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Preparation of Tetrahydrodibenzocyclooctene Lignans and Spirodienones by Hypervalent Iodine Oxidation of Phenolic Dibenzylbutyrolactones.[1]

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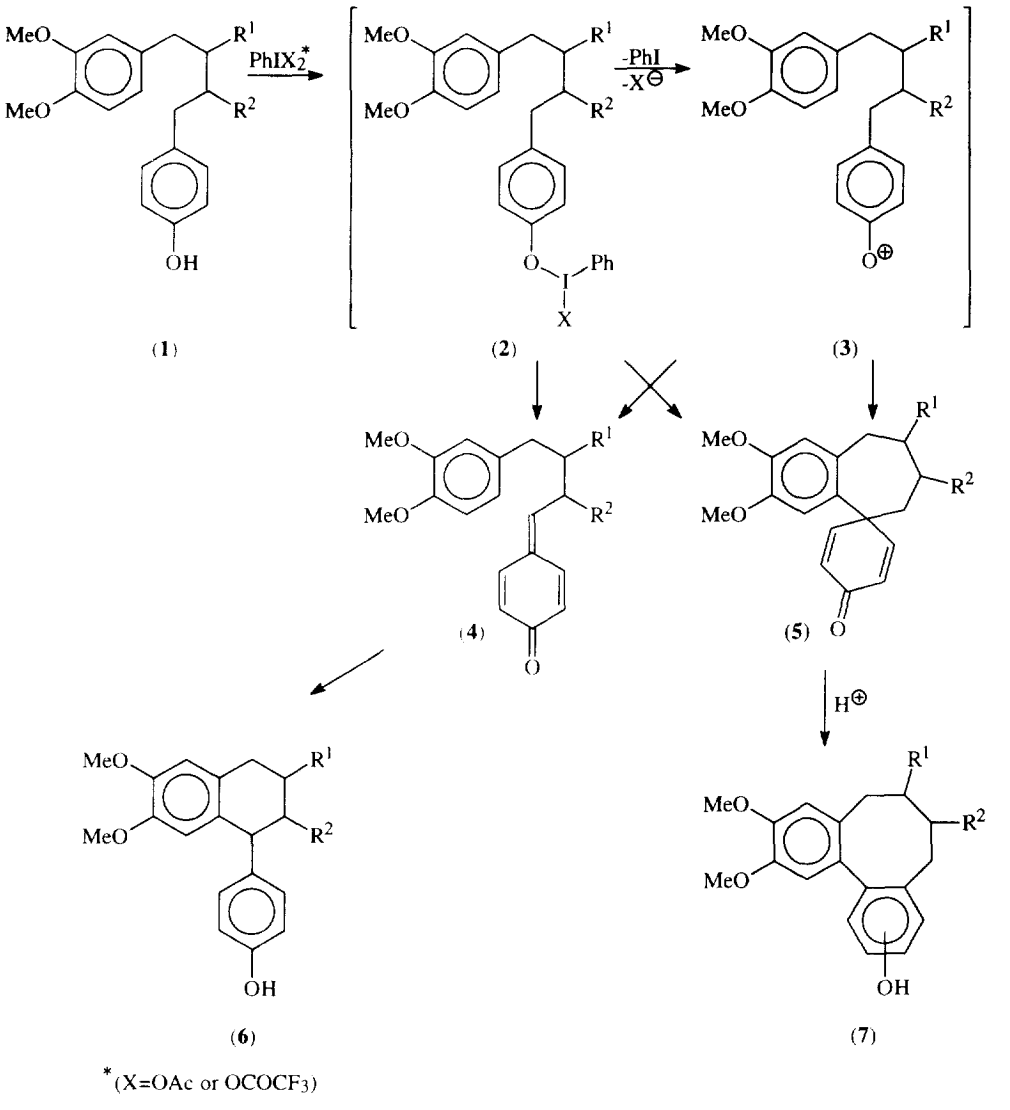
Abstract: Treatment of the dibenzylbutyrolactone **18** with $PhI(OCOCF_3)_2$ in trifluoroethanol gives as the major product either the spirodienone **28** or the tetrahydrodibenzocyclooctene **29**, depending upon the length of time allowed for the reaction. Reaction of a second dibenzylbutyrolactone **19** under the same conditions gives the products **33, 34, 36** and **38**, while **20** gives **43** directly. These reactions provide the first syntheses of spirodienones such as **28** and **33**, which have been postulated as intermediates in the biosynthesis of tetrahydrodibenzocyclooctene lignans.

INTRODUCTION

We have previously shown that phenyliodonium diacetate reacts with phenols in methanol to give cyclohexadienones and quinone ketals[2] which are valuable intermediates in organic synthesis.[3] Oxidation of phenols in less nucleophilic solvents such as acetonitrile or trifluoroethanol (TFE) allows intramolecular reactions to take place leading to cyclisation.[4,5] Of particular interest are examples in which carbon-carbon bond formation is achieved.[6-8] We have attempted to make use of this reaction to imitate the oxidatively induced cyclisations involved in the biosynthesis of various classes of lignans.[1,9]

Thus it was envisaged that a diarylbutane derivative **1** would react with phenyliodonium diacetate (PIDA) or phenyliodonium trifluoroacetate (PIFA) to give an intermediate **2** (Scheme 1). In the absence of an external nucleophile this could then react directly or *via* the phenyloxenium ion **3** to give either the quinone-methide **4** or the spirodienone **5**. The former would be expected to cyclise to give an aryltetralin **6** and the process would therefore be analogous to the biosynthetic pathway leading to such compounds.[10,11] The latter would be expected to undergo an acid-catalysed dienone-phenol rearrangement leading to a tetrahydrodibenzocyclooctene **7** which would be analogous to the presumed biosynthetic pathway leading to compounds of the steganacin and schisandrin type.[9,12]

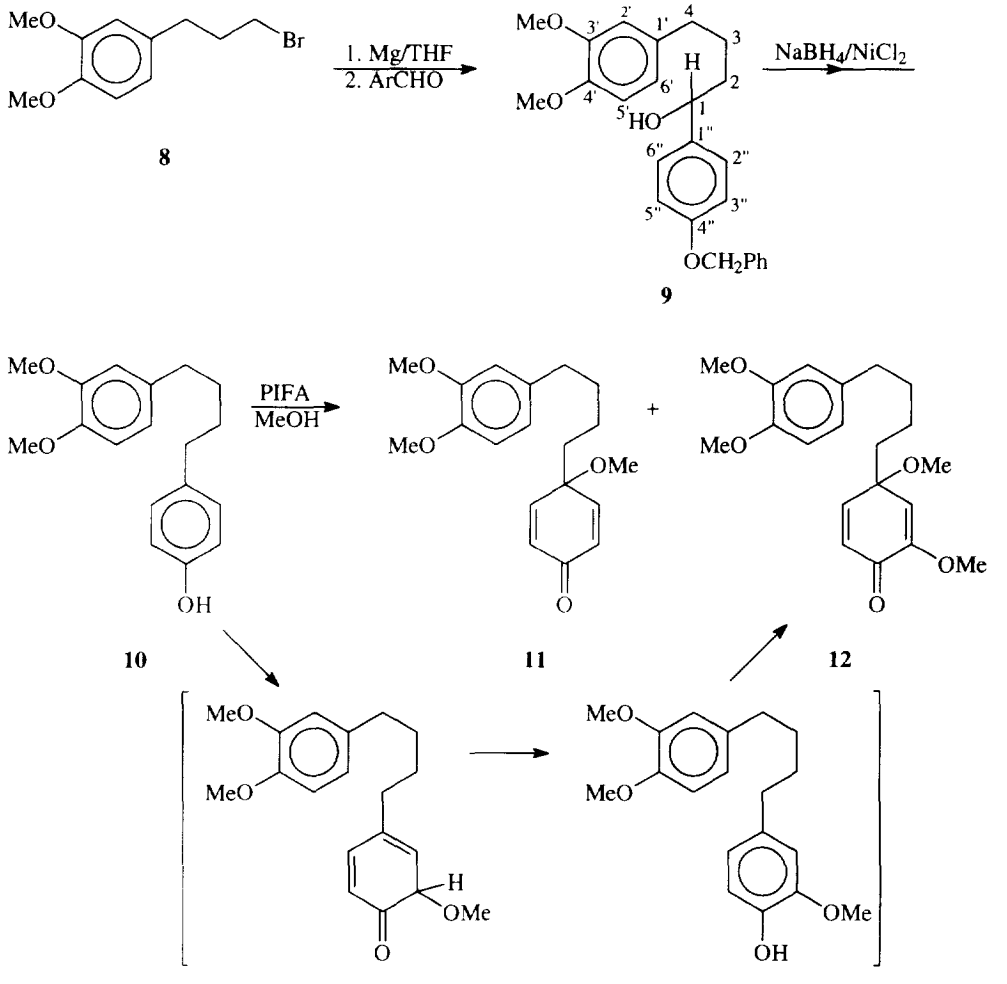


Scheme 1

RESULTS

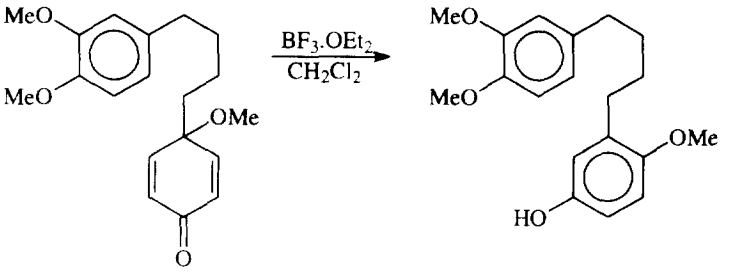
We first of all examined the reactions of the diarylbutane **10** which was conveniently prepared by reacting the Grignard reagent derived from 1-bromo-3-(3,4-dimethoxyphenyl)propane (**8**)[13,14] with 4-benzyloxybenz-aldehyde to give **9**, hydrogenation of which gave **10** in an overall yield of 52%. Reaction of **10** with PIDA (1.2 equiv.) in anhydrous methanol at room temperature gave the 4-methoxycyclohexadienone **11** in 30% yield. When the same reaction was carried out using PIFA under the same conditions **11** was again obtained in 30% yield along with a second product **12** which

was isolated in 12.5% yield. A possible pathway to account for the formation of **12** is shown in Scheme 2. The ^{1}H and ^{13}C NMR spectra of **10**, **11** and **12** are listed in Tables 1 and 2.



Scheme 2

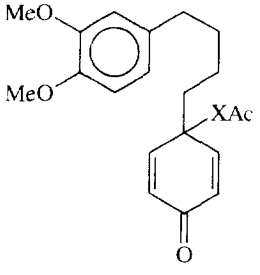
Treatment of **11** with BF_3-etherate in dry dichloromethane gave a quantitative yield of the alkyl migrated product **13**, with no hint of cyclisation (equation 1). Use of other Lewis acids and protic acids also did not lead to cyclisation.



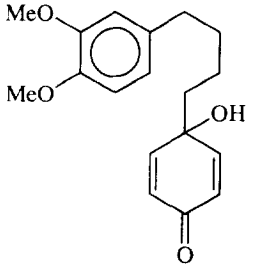
(1)

11 **13**

We therefore decided to investigate the oxidation of **10** in less nucleophilic solvents than methanol in the hope of inducing intramolecular attack leading to cyclisation. Reaction of **10** with PIDA in acetonitrile under reflux gave a complex mixture from which the acetylamino compound **14** and the acetoxy compound **15** were isolated in 23% and 16% yields respectively. Reaction of **10** with PIFA in trifluoroacetic acid at room temperature gave a complex mixture from which one fraction could be isolated (30%) which, on the basis of its NMR and mass spectra, appeared to consist of a 1:1 mixture of the starting material **10** and a tetrahydrodibenzocyclooctene **7** ($R^1 = R^2 = H$). However **7** could not be obtained in pure form and therefore was not fully characterised. Reaction of **10** with PIFA in dry dichloromethane under reflux gave a complex mixture from which on work-up 4-hydroxy-cyclohexadienone **16** was isolated in 10% yield. The ^1H and ^{13}C NMR spectra of **14**, **15** and **16** are listed in Tables 1 and 2.



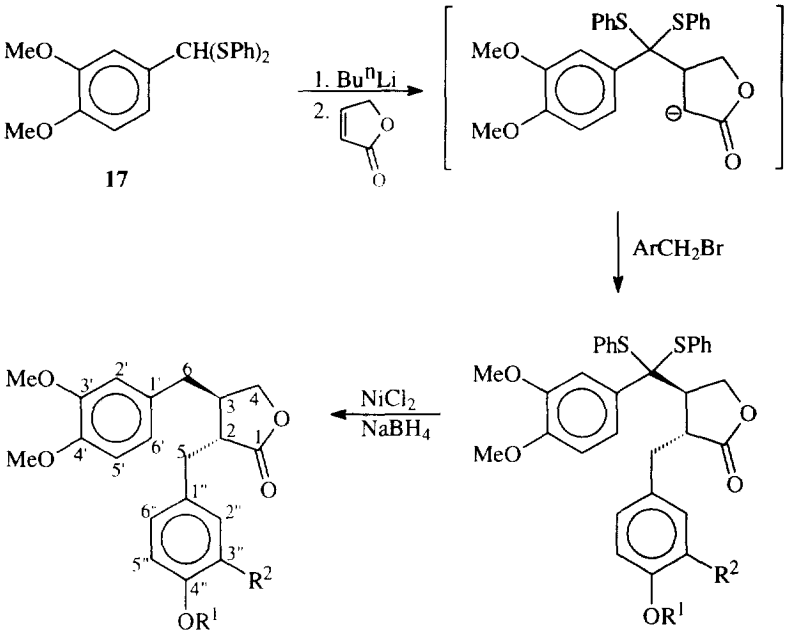
14 X = NH
15 X = O



16

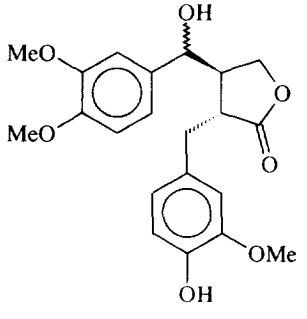
We therefore turned our attention to the phenolic dibenzylbutyrolactones **18-20** in which the two benzyl groups are held in a more rigid orientation, and which are also more closely analogous to lignan precursors than **10**. Compounds **18-20** were prepared using the tandem conjugate addition methodology developed in these laboratories (Scheme 3).[15] Lithiation of 3,4-dimethoxybenzaldehyde bis(phenylthio)acetal (**17**)[16] followed by addition of butenolide and subsequent trapping of the

enolate with the corresponding benzyl bromide gave the adducts **21-23** in 65%, 55% and 61% yields respectively. In each case only the *trans* diastereoisomer was obtained, in line with previous results.[15,16] Desulphurisation of **21-23** with nickel boride [17,18] was accompanied by debenzylation and gave the required phenolic dibenzylbutyrolactones **18-20** in 61%, 68% and 79% isolated yield respectively. Compound **22** also gave a 20% yield of the hydroxy derivative **24**. The ^{1}H and ^{13}C NMR spectra of these compounds are listed in Tables 3 and 4.



