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Oxidative cyclisation of *cis*- and *trans*-2,3-dibenzylbutyrolactones using ruthenium tetra(trifluoroacetate)

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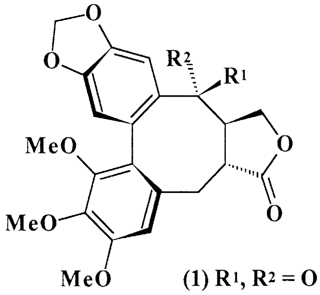
Abstract—A series of *cis*- and *trans*-2,3-dibenzylbutyrolactones have been synthesised and subjected to oxidative cyclisation using ruthenium tetra(trifluoroacetate) affording dibenzocyclooctadiene lactones belonging to the stegane and isostegane series of lignans. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

The biaryl unit is a key building block in the structures of a large number of important natural products.[1] Steganone (**1**), steganol (**2**), steganacin (**3**) and steganangin (**4**) are of interest owing to their antitumour and antiviral properties.[2]



(1) R1, R2 = O
(2) R1 = OH; R2 = H
(3) R1 = angelate; R2 = H
(4) R1 = H; R2 = OH

Successful methods that have been reported for the construction of the biaryl bond in such compounds include oxidative coupling using heavy metal oxidants, the use of hypervalent iodine reagents, and dehydrogenation by 'high potential' quinones. In this paper we report the results of our work on the oxidative cyclisation of *cis*- and *trans*-2,3-dibenzylbutyrolactones using ruthenium tetra(trifluoroacetate). Other oxidants that have been reported for such purposes include vanadium(V) oxyhalides and thallium(III) trifluoroacetate (TTFA). Thus, Kupchan[3] and Taylor and McKillop[4] have reported that vanadium(V) oxyhalides and TTFA give significant improvements when compared with other methods of oxidative coupling, and Schlessinger[5] and Cambie[6] have reported the synthesis of (**7**) and (**8**) from (**5**) and (**6**), respectively, using the vanadium and thallium reagents (Scheme 1). The synthesis of an aza analogue of isopicrostegane has also been reported utilising VOF_3 as the oxidising reagent.[7]

The use of ruthenium tetra(trifluoroacetate) was first reported by Landais and Robin[8] for the synthesis of the isosteganes (**11**) and (**12**) from the butyrolactones (**9**) and (**10**) (Scheme 2). Improved yields were obtained when the ruthenium reagent was employed.

The aims of the work described in this paper were firstly to study the cyclisation, using ruthenium tetra(trifluoroacetate), of *trans*-2,3-dibenzylbutyrolactones in which a phenolic group is located in either the 2- or the 3-benzyl group, and secondly to extend the scope of the methodology to *cis*-2,3-dibenzylbutyrolactones.

2. Results and discussion

The *trans*-compounds (**6**) and (**13–15**) were first studied. Compound (**6**)[6] was treated with ruthenium tetra(trifluoroacetate), generated *in situ* from 2 equivalents of $RuO_2\cdot 2H_2O$ in a mixture of TFA–TFAA containing a trace of $BF_3\cdot Et_2O$. The mixture was stirred at room temperature for 24 h, affording a single product in 89% yield. The structure of the product was identified as (**8**) by comparison with the data reported in the literature.[6]

The dibenzylbutyrolactones (**13–15**)[9] were similarly treated with ruthenium tetra(trifluoroacetate) and stirred at room temperature for 24 h affording (**16–18**),[9] as single diastereoisomers, in 78–82% yield (Scheme 3). The structures of (**16–18**) were assigned by analysis of their ^1H and ^{13}C NMR spectra. The aliphatic region of the ^1H NMR spectrum

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Keywords: lignans; lactones; oxidation; ruthenium and compounds.

