Synthesis of 2,6-Diaryl-4,8-dihydroxy-3,7-dioxabicyclo[3.3.0]octanes

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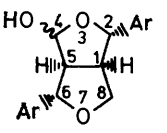
A series of 2,6-diaryl-4,8-dihydroxy-3,7-dioxabicyclo[3.3.0]octanes, including 4,8-dihydroxysesamin, a naturally occurring lignan, have been prepared *via* the corresponding dilactones. The ^1H and ^{13}C n.m.r. spectra have been compared and the bistoluene-*p*-sulphonate of 4,8-dihydroxyeudesmin has been reduced by lithium aluminium hydride to give (±)-eudesmin. Since this synthesis does not involve ring-opened intermediates and starts from a dilactone of established structure, it represents the first unequivocal synthesis of such a lignan.

FOLLOWING recent reports of the isolation and characterisation of (+)-4-hydroxysesamin (1) and (−)-4,8-dihydroxysesamin (2),[1] it was decided to attempt to synthesise compounds of this general type [*e.g.* (7)] starting from the corresponding dilactone (4).[2,3] These dilactones can be prepared directly from the corresponding cinnamic acids (see later) and their identification as the 2,6-diaryl compounds is secure inasmuch as the 2,4-diaryl isomers, perfectly possible products of the same radical mechanism, would be anhydrides which could be readily distinguished by i.r. and ^{13}C n.m.r. spectra.[4,5] The dilactones used were unequivocally *cis*-fused; hence, in the absence of reactions involving ring opening and possible epimerisation, the structures of the final products are certain. This is important in view of the various claims that 2,4-diaryl derivatives are physiologically important natural products.[6-10]

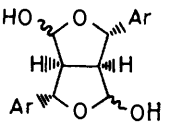
Comparison of compounds such as (7) with the naturally occurring members of this series would clearly be of interest, and it was also thought that reduction of the dilactol (7) or a derivative thereof could lead directly to the parent 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octane system (17) without involving fission of the heterocycle. This would then represent the first unambiguous synthesis of a 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octane lignan in which ring-opened intermediates are not involved. Syntheses of lignans of this type have in the past always involved intermediates which by bond rotation could give rise to either the 2,6- or the 2,4- diaryl system.

The dilactone (4) was prepared by oxidative coupling of ferulic acid with aqueous iron(III) chloride. Treatment of the resulting iron salt with concentrated hydrochloric acid gave a brown solid from which the dilactone was obtained by crystallisation from methanol. Methylation using a large excess of diazomethane in acetone gave the dimethyl ether (5), whereas treatment with methyl iodide and potassium fluoride in dimethylformamide yielded the diarylbutadiene (20) an interesting new class of lignan. Acetylation of the dilactone (4) gave the corresponding diacetate (6).

Reduction of the dilactone (6) with lithium aluminium hydride gave the tetraol (21); the corresponding reduction of (5) gave (22). However treatment of the dilactone (4) in tetrahydrofuran with a large excess of diisobutylaluminium hydride (DIBAL) in hexane at



(1)



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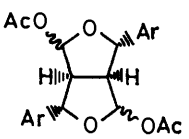
(Ar = phenyl)



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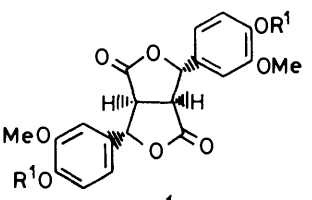
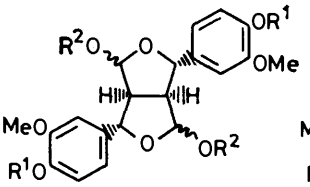
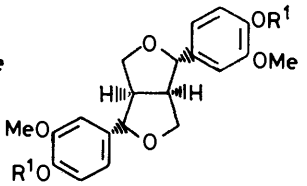


(4) R^1 = H
(5) R^1 = Me
(6) R^1 = Ac



(7) $R^1 = R^2$ = H
(8) $R^1 = R^2$ = Ac
(9) R^1 = H, R^2 = Me
(10) R^1 = H, R^2 = Et
(11) R^1 = Ac, R^2 = Me
(12) R^1 = Me, R^2 = H
(13) R^1 = Me, R^2 = Ac
(14) $R^1 = R^2$ = Me
(15) $R^1 = R^2$ = Ts
(16) R^1 = Me, R^2 = Ts

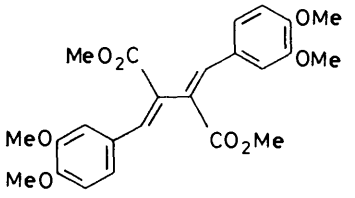


(17) R^1 = H
(18) R^1 = Me
(19) R^1 = Ac

−78 °C rapidly gave 4,8-dihydroxypinoresinol (7).† This compound yielded a tetra-acetate (8) with acetic

† In each case DIBAL reduction yielded only one product. (A wavy line indicates that the configuration of the OH group is not known. Coupling constants are notoriously unreliable in such systems [11] and cannot therefore be used to assign stereochemistry.)

anhydride and pyridine and on treatment with methanolic or ethanolic hydrogen chloride afforded the corresponding dialkyl ether (9) or (10). Acetylation of the dimethyl ether (9) gave a diacetate (11); treatment with aqueous