18 $R^1 = R^2 = H$
19 $R^1 = H$, $R^2 = OMe$
20 $R^1 = CH_3$, $R^2 = OH$

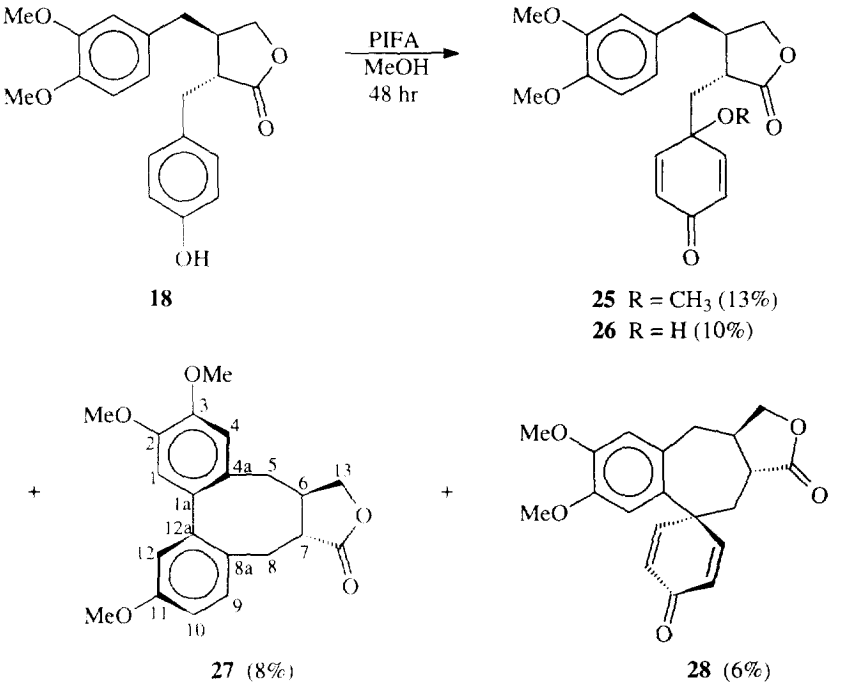
21 $R^1 = CH_2Ph$, $R^2 = H$
22 $R^1 = CH_2Ph$, $R^2 = OMe$
23 $R^1 = CH_3$, $R^2 = OCH_2Ph$



24

Scheme 3

Treatment of **18** with PIFA (3 equiv.) in methanol over 48 hours gave a mixture of products from which products **25-28** were isolated in low yield (Scheme 4). However, treatment of **18** with PIFA (1.2 equiv.) in TFE for 24 hours gave as a major product the isostegane derivative **29** (48%) together with some of the corresponding stegane isomer **31** (6%) and the spirodienone **28** (10%) (Scheme 5). When the same reaction was stopped after 1 hour the spirodienone **28** was obtained as the major product (47%), together with a minor amount of the trifluoroethanol adduct **32** (3%). The ^{1}H and ^{13}C NMR spectra of **25**, **26** and **32** are listed in Tables 3 and 4.



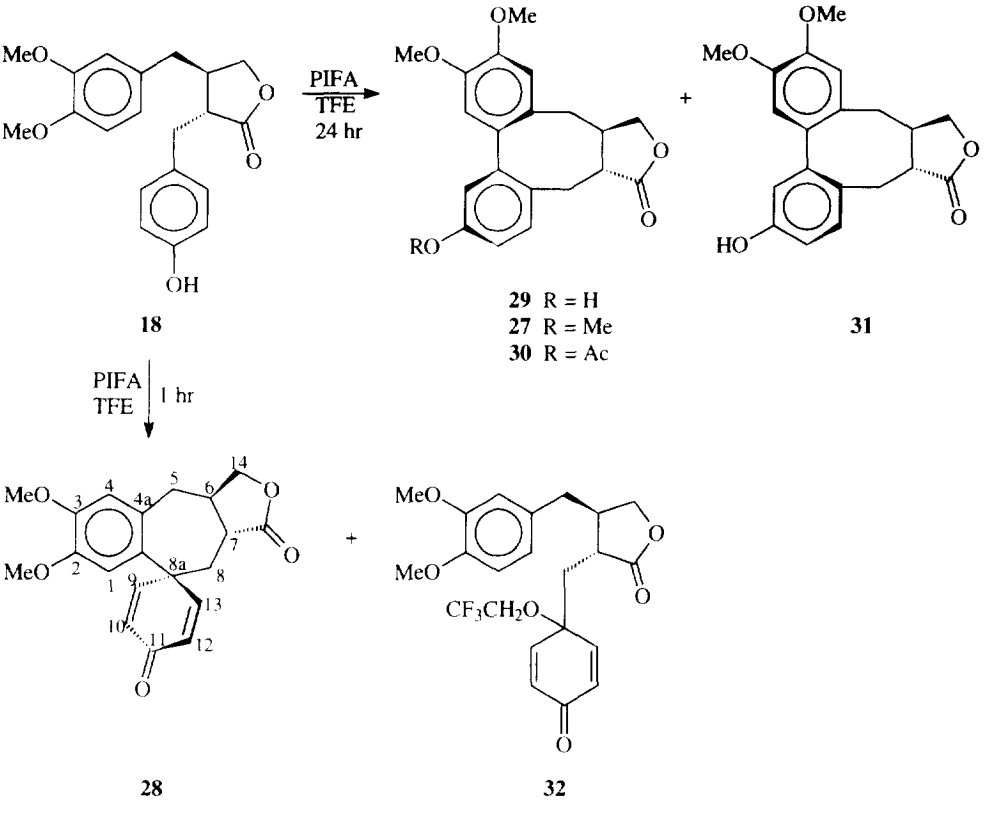
18

25 R = CH_3 (13%)
26 R = H (10%)

27 (8%)

28 (6%)

Scheme 4



Scheme 5

The structure assigned to the spirodienone **28** was based upon a detailed analysis of its ^{1}H and ^{13}C NMR spectra (Tables 5 and 6), including NOE experiments,[19] and was confirmed by X-ray analysis.[20] Dreiding models indicate the possible existence of two distinct conformers of **28** differing in the relative orientation of the cyclohexadienone ring and the aryl group. The observed NOE effects and the X-ray structure indicate that the conformation shown in Figure 1 is the preferred arrangement both in solution and in the solid state. Thus the observed NOE effects between H-1 and H-9, H-5α and H-13, H-5α and H-7, H-7 and H-13 are only consistent with this conformation.

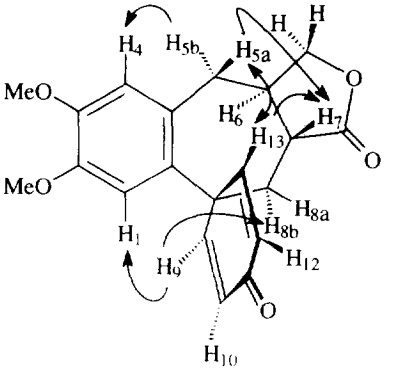
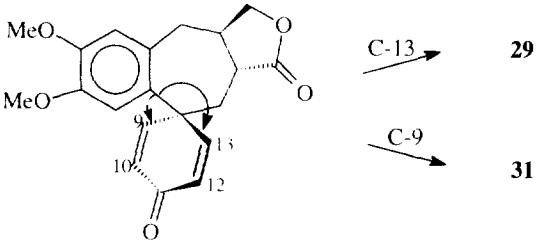


Figure 1 NOE data for 28

The structures of the tetrahydrodibenzocyclooctenes **29** and **31** were based upon a detailed analysis of their ^{1}H and ^{13}C NMR spectra (Tables 7 and 8), and comparison with the spectral data of related compounds.[21,22] In particular, the zero coupling between H-5α and H-6, and between H-8β and H-7 in the spectrum of **29** (and its methyl ether **27** and acetate **30**) is characteristic of the isostegane series. Furthermore the chemical shifts of C-6 and C-7 in the ^{13}C spectra are also characteristic of the two series, coming at *ca.* 47 and 50 ppm in the isosteganes **29**, **27** and **30**, and at *ca.* 39 and 43 ppm. in the stegane isomer **31**. The observation of a clear NOE between H-9 and H-8β in **29** and between H-9 and H-5α in **31** showed that both compounds have the phenolic OH group located at C-11. The structure assigned to **29** was subsequently confirmed by X-ray crystallography.[20]

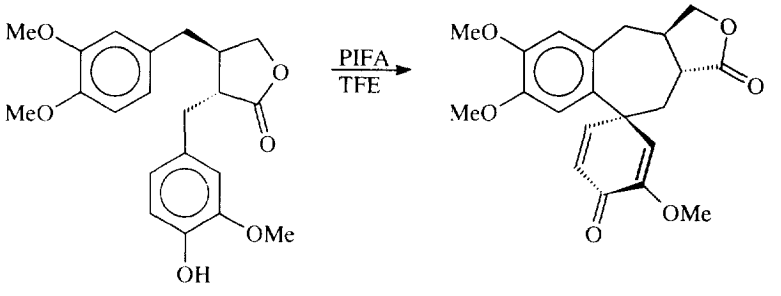
That the tetrahydrodibenzocyclooctene **29** was formed by rearrangement of spirodienone **28** was confirmed by treating **28** with trifluoroacetic acid in trifluoroethanol which gave a nearly quantitative yield of **29**. The fact that the phenolic OH group in **29** is located at C-11 indicates that **29** must be formed by an aryl rather than an alkyl migration. The structure assigned to **31** also suggests that if this compound is formed by the same pathway, then it too must be formed by an aryl migration. A model of **28** indicates that aryl migration to C-9 would give the stegane isomer **31** whereas aryl migration to C-13 would give the isostegane **29** (Scheme 6), and that the latter pathway is sterically preferred.



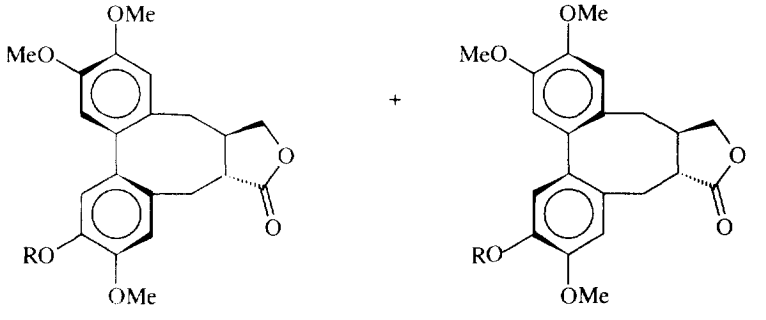
28

Scheme 6

We next turned our attention to the oxidation of arctigenin (**19**).[23] Treatment with PIFA (1.2 equiv.) in TFE for 24 hr gave a mixture of products from which two main fractions were isolated. The more polar was identified as the spirodienone **33** which was obtained in 13% yield. The second less polar fraction was shown to be a mixture containing the stegane derivative **34** and the isostegane **36** in an overall yield of 14% (Scheme 7). When the reaction was repeated in hexafluoroisopropanol for 3.5 hr. a 1:1 mixture of the stegane **34** and the isostegane **36** was obtained in 26% yield. Compounds **34** and **36** were separated by recrystallisation. The composition of the mixture differed greatly from that obtained from **18** in which the isostegane was formed in a highly preferential fashion.



19 **33**



34 R = H
35 R = Ac

36 R = H
37 R = Ac

Scheme 7

The structure assigned to the spirodienone **33** was based upon a detailed analysis of its ^{1}H and ^{13}C NMR spectra (Tables 5 and 6), including NOE experiments[19] which clearly indicated that the methoxy group was located at C-12. Thus the observed NOE effects between H-1 and H-9; H-5α and H-13; H-7 and H-13; H-7 and H-14β; H-8β and H-6; and H-8β and H-9 are only consistent with the structure **33** with the conformation shown in Figure 2.