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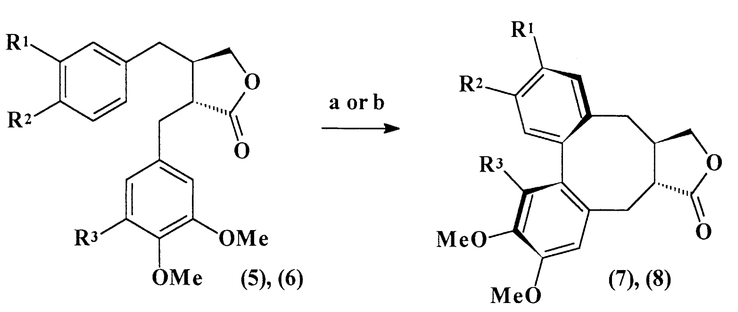
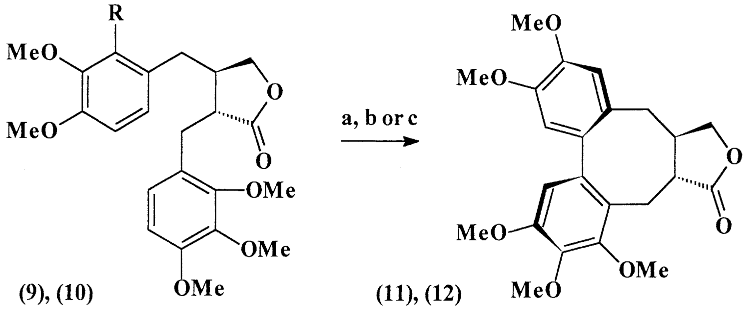


(5), (7) R1, R2 = OCH_2O; R3 = OMe
(6), (8) R1 = R2 = OMe; R3 = H

Scheme 1. *Reagents*: (a) VOF_3, TFA; (b) TTFA, $BF_3{\cdot}Et_2O$.



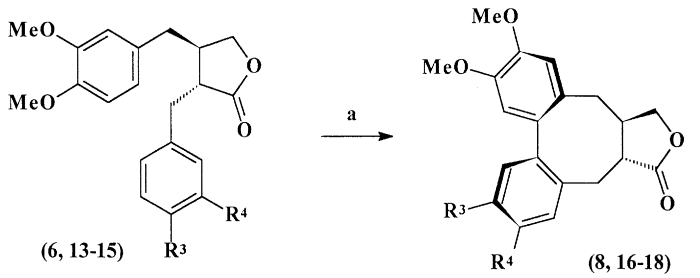
(9), (11) R = H
(10), (12) R = OMe

Scheme 2. *Reagents*: (a) $RuO_2{\cdot}2H_2O$, TFA–TFAA, $BF_3{\cdot}Et_2O$; (b) Tl_2O_3, TFA–TFAA, $BF_3{\cdot}Et_2O$; (c) VOF_3, TFA–TFAA.

was in each case retained while the aromatic region was greatly simplified, showing just four singlets for (**16**) and (**17**) and five singlets for (**18**), consistent with the dibenzocyclooctadiene skeleton. The stereochemistry about the biaryl bond was established by comparison with the data for (**8**). Thus, zero coupling was observed between H-5a and H-6 and between H-8b and H-7, characteristic of the isostegane series,[10–12] while the coupling between H-6 and H-7 [13.2 Hz for (**16**) and (**17**), and 13.3 Hz for (**18**)], indicated that the lactone was *trans*-fused.[10–12]

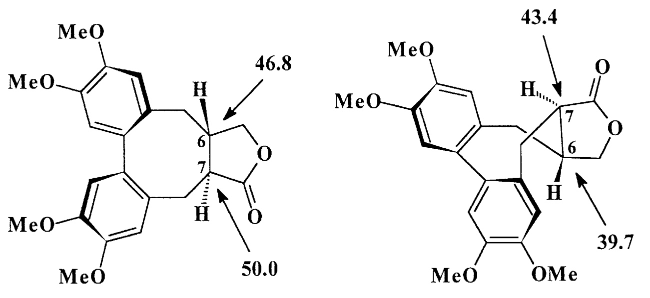
Further proof that the dibenzocyclooctadienes belonged to the isostegane series came from a comparison of the signals for C-6 and C-7 in the ^{13}C NMR spectra with those for compound (**8**) (Fig. 1). The values for (**16**) (46.9 and 50.4), (**17**) (46.9 and 50.1), and (**18**) (46.8 and 50.4) were almost identical to those for (**8**) (46.8 and 50.0), and differed from those of the stegane isomer (**19**), which come at 39.7 ppm (C-6) and 43.4 ppm (C-7), respectively.[13]

The position of the phenolic group in (**16–18**) was confirmed by examination of the ^{1}H NMR spectra, and by n.O.e experiments. The signal due to H-9 in compound (**8**) is moved downfield (6.74 ppm) due to its close proximity to the carbonyl group. Evidence for this assignment comes from comparison with the corresponding tetrahydrofuran,[14]



(6), (8) R3 = R4 = OMe
(13), (16) R3 = OH; R4 = OMe
(14), (17) R3 = OMe; R4 = OH
(15), (18) R3 = OH; R4 = H

Scheme 3. *Reagents*: (a) $RuO_2{\cdot}2H_2O$, TFA–TFAA, $BF_3{\cdot}Et_2O$ (80–90%).