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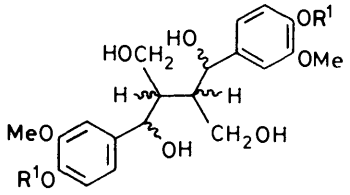
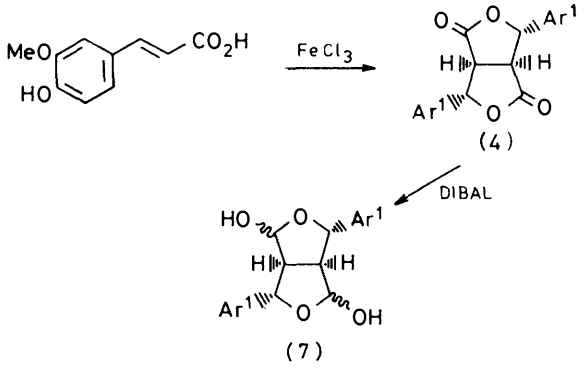


(21) $R^1 = H$
(22) $R^1 = Me$

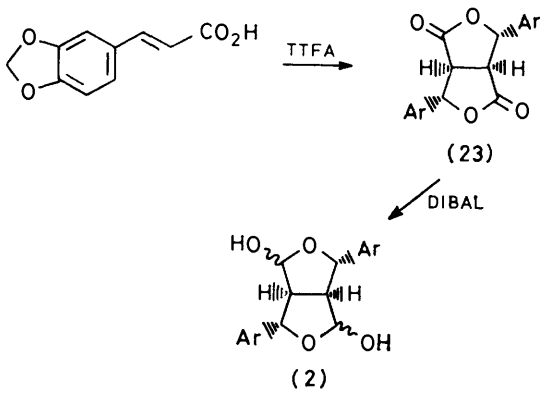
acetone containing a trace of hydrochloric acid regenerated the parent dilactol (7). Oxidation of the dilactol with chromium trioxide yielded the parent dilactone (4) showing that no rearrangement had occurred. A similar series of reactions starting from the methylated lactone (5) gave 4,8-dihydroxyeudesmin (12) and its derivatives (13) and (14).



(4)

(7)

The oxidation of ferulic acid with iron(III) chloride to give the dilactone requires that the starting acid has a free OH group at the *para*-position. It is therefore unsuitable for the synthesis of compounds such as (2) derived from sesamin. Very recently it has been shown that non-phenolic cinnamic acids can be converted into the corresponding dilactones by treatment with thallium trifluoroacetate.[12] Thus for example the dilactone (23) can be prepared from 3,4-methylenedioxycinnamic acid. The reaction is vigorous and must be quenched immediately after mixing the reactants. In our hands, and despite several attempts to modify the reaction conditions, the dilactone (23) was only obtained in 9% yield.[13] Nevertheless, reduction of (23) with DIBAL gave (±)-4,8-dihydroxysesamin (2), having spectra identical with those of the natural product.[1] The identity of the two samples was confirmed by comparison of the diacetates (3).



(23)

(2)

The ^1H n.m.r. spectra of the various 4,8-disubstituted 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octanes are listed in Table 1 along with the spectra of pinoresinol (17), its diacetate (19), eudesmin (18), and sesamin (26) for comparison. Not surprisingly there is a wide variation in the chemical shifts of the aliphatic hydrogen atoms. Thus the H-4/8 signal which appears at δ 3.8—4.3 in the spectra of the parent compounds, is shifted downfield by 1.1—1.7 p.p.m. in those of the 4,8-dihydroxy-compounds, by 0.7—1.4 p.p.m. in those of the 4,8-dimethoxy-compounds, and by 2.1—2.7 p.p.m. in those of the 4,8-diacetoxy-compounds. Furthermore the H-1/5 and H-2/6 signals are both shifted downfield by 0.9—1.2 p.p.m. in the spectra of the dilactones, relative to their positions in those of the parent compounds. Equally significant is the observation that there is apparently little or no coupling between H-1/5 and H-4/8 in any of the 4,8-dioxygenated compounds. This is in striking contrast to the situation in the 4,8-unsubstituted compounds which display coupling constants of *ca.* 4 and 7 Hz between H-1/5 and the *axial* and *equatorial* methylene hydrogens. Furthermore in the dilactones there is little or no coupling between H-1/5 and H-2/6, while in all the other compounds a coupling constant of *ca.* 6 Hz is observed between these positions.

The ^{13}C n.m.r. spectra are shown in Table 2. The 4- and 8-carbon signals which appear at 54 p.p.m. in the spectra of the parent compounds, are shifted to 101 p.p.m. in those of the dihydroxy- and diacetoxy-compounds, and to 107 p.p.m. in those of the dimethyl ethers. The same carbon signals appear at 175 p.p.m. in the spectra of the dilactones. The C-1/5 signals which occur at 72 p.p.m. in the spectra of the parent lignans, appear at 58—61 p.p.m. in those of the dihydroxy-,

TABLE 1

^{1}H N.m.r. spectra [a,b]

	(17) [c]	(7)	(9)	(10)	(4)	(19) [c]	(8)	(11)	(6)
H-1,5	3.15m	2.82d (6)	2.94d (6)	2.94d (6)	4.03d (1)	3.06m	3.27d (6)	2.91d (6)	4.20s
H-2,6	4.71d (4)	4.77d (6)	4.87d (6)	4.86d (6)	5.67s	4.76d (4)	5.29d (6)	4.97d (6)	5.88s
H-4,8	{3.8m 4.2m	5.41d (4) [d]	5.04s	5.15s		{3.90m 4.28dd (7,9)	6.52s	5.16s	
ArOMe	3.78s	3.74s	3.78s	3.78s	3.88s	3.78s	3.80s	3.72s	3.80s
ROMe			3.32s					3.31s	
ROEt				{3.56q (8) 1.16t (8)					
ArOH	6.20br, s	8.82s	8.90s	8.94s	9.03s				
ROH		6.68d (4)							
ArOAc						2.25s	2.24s	2.20s	2.26s
ROAc							2.00s		
Arom.	6.7—6.9m	6.7—7.2m	6.7—7.0m	6.7—7.0m	6.7—6.9m	6.8—7.0m	7.0—7.3m	6.9—7.2m	6.9—7.2m

