it is the first case in which we have observed removal of the menthyloxy substituent using sodium borohydride alone. The configuration of the OH group at C-7 in (**13**) was not determined. Treatment of (**13**) with TFA at 0°C gave the chiral isomer of podophyllotoxin (**14**). Preferential cyclisation involving carbocation formation adjacent to the methylenedioxyphenyl group was not unexpected in view of the greater stabilisation afforded to a carbocation by the 3,4-methylenedioxyphenyl group compared to the 3,4,5-trimethoxyphenyl group.[8-10] By varying the aromatic groups in (**13**) it should clearly be possible to control the direction of the cyclisation step in order to obtain selectively either the normal or the retro-lactone series. Plans are in hand to further investigate this aspect of the work.



13 14

Scheme 6

Table 1. ^{1}H n.m.r. spectra of butyrolactone derivatives[a,b]

	6	7	8[c]	9	10	11	12	13
H-3	2.65m	(3.05dd(17.9,4.9) (2.86dd(17.9,9.4)	)2.65m	3.57m	)3.81-3.94m))	3.00dd(8.9, 2.8)	-	3.02dd(3.6,9.7)
H-4	2.85m	4.05m	2.77m	3.72m	)	3.48dd(4.2, 9.1)	3.80d(6.1)	2.63m
H-5	5.62d(1.9)	5.71d(2.5)	6.21s/6.15s	5.44d(5.2)	5.47d(4.5)	5.54s	5.90d(1.37)	(3.58d(4.2) (3.56d(3.7)
H-6	-	-	4.93m	4.81d(8.7)	6.21d(7.0)	5.90d(8.9)	5.58s	5.28d(3.6)
H-7	-	-	-	-	-	4.80d(4.2)	4.95d(6.1)	4.37d(9.1)
H-2'	6.98d(1.9)	7.46d(1.7)	)	)	)7.29-7.35m	)		
H-5'	6.85d(8.2)	6.90d(8.2)	)6.38-6.57m	) 6.37.7.14m	)6.81d(8.1)	)6.27-6.72m	6.61-7.57m	6.54-6.70m
H-6'	7.07dd(8.2,1.9)	7.59dd(8.2,1.7)	)6.89-7.12m	)	)6.49s	)		
H-2"/6"	-	-	)	)	)	)		
OCH_2O	6.04s	6.09s	6.26m	5.95s	6.07s	(6.00d(1.4) (5.95d(1.4)	5.92d(1.4) 5.90d(1.4)	5.91ABq(1.4)
OMe	-	-	(4.07s (4.03s	3.62s[6H] 3.65s[3H]	3.78s[6H] 3.79s[3H]	(3.77s[6H] (3.80s[3H]	3.88s[6H] 3.89s[3H]	
OAc	-	-	-	-	2.00s	2.00s	-	-

a) Spectra recorded in $CDCl_3$ solution.

b) Menthyl and TBDMS groups not included.

c) Mixture of two diastereoisomers.

Table 2. ^{13}C n.m.r. spectra of butyrolactone derivatives[a,b]