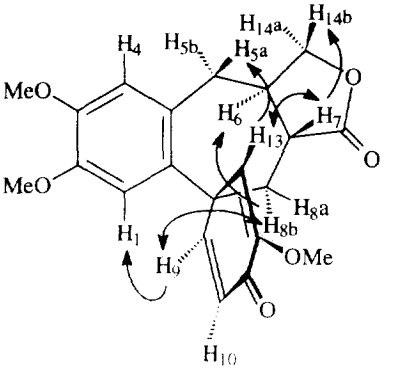
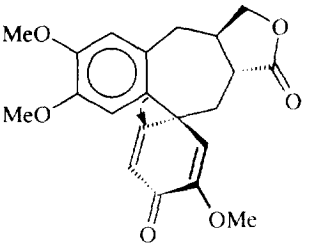


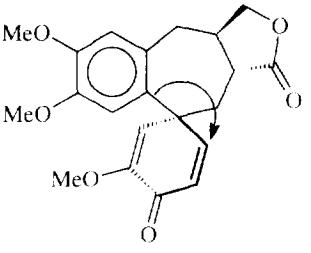
Figure 2 NOE data for 33

The structures of the tetrahydrodibenzocyclooctenes **34** and **36** were based upon a detailed analysis of their ^{1}H and ^{13}C NMR spectra (Tables 7 and 8), including NOE experiments and comparison with the spectra of related compounds **29**, **31** and **43**. This showed that **34** belongs to the stegane series and **36** belongs to the isostegane series, and that the phenolic OH group is at C-11 in both compounds. The structures of both **34** and **36** were subsequently confirmed by X-ray crystallography.[20]

Significantly, reaction of the spirodienone **33** with perchloric acid gave a quantitative yield of **34** only. This therefore suggests that two isomeric spirodienones **33** and **38** were initially produced, **33** rearranging to give **34**, and **38** (not isolated) rearranging to give **36**. Examination of molecular models shows that **34** is formed by an aryl migration to C-9, whereas **36** is formed by an aryl migration to C-13 (Scheme 8). In no case was migration to the carbon α to that bearing the methoxy group observed and this effect takes precedence over the sterically preferred migration to the "upper" position of the cyclohexadienone ring. The conversion of **33** to **34** and **38** to **36** is in line with the reported rearrangement of eupodienone-8 (**39**) to the schizandrin derivative **40** (Scheme 9).[24] In this respect however it differs from the behaviour of the other eupodienones (e.g. **41**), which undergo an alkyl migration.

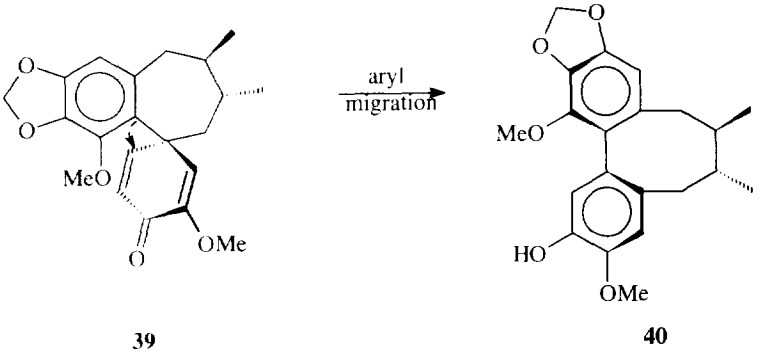


33 **34**

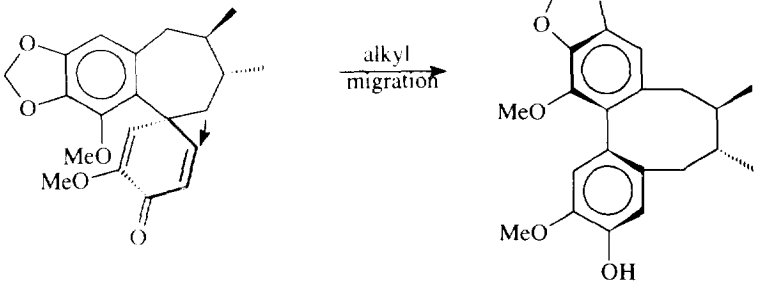


38 **36**

Scheme 8



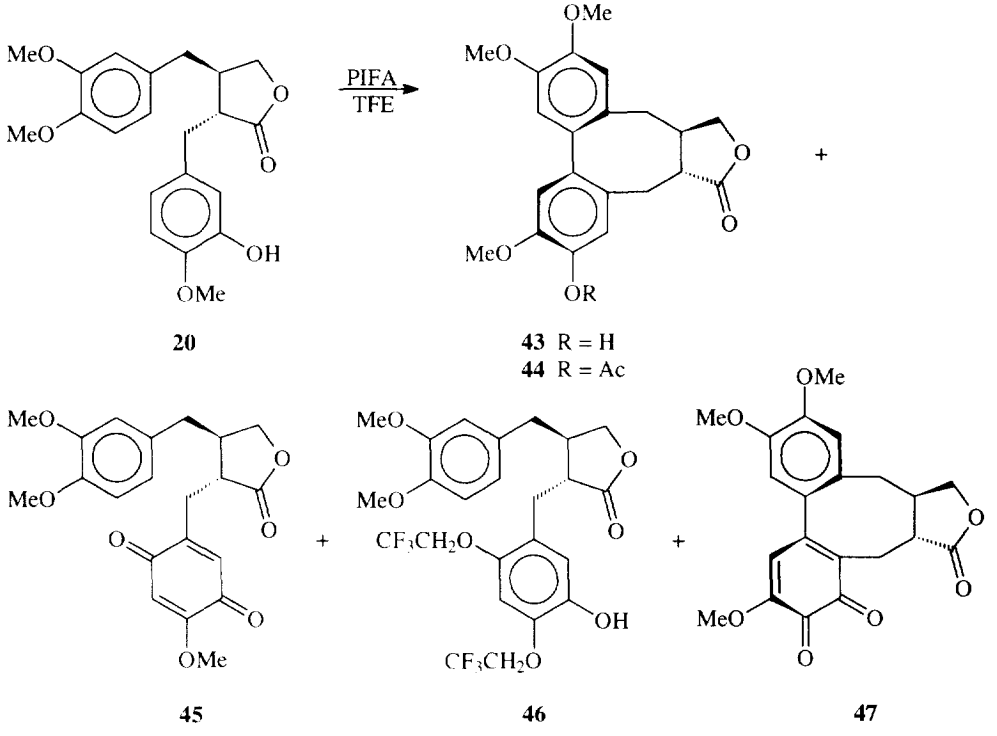
39 **40**



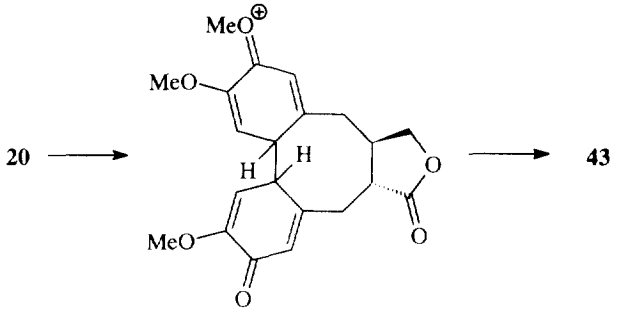
41 **42**

Scheme 9

Finally, we have examined the oxidation of prestegane A (**20**)[25] using PIFA (1.2 equiv.) in TFE. The major product formed (40%) was the isostegane derivative **43** which was obtained along with smaller amounts of **45-47** (23%, 24% and 3% respectively, Scheme 10). It is noteworthy that the formation of **43** involves direct coupling between carbon atoms 6′ and 6″ and does not require the intervention and rearrangement of a spirodienone intermediate. The preferential formation of the isostegane isomer therefore results from the coupling step itself or the subsequent enolisation of the first formed dienone **48** (Scheme 11). The isostegane derivatives **43** and **47** were also obtained in 72% and 17% yield respectively by treating **20** with ruthenium (IV) dioxide,[26] the structures being assigned on the basis of their ^{1}H and ^{13}C NMR spectra (Tables 7 and 8). The zero coupling between H-5α and H-6 and between H-8β and H-7 in both compounds is characteristic of the isostegane series,[21,22] as are the chemical shifts of C-6 and C-7 at 46.81 and 50.03 for **43**. The structure of **43** was subsequently confirmed by X-ray crystallography.[20]



Scheme 10



Scheme 11

The ^{1}H NMR spectra of **45** and **46** showed clearly the two singlet peaks for H-3″ and H-6″ at 6.54 and 5.86 ppm for **45** and at 6.83 and 6.45 for **46**. Compound **46** also showed quartets at 4.26 and 4.42 ppm for the two trifluoroethoxy groups (Table 3). The ^{13}C NMR spectrum showed clearly the two carbonyl carbon atoms (C-2″ and C-5″) at 187.02 and 181.63 ppm for **45** and the expected peaks for the trifluoroethoxy groups for **46** (Table 4). The ^{1}H NMR of **47** showed a large degree of shielding at positions H-7 and H-8α and also a large degree of deshielding at position H-8β as compared to **43**. The ^{13}C NMR of **47** showed also a large degree of shielding of C-7 (46.31) and C-8 (24.28) as compared to **43** (50.03 and 31.67 respectively) (Tables 7 and 8). The UV spectrum of **47** showed a new peak at 360.8 nm (ε=4284) when a small amount of aluminium chloride was added to the methanol solution, as compared to λ_{max} 327.6 nm (ε =1428) without aluminium chloride. The bathochromic shift resulted from the chelation of aluminium chloride with the two adjacent carbonyl groups of the quinone.

Conclusion. The oxidation of phenols to substituted 1,4-cyclohexadienones by phenyliodonium derivatives has been applied to 2,3-dibenzylbutyrolactones which yield spirodienones which have undergone oxidative cyclisation. On exposure to acid, the spirodienones give tetrahydrodibenzocyclooctene lignans by an aryl migration, the stereochemistry of which is elucidated. These reactions provide models for possible biosynthetic pathways as well as giving access to a variety of 8-membered ring lignans.

Table 1. ^{1}H NMR spectra of **10** and **11**-**16**.[a,b]

	10	**11**	**12**	**13**	**14**	**15**	**16**
H-1		2.52 t (7.67)	2.53 t (7.77)		1.80-1.87 m	1.81-1.89 m	1.74-1.81 m
H-4	}2.55-2.56 m [4H]	1.71-1.78 m	1.76-1.83 m	}2.57 t (7) [2H]	2.45-2.56 m	2.07-2.57 m	2.52 t (7.9)
H-2		1.25-1.33 m	1.25-1.34 m			1.24-1.38 m	1.26-1.34 m
H-3	}1.58-1.64 m [4H]	1.57 m	1.53-1.62 m	}1.61 m [2H]	}1.30-1.62 m [2H]	1.56-1.65 m	1.56-1.65 m
H-2″			5.55 d (2.71)	—			
H-6″	}7.00 d (8.46) [2H]	}6.68 d (10.4) [2H]	6.72 dd (2.71, 10.13)	6.76 s	}6.81 d (10) [2H]	}6.83 d (10) [2H]	}6.81 d (10) [2H]
H-4″	—	—	—		—	—	—
H-3″			—	}6.66-6.75 m [2H]	}6.25 d (10) [2H]	}6.27 d (10) [2H]	}6.13 d (10) [2H]
H-5″	}6.74 d (8.46) [2H]	}6.35 d (10.4) [2H]	6.36 d (10.13)	—			
H-2′		6.65 s	6.67 s	6.63 s			
H-5′	}6.70 m [3H]	6.73 d (8.5)	6.68 d (8.6)	}6.66-6.75 m [2H]	}6.63-6.77 m [3H]	}6.66-6.80 m [3H]	}6.66-6.73 m [3H]
H-6′		6.78 d (8.5)	6.78 d (8.6)				
OMe	3.83 s	3.85 s	3.85 s	3.74 s	3.82 s	3.85 s	3.84 s
OMe	3.86 s	3.85 s	3.85 s	3.83 s	3.83 s	3.85 s	3.85 s
OMe	—	3.21 s	3.19 s	3.84 s	—	—	—
OMe	—	—	3.69 s	—	—	—	—
OH	5.63 s	—	—	3.63 s	—	—	2.86 br. s
$COCH_3$	—	—	—	—	1.92 s	2.06 s	—
NH	—	—	—	—	6.45 s	—	—

[a] Spectra run in $CDCl_3$. [b] δ values (coupling constants, Hz).

Table 2. ^{13}C NMR spectra of **10** and **11**-**16**.[a,b]

	10	**11**	**12**	**13**	**14**	**15**	**16**
C-1	34.85	39.26	40.40	31.38	37.93	35.17	35.24
C-2	31.14	23.05	23.41	29.38	22.83	22.94	23.23
C-3	31.23	31.73	31.82	29.85	31.41	31.53	31.74
C-4	35.35	35.14	35.23	35.35	35.07	39.05	39.73
C-1′	134.48	134.77	134.89	129.39	134.61	134.65	134.85
C-2′	111.16	111.27	111.33	112.69	111.41	111.41	111.43
C-3′	148.59	148.77	148.85	148.76	148.84	148.89	148.85
C-4′	146.85	147.12	147.21	147.02	147.22	147.30	147.21
C-5′	111.71	111.73	111.80	111.69	111.85	111.83	111.86
C-6′	120.21	120.04	116.57	120.30	120.14	120.19	120.18
C-1″	135.36	75.72	76.66	129.74	56.00	76.93	69.84
C-2″	129.39	151.07	120.15	151.60	150.55	148.50	151.65
C-3″	115.10	131.36	152.47	111.98	128.87	128.86	128.09
C-4″	153.59	185.35	180.89	111.39	185.57	185.32	185.79
C-5″	115.10	131.36	130.47	149.44	128.87	128.86	128.09
C-6″	129.39	151.07	151.88	117.07	150.55	148.50	151.65
OMe	55.72	55.75	55.84	55.84	55.81	55.86	55.85
OMe	55.87	55.78	55.96	55.96	55.91	55.96	55.96
OMe	—	52.96	55.05	56.08	—	—	—
OMe	—	—	52.41	—	—	—	—
$COCH_3$	—	—	—	—	170.01	169.44	—
$COCH_3$	—	—	—	—	23.34	21.23	—

[a] Spectra run in $CDCl_3$. [b] All assignments supported by DEPT spectra.