	(18) [c]	(12)	(13)	(14) [c]	(5)	(26) [c]	(2)	(3) [c]	(23)
H-1,5	3.15m	2.84d (5)	3.15d (6)	3.18dd (6,2)	4.22s	3.05m	2.83d (5)	3.19dd (5,2)	3.51s
H-2,6	4.76d (4)	4.93d (5)	5.14d (6)	4.89d (6)	5.78s	4.71d (4.5)	4.79d (5)	5.09d (6)	5.79s
H-4,8	{3.9m 4.3m	5.46d (4) [d]	6.38s	5.01s		{3.86dd (4,9) 4.23dd (7,9)	5.43d (4) [d]	6.40s	
ArOMe	{3.88s 3.84s	{3.74s 3.72s	{3.72s 3.69s	{3.87s 3.85s	{3.77s 3.74s				
ROH		6.64d (4)					6.54d (4)		
ROAc			1.98s					2.05s	
Arom.	6.8—7.0m	6.8—7.2m	6.9—7.1m	6.7—7.1m	6.8—7.0m	6.7—6.9m	6.6—7.1m	6.6—6.9m	6.7—6.9m
OCH_2O						5.93s	5.93s	5.93s	5.95s

[a] Shifts given as δ values, coupling constants (in parentheses) in Hz. [b] All spectra run in $(CD_3)_2SO$ unless otherwise indicated. [c] Run in $CDCl_3$. [d] Becomes singlet after D_2O exchange

TABLE 2

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

	(17) [c]	(7)	(9)	(4)	(19) [c]	(8)	(11)	(6)
C-1,5	54.2	60.9	59.2	48.1	54.4	58.5	59.1	47.9
C-2,6	85.9	84.2	84.8	82.1	85.5	85.0	84.2	81.2
C-4,8	71.7	100.2	107.1	175.4	72.0	101.1	107.5	175.1
C-1′	133.0	134.2	133.4	129.0	139.2	139.3	139.1	137.2
C-2′	108.5 †	110.8	110.5	110.6	110.0	110.9	111.1	110.8
C-3′	145.4 ‡	145.8 ‡	146.3 ‡	147.4 ‡	151.3	151.4	151.1	151.3
C-4′	146.8 ‡	147.5 ‡	147.8 ‡	147.9 ‡	140.2	141.1	141.5	139.8
C-5′	108.8 †	114.9	115.2	115.5	122.7	122.8	122.8	123.3
C-6′	119.0	118.9	119.3	119.1	111.9	118.3	118.5	118.3
ArOMe	56.0	55.5	55.4	55.8	55.9	55.8	55.9	56.0
ROMe			54.3				54.5	
ArOAc					{169.0 20.6	{169.1 20.3	{168.4 20.3	{168.4 20.3
ROAc						{170.1 20.9		

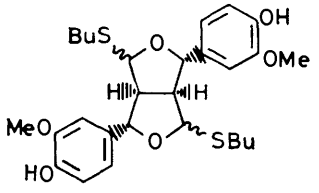
	(18) [c]	(12)	(13)	(14)	(5)	(26) [c]	(2) [d]	(3) [d]	(23) [d]
C-1,5	54.3	60.9	58.2	59.2	48.1	54.2	60.4	58.5	48.2
C-2,6	85.8	84.2	85.1	84.7	81.7	85.6	85.3	85.9	81.9
C-4,8	71.7	100.4	100.4	107.1	175.3	71.6	101.2	100.3	174.9
C1′	134.0	135.9	133.8	135.0	130.5	134.9	136.5	134.7	131.7
C2′	109.7 †	110.4 †	109.7 †	110.1 †	110.0 †	106.3 †	107.3 †	106.4 †	105.6 †
C3′	148.9 ‡	148.2 ‡	148.5 ‡	148.5 ‡	146.3 ‡	146.9 ‡	147.2 ‡	147.6 ‡	148.3 ‡
C4′	149.5 ‡	148.9 ‡	148.9 ‡	149.1 ‡	149.4 ‡	147.7 ‡	147.9 ‡	148.2 ‡	148.5 ‡
C5′	111.5 †	111.5 †	111.6 †	111.6 †	111.7 †	108.0 †	107.9 †	108.2 †	108.6 †
C6′	118.4	118.6	118.5	118.9	118.8	119.1	119.0	119.8	119.0
ArOMe	{55.6 55.9	{55.4 55.6	{55.3 55.6	{55.3 55.6	{55.6 55.7				
ROMe				54.3					
ROAc			{169.4 21.0					{169.8 21.2	
OCH_2O						100.9	101.0	101.2	101.5

[a] Chemical shifts given in p.p.m. downfield from Me_4Si. [b] All spectra run in $(CD_3)_2SO$ unless otherwise indicated [c] Run in $CDCl_3$. [d] Run in $CDCl_3/(CD_3)_2SO$. †, ‡ Similarly marked signal assignments could be interchanged

diacetoxy-, and dialkoxy-derivatives, but at 48 p.p.m. in that of the dilactone. The C-2/6 signals are, by comparison, little affected by the substitution pattern at the 4/8-positions, except in the dilactone where they are shifted upfield by *ca.* 4 p.p.m.