	6	7	8[c]	9	10	11	12	13
C-2	174.41	173.53	177.09/177.00	175.94	172.29	174.82	164.87	176.20
C-3	29.26	29.17	57.21/56.87	52.13	51.65	51.58	123.56	52.74
C-4	54.61	47.96	49.51	51.90	48.71	47.93	52.33	43.86
C-5	100.92	100.25	100.89/100.20	102.08	100.66	101.46	99.40	67.82
C-6	75.13	192.35	74.64/74.47	74.39	73.16	72.81	106.66	76.24
C-7	-	-	75.72	193.61	193.61	74.66	72.71	71.69
C-1'	131.24	128.60	137.98/137.77	130.38	130.15	132.68	129.33	134.30
C-1"	-	-	134.54/134.42	134.41	131.89	134.42	134.03	135.55
C-2'	106.19	107.36	105.16/105.10	107.59	107.84	107.75	108.16	106.29
C-2"/6"	-	-	103.81/103.48	107.89	104.23	104.19	107.12	103.68
C-5'	108.28	107.13	107.14/106.95	108.04	108.14	105.72	107.51	108.22
C-6'	119.65	124.48	119.83/119.60	125.21	125.65	118.54	119.83	119.88
C-3'	148.71	151.80	148.47	153.15	153.30	152.91	153.16	152.97
C-3"/5"	-	-	148.56	148.12	148.42	147.93	147.89	148.12
C-4'	148.42	147.62	148.86	152.56	152.82	147.77	152.39	147.83
C-4"	-	-	153.03/152.97	137.77	137.98	137.71	139.83	136.97
OCH_2O	101.18	101.19	102.45/102.34	103.81	102.22	101.63	101.22	101.32
OMe	-	-	55.90/55.84 60.74	55.85 60.64	56.00 60.74	55.87 60.75	56.19 60.96	56.03 60.81
OAc	-	-	-	-	169.44 20.83	169.59 21.11	-	-
CN	119.6	-	129.92/129.83	-	-	-	-	-

a) Spectra recorded in $CDCl_3$ solution.

b) Menthyl and TBDMS groups not included.

c) Mixture of two diastereoisomers.

Table 3. ^{1}H and ^{13}C n.m.r. spectra for compound (14)[a]

H-1	4.01d(9.7)	C-1	47.38
H-2	)2.31-2.43m	C-2	)46.23
H-3	)	C-3	)46.14
H-4	5.07d(8.8)	C-4	68.66
H-5	7.08s	C-4a	135.27
H-9	4.98-4.30m	C-8a	124.77
H-2'	)	C-5	104.51
H-5'	)6.73d(7.9)	C-6	)139.59
H-6'	)6.52m[2H]	C-7	)141.98
OCH_2O	5.92s	C-8	)146.00
OMe	3.91s	C-1'	)147.85
	3.75s	C-3'	)151.65
	3.19s	C-4'	)153.21
OH	3.20br.s	C-2'	108.39
		C-5'	106.95
		C-6'	119.51
		C-9	71.70
		CO	176.76
		OCH_2O	100.98
		OMe	60.43
			59.55
			55.87

[a] Spectra recorded in $CDCl_3$ solution.

Experimental

NMR spectra were recorded on a Bruker 250WM spectrometer at 250 MHz (proton) or 62.9 MHz (carbon) using tetramethylsilane as internal standard and deuterated chloroform as solvent. All carbon spectra were recorded using both proton noise decoupled and DEPT 135 techniques. Mass spectra were obtained on a VG-12-250 low resolution quadrupole mass spectrometer, while accurate mass measurements were obtained on a ZAB-E high resolution double focusing instrument. Infrared spectra were obtained on a Perkin-Elmer 1725X FTIR spectrometer equipped with Perkin-Elmer's IR data manager. Ultraviolet spectra were obtained using a Philips PU8720 scanning spectrometer, while optical rotations were recorded on a Perkin-Elmer 141 polarimeter using a sodium lamp at 589 nm. $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Melting points were obtained on an Electrothermal digital melting point apparatus, and are uncorrected.

HPLC analyses were carried out using a Milton Roy 3100 spectroMonitor and 3100 constaMetric pump, coupled to a CI-4100 integrator, and using a reverse phase (methanol-water) Apex II ODS 5μ column.

All reactions under an inert atmosphere were carried out in flame dried apparatus which was cooled under an inert gas stream; inert gas refers to oxygen-free nitrogen or argon.

THF and ether were dried by passage through an alumina column, followed by distillation from sodium/benzophenone. Dichloromethane was dried by passage through alumina, followed by distillation from calcium hydride.

Low temperature baths were formed using ice/sodium chloride (-20°C) or solid carbon dioxide/acetone (-78°C).