(8) (19)

Figure 1.

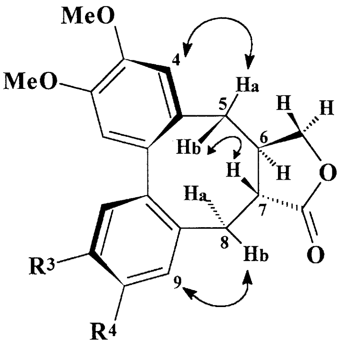


Figure 2.

where the corresponding proton appears at 6.65 ppm. The presence of a hydroxyl group also results in a downfield shift of the proton located next to it, with the result that in the ^{1}H NMR spectrum of (**16**), where the hydroxyl group is located at C-11, two singlets, corresponding to H-9 and H-12, appear downfield, while in the ^{1}H NMR spectrum of (**17**), where the hydroxyl group is located at C-10, only one singlet, corresponding to H-9, is moved downfield.

The ^{1}H NMR spectrum of (**18**) reflected the fact that it has only one substituent located on the phenolic ring. However, the presence of two doublets, at 6.63 and 6.75 ppm, and a double doublet at 7.11 ppm is consistent with the hydroxyl group being located at C-11. Furthermore, the observation of a clear n.O.e between H-9 and H-8b in all three compounds (**16–18**) showed that the phenolic group was located at C-11, C-10 and C-11, respectively. The observed n.O.e effects between H-5b and H-7 and H-5a and H-4 were also consistent with the structures of (**16–18**), as shown in Fig. 2.

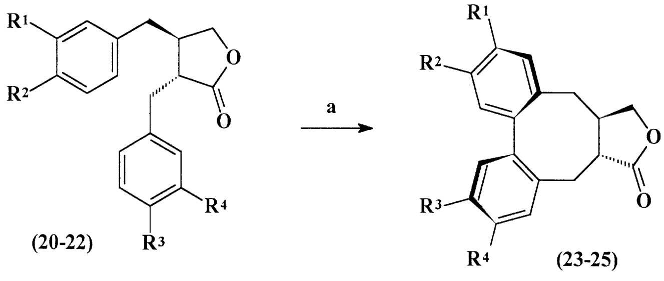
The oxidation of the dibenzylbutyrolactones (**20–22**),[15] under the same reaction conditions, afforded the dibenzocyclooctadienes (**23–25**), as single diastereoisomers, in 81–87% yield (Scheme 4).

Evidence for their structures was based on comparison with the spectral data for the previous compounds. The aliphatic regions of the NMR spectra were retained, while the aromatic regions were simplified, showing four singlets, corresponding to H-1, H-4, H-9 and H-12. Evidence that the dibenzocyclooctadienes possessed an isostegane structure came from the zero coupling observed between H-5a and H-6 and H-8b and H-7, while the signals due to C-6 and C-7 were almost identical to those for the previous compounds, resonating at 47.1 and 50.1, 47.0 and 50.1, and 46.9 and 50.3 ppm, respectively. The coupling between H-6 and H-7 was in line with previous results, and was found to be 13.2 Hz for all 3 compounds, indicating that the lactone was *trans*-fused.

The position of the phenolic moiety in each compound was confirmed from observations similar to those for compounds (**8**), (**16–18**), including n.O.e experiments. Other evidence came from the IR spectra, which showed the necessary γ-lactone and hydroxyl peaks, while high-resolution mass spectrometry confirmed molecular formulas as $C_{21}H_{22}O_6$ for compounds (**23**) and (**24**) and $C_{20}H_{20}O_6$ for compound (**25**).