Reaction of the dilactol (7) with butanethiol and boron trifluoride gave the thioacetal derivative (24). However despite numerous attempts to reduce this compound with Raney nickel in ethanol the unsubstituted compound (17) was not obtained. We therefore converted the dilactols

(7) and (10) into their corresponding tosylates (15) and (16). Reduction of the last compound with lithium aluminium hydride gave (±)-eudesmin (18). Since exposure of the tetraol (22) to lithium aluminium hydride under similar conditions does not yield eudesmin, we conclude that reduction of the ditosylate involves a direct displacement of the tosylate group by hydride. The possibility of reduction of an oxonium ion produced by elimination of the tosylate group cannot be exluded, but it is difficult to envisage any ring-opened intermediates being involved. Hence the sequence from ferulic acid to the lignan represents the first unambiguous synthesis of a 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octane.



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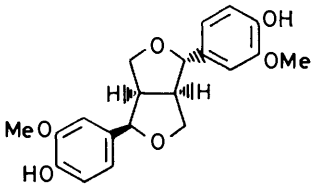

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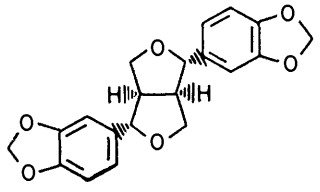

(26)

It is of interest that exposure of the tetraols (21) and (22) to a variety of acidic reagents converts them into (±)-pinoresinol (7) and (±)-eudesmin (18), respectively. Cyclisation can be achieved in low yield by high temperature vacuum distillation or by heating with potassium hydrogen sulphate at 200 °C under vacuum. However the best yields were obtained by treating the tetraols with ethanolic hydrogen chloride. Thus treatment of the crystalline tetraol (21) with ethanolic hydrogen chloride at 0 °C for 1 h gave a mixture of (±)-pinoresinol (17) and (±)-epipinoresinol (25) in 52% yield. Cyclisation of the crystalline tetraol (22) was achieved by refluxing in ethanolic hydrogen chloride for 1 h, which gave (±)-eudesmin (18) in 43% yield.

EXPERIMENTAL

I.r. and u.v. spectra were recorded on Pye Unicam SP1050 and Perkin–Elmer 402 spectrometers, respectively. N.m.r. (^{1}H and ^{13}C) spectra were recorded on Varian HA100 and XL100 instruments using tetramethylsilane as internal standard. Mass spectra were obtained on an A.E.I. MS9 double-focusing instrument at 250 °C and 70 eV.

2,6-*Bis*-(3,4-*dimethoxyphenyl*)-3,7-*dioxabicyclo*[3.3.0]-*octane*-4,8-*dione* (5).—The dilactone (4) (1 g) dissolved in dry acetone (100 ml) was added to a solution of diazomethane in diethyl ether (60 ml; 0.16M) at room temperature under nitrogen. This was stirred at room temperature for 24 h. The excess of diazomethane was then destroyed with a few drops of concentrated hydrochloric acid. The solution was evaporated giving a pale yellow solid, which was recrystallised from ethyl acetate–ethanol (7 : 10) giving white *crystals* (0.88 g, 82%), m.p. 207—208 °C (Found: C, 63.6; H, 5.1. $C_{22}H_{22}O_8$ requires C, 63.8; H, 5.35%); $\nu_{max.}$(KBr) 3 010—2 800, 1 770, and 1 610 cm^{-1}; *m/z* 414.1315 ($M^{+\cdot}$, $C_{22}H_{22}O_8$).

Dimethyl 2,3-*Bis*-(3,4-*dimethoxybenzylidene*)*butanedioate* (20).—Potassium fluoride (480 mg) was dissolved in dimethylformamide (2 ml) and a solution of the dilactone (4) (390 mg) in dimethylformamide (2 ml) was added. The mixture was stirred at room temperature for 2 h and then methyl iodide (0.5 ml) added. The mixture was stirred at 110 °C for 3 h, poured into ethyl acetate (30 ml), washed with water (3 × 10 ml), dried ($MgSO_4$), and evaporated under reduced pressure. Chromatography of the product on silica gel eluted with dichloromethane gave unchanged dilactone and the product as a bright yellow *oil* which did not crystallise (250 mg, 57%) (Found: $M^{+\cdot}$ 442.1628. $C_{24}H_{26}O_8$ requires *M*, 442.1628); $\nu_{max.}$(film) 3 040—2 820, 1 705, 1 630, and 1 600 cm^{-1}; δ($CDCl_3$) 7.94 (s, H-1/4), 3.84(s) and 3.75(s) (OMe), 3.71 (s, CO_2Me), and 6.6—7.4 (m, arom.); $\lambda_{max.}$ 246 (log ε 4.07), 297 (4.11), and 336 (4.18) nm.

2,6-*Bis*-(4-*acetoxy*-3-*methoxyphenyl*)-3,7-*dioxabicyclo*-[3.3.0]*octane*-4,8-*dione* (6).—The dilactone (4) (2.6 g) was dissolved in dry pyridine (25 ml) together with acetic anhydride (2.9 g) and the solution stirred overnight at room temperature. The mixture was poured into water (200 ml) and filtered. The resulting white *solid* was dried under vacuum and recrystallised from methanol (yield 3 g, 95%); m.p. 230—231 °C (Found: C, 61.3; H, 4.4. $C_{24}H_{22}O_{10}$ requires C, 61.3; H, 4.7%); $\nu_{max.}$(KBr) 3 100—2 800, 1 760, and 1 610 cm^{-1}.