Chromatography was performed on Merck 9385 Kieselgel 60 (230-400 mesh) or for small scale separations on a chromatotron 7924 using plates prepared from Merck 7749 Kieselgel 50 F_{254} Gipshaltig. Thin layer chromatography was carried out on Merck 5554 Kieselgel 60 F_{254} plates.

Synthesis of (-)-(4*R*,5*R*)-4-(α-[*tert*-butyldimethylsiloxy]-3',4'-methylenedioxyphenyl-acetonitrile-5-(1-menthyloxy)butyrolactone (6).

To freshly distilled diisopropylamine (2.7ml, 0.19 mmoles) in dry THF (20ml) at 0°C under an inert atmosphere was added dropwise *n*-BuLi (10.32ml, 1.84M, 19 mmoles) and the reaction stirred for 45 minutes. The temperature was then lowered to -78°C and a precooled solution of (**4**)[6] (5.12g, 17.6 mmoles) in dry THF (50ml) was added *via* double-ended needle. After two hours at -78°C a precooled solution of (-)-5-(1-menthyloxy)furan-2(5*H*)-one (5.45g, 23 mmoles, 1.3 equivalents) in THF (50 ml) was added *via* double-ended needle, and the reaction stirred for a further two hours at -78°C before being quenched with 10% aqueous sodium chloride (10ml) and allowed to warm to room temperature over one hour. The organic layer was removed and the aqueous layer extracted with ether. The organic layers were combined, dried ($MgSO_4$), and evaporated to give the crude product which was purified on silica (eluant 50/50 dichloromethane/petroleum spirit) to give (**6**) as a light green gum (7.79g, 84%). For ^1H and ^{13}C NMR data see Tables 1 and 2. ν_{max}/cm^{-1} (film): 2956, 2930, 2362 (C≡N), 1795 (C=O), 1614 (C=C, aromatic), 1506, 1491, 1445, 1250, 1170, 1110. $[\alpha]_D^{23}$ = -47.83° (c = 0.16, $CHCl_3$). Found: C, 66.30; H, 8.36; N, 2.54. $C_{29}H_{23}O_6SiN$ requires C, 65.78; H, 8.13; N, 2.65%. λ_{max}/nm (MeOH) 238.1 (ε/dm^3 mol^{-1} cm^{-1} 5034), 288.7 (3076). *m/z* (EI) 365(13,), 334(15), 290(14), 159(63), 149(68%). *m/z* (CI) 547(M + NH_4, 28), 365(100), 290(52%).

Synthesis of (-)-(4*R*,5*R*)-4-(3,4-methylenedioxybenzoyl)-5-(1-menthyloxy)butyrolactone (7).

To (**6**) (0.055g, 10.4 mmoles) in THF (10ml) at -78°C was added dropwise a solution of tetrabutyl ammonium fluoride in THF (0.11ml, 1M, 11.0 mmoles, 1.06 equiv.) and the reaction stirred for fifteen minutes. Water was then added, and the reaction was allowed to warm to room temperature over one hour. Ether was added, and the aqueous layer was separated and extracted twice with ether. The organic layers were combined, dried ($MgSO_4$), and the solvent evaporated under reduced pressure at room temperature to afford the crude product (**7**) as a clear gum (0.040g, 100%). (**7**) was kept at -18°C, to prevent decomposition. For ^1H and ^{13}C NMR data see Tables 1 and 2. ν_{max}/cm^{-1} (film): 2955, 2920, 1785 (C=O, lactone), 1670 (C=O, ketone), 1600 C=C, aromatic), 1440, 1250, 1095.

Synthesis of (-)-(3*S*,4*R*,5*R*)-3-(3",4",5"-trimethoxy-α-hydroxybenzyl)-4-(α-[*tert*-butyl-dimethylsiloxy]-3',4'-methylenedioxyphenylacetonitrile)-5-(1-menthyloxy)butyrolactone (8).