When yatein (**5**)[5] was treated with ruthenium tetra(trifluoroacetate) and stirred at room temperature for 24 h, the dibenzocyclooctadiene (**7**) was obtained, as a single diastereoisomer, in 59% yield (Scheme 5). The structure of the product was established by comparison with the data for (**8**), (**16–18**), and (**23–25**), and with the data given in the literature.[5]

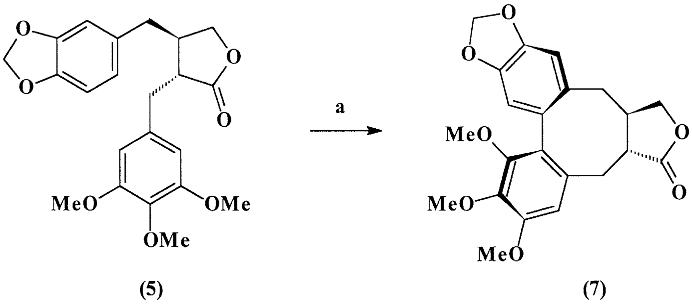
It is of interest to note, however, that Robin et al.[16] reported that oxidation of (**5**), using ruthenium tetra(trifluoroacetate), gave only degradation products, probably due to the cleavage of the methylenedioxy group. The same authors[16] reported that when the reaction was carried out using TTFA, the isostegane (**7**) was obtained, but in only 30%



(20-22) (23-25)

(20), (23) R1 = R3 = R4 = OMe; R2 = OH
(21), (24) R1 = OH; R2 = R3 = R4 = OMe
(22), (25) R1 = R3 = OH; R2 = R4 = OMe

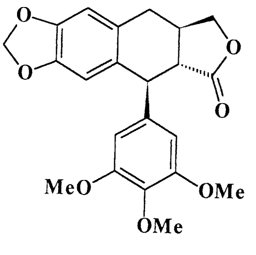
Scheme 4. *Reagents*: (a) $RuO_2{\cdot}2H_2O$, TFA–TFAA, $BF_3{\cdot}Et_2O$ (81–87%).



Scheme 5. *Reagents*: (a) $RuO_2 \cdot 2H_2O$, TFA–TFAA, $BF_3 \cdot Et_2O$ (59%).

yield. Schlessinger et al.[5] reported that the reaction of (**5**) with vanadium oxyfluoride, in TFA and $BF_3 \cdot Et_2O$, afforded (**7**) in 65–70% yield, while the use of thallium(III) oxide as the oxidising agent, in TFA and $BF_3 \cdot Et_2O$, afforded (**7**) in 65% yield.

Cambie et al.[17] reported that oxidation of (**5**) in neat TFA, without $BF_3 \cdot Et_2O$, afforded deoxypodophyllotoxin (**26**) as the major product. Treatment of the isostegane (**7**) with thallium(III) oxide in TFA cleaved the methylenedioxy group to give the *o*-benzoquinone (**27**) in 61% yield. In the current work (**27**) was not isolated, even though the yield of (**7**) was only 59%.



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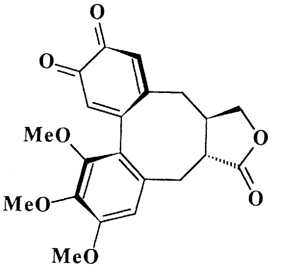


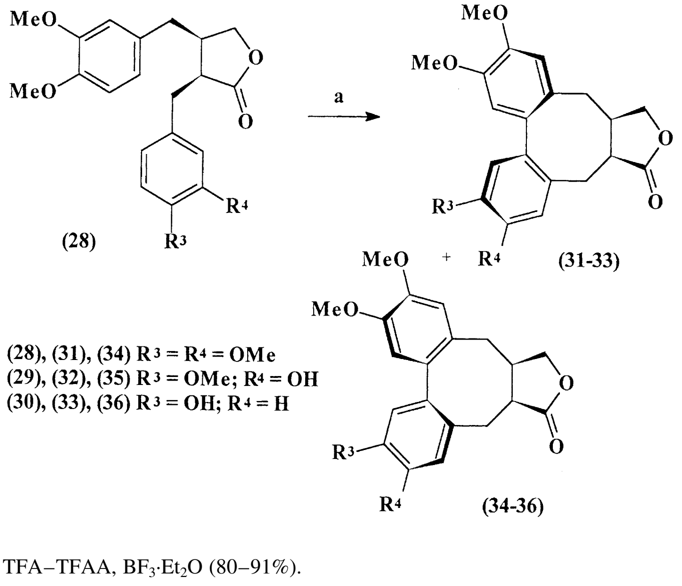
(27)

The *cis*-dibenzylbutyrolactones (**28–30**) were synthesised using the route reported by Moritani et al.[15,18] Treatment of (**28–30**) with ruthenium tetra(trifluoroacetate) at room temperature for 24 h afforded, in each case, a mixture of products. Purification by flash chromatography afforded one major fraction containing two components having almost identical R_f values. Further attempts to separate these compounds by chromatography failed. The ^{13}C NMR spectra showed two carbonyl peaks, in each case, which led to the conclusion that both the stegane and isostegane isomers had been formed (Scheme 6).