threo-2,3-*Bis*-(α-*hydroxy*-3,4-*dimethoxybenzyl*)*butane*-1,4-*diol* (22).—2,6-Bis-(3,4-dimethoxyphenyl)-3,7-dioxabicyclo-[3.3.0]octane-4,8-dione (5) (415 mg) dissolved in dry tetrahydrofuran (50 ml) was added to a suspension of lithium aluminium hydride (340 mg) in dry tetrahydrofuran (30 ml) under nitrogen. The mixture was stirred and heated under reflux for 5 h. It was then cooled in an ice-bath and wet tetrahydrofuran (50 ml) was added to destroy any residual lithium aluminium hydride. The mixture was filtered and the resulting clear solution evaporated to give an oil, which was dissolved in ethyl acetate and dried ($MgSO_4$). The solution was again evaporated and the resulting *oil* crystallised when kept in ethanol solution for 2 weeks at 0 °C (yield 190 mg, 45%); m.p. 115—120 °C; $\nu_{max.}$(KBr) 3 400—3 200, 3 000—2 800, and 1 610 cm^{-1}; δ[$(CD_3)_2SO$] 2.14 (m, H-2/3), 3.44 (m, H-1/4), 4.62 (t, *J* 5 Hz, C*H*OH), 5.40 (d, *J* 5 Hz, CHO*H*), 5.14 (s, CH_2OH), 3.68(s) and 3.64(s, OMe), and 6.5—6.9 (m, arom.).

threo-2,3-*Bis*-(α-*hydroxy*-4-*hydroxy*-3-*methoxybenzyl*)-*butane*-1,4-*diol* (21).—2,6-Bis-(4-acetoxy-3-methoxyphenyl)-3,7-dioxabicyclo[3.3.0]octane-4,8-dione (6) (2.35 g) dissolved in hot dry tetrahydrofuran (200 ml) was added carefully to a refluxing suspension of lithium aluminium hydride (1.52 g) in dry tetrahydrofuran (200 ml) under nitrogen. The mixture was stirred for 5 h under reflux and then cooled. The excess of lithium aluminium hydride was destroyed with wet tetrahydrofuran (50 ml) followed by powdered frozen carbon dioxide. The resulting suspension was filtered and

the solid was washed with hot tetrahydrofuran (100 ml). The combined solutions were dried (Na_2SO_4) and evaporated to give a clear *oil* which was crystallised from acetone–diethyl ether (2 : 1) (yield 1 g, 51%); m.p. 155—157 °C (Found: C, 60.8; H, 6.7. $C_{20}H_{26}O_8$ requires C, 60.9; H, 6.65%); $\nu_{max.}$(KBr) 3 400—3 200, 3 000—2 800, 1 610 cm^{-1}; δ[$(CD_3)_2SO$] 2.12 (m, H-2/3), 3.43 (m, H-1/4), 4.60 (t, *J* 5 Hz, C*H*OH), 5.31 (d, *J* 5 Hz, CHO*H*), 5.06 (s, CH_2O*H*), 8.55 (s, ArO*H*), 3.64 (s, OMe), and 6.5—6.8 (m, arom.); *m/z* 376.1522 (*M* − H_2O, $C_{20}H_{24}O_7$) and 358.1416 (*M* − $2H_2O$, $C_{20}H_{22}O_6$).

4,8-*Dihydroxypinoresinol* (7).—The dilactone (4) (390 mg) was dissolved in dry tetrahydrofuran (100 ml) at −68 °C under nitrogen. A solution of di-isobutylaluminium hydride in hexane (7 ml; 1.4M) was added and the resulting solution stirred at −68 °C for 1 h. Water (10 ml) was added to the cold solution, which was then allowed to warm slowly to room temperature. It was then extracted with ethyl acetate (3 × 50 ml) and the combined extracts were dried (Na_2SO_4) and evaporated to give a pale blue *powder* which was recrystallised from ethyl acetate (yield 310 mg, 80%); m.p. 186—192 °C (Found: C, 61.8; H, 5.5. $C_{20}H_{22}O_8$ requires C, 61.5; H, 5.6%); $\nu_{max.}$(KBr) 3 600—3 000, 3 000—2 800, and 1 610 cm^{-1}.

4,8-*Diacetoxypinoresinol diacetate* (8).—4,8-Dihydroxypinoresinol (7) (130 mg) was dissolved in dry pyridine (8 ml) and dry acetic anhydride (1 ml) added. The resulting solution was stirred for 16 h at room temperature, poured into water (60 ml), and extracted with ethyl acetate (3 × 25 ml). The combined extracts were washed with diluted hydrochloric acid (2 × 20 ml; 1M), and the ethyl acetate solution dried (Na_2SO_4) and evaporated to give a yellow powder. This was recrystallised from ethyl acetate to give white *crystals* (142 mg, 85%); m.p. 210—214 °C (Found: C, 60.2; H, 5.67. $C_{28}H_{30}O_{12}$ requires C, 60.2; H, 5.41%); $\nu_{max.}$(KBr) 3 000—2 800, 1 765, 1 740, 1 610 cm^{-1}.

4,8-*Dimethoxypinoresinol* (9).—4,8-Dihydroxypinoresinol (7) (130 mg) was dissolved in hot methanol (2 ml) and 1 drop of concentrated hydrochloric acid added. This solution was refluxed for 30 min and then cooled to 0 °C. White *crystals* separated and were filtered off, washed with ice-cold methanol and dried under vacuum (yield 83 mg, 66%); m.p. 208—210 °C (Found: C, 63.0; H, 5.9. $C_{22}H_{26}O_8$ requires C, 63.2; H, 6.2%); $\nu_{max.}$(KBr) 3 600—3 400, 3 040—2 820, and 1 605 cm^{-1}.