To freshly distilled diisopropylamine (1.50ml, 11 mmoles) in dry THF (15ml) at 0°C under an inert atmosphere was added dropwise *n*-BuLi (5.85ml, 1.88M, 11 mmoles) and the reaction stirred for 45 minutes. The temperature was then lowered to -78°C and a precooled solution of (**4**)[6] (9.72 mmoles) in dry THF (30ml) was added *via* double-ended needle. After two hours at -78°C a precooled solution of (-)-5-(1-menthyloxy)furan-2(5*H*)-one (3.007g, 13 mmoles, 1.3 equivalents) in dry THF (30ml) was added and the reaction stirred for a further two hours before a precooled solution of freshly distilled 3,4,5-trimethoxybenzaldehyde (2.470g, 13 mmoles, 1.3 equivalents) in dry THF (30ml) was added. After one hour the reaction was quenched by the addition of 10% aqueous sodium chloride (10ml) and allowed to warm to room temperature over one hour. The organic layer was removed and the aqueous layer extracted with ether. The organic layers were combined, dried ($MgSO_4$), the solvent evaporated and the product purified on silica (eluant dichloromethane) to yield (**8**) as a white foam (7.05g, 84%). For ^1H and ^{13}C NMR data see Tables 1 and 2. ν_{max}/cm^{-1} (KBr disc): 3512(OH), 2956,

2932, 1173 (C=O), 1595, 1508, 1465, 1365, 1330, 1248, 1178, 1130. $[\alpha]_D^{23}$ = 48.00° (c = 0.033, $CHCl_3$). Found: C, 64.58; H, 7.71; N, 1.93. $C_{39}H_{55}O_{10}SiN$ requires C, 64.55; H, 7.59; N, 1.93%. λ_{max}/nm (MeOH) 211.3 (ε/dm³ mol⁻¹ cm⁻¹ 33275), 285.7 (4128). *m/z* (EI) 365(20), 290(24), 197(80), 196(100), 159(52), 149(45%). *m/z* (CI) 334(18), 307(25), 197(44), 196(62), 159(79), 149(100%).

Synthesis of (-)-(3*S*,4*R*,5*R*,6*R*(-3-)3",4",5"-trimethoxy-α-hydroxybenzyl)-4-(3',4'-methylenedioxy-benzoyl)-5-(1-menthyloxy)butyrolactone (9).

To the conjugate addition product (**8**) (4.46g, 6.15 mmoles) in THF (90ml) at -78°C was added dropwise a solution of tetrabutylammonium fluoride in THF (6.8ml, 1M, 6.80 mmoles, 1.1 equivalents). After the addition the reaction was stirred for fifteen minutes before being quenched with water, and was then allowed to warm to room temperature over one hour. The product was extracted into ether, dried ($MgSO_4$), and evaporated. Flash chromatography on silica (eluant 80/20 dichloromethane/ethyl acetate) afforded the desired product (**9**) as a white foam (2.87g, 80%). For ^1H and ^{13}C NMR data see Tables 1 and 2. ν_{max}/cm⁻¹ (KBr disc): 3495(OH), 2955 , 2928, 1770 (C=O, lactone), 1673 (C=O, ketone), 1596, 1507, 1448, 1331, 1256, 1173, 1129, 1039. $[\alpha]_D^{23}$ = 113.73° (c = 0.026, $CHCl_3$). Found: C, 65.04; H, 7.09. $C_{32}H_{40}O_{10}$ requires C, 65.75; H, 6.85%. λ_{max}/nm (MeOH) 232.7 (ε/dm³ mol⁻¹ cm⁻¹ 19651), 278.5 (6464), 318.4 (7589). *m/z* (EI) 584(M^+, 1), 566(M-H_2O, 3), 410(15), 382(28), 149(100%). *m/z* (CI) 523(4), 385(13), 251(27), 197(100), 149(30%). Acc. Mass 584.262 (M^+, calc. 584.262).