Table 3. ^{1}H NMR spectra of **18-20**, **21-26**, **32**, **45** and **46**.[a,b]

	18	**19**	**20**	**21**	**22**	**23**
H-2				3.33 m	3.33 m	3.32 m
H-3	}2.47-2.62 m [4H]	}2.48-2.61 m [4H]	}2.44-2.61 m [4H]	2.90 m	2.90 m	2.92 m
H-6				—	—	—
H-4α	4.11 dd (6.55, 9.12)	4.12 dd (6.73, 9.37)	4.11 dd (6.47, 8.98)	4.40 dd (2.30, 10.09)	4.40 dd (2.99, 9.96)	4.39 dd (2.98, 9.90)
H-4β	3.88 m	3.89 dd (2.23, 9.37)	3.89 m	3.46 t (9.22)	3.46 dd (8.55, 9.96)	3.49 dd (8.73, 9.90)
H-5α			2.98 dd (4.74, 13.96)	3.08 dd (4.51, 13.71)	3.10 dd (4.60, 13.75)	3.08 dd (4.50, 13.76)
H-5β	}2.91 m [2H]	}2.91 m [2H]	2.82 dd (6.84, 13.96)	2.78 dd (5.44, 13.71)	2.78 dd (5.58, 13.75)	2.75 dd (5.71, 13.76)
H-5′	6.76 d (8.20)	6.75 d (8.13)	6.75 d (8.20)	6.73 d (8.60)	6.75 d (8.57)	6.74 d (8.55)
H-6′	6.57 dd (1.80, 8.20)	6.55 dd (1.95, 8.13)	6.56 dd (1.89, 8.20)		7.08 dd (2.17, 8.57)	7.08 dd (2.06, 8.55)
H-2′	6.47 d (1.80)	6.47 d (1.95)	6.49 d (1.89)			
H-2″		6.63 d (1.83)	6.74 d (2.18)		6.57 d (1.80)	6.61 d (1.70)
H-6″	}6.97 d (8.46) [2H]	6.58 dd (1.83, 7.56)	6.63 dd (2.18, 8.31)	}6.77-7.43 m [21H]	6.31 dd (1.80, 8.14)	6.45 dd (1.70, 8.16)
H-3″		—	—		—	—
H-5″		6.82 d (7.56)	6.76 d (8.31)		6.67 d (8.14)	6.67 d (8.16)
Ph	}6.77 d (8.46) [2H]	—	—		7.18-7.46 m [16H]	7.16-7.44 m [16H]
	—					
OMe	3.79 s	3.80 s	3.85 s	3.72 s	3.73 s	3.73 s
OMe	3.83 s	3.84 s	3.85 s	3.82 s	3.86 s	3.86 s
OMe	—	3.81 s	3.83 s	—	3.77 s	3.86 s
OCH_2Ph	—	—	—	5.01 s	5.14 s	5.00 s
OH	6.75 s	5.78 s	5.72 s	—	—	—
OCH_2CF_3	—	—	—	—	—	—

[a] Spectra run in $CDCl_3$. [b] δ values (coupling constants, Hz).

Table 3. ^{1}H NMR spectra of **18-20, 21-26, 32, 45** and **46**.[a,b]

	24	**25**	**26**	**32**	**45**	**46**
H-2		2.56 m		2.75 m		
H-3	}2.51-2.71 m [2H]	2.30 m	}2.49-2.61 m [3H]	2.37 m	}2.47-2.73 m [4H]	
H-6α		2.60 m		2.79 m		}2.43-2.66 m [4H]
H-6β	}4.40 m	2.66 dd (3.86, 12.17)	}2.90 m	2.82 m		
H-4α	4.14 dd (7.56, 9.48)	4.18 dd (6.80, 9.21)	4.28 m	4.19 dd (3.03, 9.04)	4.31 dd (9.19, 7.68)	4.18 dd (8.93, 6.54)
H-4β	3.91-3.97 m	3.94 m	3.98 t (8.53)	3.93 dd (4.67, 9.04)	3.94 dd (12.55, 7.68)	3.90 dd (9.25, 6.54)
H-5α		2.22 dd (5.73, 13.86)	2.17 dd (7.61, 14.48)	2.25 dd (9.17, 13.42)		3.12 dd (5.18, 13.61)
H-5β	}2.87-3.05 m [2H]	1.94 dd (4.34, 13.86)	1.78 dd (3.07, 14.48)	1.90 dd (8.21, 13.42)	}2.82 m [2H]	2.77 dd (8.23, 13.61)
H-5′			6.77 d (6.32)	6.82 d (7.99)	6.75 d (8.02)	6.73 d (8.12)
H-6′		}6.68 m [2H]	6.65 dd (1.74, 6.32)	6.71 dd (1.77, 7.99)	6.64 dd (1.77, 8.02)	6.53 dd (1.73, 8.12)
H-2′			6.64 d (1.74)	6.68 d (1.77)	6.61 d (1.77)	6.45 d (1.73)
H-2″		6.66 d (1.88)	6.95 dd (3.08, 10.29)	7.03 dd (3.22, 10.04)	—	—
H-6′	}6.48-6.85 m [6H]	6.81 dd (3.34, 10.25)	6.83 dd (3.08, 10.25)	6.83 dd (3.22, 10.17)	5.86 s	6.45 s
H-3′		6.74 dd (3.34, 10.17)	6.15 dd (1.84, 10.29)	6.17 dd (1.86, 10.04)	6.54 s	6.83 s
H-5′		6.40 dd (1.98, 10.25)	6.12 dd (1.84, 10.25)	6.13 dd (1.86, 10.17)	—	—
Ph		6.37 dd (1.98, 10.17)	—	—	—	—
	—	—				
OMe	3.88 s	3.21 s	—	—	3.83 s	3.79 s
OMe	3.85 s	3.87 s	3.85 s	3.86 s	3.85 s	3.84 s
OMe	3.81 s	3.88 s	3.85 s	3.88 s	3.86 s	—
OCH_2Ph	—	—	—	—	—	—
OH	5.51 br.s	—	6.79 s	—	—	—
OCH_2CF_3	—	—	—	4.08 m	—	4.26 q (8.06), 4.42 q (8.09)

Table 4. ^{13}C NMR spectra of **18-20, 21-26, 32, 45** and **46**.[ab]

	18	**19**	**20**	**21**[c]	**22**[c]	**23**[c]	**24**[d]	**25**	**26**	**32**	**45**	**46**
C-1	179.61	178.89	178.71	178.50	178.76	178.70	179.88	177.68	180.25	184.88	177.62	178.85
C-2	46.53	46.55	46.32	47.46	47.55	47.66	45.07	43.26	44.04	47.70	44.14	45.11
C-3	41.06	40.91	41.38	44.73	44.82	44.81	43.32	39.91	41.92	51.34	42.83	41.97
C-4	71.57	71.34	71.25	68.05	68.23	68.22	68.87	70.19	72.04	73.19	71.25	71.43
C-5	33.99	34.47	34.49	36.20	36.73	36.58	35.02	36.76	37.09	37.79	29.30	29.29
C-6	38.02	38.11	38.14	73.19	73.14	73.17	74.44	37.64	39.30	41.67	38.18	38.17
C-1′	130.53	130.48	131.56	130.71	130.83	130.98	134.21	129.21	129.59	131.89	130.05	130.58
C-2′	111.33	111.22	110.74	110.45	110.43	110.42	108.87	119.60	120.61	120.69	111.26	111.27
C-3′	148.89	148.94	149.00	148.83	148.91	148.68	148.94	148.09	148.99	148.97	148.93	148.97
C-4′	147.65	147.74	147.77	148.47	148.51	148.50	148.50	146.95	147.88	147.68	147.78	147.71
C-5′	111.72	111.72	111.66	112.80	112.98	113.04	111.96	130.57	127.47	127.30	111.73	118.48
C-6′	120.67	120.57	120.57	120.77	120.80	120.78	118.04	131.04	127.67	128.63	120.69	120.66
C-1″	129.01	129.48	130.83	132.42	132.39	132.39	129.36	73.69	68.36	80.31	145.96	123.00
C-2″	130.36	111.57	111.23	130.41	112.74	111.72	110.92	148.50	150.58	147.59	187.02	148.74
C-3″	115.54	146.75	145.51	114.95	147.00	148.89	146.59	110.37	111.29	111.34	107.40	101.60
C-4″	155.06	144.54	145.59	157.71	149.62	148.09	144.33	183.94	185.28	184.88	158.56	143.65
C-5″	115.54	114.19	115.48	114.95	114.10	114.84	114.13	110.71	111.59	112.00	181.63	141.70
C-6″	130.36	122.04	120.66	130.41	121.42	112.18	122.33	149.53	151.32	148.24	132.72	111.57
OMe	55.76	55.76	55.79	55.70	55.76	55.78	55.71	54.91	55.79	55.87	55.76	55.70
OMe	55.90	55.81	55.90	55.81	55.88	55.87	55.75	54.91	55.79	55.87	55.76	55.90
OMe	—	55.87	55.90	—	55.88	55.96	55.84	52.17	—	—	56.25	—
OCH_2Ph	—	—	—	69.87	71.01	70.88	—	—	—	—	—	—
OCH_2CF_3	—	—	—	—	—	—	—	—	—	60.54	—	67.38, 67.56
OCH_2CF_3	—	—	—	—	—	—	—	—	—	131.54	—	125.41, 125.49

[a] Spectra run in $CDCl_3$. [b] All assignments supported by DEPT spectra. [c] Signals due to Ph groups omitted. [d] Major isomer only listed.

Table 5. ^{1}H NMR spectra of spirodienones **28** and **33**.[a,b]

	28	**33**
H-1	6.70 s	6.71 s
H-4	6.74 s	6.75 s
H-5α	3.11 dd (11.49, 15.06)	3.13 dd (11.08, 14.92)
H-5β	2.97 dd (1.81, 15.06)	3.01 dd (2.07, 14.92)
H-6	2.37 m	2.43 m
H-7	2.68 dt (2.60, 12.78)	2.74 dt (2.53, 12.60)
H-8α	2.13 dd (2.60, 13.55)	2.25 dd (2.53, 13.52)
H-8β	1.93 dd (13.02, 13.55)	1.99 dd (12.60, 13.52)
H-9	7.23 dd (3.14, 10.17)	7.33 dd (2.69, 10.06)
H-10	6.20 dd (1.88, 10.17)	6.51 d (10.06)
H-12	6.45 dd (1.88, 10.12)	—
H-13	7.27 dd (3.14, 10.12)	6.10 d (2.69)
H-14α	4.49 dd (7.10, 8.67)	4.53 dd (7.13, 8.69)
H-14β	3.95 dd (11.14, 8.67)	4.00 dd (11.06, 8.69)
OMe	3.84 s	3.87 s
OMe	3.76 s	3.79 s
OMe	—	3.65 s

[a] Spectra run in $CDCl_3$. [b] δ values (coupling constants, Hz)

Table 6. ^{13}C NMR spectra of spirodienones **28** and **33**.[a,b]

	28	**33**
C-1	127.86	115.98
C-2	147.95	147.80
C-3	147.44	147.38
C-4	127.51	115.72
C-4a	131.01	132.48
C-5	38.18	38.94
C-6	45.85	46.58
C-7	43.17	43.26
C-8	38.15	38.45
C-8a	47.93	48.40
C-1a	130.80	130.22
C-9	154.85	155.18
C-10	116.01	112.67
C-11	185.08	180.23
C-12	113.10	150.09
C-13	148.88	126.86
C-14	70.25	70.19
C-15	176.85	176.97
OMe	55.93	55.93
OMe	56.02	55.99
OMe	—	54.78

[a] Spectra run in $CDCl_3$.

[b] All assignments supported by DEPT spectra.

Table 7. ^{1}H NMR spectra of stegane and isostegane derivatives.[a,b]

	27	**29**	**30**	**31**	**34**	**35**
H-1	6.71 s	6.66 s	6.68 s	6.67 s	6.64 s	6.66 s
H-4	6.72 s	6.66 s	6.69 s	6.60 s	6.60 s	6.60 s
H-5α	2.69 d (13.02)	2.64 d (13.24)	2.68 d (13.03)	2.99 m		
H-5β	2.40 dd (9.58, 13.02)	2.38 dd (9.81, 13.24)	2.55 m	2.94 dd (5.63, 14.94)		
H-6	2.23 m	2.20 m	2.24 m	2.53 m	}3.01 m [3H]	}3.03 m [3H]
H-7	2.12 dd (9.33, 12.89)	2.10 dd (9.38, 13.22)	2.15 dd (9.11, 12.78)	2.45 m	}2.48 m [3H]	}2.45 m [3H]
H-8α	2.30 dd (9.33, 13.40)	2.26 dd (9.38, 13.59)	2.41 dd (9.11, 13.29)	2.48 m		
H-8β	3.20 d (13.40)	3.17 d (13.59)	3.27 d (13.29)	3.03 dd (6.29, 8.43)		
H-9	7.22 d (8.42)	7.13 d (8.29)	7.33 d (8.32)	7.01 d (8.20)	6.64 s	6.76 s
H-10	6.89 dd (2.77, 8.42)	6.81 dd (2.71, 8.29)	7.08 dd (2.48, 8.32)	6.74 dd (2.90, 8.20)	—	—
H-12	6.76 d (2.77)	6.68 d (2.71)	6.95 d (2.48)	6.69 d (2.90)	6.79 s	6.86 s
H-13α	4.40 dd (6.37, 8.44)	4.39 dd (6.69, 8.43)	4.41 dd (6.17, 8.47)	4.28 dd (6.89, 8.37)	4.28 dd (6.39, 8.40)	4.29 m
H-13β	3.76 dd (11.00, 8.44)	3.77 dd (11.25, 8.43)	3.78 dd (10.48, 8.47)	3.77 dd (10.54, 8.37)	3.79 dd (10.29, 8.40)	3.75 m
OMe	3.93 s	3.90 s	3.93 s	3.91 s	3.91 s	3.90 s
OMe	3.82 s	3.81 s	3.86 s	3.85 s	3.91 s	3.84 s
OMe	3.86 s	—	—	—	3.85 s	3.84 s
OH	—	6.06 br s	—	4.98 s	5.56 s	—
OAc	—	—	2.31 s	—	—	2.30 s