4,8-*Diethoxypinoresinol* (10).—4,8-Dihydroxypinoresinol (7) (130 mg) was dissolved in ethanol (2 ml) and 1 drop of concentrated hydrochloric acid added. This solution was refluxed for 30 min and then cooled to 0 °C. White *crystals* separated and were filtered off, washed with ice-cold ethanol and dried under vacuum (yield 124 mg, 93%); m.p. 190—192 °C (Found: C, 64.4; H, 7.1. $C_{24}H_{30}O_8$ requires C, 64.6; H, 6.7%); $\nu_{max.}$(KBr) 3 500—3 300, 3 000—2 800, and 1 610 cm^{-1}.

Hydrolysis of 4,8-*Dimethoxypinoresinol* (9).—4,8-Dimethoxypinoresinol (20 mg) was dissolved in acetone (10 ml) and diluted hydrochloric acid (5 ml; 0.1M) added. This mixture was refluxed for 1 h and then extracted with ethyl acetate (3 × 10 ml). The ethyl acetate solution was dried (Na_2SO_4) sulphate and evaporated to give a white solid (15 mg), identical with 4,8-dihydroxypinoresinol (7).

4,8-*Dimethoxypinoresinol Diacetate* (11).—4,8-Dimethoxypinoresinol (9) (104 mg) was dissolved in dry pyridine (8 ml) and dry acetic anhydride (1 ml) added. The solution was left for 16 h at room temperature and then poured into water (50 ml). The mixture was extracted with ethyl acetate (3 × 20 ml) and the combined extracts washed with water (15 ml), dried (Na_2SO_4), and then evaporated to give a yellow oil which was dried under vacuum and slowly solidified. The resulting yellow *solid* was recrystallised from ethyl acetate giving white crystals (110 mg, 88%); m,p. 100—101 °C (Found: C, 62.4; H, 5.6. $C_{26}H_{30}O_{10}$ requires C, 62.2; H, 6.0%); $\nu_{max.}$(KBr) 3 100—2 800, 1 765, and 1 615 cm^{-1}.

Oxidation of 4,8-*Dihydroxypinoresinol* (7).—4,8-Dihydroxypinoresinol (7) (50 mg) was dissolved in dry pyridine (2 ml) and added to a solution of dry chromium trioxide (52 mg) in dry pyridine (2 ml). This mixture was refluxed for 4 h and was then poured into water (20 ml). The mixture was extracted with ethyl acetate (2 × 15 ml), the combined extracts were dried (Na_2SO_4) and evaporated to give a yellow oil which solidified on washing with light petroleum. Crystallisation from methanol gave white plates (21 mg), identical with the dilactone (4).

4,8-*Dihydroxyeudesmin* (12).—2,6-Bis-(3,4-dimethoxyphenyl)-3,7-dioxabicyclo[3.3.0]octane-4,8-dione (5) (410 mg) was dissolved in dry tetrahydrofuran (100 ml) at −68 °C under nitrogen. A solution of di-isobutylaluminium hydride in hexane (11.2 ml; 0.89M) was added and the resulting solution stirred at −68 °C for 3 h. Ethyl acetate (100 ml) was added together with water (60 ml) and the mixture then allowed to warm to room temperature. The organic layer was separated and the aqueous layer extracted with ethyl acetate (50 ml). The organic layers were combined and dried (Na_2SO_4). Evaporation gave a white solid which was recrystallised from ethyl acetate (yield 401 mg, 96%); m.p. 218—220 °C; $\nu_{max.}$(KBr) 3 400—3 100, 3 000—2 800, and 1 610 cm^{-1}.

4,8-*Diacetoxyeudesmin* (13).—4,8-Dihydroxyeudesmin (140 mg) was dissolved in dry pyridine (8 ml) and dry acetic anhydride (1 ml) added. The resulting solution was stirred for 16 h at room temperature and was then poured into water (60 ml). This was extracted with ethyl acetate (3 × 20 ml). The extracts were combined and washed with diluted hydrochloric acid (2 × 15 ml; 1M) and with water (20 ml), dried (Na_2SO_4), and evaporated to give a clear *oil*. This solidified on washing with light petroleum and was recrystallised from ethyl acetate (yield 140 mg, 93%); m.p. 137—139 °C (Found: C, 62.3; H, 5.85. $C_{26}H_{30}O_{10}$ requires C, 62.1; H, 6.0%); $\nu_{max.}$(KBr) 3 030—2 800, 1 740, and 1 610 cm^{-1}.

4,8-*Dimethoxyeudesmin* (14).—4,8-Dihydroxyeudesmin (12) (140 mg) was dissolved in hot methanol (2 ml) and 1 drop of concentrated hydrochloric acid added. This solution was refluxed for 30 min and was then cooled to 0 °C. White *crystals* separated and were filtered off, washed with ice-cold methanol and dried under vacuum (yield 82 mg, 61%); m.p. 98—100 °C (Found: C, 65.0; H, 6.5. $C_{24}H_{30}O_8$ requires C, 64.6; H, 6.7%); $\nu_{max.}$(KBr) 3 000—2 800 and 1 605 cm^{-1}.

Hydrolysis of 4,8-*Dimethoxyeudesmin* (14).—4,8-Dimethoxyeudesmin (20 mg) was dissolved in acetone (5 ml) and diluted hydrochloric acid (2 ml; 1M) added. This solution was refluxed for 1 h and extracted with ethyl acetate (10 ml). The extract was dried (Na_2SO_4) and evaporated leaving a white solid. This was recrystallised from ethyl acetate giving white crystals (9 mg) having physical properties identical with those of 4,8-dihydroxyeudesmin (12).