Synthesis of (-)-(3*S*,4*R*,5*R*,6*R*)-3-(3,4",5"-trimethoxy-α-acetoxybenzyl)-4-(3',4'-methylenedioxy-benzoyl)-5-(1-menthyloxy)butyrolactone (10).

To (**9**) (0.5855g, 1.00 mmole) in dry dichloromethane (50ml) was added acetic anhydride (0.14ml, 1.50 mmoles, 1.5 equivalents) and DMAP, and the reaction stirred for two hours, before being washed with saturated sodium bicarbonate solution, dried ($MgSO_4$), and the solvent evaporated. Flash chromatography on silica (eluant dichloromethane) yielded the desired product (**10**) as a yellow foam (0.57g, 91%). For ^1H and ^{13}C NMR data see Tables 1 and 2. ν_{max}/cm⁻¹ (KBr disc): 2956, 2926, 1780 (C=O, lactone), 1753 (C=O, ester), 1675 (C=O, ketone), 1596, 1509, 1449, 1255, 1130, 1038. $[\alpha]_D^{23}$ = -43.92° (c = 0.26, $CHCl_3$). Found: C, 65.35; H, 6.95. $C_{34}H_{42}O_{11}$ requires C, 65.18; H, 6.71. λ_{max}/nm (MeOH) 232.8 (ε/dm³ mol⁻¹ cm⁻¹ 1459), 281.6(5532), 316.89(283). *m/z* (EI) 626(M^+, 15), 566(M-HOAc, 6), 410(28), 236(24), 149(100%). *m/z* (CI) 411(15), 383(32), 245(100%). Acc. Mass 626.273 (M^+, calc. 626.273).

Synthesis of (-)-(3*S*,4*R*,5*R*,6*R*)-3-(3",4",5"-trimethoxy-α-acetoxybenzyl)-4-(3',4'-methylene-dioxy-α-hydroxybenzyl)-5-(1-menthyloxy)butyrolactone (11).

To (**10**) (0.1072g, 0.17 mmoles) in ethanol (16ml) at -20°C was added a solution of sodium borohydride in ethanol (1.20ml, 0.14M, 0.17 mmoles, 1 equivalent), and the reaction stirred for seventy minutes before being quenched by the dropwise addition of 45% aqueous sodium hydrogen sulphite. The product was extracted into ether which was dried ($MgSO_4$), and the solvent removed *in vacuo*. Purification on a chromatotron gave the desired product (**11**) (0.0327g, 30%) plus unreacted starting material (**10**) (0.0517g), corresponding to a 59% conversion. For ^1H and ^{13}C NMR data see Tables 1 and 2. ν_{max}/cm⁻¹ (film): 3492 (OH), 2954, 2929, 1769 (C=O, lactone), 1754 (C=O, ester), 1595, 1507, 1493, 1462, 1371, 1331, 1240, 1158, 1129, 1039. $[\alpha]_D^{22}$ = -66.43° (c = 0.14, $CHCl_3$). *m/z* (EI) 628(M^+, 6), 418(32), 280(61), 262(37), 196(27), 181(90), 149(100%). *m/z* (CI) 628(M^+, 3), 569(M-OAc, 13), 413(77), 369(23), 281(66), 263(100), 197(24), 151(82%). Acc. Mass 628.2883 (M^+, calc. 628.2884).

Synthesis of (-)-(4*R*,5*R*)-3-(3",4",5"-trimethoxybenzylidene)-4-(3',4'-methylenedioxy-α-hydroxybenzyl)-5-(1-menthyloxy)butyrolactone (12).