Table 7. ^{1}H NMR spectra of stegane and isostegane derivatives.[a,b]

	36	**37**	**43**	**44**	**47**
H-1	6.64 s	6.65 s	6.66 s	6.70 s	6.10 s
H-4	6.67 s	6.68 s	6.67 s	6.73 s	6.55 s
H-5α	2.67 d (13.09)	2.67 d (13.06)	2.64 d (13.19)	2.68 d (13.15)	2.76 d (13.48)
H-5β	2.42 dd (13.09, 9.37)		2.40 dd (9.65, 13.19)	2.44 dd (9.35, 13.15)	2.42 dd (9.92, 13.48)
H-6	2.23 m		2.19 m		2.18 m
H-7	2.16 dd (9.12, 12.59)	}2.20-2.44 m [4H]	2.12 dd (9.19, 13.24)	}2.14-2.33 m [3H]	1.96 dd (9.75, 13.33)
H-8α	2.32 dd (9.12, 13.43)		2.26 dd (9.19, 13.41)		1.74 dd (9.75, 12.18)
H-8β	3.16 d (13.43)		3.13 d (13.41)	3.16 d (13.36)	3.67 d (12.18)
		2.23 d (13.24)			
H-9	6.79 s	6.91 s	6.87 s	7.00 s	—
H-10	—	—	—	—	—
H-12	6.79 s	6.90 s	6.68 s	6.80 s	6.71 s
H-13α	4.42 dd (6.30, 8.52)	4.38 dd (6.25, 8.50)	4.38 dd (6.60, 8.47)	4.40 dd (6.23, 8.47)	4.42 dd (6.80, 8.22)
H-13β	3.79 dd (10.71, 8.52)	3.79 m	3.77 dd (11.13, 8.47)	3.78 dd (10.87, 8.47)	3.78 m
OMe	3.92 s	3.92 s	3.92 s	3.94 s	3.92 s
OMe	3.85 s	3.85 s	3.86 s	3.87 s	3.84 s
OMe	3.94 s	3.88 s	3.87 s	3.82 s	3.87 s
OH	5.57 s	—	5.59 s	—	—
OAc	—	2.32 s	—	2.35 s	—

[a] Spectra run in $CDCl_3$. [b] δ values (coupling constants, Hz).

Table 8. ^{13}C spectra of stegane and isostegane derivatives.[a,b]

	17	29	30	31	34	35	36	37	43	44	47
C-1	112.05	112.01	112.07	113.11	111.87	112.22	111.16	111.02	114.18	112.01	112.37
C-2	147.22	147.15	147.30	147.34	147.30	146.44	147.19	146.27	147.15	147.30	146.97
C-3	148.78	148.68	147.30	148.01	147.86	147.06	148.56	147.06	148.59	148.91	150.06
C-4	113.67	114.04	113.95	114.06	113.22	112.53	111.98	111.74	114.86	114.08	113.39
C-4a	132.17	131.83	131.54	129.15	128.51	131.30	131.48	130.35	131.97	131.89	130.95
C-5	34.12	34.09	34.08	31.26	31.79	31.32	34.23	33.17	34.11	34.08	34.26
C-6	46.74	46.73	46.64	39.34	39.35	38.49	46.82	45.79	46.81	47.73	46.14
C-7	50.39	50.49	49.90	43.58	43.88	42.49	50.32	48.79	50.03	49.99	46.31
C-8	31.51	31.43	31.79	34.11	34.53	33.37	32.13	31.47	31.67	31.52	24.28
C-8a	141.66	141.77	141.80	143.17	133.04	133.10	133.23	131.30	132.41	138.56	131.54
C-9	130.20	130.36	128.30	128.13	114.51	113.48	114.18	113.18	113.21	123.24	185.97
C-10	116.41	117.68	123.81	117.37	145.88	137.01	146.45	136.85	144.88	149.27	182.05
C-11	157.96	154.34	148.95	154.14	143.98	149.27	143.78	149.80	145.41	139.33	158.38
C-12	114.03	115.36	121.51	114.36	116.75	123.80	116.98	124.13	111.92	115.01	107.60
C-12a	132.46	132.39	137.39	130.78	134.69	134.60	133.28	131.83	132.68	132.33	143.65
C-1a	130.61	130.51	130.62	133.10	128.36	127.45	130.63	129.80	130.91	130.74	122.45
C-13	70.04	70.22	70.02	70.83	71.11	69.99	70.17	69.96	69.98	69.98	69.78
C-14	176.72	177.21	176.44	178.48	178.68	177.35	176.92	177.56	176.58	176.35	174.85
OMe	55.36	56.02	56.02	55.90	55.94	55.02	55.94	54.99	55.99	56.05	55.93
OMe	56.02	56.02	56.02	55.90	55.99	55.02	55.99	54.99	55.99	56.05	55.93
OMe	—	—	—	—	56.05	55.02	56.11	54.99	55.99	56.10	56.02
$COCH_3$			169.53			168.03		168.03		169.11	
$COCH_3$			21.14			19.67		19.67		20.70	

[a] Spectra run in $CDCl_3$. [b] All assignments supported by DEPT spectra.

EXPERIMENTAL[27]

Infra-red spectra were recorded on a Pye Unicam SP1050 spectrometer. Ultra-violet spectra were recorded on a Philips PU8720 scanning spectrometer. ^{1}H NMR spectra were recorded on a Bruker 250WM spectrometer at 250 MHz and, where indicated, a Hitachi Perkin-Elmer R24B spectrometer at 60 MHz. The high field spectra were recorded using a Bruker spectrometer at 400 MHz. ^{13}C NMR spectra were recorded on a Bruker 250WM spectrometer at 62.9 MHz. All NMR spectra used tetramethylsilane as the internal standard, and were run in deuterated chloroform, unless otherwise stated. The mass spectra were recorded on a VG-12-250 low resolution quadruple mass spectrometer, whilst accurate mass measurements were obtained from a ZAB-E, high resolution, double focussing mass spectrometer. Melting points were recorded on a Electrothermal digital melting point apparatus, and are uncorrected.

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

Reactions carried out under an inert atmosphere refer to the use of argon or 'white spot' nitrogen used directly from the cylinder. Tetrahydrofuran was dried by being stirred overnight over calcium hydride, passed down a dry alumina column, and then distilled from sodium wire and benzophenone. Diethyl ether and dichloromethane were dried by passing down a dry alumina column and then distilled from calcium hydride. Triethylamine was distilled from calcium hydride, whilst dry acetonitrile was prepared by distillation from phosphorus pentoxide. Methanol and ethanol were dried by treatment with magnesium activated with iodine followed by heating under reflux and distillation. Solutions of *n*-butyllithium in hexane were obtained from Aldrich and were regularly estimated.[28,29] Lithium aluminium hydride was used as a solution in dry tetrahydrofuran, estimated as described by Brown.[30] Low temperature baths were prepared by making a slurry of solid carbon dioxide with acetone (-78°C) or using a mixture of solid carbon dioxide with acetone monitored using a digital temperature probe (-25 to -30°C). All other reagents were purified by distillation under nitrogen prior to use, the pressure being reduced if the boiling point of the compound was >110°C at atmospheric pressure.

*1-(4″-Benzyloxyphenyl)-4-(3′,4′-dimethoxyphenyl)butan-1-ol (**9**)*

A solution of 1-bromo-3-(3′,4′-dimethoxyphenyl)propane (**8**)[13,31] (2.59 g, 0.01 mol) in dry THF (10 ml) was added slowly with stirring to magnesium turnings (0.96 g, 0.04 mol, 4 mol equiv.) (preactivated with two crystals of iodine) under dry THF (5 ml), in a nitrogen atmosphere. The reaction mixture was heated under reflux for half an hour and cooled to rt. A solution of 4-benzyloxybenzaldehyde[32] (2.12 g, 0.01 mol, 1 mol equiv) in dry THF (10 ml), was then added slowly to the stirred solution. The reaction mixture was left at room temperature for 5 hours and poured onto ice (75 g), neutralised with dilute HCl, and extracted with diethyl ether (2 x 75 ml). The combined ether extracts were washed with water (2 x 20 ml), dried ($MgSO_4$) filtered and evaporated, to give a beige paste. Purification by flash chromatography on neutral alumina with

petroleum spirit (40-60°C)/EtOAc (65:35) afforded **9** (2.27 g, 58%) as a white solid, mp 75-77°C. ν_{max} (KBr): 3230 cm^{-1} (OH): δ_H 1.66-1.71 (4H, m, H-2, H-3), 2.16 (1H, s, OH), 2.54 (2H, m, H-4), 3.80 (3H, s, OMe), 3.80 (3H, s, OMe), 4.56 (1H, m, H-1), 5.01 (2H, s, OCH_2Ph), 3.80 (3H, s, OMe), 6.64-6.75 (3H, m, H-2′, H-5′, H-6′), 6.91 (2H, d, J = 8.66, H-3″, H-5″), 7.20 (2H, d, J = 8.66, H-2″, H-6″), 7.29-7.42 (5H, m, Ph). δ_C 73.99 (C-1), 38.41 (C-2), 27.76 (C-3), 35.29 (C-4), 134.98 (C-1′), 111.31 (C-2′), 148.80 (C-3′), 147.12 (C-4′), 111.83 (C-5′), 120.21 (C-6′), 137.01 (C-1″), 128.54 (C-2″, C-6″), 114.74 (C-3″, C-5″), 158.18 (C-4″), 55.78 (OMe), 55.90 (OMe), 70.02 ($O\underline{C}H_2Ph$), 137.24, 127.14, 127.42, 127.92 (Ph). *m/z* (e.i.) 392 (3%, M^+), 374 (3%, M-H_2O), 151 (24%, Ar′CH_2^+), 164 (29%, Ar′CH = CH_2^+), 91 (100%, $PhCH_2^+$). *m/z* (c.i.) 392 (77%, M + NH_4 - H_2O), 375 (100%, M + H - H_2O). Found: M^+ 392.1988; $C_{25}H_{28}O_4$ requires 392.1988.

*1-(3′,4′-Dimethoxyphenyl)-4-(4″-hydroxyphenyl)butane (**10**)*

1-(4′-Benzyloxyphenyl)-4-(3″,4′-dimethoxyphenyl)butan-1-ol (**9**) (4.02 g, 0.01 mol) was dissolved in dry EtOH (120 ml), and hydrogenolysed over 10% Pd/C (1.14 g) at room temperature and atmospheric pressure. After 24 hours, the mixture was filtered through a short column of celite, dried ($MgSO_4$), filtered and evaporated, to give a dark brown gum. Crystallisation from EtOAc containing a small amount of petroleum spirit (40-60°C) gave **10** (2.64 g, 90%), mp 84-88°C; (Found: C, 75.62; H, 7.69; $C_{18}H_{22}O_3$ requires C, 75.52; H, 7.69); ν_{max} (KBr): 3480 cm^{-1} (OH); λ_{max} (MeOH), 226.3 nm (ε, 14 757); See Tables 1 and 2 for ^1H and ^{13}C NMR data; *m/z* (e.i.) 286 (60%, M^+), 107 (57%, Ar″CH_2^+), 151 (100%, Ar′CH_2^+). *m/z* (c.i.) 304 (66%, M + NH_4), 287 (100%, M + H). Found: M^+ 286.1570. $C_{18}H_{22}O_3$ requires 286.1569.

*1-(1″-Methoxy-4″-oxocyclohexa-2″,5″-dienyl)-4-(3′,4′-dimethoxyphenyl)butane (**11**)*

Diarylbutane **10** (0.62g, 0.0022 mol) was dissolved in dry MeOH (10 ml) under a nitrogen atmosphere and stirred. To this solution, PIDA (1.288 g, 0.0040 mol, 1.8 mol equiv.) dissolved in dry MeOH (20 ml) was added, *via* syringe and stirring was continued at rt for 1 h. After this time the reaction mixture was neutralised by addition of powdered $NaHCO_3$, the mixture was concentrated *in vacuo* and the residue was dissolved in EtOAc and filtered. The filtrate was evaporated and the residue was purified by flash chromatography on neutral alumina by gradient elution using petroleum spirit (40-60°C) and EtOAc. Elution with a 4:1 mixture afforded **11** (0.206 g, 30%) as a light brown gum; ν_{max} (film): 1670 cm^{-1} (C=O); λ_{max} (MeOH), 210.3 nm (ε, 17 648), 277.9 nm (ε, 5 224); see Tables 1 and 2 for ^1H and ^{13}C NMR data; *m/z* (e.i.) 316 (23%, M^+), 284 (4%, M-MeOH), 193 (12%, Ar′$(CH_2)_4^+$), 151 (100%, Ar′CH_2^+) *m/z* (c.i.) 334 (88%, M + NH_4), 317 (100%, M + H). Found: M^+ 316.1675. $C_{19}H_{24}O_4$ requires 316.1675.

*1-(1″-Methoxy-4″-oxocyclohexa-2″,5″-dienyl)-4-(3′,4′-dimethoxyphenyl)butane (**11**) and 1-(1″,3″-dimethoxy-4″-oxocyclohexa-2″,5″-dienyl)-4-(3′,4′-dimethoxyphenyl)butane (**12**)*

Diarylbutane **10** (0.66 g, 2.3 mmol) was dissolved in dry MeOH (14 ml), under a nitrogen atmosphere and stirred. To this solution PIFA (1.2 g, 2.8 mmol, 1.2 mol equiv.) dissolved in dry MeOH (15 ml) was added, *via* syringe. Stirring was continued at rt for 1 h. After this time, the reaction mixture was neutralised by addition of powdered $NaHCO_3$, the mixture was concentrated *in vacuo* and the residue was dissolved in ethyl acetate and filtered. The filtrate was evaporated and the residue was purified by flash chromatography on neutral alumina using gradient elution with petroleum spirit (40-60°C) and EtOAc. Elution with petroleum

spirit (40-60°C)/EtOAc(4:1) afforded **11** (0.22 g, 30%) as a light brown gum. See above for spectroscopic data.