4,8-*Bisbutylthiopinoresinol* (24).—4,8-Dihydroxypinoresinol (7) (200 mg) was dissolved in dry tetrahydrofuran (5 ml) with boron trifluoride–ether complex (1 ml) at room

temperature. Butanethiol (180 mg) was added and the solution stirred at room temperature for 1 h. Dichloromethane (50 ml) was added and the mixture washed with water (4 × 10 ml). It was then dried ($MgSO_4$) and evaporated to give a pale yellow oil. This material was placed on a silica gel column which was eluted with diethyl ether to remove any remaining butanethiol. The desired product was then obtained by washing the column with dichloromethane. This gave a clear oil which did not crystallise (yield 248 mg, 91%); $\nu_{max.}$(film) 3 500—3 300, 3 000—2 800, and 1 610 cm^{-1}; $\delta(CDCl_3)$ 5.02 (d, *J* 6 Hz, H-2/6), 3.04 (m, H-1/5), 5.36 (H-4/8), 2.68 (t, *J* 7 Hz, SCH_2), 1.4 (m, CH_2CH_2), 0.95 (t, *J* 7 Hz, CH_3), 3.88 (s, OMe), 5.2 (br, s, ArO*H*), and 6.6—7.2 (m, arom.).

Attempted Reduction of 4,8-*Bisbutylthiopinoresinol* (24).—4,8-Bisbutylthiopinoresinol (120 mg) dissolved in ethanol (20 ml) was added to a suspension of freshly prepared Raney nickel (1 g) in ethanol (20 ml). This mixture was stirred for 1 h and was then filtered and evaporated to leave a yellow oil from which white crystals were obtained (from ethyl acetate) of 4,8-diethoxypinoresinol (10). T.l.c. of the mother liquor showed the presence of only this and starting material.

This experiment was repeated in the presence of hydrogen at 140 lb in^{-2} for 16 h. The same product was obtained.

Eudesmin (18).—4,8-Dihydroxyeudesmin (12) (102 mg) was dissolved in dry pyridine (2 ml) at 0 °C and toluene-*p*-sulphonyl chloride (114 mg) added. The mixture was kept at 0 °C for 48 h and then poured into water (20 ml) and extracted with ethyl acetate (3 × 15 ml). The combined extracts were dried (Na_2SO_4) and evaporated to give the ditosylate (16) as a yellow oil. This oil was dissolved in dry tetrahydrofuran (40 ml) and added to a suspension of lithium aluminium hydride (152 mg) in tetrahydrofuran (20 ml). The mixture was stirred for 30 min at room temperature and then water (5 ml) was added. The resulting suspension was extracted with ethyl acetate (3 × 50 ml) and the combined extracts were dried (Na_2SO_4) and then evaporated to give an oil. This material was purified by preparative t.l.c. on silica to give (±)-eudesmin (19 mg, 20%); m.p. 104—106 °C (lit.,[14] 107 °C) (Found: C, 68.4; H, 6.9. $C_{22}H_{26}O_6$ requires C, 68.4; H, 6.8%); $\nu_{max.}$(KBr) 3 000—2 800 and 1 610 cm^{-1}.

4,8-*Bistosyloxypinoresinol Ditosylate* (15).—4,8-Dihydroxypinoresinol (7) (100 mg) was dissolved in dry pyridine (2 ml) at 0 °C and toluene-*p*-sulphonyl chloride (228 mg) was added. The mixture was kept at 0 °C for 48 h, then poured into water (20 ml) and filtered to give a white solid which was dried under vacuum (yield 245 mg, 92%).

Pinoresinol (17) *and Epipinoresinol* (25).—*threo*-2,3-Bis-(α-hydroxy-4-hydroxy-3-methoxybenzyl)butane-1,4-diol (21) (5 g) was dissolved in dry ethanol (25 ml) and cooled to 0 °C. The solution was then added to dry ethanolic hydrogen chloride (25 ml; 3M) at 0 °C and kept at this temperature for 10 min with occasional swirling. Ethyl acetate (300 ml) at 0 °C was then added and the resulting solution was extracted with sodium hydrogen carbonate solution (2 × 30 ml; 1M) and washed with water (2 × 30 ml). The resulting solution was dried (Na_2SO_4) and then evaporated to give a clear oil. Chromatography of this oil on silicic acid eluted with dichloromethane gave an oil which slowly solidified (yield 2.36 g, 52%). T.l.c. showed two products which were separated by preparative t.l.c. to yield (±)-pinoresinol (1.08 g), m.p. 118—121 °C (lit.,[15] 120—121 °C) (Found: C, 67.1; H, 5.95. $C_{20}H_{22}O_6$ requires C, 67.0; H, 6.15%); $\nu_{max.}$(KBr) 3 600—3 200, 3 000—2 800, and 1 610 cm^{-1}, and (±)-epipinoresinol (1.13 g), m.p. 135—137 °C (lit.,[15] 137—138 °C); $\nu_{max.}$(KBr) 3 600—3 200, 3 000—2 800, and 1 610 cm^{-1}; $\delta(CDCl_3)$ 4.44 (d, *J* 7 Hz, H-2), 4.84 (d, *J* 5 Hz, H-6), 2.9 (m, H-1), 3.1 (m, H-5), 3.35 [m, H-4(a)], 3.80 [m, H-8(a)], 3.80 [m, H-4(e)], 4.12 [d, *J* 10 Hz, H-8(e)], 3.82 (s, OMe), 5.6 (br, s, OH), and 6.7—6.9 (m, arom.).