To (**10**) (0.1265g, 0.20 mmoles) in ethanol (7ml) at 0°C was added a solution of sodium borohydride in ethanol (1ml, 0.20M, 0.20 mmoles, 1 equivalent) and the reaction stirred at 0°C for five hours before being allowed to warm to room temperature overnight. Aqueous sodium hydrogen sulphite was added to quench the reaction, and the product was extracted into ether. The latter was dried ($MgSO_4$), and the solvent evaporated. Purification by chromatotron gave the product (**12**) as a colourless gum (0.0586g, 50%). For ^1H and ^{13}C NMR data see Tables 1 and 2. ν_{max}/cm^{-1} (film): 3470 (OH), 2956, 1755 (C=O), 1649 (C=C), 1584, 1507, 1454, 1334, 1244, 1129. $[\alpha]_D^{22} = 66.55°$ (c = 0.28, $CHCl_3$). *m/z* (EI) 568(M^+, 1), 418(30), 280(100), 262(49), 169(53), 151(56). *m/z* (CI) 419(42), 281(87), 263(100), 151(39%). Acc. Mass 568.267 (M^+, calc. 568.267).

Synthesis of (-)-(3*S*,4*R*,6*R*)-3-(3",4",5"-trimethoxy-α-hydroxybenzyl)-4-(3',4'-methylenedioxy-α-hydroxybenzyl)butyrolactone (13).

To (**9**) (1.46g, 2.5 mmoles) in ethanol (50ml) at 0°C was added sodium borohydride (0.12g, 3.25 mmoles, 1.3 equivalents) and the reaction stirred for five hours at 0°C before being allowed to warm up slowly to room temperature while being stirred overnight. The reaction was quenched by the dropwise addition of 45% aqueous sodium hydrogen sulphite, and the product extracted into ether, dried ($MgSO_4$), and evaporated. Purification on silica (eluant dichloromethane to 50/50 dichloromethane/ethyl acetate) afforded the product (**13**) as a white foam (0.542g, 50%). For ^1H and ^{13}C NMR data see Tables 1 and 2. ν_{max}/cm^{-1} (KBr disc): 3415 (OH), 2942, 1764 (C=O), 1595, 1507, 1492, 1463, 1449, 1423, 1331, 1245, 1127, 1037. $[\alpha]_D^{23} = -27.08°$ (c = 0.048, $CHCl_3$). Found: C, 61.11; H, 5.60. $C_{22}H_{24}O_9$ requires C, 61.11; H, 5.56%. λ_{max}/nm (MeOH) 214.3 (ε/dm^3 mol^{-1} cm^{-1} 20344), 284(3654). *m/z* (EI) 432(M^+, 1), 414(M-H_2O, 1), 236(M-ArCO, 17), 196($ArCO^+$, 53), 181(31), 151(100%). *m/z* (CI) 450(M+NH_4, 1), 432(M+NH_4-H_2O, 2), 415(M-OH, 20), 254(86), 237(31), 219(25), 197(100%). Acc. Mass 432.1420 (M^+, calc. 432.1420).

Synthesis of 1,2,3,4-Tetrahydro-4-hydroxy-2-hydroxymethyl-6,7,8-trimethoxy-1-(3,4-methylene dioxyphenyl)-naphthalene-3-carboxylic acid lactone (14).

To (**13**) (0.1101g, 0.255 mmoles) at 0°C was added precooled TFA (10ml) and the reaction left to stand for one hour at the same temperature. Dichloromethane was then added, followed by the dropwise addition of saturated sodium bicarbonate solution. The organic layer was dried ($MgSO_4$), and the solvent removed *in vacuo*. Purification by chromatotron gave the product (**14**) as a white solid 90.0453g, 43%). For ^1H and ^{13}C NMR data see Table 3. ν_{max}/cm^{-1} (film): 3442 (OH), 2941, 2900, 1778 (C=O), 1599, 1567, 1489, 1451, 1406, 1330, 1245, 1198, 1119, 1037. $[\alpha]_D^{22} = -49.03°$ c = 0.31, $CHCl_3$). *m/z* (EI) 414(M^+, 100), 135(59%). *m/z* (CI) 432(M + NH_4, 27), 415(M + H, 15), 397(M-OH, 100%). Acc. Mass 414.1315 (M^+, calc. 414.1315).

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