Further elution with petroleum spirit (40-60°C)/EtOAc (3:1) gave **12** (0.1 g, 12.5%) as a light brown gum. ν_{max} (film): 1660 cm^{-1} (C=O); λ_{max} (MeOH), 204.6 nm (ε, 16 397), 228 nm (ε, 6 338), 280.4 nm (ε, 2 132); See Tables 1 and 2 for ^1H and ^{13}C NMR data; *m/z*, (e.i.) 346 (34%, M^+), 314 (21%, M-MeOH), 283 (8%, M-2OMe), 151 (100%, $Ar'CH_2^+$) *m/z* (c.i.) 364 (100%, M + NH_4), 347 (73%, M + H). Found: M^+ 346.1780. $C_{20}H_{26}O_5$ requires 346.1780.

*1-(5″-Hydroxy-2″-methoxyphenyl)-4-(3′,4′-dimethoxyphenyl)butane (**13**)*

Compound **11** (0.21 g, 0.66 mmol) was dissolved in dry CH_2Cl_2 (3 ml) and stirred under nitrogen. To this solution was added $BF_3.OEt_2$ (0.71 g, 0.62 ml, 5 mmol, 7.57 mol equiv.) dropwise *via* syringe and stirring was continued at room temperature under a nitrogen atmosphere for 2.5 h. The reaction mixture was then poured into CH_2Cl_2 (100 ml) and washed with saturated aq. $NaHCO_3$ (35 ml). The organic layer was washed with water (20 ml), dried ($MgSO_4$) filtered and evaporated to give **13** (0.192 g, 91%) as a brown solid mp 75-78°C. ν_{max} (film): 3500 cm^{-1} (br, OH); λ_{max} (MeOH), 211.2 nm (ε, 16 015), 225.3 nm (ε, 15 879), 285.6 nm (ε, 6 851); See Tables 1 and 2 for ^1H and ^{13}C NMR data; *m/z* (e.i.) 316 (76%, M^+), 284 (10%, M-MeOH), 151 (100%, $Ar'CH_2^+$). *m/z* (c.i.) 334 (100%, M + NH_4). Found: M^+ 316.1675. $C_{19}H_{24}O_4$ requires 316.1675.

*1-(1″-Acetylamino-4″-oxocyclohexa-2″,5″-dienyl)-4-(3′,4′-dimethoxyphenyl)butane (**14**) and 1-(1″-acetoxy-4″-oxocyclohexa-2″,5″-dienyl)-4-(3′,4′-dimethoxyphenyl)butane (**15**)*

Diarylbutane **10** (0.58 g, 2 mmol) was dissolved in dry CH_3CN (10 ml), and stirred under a nitrogen atmosphere. A solution of PIDA (1.31 g, 4 mmol, 2.00 equiv), in dry CH_3CN (10 ml) *via* syringe, and the reaction mixture was heated under reflux for four hours, then neutralised by addition of powdered $NaHCO_3$. The mixture was concentrated *in vacuo* and the residue dissolved EtOAc and filtered. The filtrate was evaporated and the residue purified by Chromatotron on silica using gradient elution with petroleum spirit (40-60°C) and EtOAc. Elution with petroleum spirit (40-60°C)/EtOAc(60:40) afforded **14** (0.16 g, 23%) as a brown gum. ν_{max} (film): 3400 cm^{-1} (NH), 1675 cm^{-1} (C=O); See Tables 1 and 2 for ^1H and ^{13}C NMR data, *m/z* (e.i.) 343 (10%, M^+), 151 (100%, $Ar'CH_2^+$). *m/z* (c.i.) 344 (16%, M + H), 152 (19%, $Ar'CH_2$ + H), 60 (100%). Found: M^+ 343.1784. $C_{20}H_{25}O_4N$ requires 343.1784.

Further elution with petroleum spirit (40-60°C)/EtOAc (30:70) gave **15** (0.11 g, 15.7%) as a light brown gum. ν_{max} (film): 1675 cm^{-1} (C=O); See Tables 1 and 2 for ^1H and ^{13}C NMR data; *m/z* (e.i.) 344 (9%, M^+), 151 (100%, $Ar'CH_2^+$). *m/z* (c.i.) 345 (48%, M + H), 364 (56%, M + NH_4), 285 (100%, M - OAc). Found: M^+ 344.1624. $C_{20}H_{24}O_5$ requires 344.1624.

*Reaction of **10** with PIFA in TFA*

Diarylbutane **10** (0.338 g, 1.2 mmol) was dissolved in TFA (2 ml) under a nitrogen atmosphere and stirred. To this solution PIFA (0.61 g, 1.4 mmol, 1.2 mol equiv.) dissolved in TFA (4 ml) was added, *via* syringe. Stirring was continued at rt for 45 min. After this time the TFA was evaporated and the residue purified by flash chromatography on silica by gradient elution with petroleum spirit (40-60°C) and EtOAc. Elution with a 60:40 mixture afforded a mixture (0.101 g, 30%) of **10** and a second compound tentatively

identified as **7** (R^1=R^2=H). δ_H 6.71 (1H, s, H-1), 6.73 (1H, s, H-4), 2.01-2.12 (4H, m, H-5, H-8), 1.26-1.43 (4H, m, H-6, H-7), 6.81 (1H, dd, J = 2.72, 8.18, H-9), 6.75 (1H, d, J = 2.93, H-10), 7.09 (1H, d, J = 8.22, H-12), 3.80 (3H, S, OMe), 3.89 (3H, S, OMe). δ_C 111.45 (C-1), 146.50 (C-2), 148.44 (C-3), 112.22 (C-4), 35.34 (C-5), 29.82 (C-6), 29.32 (C-7), 34.84 (C-8), 130.39 (C-9), 115.65 (C-10), 153.48 (C-11), 114.77 (C-12), 132.68 (C-1a), 134.92 (C-4a), 141.47 (C-8a), 135.00 (C-12a). *m/z* (e.i.) 284 (100%, M^+), 253 (7%, M-OMe), 211 (3%), 165 (9%). *m/z* (c.i.) 302 (40%, M+18), 285 (52%, M+1), 269 (6%), 241 (3%).

*1-(1″-Hydroxy-4″-oxocyclohexa-2″,5″-dienyl)-4-(3′,4′-dimethoxyphenyl)butane (**16**)*

Diarylbutane **10** (0.48 g, 1.7 mmol) was dissolved in dry CH_2Cl_2 (6.5 ml) and anhydrous K_2CO_3 (0.46 g, 3.3 mmol, 1.94 mol equiv), was added and the mixture stirred under nitrogen. A solution of PIFA (0.86 g, 2.0 mmol, 1.18 mol equiv) in dry CH_2Cl_2 (6 ml) was added *via* syringe and stirring was continued at rt for 12h after which, because there was no reaction, it was heated under reflux for 4 h. The reaction mixture was filtered and concentrated *in vacuo* and the residue was purified by flash chromatography on silica, using gradient elution with CH_2Cl_2/EtOAc. Elution with a (60:40) mixture of CH_2Cl_2/EtOAc afforded **16** (0.05 g, 10%) as a light brown gum. ν_{max} (film): 1675 cm^{-1} (C=O), 3490 cm^{-1} (OH); λ_{max} (MeOH), 210.2 nm (ε, 50 711), 213.6 nm (ε, 47 111), 285.8 nm (ε, 17 533); See Tables 1 and 2 for ^1H and ^{13}C NMR data; *m/z* (e.i.) 302 (32%, M^+), 151 (100%, $ArCH_2^+$). *m/z* (c.i.) 320 (61%, M + NH_4), 303 (100%, M + H), 285 (17%, M + H - H_2O). Found: M^+ 302.1518. $C_{18}H_{22}O_4$ requires 302.1518.

trans-*2-(4″-Benzyloxybenzyl)-3-(3′,4′-dimethoxy-α,α-bis[phenylthio]benzyl)butyrolactone (**21**)*

3,4-Dimethoxybenzaldehyde bis(phenylthio)acetal (**17**)[16] (4.00 g, 10.87 mmol) was dissolved in dry THF (20 ml), under an argon atmosphere, and then cooled and stirred at -78°C. To this was added *n*-BuLi (3.75ml of 2.90M, 10.87 mmol, 1 mol equiv), *via* syringe, and stirring was continued at -78°C for 2.5 hours. After this time, pre-cooled butenolide (1.09g, 0.9ml, 13.00 mmol, 1.2 mol equiv), was added *via* syringe to the orange solution. The mixture was stirred at -78°C for 2.5 hours before pre-cooled DMI (1.24g, 1.18ml, 10.87 mmol, 1.00 mol equiv) was added *via* syringe, immediately followed by pre-cooled (-78°C) 4-benzyloxybenzyl bromide[33] (3.01g, 10.87 mmol, 1.00 mol equiv) dissolved in dry THF (7 ml), added *via* a double-ended needle. The reaction mixture was stirred at -78°C, and then allowed to warm to room temperature overnight, before adding aqueous NaCl (60 ml) and extracting with EtOAc (3 x 100 ml). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated yielding a yellowish foam. Crystallisation from EtOAc afforded **21** (4.75 g, 65%) as white crystals, mp 88-91°C. Found: C, 72.38; H, 5.77; $C_{39}H_{36}O_5S_2$ requires C, 72.22; H, 5.55; ν_{max} (film): 1770 cm^{-1} (γ-lactone); See Tables 3 and 4 for ^1H and ^{13}C NMR data; *m/z* (e.i.) 539 (3%, M - SPh), 430 (3%, M - 2SPh), 151 (13%, $Ar'CH_2^+$), 91 (100%, $PhCH_2^+$), *m/z* (c.i.) 666 (6%, M + NH_4) 649 (3%, M + H), 431 (70%, M + H - 2SPh), 91 (100%, $PhCH_2^+$). Found: $(M + NH_4)^+$ 666.2350. $C_{39}H_{40}O_5NS_2$ requires 666.2348.

trans-*2-(4″-Benzyloxy-3-″methoxybenzyl)-3-(3′,4′-dimethoxy-α,α-bis[phenylthio]benzyl) butyrolactone (**22**)*

The same experimental procedure as for the preparation of **21** was followed.

Crystallisation from EtOAc afforded **22** (4.05 g, 55%) as white crystals, mp 102-102.5°C. Found: C, 70.51; H, 5.61. $C_{40}H_{38}O_6S_2$ requires C, 70.79; H, 5.60; ν_{max} (film): 1770 cm^{-1} (γ-lactone); See Tables 3 and

4 for ^1H and ^{13}C NMR data; *m/z* (e.i.) 539 (3%, M-SPh), 430 (3%, M-2SPh), 151 (13%, $Ar'CH_2^+$), 91 (100%, $PhCH_2^+$). *m/z* (c.i.) 666 (6%, M + NH_4), 649 (3%, M + H), 431 (70%, M + H - 2SPh), 91 (100%, $PhCH_2^+$). Found: $[M-H-2xSPh]^+$ 459.1808. $C_{28}H_{27}O_6$ 459.1808.

trans-*2-(3″-Benzyloxy-4″-methoxybenzyl)-3-(3′,4′-dimethoxy-α,α-bis[phenylthio]benzyl) butyrolactone (23)*

The same experimental procedure as for the preparation of **21** was followed. Crystallisation from EtOAc afforded **23** (4.5 g, 61%) as white crystals, mp 90-91°C; Found: C, 70.84; H, 5.70. $C_{40}H_{38}O_6S_2$ requires C, 70.79; H, 5.60. ν_{max} (film): 1770 cm^{-1} (γ-lactone); See Tables 3 and 4 for ^1H and ^{13}C NMR data; *m/z* (e.i.) 227 (11%, $Ar''CH_2^+$), 151 (23%, $Ar'CH_2^+$), 91 (100%, $PhCH_2^+$). *m/z* (c.i.) 696 (3%, M + NH_4), 588 (34%, M + H - $PhCH_2$), 461 (79%, M + H - 2SPh), 259 (50%, Ar'CHSPh+), 91 (100%, $PhCH_2$). Found: $[M-H-2xSPh]^+$ 459.1808. $C_{28}H_{27}O_6$ 459.1801.

trans-*2-(4″-Hydroxybenzyl)-3-(3′,4′-dimethoxybenzyl)butyrolactone (18)*

Compound **21** (1.22g, 1.88 mmol) was dissolved in MeOH (220 ml) and THF (73 ml), and $NiCl_2.6H_2O$ (8.94g, 37.6 mmol, 20 mol equiv) added. The stirred green solution was then cooled to 0°C and $NaBH_4$ (4.27g, 112.8 mmol, 60 mol equiv) was added carefully, in order to minimize the effervescence produced. The black suspension was then removed from the ice-bath and thoroughly stirred for 3 hours at room temperature. After this time, water (20 ml) was added and the reaction mixture passed through a short Celite column, in order to remove the nickel salts. Water (80ml) was added to the resulting solution and $CHCl_3$ (3 x 150 ml) used for the extraction. The combined organic layers were dried ($MgSO_4$), filtered and evaporated yielding a yellowish gum. Crystallization from EtOAc containing a small amount of petroleum spirit (40-60°C) afforded **18** (0.393 g, 61%) as white crystals, mp 148.4-148.8°C. Found: C, 69.95; H, 6.41. $C_{20}H_{22}O_5$ requires C, 70.17; H, 6.43; ν_{max} (film): 1766 cm^{-1} (γ-lactone), 3423 cm^{-1} (OH); ν_{max} (MeOH), 209.5 nm (ε, 14 791), 226.9 nm (ε, 16 330), 279.7 nm (ε, 5 578); See Tables 3 and 4 for ^1H and ^{13}C NMR data; *m/z* ((e.i.) 342 (36%, M^+), 178 (10%), 107 (73%, $Ar''CH_2^+$), 151 (100%, $Ar'CH_2^+$). *m/z* (c.i.) 360 (91%, M + NH_4), 343 (100%, M + H). Found: M^+ 342.1470. $C_{20}H_{22}O_5$ requires 342.1467.