Further evidence that oxidative coupling had taken place came from the high-resolution mass spectra which confirmed the molecular formulas of the products.

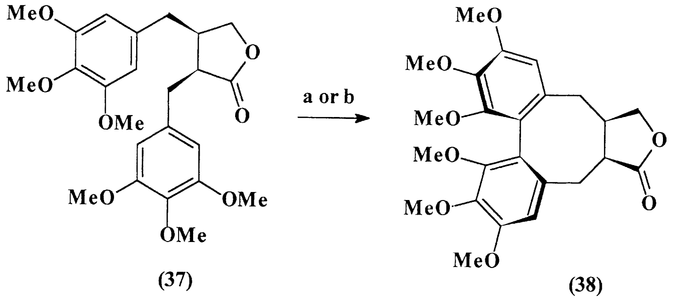
It was evident from the aromatic regions in the ^1H NMR spectra, that coupling of the phenolic dibenzylbutyrolactones (**29**) and (**30**) afforded a mixture of the stereoisomers in an approximate 1:1 ratio, whereas coupling of the non-phenolic dibenzylbutyrolactone (**28**) afforded the stereoisomers in a 1.6:1 ratio.

The coupling of (**28–30**) is in marked contrast to the findings of Robin et al.[16] who reported that the coupling of (**37**) using ruthenium tetra(trifluoroacetate) and TTFA afforded only the stegane isomer (**38**) (Scheme 7).



(28), (31), (34) $R^3 = R^4 = OMe$
(29), (32), (35) $R^3 = OMe$; $R^4 = OH$
(30), (33), (36) $R^3 = OH$; $R^4 = H$

Scheme 6. *Reagents*: (a) $RuO_2 \cdot 2H_2O$, TFA–TFAA, $BF_3 \cdot Et_2O$ (80–91%).



Scheme 7. *Reagents*: (a) $RuO_2{\cdot}2H_2O$, TFA–TFAA, $BF_3{\cdot}Et_2O$; (b) TTFA, $BF_3{\cdot}Et_2O$.

3. Experimental

^1H and ^{13}C NMR spectra were recorded on a Bruker AC 400 instrument and were run in $CDCl_3$ unless otherwise stated. Mass spectra were recorded on a VG 12-250 low-resolution quadrupole instrument or on a VG Micromass Quattro II instrument. Accurate mass measurements were made using either a ZAB-E high-resolution double-focusing instrument or a Finnigan Mat 900 instrument. IR spectra were recorded on a Perkin–Elmer FT 1725X spectrometer and were measured using KBr discs unless otherwise stated. Melting points were recorded on an Electrothermal 9100 apparatus and are uncorrected.

Flash chromatography was performed on silica gel (Fisons Matrex, 35–70μ). Ether and dichloromethane were dried by passing them down an alumina column and distillation from calcium hydride. Ethyl acetate was dried over anhydrous potassium carbonate and distilled from calcium hydride. TFE was dried by distillation from calcium hydride and stored over molecular sieves.

3.1. Preparation of *trans*-6-(hydroxymethyl)-2,3,10,11-tetramethoxydibenzo[1a,4a:8a,12a]cyclooctadiene-7-carboxylic acid lactone (8) using ruthenium tetra-(trifluoroacetate)