Eudesmin (18).—*threo*-2,3-Bis-(α-hydroxy-3,4-dimethoxybenzyl)butane-1,4-diol (22) (210 mg) dissolved in dry ethanol (10 ml) was added to dry ethanolic hydrogen chloride (10 ml; 1M). This solution was refluxed for 1 h, then cooled and ethyl acetate (150 ml) was added. The resulting solution was extracted with aqueous sodium hydrogen carbonate (2 × 15 ml; 1M) and washed with water (2 × 15 ml), then dried (Na_2SO_4) and evaporated to an oil. Column chromatography of this oil over silicic acid eluted with dichloromethane gave (±)-eudesmin as a white crystalline solid (92 mg, 43%); m.p. 104—106 °C (lit.,[15] 107 °C).

2,6-*Bis*-(3,4-*methylenedioxyphenyl*)-3,7-*dioxabicyclo*-[3.3.0]*octane*-4,8-*dione* (23).—A solution of 3,4-methylenedioxycinnamic acid (1.54 g) in trifluoroacetic acid (20 ml) and dichloromethane (80 ml) was added all at once to a vigorously stirred solution of thallium(III) trifluoroacetate (4.8 g) in trifluoroacetic acid (3 ml) and dichloromethane (10 ml) containing boron trifluoride–ether (2 ml) at room temperature. The reaction was immediately quenched with t-butyl alcohol (60 ml). Chloroform (300 ml) was then added to the mixture, which was then washed with water (4 × 150 ml), followed by aqueous 5% sodium hydrogen carbonate (3 × 100 ml) and dried (Na_2SO_4). The reaction was repeated two more times and the products were combined (3.16 g) and purified on a column of alumina eluted with chloroform–pentane (1 : 1) to give the pure product (23) (0.4 g, 9%); m.p. 192—193 °C (lit.,[1] 199 °C); $\nu_{max.}$(KBr) 1 773 cm^{-1}; *m/z* 382 (40%, $M^{+\cdot}$), 188 (26), and 149 (100).

4,8-*Dihydroxysesamin* (2).—2,6-Bis-(3,4-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octane-4,8-dione (23) (382 mg) was dissolved in dry tetrahydrofuran (100 ml) at room temperature under nitrogen. The temperature was lowered to −78 °C and a solution of di-isobutylaluminium hydride in hexane (10 ml; 2.6M) was added and the solution stirred for 8 h. Ethyl acetate (100 ml) and water (60 ml) were added and the mixture allowed to warm to room temperature. The layers were separated and the aqueous layer extracted with ethyl acetate (3 × 50 ml). The organic extracts were combined, dried (Na_2SO_4) and evaporated to give a light brown crystalline material (360 mg). This had ^1H n.m.r., i.r. and mass spectra identical with those of the natural product and on recrystallisation from ethyl acetate gave a pure sample with m.p. 147—149 °C (164 mg, 43%) (lit.,[1] 150 °C); $\nu_{max.}$(KBr) 3 500—3 100 cm^{-1}; *m/z* 236 (1%, $M^{+\cdot}$) and 149 (100).

4,8-*Diacetoxysesamin* (3).—4,8-Dihydroxysesamin (100 mg) was added to a mixture of acetic anhydride (2 ml) and pyridine (4 ml). The mixture was stirred for 60 h before being added to iced water (50 ml); a crystalline product separated. The crystals were washed with ether (yield 82 mg, 69%); m.p. 207—209 °C; $\nu_{max.}$(KBr) 1 745 cm^{-1}; *m/z* 470 (41%, $M^{+\cdot}$), 410 (2), 219 (24), 177 (67), 159 (57), and 149 (81).

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REFERENCES

[1] A. S. R. Anjaneyulu, A. Madhusudhana Rao, V. Kameswara Rao, L. Ramachandra Row, A. Pelter, and R. S. Ward, *Tetrahedron*, 1977, **33**, 133.
[2] H. Erdtman, *Svensk. Kem. Tids.*, 1935, **47**, 223.
[3] N. J. Cartwright and R. D. Haworth, *J. Chem. Soc.*, 1944, 535.
[4] L. J. Bellamy, ' The Infrared Spectra of Complex Molecules,' Methuen, London, 1958.
[5] G. C. Levy, R. L. Lichter, and G. L. Nelson, ' Carbon-13 Nuclear Magnetic Resonance Spectroscopy,' 2nd edn., Wiley, New York, 1980.
[6] D. Lavie, E. C. Levy, M. Evenari, and T. Gutterman, *Nature*, 1974, **249**, 388.
[7] R. Cooper, E. C. Levy, and D. Lavie, *J. Chem. Soc., Chem. Commun.*, 1977, 794.
[8] R. Cooper, H. E. Gottlieb, D. Lavie, and E. C. Levy, *Tetrahedron*, 1979, **35**, 861.
[9] C. H. Brieskorn and H. Huber, *Tetrahedron Lett.*, 1976, 2221.
[10] D. Takaoka, N. Kakamatsu, Y. Saheki, K. Kono, C. Nakaoka, and M. Hiroi, *Nippon Kagaku Kaishi*, 1975, 2192.
[11] A. Pelter and R. S. Ward, ' Chemistry of Lignans,' ed. C. B. S. Rao, Andhra Univ. Press, Visakhapatnam, India, 1978, ch. 7.
[12] E. C. Taylor, J. G. Andrade, G. J. H. Rall, and A. McKillop, *Tetrahedron Lett.*, 1978, 3623.
[13] A. Pelter, R. S. Ward, D. J. Watson, P. Collins, and I. T. Kay, *Tetrahedron Lett.*, 1979, 2275.
[14] R. Robinson and H. G. Smith, *Proc. R. Soc. N.S.W.*, 1914, 449.
[15] K. Weinges, *Tetrahedron Lett.*, 1960, 1; *Chem. Ber.*, 1961, 2522.