trans-*2-(4″-Hydroxy-3″-methoxybenzyl)-3-(3′,4′-dimethoxybenzyl)butyrolactone (19) and trans-2-(4″-hydroxy-3″-methoxybenzyl)-3-(3′,4′-dimethoxy-α-hydroxybenzyl)butyrolactone (24)*

Compound **22** (1.82 g, 2.68 mmol) was dissolved in MeOH (321 ml) and THF (107 ml) and $NiCl_2.6H_2O$ (12.76 g, 53.68 mmol, 20.03 mol equiv) was added. The stirred green solution was then cooled to 0°C and $NaBH_4$ (6.09 g, 160.94 mmol, 60.05 mol equiv) was added carefully, in order to minimize the effervescence produced. The black suspension was then removed from the ice-bath and thoroughly stirred for 3 h at room temperature. After this time, water (20 ml) was added and the reaction mixture passed through a short Celite column, in order to remove nickel salts. Water (120ml) was added to the resulting solution which was then extracted with $CHCl_3$ (3 x 200 ml). The combined organic layers were dried ($MgSO_4$), filtered and evaporated yielding a yellowish gum. Purification by flash chromatography on silica using gradient elution with CH_2Cl_2/EtOAc (7:3) afforded **19** (0.68 g, 68%) as white crystals, mp 50-55°C; Found: C, 67.81; H, 6.44; $C_{21}H_{24}O_6$ requires C, 67.74; H, 6.45; ν_{max} (film): 3432 cm^{-1} (OH), 1767 cm^{-1} (γ-lactone); λ_{max} (MeOH), 210.6 nm (ε, 16 212), 230.3 nm (ε, 13 437), 280.9 nm (ε, 6 197); See Tables 3 and 4 for ^1H and ^{13}C NMR

data; *m/z* (e.i.) 372 (29%, M^+), 235 (2%, M - $Ar''CH_2^+$), 151 (70%, $Ar'CH_2^+$), 137 (100%, $Ar''CH_2^+$). *m/z* (c.i.) 390 (81%, M + NH_4), 373 (100%, M + H), 355 (11%, M + H H_2O), 107 (8%). Found: M^+ 372.1570. $C_{21}H_{24}O_6$ requires 372.1573.

Further elution with CH_2Cl_2/EtOAc (7:3) gave **24** (0.21 g, 20%) as a brownish foam. ν_{max} (film): 3500 cm^{-1} (OH), 1765 cm^{-1} (γ-lactone): See Tables 3 and 4 for ^1H and ^{13}C NMR data; *m/z* (e.i.) 388 (48%, M^+), 371 (6%, M - OH), 251 (6%, M - $Ar''CH_2^+$), 233 (27%, M - Ar' - H_2O), 167 (100%, $Ar'CHOH^+$), 151 (17%, $Ar'CH_2^+$), 137 (61%, $Ar''CH_2^+$). *m/z* (c.i.) 406 (63%, M + NH_4), 371 (28%, M - OH), 167 (100%, $Ar'CHOH^+$). Found: M^+ 388.1522. $C_{21}H_{24}O_7$ requires 388.1522.

trans-*2-(3″-Hydroxy-4″-methoxybenzyl)-3-(3′,4′-dimethoxybenzyl)butyrolactone (20)*

The same experimental procedure as for **19** was used. Purification by column chromatography on silica and elution with CH_2Cl_2/EtOAc (85:15) afforded **20** (2.5 g, 78.6%) as white crystals. mp 40-45°C; ν_{max} (film): 3431 cm^{-1} (OH), 1767 cm^{-1} (γ-lactone); λ_{max} (MeOH), 211.3 nm (ε, 16 767), 228.2 nm (ε, 14 595), 281.4 nm (ε, 6 696); See Tables 3 and 4 for ^1H and ^{13}C NMR data: *m/z* (e.i.) 372 (25%, M^+), 151 (100%, $Ar'CH_2^+$), 137 (98%, $Ar''CH_2^+$). *m/z* (c.i.) 390 (100%, M + NH_4), 373 (21%, M + H). Found: M^+ 372.1570. $C_{21}H_{24}O_6$ requires 372.1573.

trans-*2-([1″-Methoxy-4″-oxocyclohexa-2″,5″-dienyl]methylene)-3-(3′,4′-dimethoxybenzyl)butyrolactone (25)* *and* trans-*2-([1″-hydroxy-4″-oxocyclohexa-2″,5″-dienyl]methylene)-3-(3′,4′-dimethoxybenzyl)butyrolactone (26)*

Compound **18** (0.5g, 1.46 mmol) was dissolved in dry MeOH (20ml), under nitrogen. To this stirred solution was added PIFA (0.75 g, 1.74 mmol, 1.19 mol equiv) dissolved in dry MeOH (3 ml), *via* syringe, and stirring was continued at room temperature for 15 h. The reaction was monitored by hplc, which showed that after this time there remained a large peak due to starting material. Therefore more PIFA (0.55 g, 1.28 mmol, 0.88 mol equiv) dissolved in dry MeOH (2 ml) was added, and stirring was continued for another 18 h. Because starting material was still present, another portion of PIFA (0.55 g, 1.28 mol, 0.88 mol equiv) dissolved in dry MeOH (2 ml) was added and stirring was continued for another 15 h. After this time, the reaction mixture was neutralised by addition of powdered $NaHCO_3$, and the mixture was concentrated *in vacuo*. The residue was dissolved in ethyl acetate and filtered. The filtrate was evaporated and the residue was purified by flash chromatography on silica using gradient elution with CH_2Cl_2/EtOAc. Elution with CH_2Cl_2/EtOAc (4:1) gave **27** (0.043 g, 8%) as a brown gum. The compound was identified by comparison with an authentic sample prepared from **29** (see later for experimental details).

Elution CH_2Cl_2/EtOAc (3:1) afforded **25** (0.072 g, 13%) as a brown gum. ν_{max} (film): 1672 cm^{-1} (C=O), 1770 cm^{-1} (γ-lactone); λ_{max} (MeOH), 206.1 nm (ε, 21 173), 228.8 nm (ε, 15 489), 277.7 nm (ε, 4 185); See Tables 3 and 4 for ^1H and ^{13}C NMR data; *m/z* (e.i.) 372 (29%, M^+), 137 (14%, Ar'^+), 151 (100%, $Ar'CH_2^+$). *m/z* (c.i.) 373 (100%, M + H), 390 (50%, M + NH_4). Found: M^+ 372.1570. $C_{21}H_{24}O_6$ requires 372.1573.

Further elution with CH_2Cl_2/EtOAc (3:1) gave **28** (0.03 g, 6%) as a brownish gum (see below for spectral data).

Elution with CH_2Cl_2/EtOAc (6:4) gave **26** (0.051 g, 10%) as a brown gum. ν_{max} (film): 3442 cm^{-1} (OH), 1770 cm^{-1} (γ-lactone), 1671 cm^{-1} (C=O); λ_{max} (MeOH), 220.9 nm (ε, 29 918); See Tables 3 and 4 for ^1H and ^{13}C NMR data; *m/z* (e.i.) 358 (7%, M^+), 249 (1%, M - Ar″), 137 (9%, Ar′), 151 (100%, Ar′CH_2). *m/z* (c.i.) 376 (8%, M + NH_4), 360 (100%), 342 (67%, M + H - OH), 152 (20%).

Spirodienone ***(28)*** *and* trans-*2-([1″-trifluoroethoxy-4″-oxocyclohexa-2″,5″-dienyl]methylene)-3-(3′,4′-dimethoxybenzyl)butyrolactone* ***(32)***

Compound **18** (1.00 g, 2.92 mmol) was dissolved in dry TFE (16 ml), under nitrogen. To the stirred solution was added PIFA (1.51 g, 3.51 mmol, 1.2 mol equiv) dissolved in dry TFE (13 ml), *via* syringe and stirring was continued at rt for 1 h. After this time, the reaction mixture was neutralised by addition of powdered $NaHCO_3$, and concentrated *in vacuo*. The residue was dissolved in EtOAc and filtered. The filtrate was evaporated and the residue purified by flash chromatography on silica using gradient elution with CH_2Cl_2/EtOAc. Elution with CH_2Cl_2/EtOAc (95:5) gave **32** (0.04 g, 3%), as a brown gum. ν_{max} (film): 1672 cm^{-1} (C=O), 1770 cm^{-1} (γ-lactone); λ_{max} (MeOH), 207.4 nm (ε, 24 959), 227.2 nm (ε, 20 636), 280 nm (ε, 5 533); See Tables 3 and 4 for ^1H and ^{13}C NMR data; *m/z* (e.i.) 440 (15%, M^+), 249 (2%, M - Ar″), 151 (100%, Ar′$CH2^+$). *m/z* (c.i.) 441 (12%, M + H), 360 (100%, M + NH_4 - $OCHCF_3$), 341 (70%, M - OCH_2CF_3), 152 (22%). Found: M^+ 440.1447. $C_{22}H_{23}O_6F_3$ requires 440.1447.

Elution with a 4:1 mixture afforded **28** (0.466 g, 47%), which crystallised from EtOAc as colourless crystals mp 193-194°C. Found: C, 70.36; H, 5.94; $C_{20}H_{20}O_5$ requires C, 70.59; H, 5.88; ν_{max} (KBr): 1670 cm^{-1} (C=O), 1780 cm^{-1} (γ-lactone); λ_{max} (MeOH), 208.8 nm (ε, 53 574), 235.1 nm (ε, 36 137), 279.7 nm (ε, 5 731); See Tables 5 and 6 for ^1H and ^{13}C NMR data; *m/z* (e.i.) 370 (M^+, 13%), Found: M^+ 340.1310. $C_{20}H_{20}O_5$ requires 340.1311).

rel*(1a,12a*R_a*,6R,7R)-11-Hydroxy-6-hydroxymethyl-2,3-dimethoxy-5,6,7,8-tetrahydrodibenzo[1a,4a:8a,12a]cyclooctene-7-carboxylic acid lactone* ***(29)*** *and* rel*(1a,12a*S_a*,6R,7R)-11-hydroxy-6-hydroxymethyl-2,3-dimethoxy-5,6,7,8-tetrahydrodibenzo[1a,4a:8a,12a]cyclooctene-7-carboxylic acid lactone* ***(31)***

Compound **18** (0.5 g, 1.46 mmol) was dissolved in dry TFE (8 ml), under nitrogen. To the stirred solution was added PIFA (0.75 g, 1.74 mmol, 1.19 mol equiv) dissolved in dry TFA (7 ml) *via* syringe. The reaction mixture was stirred at rt for 24 h, after which it was neutralised by addition of powdered $NaHCO_3$. The mixture was concentrated *in vacuo*, the residue dissolved in EtOAc, filtered and the filtrate was evaporated and the residue was purified by flash column chromatography on silica by gradient elution with CH_2Cl_2 and EtOAc. Elution with a 7:3 mixture gave **29** together with **31** in an 8:1 ratio respectively. Crystallisation from EtOAc gave colourless crystals of **29** (0.27 g, 54%), mp 190-192°C; Found: C, 70.43; H, 6.09. $C_{20}H_{20}O_5$ requires C, 70.59; H, 5.88; ν_{max} (KBr): 1745 cm^{-1} (γ-lactone), 3400 cm^{-1} (OH); λ_{max} (MeOH), 216.8 nm (ε, 44 038), 280.8 nm (ε, 10 934); See Tables 7 and 8 for ^1H and ^{13}C NMR data; *m/z* (e.i.) 340 (M^+, 100%). It was not possible to obtain a completely pure sample of compound **31** and the spectral data given in Tables 7 and 8 are obtained by difference.

Further elution with CH_2Cl_2/EtOAc (7:3) gave **28** (0.05 g, 10%) as a brownish gum (see above for spectral data).

Compound **29** was also prepared using a different procedure as follows. Compound **28** (0.06 g, 0.00017 mol) was dissolved in dry TFE (2 ml) and stirred under a nitrogen atmosphere. To this solution TFA (0.5 ml) was added, *via* syringe and stirring was continued at rt for 1 h. After this time HPLC indicated that **28** had been converted into **29**, identified by coinjection with an authentic sample. Water (3 ml) was added and the mixture extracted with EtOAc (20 ml). The organic layer was separated, dried ($MgSO_4$) and evaporated to give **29** (0.06 g, 100%).

rel(*1a,12a*R_a,6R,7R)-*6-Hydroxymethyl-2,3,11-trimethoxy-5,6,7,8-tetrahydrodibenzo[1a,4a: 8a,12a] cyclooctene-7-carboxylic acid lactone (27)*

Compound **29** (0.05g, 0.147 mmol) was dissolved in dry acetone (0.5 ml) under a nitrogen atmosphere and anhydrous K_2CO_3 (0.37 g, 2.68 mmol, 18.23 mol equiv) was added quickly to the solution. To this stirred mixture was added Me_2SO_4 (0.085 g, 0.674 mmol, 4.58 ml equiv) *via* syringe and stirring was continued at room temperature for 7 h. After this time, the acetone was removed by distillation while maintaining a steady nitrogen flow. EtOAc (30 ml) was then added and the mixture was filtered from K_2CO_3. The organic layer was washed with water (2 x 5 ml), saturated aq. K_2CO_3 (8 ml) and with water until the washings were neutral. The organic layer was dried ($MgSO_4$), filtered, and evaporated to yield **27** (0.047 g, 91%), as a brown gum. ν_{max} (film): 1771 cm^{-1} (γ-lactone); λ_{max} (MeOH), 220 nm (ε, 19 448), 223 nm (ε, 19 887), 225.2 nm (ε, 19250); See Tables 7 and 8 for ^1H and ^{13}C NMR data; *m/z* (e.i.) 354 (M^+, 100%). Found: M^+ 354.1466. $C_{21}H_{22}O_5$ requires 354.1467.