To a stirred solution of $RuO_2{\cdot}2H_2O$ (0.064 g, 0.480 mmol, 2 mol equiv.), in CH_2Cl_2 (15 ml), TFA (1 ml) and TFAA (0.5 ml) was added, at −10°C, a solution of (**6**)[6] (0.091 g, 0.240 mmol) in CH_2Cl_2 (10 ml) followed immediately by $BF_3{\cdot}Et_2O$ (0.2 ml). The mixture was stirred at room temperature overnight before addition of a cold saturated solution of $NaHCO_3$ (10 ml). The mixture was then passed through a short celite column to remove the metallic salts. The organic layer was decanted and the aqueous layer was extracted with EtOAc (4×40 ml). The combined organic extracts were washed with brine (2×40 ml), water (2×40 ml), dried ($MgSO_4$), filtered and evaporated *in vacuo* to afford an off-white foam. Purification via flash chromatography on silica and elution with CH_2Cl_2/EtOAc (90:10), followed by crystallisation from diethyl ether, afforded (**8**) as a white solid (0.083 g, 90%), m.p. 208–210°C (Lit.[16] 212–213°C); IR (film): 1795 cm^{-1} (γ-lactone); δ_H (400 MHz, $CDCl_3$) 6.74 (1 H, s, H-9), 6.63 (2 H, s, H-1,4), 6.62 (1 H, s, H-12), 4.35 (1 H, dd, *J* 6.7, 8.5 Hz, H-13a), 3.87 (3 H, s, OMe), 3.86 (3 H, s, OMe), 3.80 (3 H, s, OMe), 3.78 (3 H, s, OMe), 3.73 (1 H, dd, *J* 8.5, 11.3 Hz, H-13b), 3.11 (1 H, d, *J* 13.4 Hz, H-8a), 2.60 (1 H, d, *J* 13.2 Hz, H-5a), 2.35 (1 H, dd, *J* 9.7, 13.2 Hz, H-5b), 2.26 (1 H, dd, *J* 9.1, 13.4 Hz, H-8b), 2.17 (1 H, m, H-6), 2.09 (1 H, dd, *J* 9.1, 13.2 Hz, H-7); δ_C (100.6 MHz, $CDCl_3$) 176.7 (C-14), 148.9 (C-3), 148.7 (C-2), 147.3 (C-11), 147.2 (C-10), 132.4 (C-12a), 132.0 (C-8a), 131.7 (C-4a), 130.9 (C-1a), 114.2 (C-9), 114.0 (C-12), 112.0 (C-4), 111.7 (C-7), 70.1 (C-13), 56.1 (4×OMe), 50.2 (C-7), 46.9 (C-6), 34.3 (C-5), 32.1 (C-8); *m/z*: (EI) 385 (4), 384 (M^+, 18), 207 (4%); (CI) 402 ($M+NH_4^+$, 100), 372 (16), 152 (9), 117 (33%); [Found: $(M+NH_4)^+$ 402.1923, $C_{22}H_{24}O_6$ requires 402.1917].

3.2. Preparation of *trans*-11-hydroxy-6-(hydroxymethyl)-2,3,10-trimethoxydibenzo[1a,4a:8a,12a]cyclooctadiene-7-carboxylic acid lactone (16) using ruthenium tetra-(trifluoroacetate)

The above experimental procedure was employed using as starting material the dibenzylbutyrolactone (**13**)[9] (0.152 g, 0.409 mmol). Purification via flash chromatography on silica using a gradient elution of CH_2Cl_2/EtOAc (80:20), followed by crystallisation from EtOAc, afforded (**16**) as a white solid (0.121 g, 80%), m.p. 240–243°C (Lit.[9] 245–250°C); IR (film): 3438 cm^{-1} (OH), 1770 cm^{-1} (γ-lactone); δ_H (400 MHz, $CDCl_3$) 6.73 (1 H, s, H-12), 6.72 (1 H, s, H-9), 6.61 (1 H, s, H-4), 6.60 (1 H, s, H-1), 5.50 (1 H, s, OH), 4.34 (1 H, dd, *J* 6.7, 8.4 Hz, H-13a), 3.86 (3 H, s, OMe), 3.85 (3 H, s, OMe), 3.78 (3 H, s, OMe), 3.73 (1 H, dd, *J* 8.4, 11.2 Hz, H-13b), 3.09 (1 H, d, *J* 13.4 Hz, H-8a), 2.59 (1 H, d, *J* 13.2 Hz, H-5a), 2.35 (1 H, dd, *J* 9.7, 13.2 Hz, H-5b), 2.25 (1 H, dd, *J* 9.2, 13.4 Hz, H-8b), 2.17 (1 H, m, H-6), 2.08 (1 H, dd, *J* 9.2, 13.2 Hz, H-7); δ_C (100.6 MHz, $CDCl_3$) 177.4 (C-14), 147.5 (C-3), 146.2 (C-2), 145.5 (C-11), 142.9 (C-10), 133.8 (C-12a), 132.5 (C-8a), 131.9 (C-4a), 130.6 (C-1a), 116.9 (C-12), 114.2 (C-9), 112.0 (C-4), 111.1 (C-7), 70.1 (C-13), 56.1 (OMe), 56.0 (2×Me), 50.4 (C-7), 46.9 (C-6), 34.3 (C-5), 32.1 (C-8); *m/z*: (EI) 371 (20), 370 (M^+, 100), 151 (24), 137 (25%); (CI) 388 ($M+NH_4^+$, 100), 370 (11), 358 (4%); [Found: $(M+NH_4)^+$ 388.1764, $C_{21}H_{22}O_6$ requires 388.1760].