Spirodienone (33)

Compound **19** (0.22 g, 0.59 mmol) was dissolved in dry TFE (2 ml), under nitrogen. To the stirred solution was added PIFA (0.31 g, 0.72 mmol, 1.22 mol equiv), dissolved in dry TFE (4 ml) *via* syringe. Stirring was continued at room temperature for 24 h, after which, the reaction mixture was neutralised by addition of powdered $NaHCO_3$, and the mixture was concentrated *in vacuo*. The residue was dissolved in EtOAc, filtered, and the filtrate evaporated. The residue was purified by flash column chromatography on silica using gradient elution with CH_2Cl_2 and EtOAc. Elution with a 9:1 mixture gave a mixture containing **34** and **36** (0.025 g, 11.5%) as a brown gum. See experiment below for spectral data of **34** and **36**.

Further elution with CH_2Cl_2/EtOAc (85:15) mixture afforded **33** (0.032 g, 15%), which recrystallised from MeOH as small brown crystals, mp 252-260°C: ν_{max}(film): 1772 cm^{-1} (γ-lactone), 1669 cm^{-1} (C=O); λ_{max} (MeOH), 212.3 nm (ε, 36 748), 281.1 (ε, 7 918); See Tables 5 and 6 for ^1H and ^{13}C NMR data; *m/z* (e.i.) 370 (M^+, 100%); *m/z* (c.i.) 388 (M+18, 100%), 371 (M+1, 40%). Found: M^+ 370.1416. $C_{21}H_{22}O_6$ requires 370.1416.

rel(*1a,12a* S_a,6R,7R)-*11-Hydroxy-6-hydroxymethyl-2,3,10-trimethoxy-5,6,7,8-tetrahydro-dibenzo [1a,4a:8a,12a]cyclooctene-7-carboxylic acid lactone (34) and* rel(*1a,12a,* R*a*,6R,7R)-*11-hydroxy-6-hydroxymethyl-2,3,10-trimethoxy-5,6,7,8-tetrahydrodibenzo[1a,4a:8a,12a]cyclooctene-7-carboxylic acid lactone (36)*

Compound **19** (0.51 g, 1.37 mmol) was dissolved in dry hexafluoroisopropanol (2 ml), under an argon atmosphere. To the stirred solution was added PIFA (0.70 g, 1.63 mmol, 1.19 mol equiv), dissolved in dry

TFE (2 ml), *via* syringe and stirring was continued at rt for 3.5 h. After this time, the reaction mixture was neutralised by addition of powdered $NaHCO_3$, and the mixture was concentrated *in vacuo*. The residue was dissolved in EtOAc, filtered, and the filtrate was evaporated and the residue purified by flash chromatography on silica using a gradient of petroleum spirit (60-80°C) and EtOAc. The (1:1) eluate afforded a mixture of **33** and **34** in 1:1 ratio (0.13 g, 26%) (hplc yield 36.8%) which were separated by recrystallisation from EtOAc. In this way were obtained the stegane **34** mp 246-248°C and the isostegane **36** mp 245-250°C as colourless crystals. For the mixture of **34** and **36**, analysis gave C, 68.17; H, 5.98. $C_{21}H_{22}O_6$ requires C, 68.11; H, 5.95; ν_{max} (film): 3436 cm^{-1} (OH), 1770 cm^{-1} (γ-lactone); λ_{max} (MeOH), 208.8 nm (ε, 129 438), 211.4 nm (ε, 132 521), 283.2 nm (ε, 28 736); See Tables 7 and 8 for ^1H and ^{13}C NMR data; *m/z* (e.i.) 370 (M^+, 100%) *m/z* (c.i.) 388 (M+18, 27%), 371 (M+1, 100%). Found M^+ 370.1416. $C_{21}H_{22}O_6$ requires 370.1416.

The stegane **34** was also prepared by protonation of spirodienone **33**. Compound **33** (0.02 g, 0.054 mmol) was dissolved in Analar $CHCl_3$ (0.5 ml), and to the stirred solution was added one small drop of 71-73% Analar perchloric acid ($HClO_4$). Stirring was continued at rt for 1 h, the reaction being monitored by hplc. After this time, the reaction mixture was neutralised by addition of saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$ (2 x 20 ml). The combined organic layers were washed with water (10 ml), dried ($MgSO_4$), filtered and evaporated to give **34** (0.002 g, 100%), as a hard, white gum, with HPLC retention time exactly the same as for the previously prepared sample.

rel(1a,12a R_a*,6R,7R)-10-Hydroxy-6-hydroxymethyl-2,3,11-trimethoxy-5,6,7,8-tetrahydro-dibenzo[1a,4a:8a,12a]cyclooctene-7-carboxylic acid lactone (**43**),* trans*-2-(2″,4″-bis[trifluoro-ethoxy]-5″-hydroxybenzyl)-3-(3′,4′-dimethoxybenzyl)butyrolactone (**46**) and benzoquinones (**45**) and (**47**)*

The dibenzylbutyrolactone **20** (0.27 g, 0.726 mmol) was dissolved in dry TFE (2 ml) under an argon atmosphere. To this stirred solution was added PIFA (0.37 g, 0.86 mmol, 1.18 mol equiv) dissolved in dry TFE (4 ml), *via* syringe. The solution was stirred at rt for 24 h, after which time, it was neutralised by addition of powdered $NaHCO_3$. The mixture was concentrated *in vacuo*, and the residue was purified by flash chromatography on silica by gradient elution with petroleum spirit (60-80°C)/EtOAc. The (1:1) mixture afforded **43** (0.107 g, 40%), which crystallised from EtOAc as colourless crystals mp 210-215°C; Found: C, 68.13; H, 6.07. $C_{21}H_{22}O_6$ requires C, 68.11; H, 5.95; ν_{max}(film): 3434 cm^{-1} (OH), 1773 cm^{-1} (γ-lactone); λ_{max} (MeOH), 217.1 nm (ε, 38 453), 281.5 nm (ε, 15 197), See Tables 7 and 8 for ^1H and ^{13}C NMR data; *m/z* (e.i.) 370 (M^+, 100%). Found: M^+ 370.1416. $C_{21}H_{22}O_6$ requires 370.1416.

Further elution with petroleum spirit (60-80°C)/EtOAc (45:55) gave **45**, **46** and **47**. Compound **45** was a brown gum (0.064 g, 22.8%). ν_{max} R (film): 1768 cm^{-1} (γ-lactone), 1679 cm^{-1} (C=O), 1652 cm^{-1} (C=O); λ_{max} (MeOH), 208.1 nm (ε, 16 160), 209.6 nm (ε, 16 617), 258.4 (ε, 5 764), 348.2 nm (ε, 1 576); See Tables 3 and 4 for ^1H and ^{13}C NMR data; *m/z* (e.i.) 388 (39%, M + 2), 370 (3%, M + 2 - H_2O), 237 (45%, M + 2 - $Ar'CH_2^+$), 219 (25%, M + 2 - $Ar'CH_2$ - H_2O), 151 (100%, $Ar'CH_2^+$), 137 (15%, Ar'^+). *m/z* (c.i.) 406 (41%, M + 2 + NH_4), 389 (100%, M + 2 + H), 371 (6%, M + 2 + H - H_2O). Found: $(M + 2H)^+$ 388.1522. $C_{21}H_{24}O_7$ requires 388.1522. Compound **46** was a brown gum (0.092g, 23.5%). ν_{max} (film): 3416 cm^{-1} (OH), 1767 cm^{-1} (γ-lactone); λ_{max} (MeOH), 209.9 nm (ε, 25084), 226.1 nm (ε, 19 536), 284.8 nm (ε, 8 955); See Tables 3 and 4 for ^1H and ^{13}C NMR data; *m/z* (e.i.) 538 (48%, M^+), 456 (3%, M + H - CF_3CH_2), 151 (100%, $Ar'CH_2^+$). *m/z* (c.i.) 556 (100%, M + NH_4), 539 (44%, M + H), 521 (4%, M - OH), 303 (12%, M + H

Ar′ - CF_3CH_2O). Found: M^+ 538.1426. $C_{24}H_{24}O_7F_6$ requires 538.1426. Compound **47** was a brown gum (MeOH), 208 nm (ε, 32 945), 274.1 nm (ε, 11 329), 327.6 nm (ε, 1 428); See Tables 7 and 8 for ^1H and ^{13}C NMR data; *m/z* (e.i.) 386 [$(M+2)^+$, 100%]. Found: $(M+2)^+$ 386.1366. $C_{21}H_{22}O_7$ requires 386.1366.

Compound **43** was also prepared by another procedure as follows.[26] To a stirred solution of $RuO_2.2H_2O$ (0.072 g, 0.54 mmol) in CH_2Cl_2 (4 ml), TFA (1.2 ml) and TFAA (0.6 ml) at -10°C was added a solution of **20** (0.1 g, 0.27 mmol) in CH_2Cl_2 (4 ml), immediately followed by BF_3-Et_2O (0.3 ml). The mixture was stirred vigorously at room temperature for 16 hours, after which time it was treated with a cold solution of saturated $NaHCO_3$. The organic layer was separated and the aqueous layer extracted with EtOAc (3 x 20 ml). The combined organic extracts were washed with saturated brine (10 ml), dried ($MgSO_4$), filtered and evaporated. The residue was purified by flash chromatography on silica using gradient elution with toluene/EtOAc. The (7:3) mixture afforded **43** (0.071 g, 71.6%), which was crystallised from EtOAc as colourless crystals mp 210-215°C (Lit.[26] 203-205°C). Further elution with toluene/EtOAc (65:35) gave **47** as a brown gum (0.017 g, 17%) (See above).

rel(*1a,12a* S_a,6R,7R)-*11-Acetoxy-6-hydroxymethyl-2,3,10-trimethoxy-5,6,7,8-tetrahydro-dibenzo [1a,4a:8a,12a] cyclooctene-7-carboxylic acid lactone (35)*

Compound **34** (0.02 g, 0.054 mmol) was dissolved in pyridine (2 ml) under a nitrogen atmosphere. Acetic anhydride (Ac_2O) (0.016 g, 0.157 mmol, 2.91 mol equiv) was added to the stirred solution *via* syringe. The mixture was stirred at rt for 24 h, after which time, the reaction mixture was poured onto ice (2 g) and was left stirring for 3 h. The reaction mixture was then extracted with EtOAc (20 ml), and the organic layer washed with 2 M HCl (2 x 7 ml), saturated aq. $CdCl_2$ (7 ml), saturated aq. $NaHCO_3$ (2 x 5 ml) and water (2 x 7 ml), dried ($MgSO_4$), filtered and evaporated yielding **35** as a brown gum (0.022 g, 100%). ν_{max} (film): 1770 cm^{-1} (γ-lactone); λ_{max} (MeOH), 211.6 nm (ε, 22 379), 214.5 nm (ε, 23 063), 217.6 nm (ε, 22 519), 280.9 nm (ε, 6 212); See Tables 7 and 8 for ^1H and ^{13}C NMR data; *m/z* (e.i.) 412 (M^+, 16%). Found: M^+ 412.1522. $C_{23}H_{24}O_7$ requires 412.1522.

rel(*1a,12a* R_a,6R,7R)-*11-Acetoxy-6-hydroxymethyl-2,3,10-trimethoxy-5,6,7,8-tetrahydrodibenzo [1a,4a:8a,12a]cyclooctene-7-carboxylic acid lactone (37)*

The experimental procedure was the same as that for **35**, starting with **36**. This afforded **37** (0.026 g, 100%); *m/z* (e.i.) 412 (M^+, 100%); See Tables 7 and 8 for ^1H and ^{13}C NMR data.

rel(*1a,12a* Ra,6R,7R)-*10-Acetoxy-6-hydroxymethyl-2,3,11-trimethoxy-5,6,7,8-tetrahydro-dibenzo [1a,4a:8a,12a]cyclooctene-7-carboxylic acid lactone (44)*

The experimental procedure was the same as that for **35**, starting from **43**. This afforded **44** (0.11 g, 100%). ν_{max} (film): 1776 cm^{-1} (γ-lactone); λ_{max} (MeOH), 209 nm (ε, 24 237), 213 nm (ε, 25 122), 215.4 nm (ε, 25 590), 218.2 nm (ε, 25 185), 278.9 nm (ε, 8 427); See Tables 7 and 8 for ^1H and ^{13}C NMR data; *m/z* (e.i.) 412 (M^+, 11%). Found: M^+ 412.1522. $C_{23}H_{24}O_7$ requires 412.1522.

Rel(*1a,12a*R_a,6R,7R)-*11-Acetoxy-6-hydroxymethyl-2,3-dimethoxy-5,6,7,8-tetrahydrodibenzo [1a,4a:8a,12a]cyclooctene-7-carboxylic acid lactone (30)*

The experimental procedure was the same as that for **35**, starting from **29**. This afforded **30** (0.056 g, 100%). ν_{max} (film): 1767 cm^{-1} (γ-lactone); λ_{max} (MeOH), 216.8 nm (ε, 32 295), 219.1 nm (ε, 32 742), 224.5 nm (ε 32 742), 227.9 nm (ε, 34513); See Tables 7 and 8 for NMR data. *m/z* (e.i.) 382 (M^+, 47%). Found: M^+ 382.1416. $C_{22}H_{22}O_6$ requires 382.1416.

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