3.3. Preparation of *trans*-10-hydroxy-6-(hydroxymethyl)-2,3,11-trimethoxydibenzo[1a,4a:8a,12a]cyclooctadiene-7-carboxylic acid lactone (17) using ruthenium tetra-(trifluoroacetate)

The above experimental procedure was employed using as starting material the dibenzylbutyrolactone (**14**)[9] (0.126 g, 0.339 mmol). Purification via flash chromatography on silica using a gradient elution of CH_2Cl_2/EtOAc (80:20), followed by crystallisation from EtOAc, afforded (**17**) as a white solid (0.103 g, 82%), m.p. 213–215°C (Lit.[9] 210–215°C); IR (film): 3434 cm^{-1} (OH), 1771 cm^{-1} (γ-lactone); δ_H (400 MHz, $CDCl_3$) 6.80 (1 H, s, H-9), 6.63 (1 H, s, H-12), 6.62 (1 H, s, H-4), 6.61 (1 H, s, H-1), 5.63 (1 H, s, OH), 4.32 (1 H, dd, *J* 6.7, 8.4 Hz, H-13a), 3.86 (3 H, s, OMe), 3.81 (3 H, s, OMe), 3.80 (3 H, s, OMe), 3.70 (1 H, dd, *J* 8.4, 11.1 Hz, H-13b), 3.06 (1 H, d, *J* 13.5 Hz, H-8a), 2.60 (1 H, d, *J* 13.3 Hz, H-5a), 2.34 (1 H, dd, *J* 9.7, 13.3 Hz, H-5b), 2.20 (1 H, dd, *J* 9.2, 13.5 Hz, H-8b), 2.13 (1 H, m, H-6), 2.06 (1 H, dd, *J* 9.2, 13.2 Hz, H-7); δ_C (100.6 MHz, $CDCl_3$) 176.5 (C-14), 148.7 (C-3), 147.3 (C-2), 145.5 (C-11), 144.9 (C-10), 132.8 (C-12a), 132.5 (C-8a), 132.0 (C-4a), 131.0 (C-1a), 114.9 (C-12), 114.3 (C-9), 113.3 (C-4), 112.0 (C-7), 70.0 (C-13), 56.1 (3× OMe), 50.1 (C-7), 46.9 (C-6), 34.2 (C-5), 31.7 (C-8); *m/z*: (EI) 371 (25), 370 (M$^+$, 100), 281 (15), 207 (84), 191 (11), 165 (15%); (CI) 388 (M+NH$_4^+$, 100), 372 (8), 358 (7%); [Found: (M+NH$_4$)$^+$ 388.1759, $C_{21}H_{22}O_6$ requires 388.1760].

3.4. Preparation of *trans*-11-hydroxy-6-(hydroxymethyl)-2,3-dimethoxydibenzo[1a,4a:8a,12a]cyclooctadiene-7-carboxylic acid lactone (18) using ruthenium tetra-(trifluoroacetate)

The above experimental procedure was employed using as starting material the dibenzylbutyrolactone (**15**)[9] (0.118 g, 0.346 mmol). Purification via flash chromatography on silica using a gradient elution of CH_2Cl_2/EtOAc (80:20), followed by crystallisation from EtOAc, afforded (**18**) as a white solid (0.094 g, 80%), m.p. 194–195°C (Lit.[9] 190–192°C); IR (film): 3400 cm^{-1} (OH), 1745 cm^{-1} (γ-lactone); δ_H (400 MHz, $CDCl_3$) 7.11 (1 H, d, *J* 8.3 Hz, H-9), 6.75 (1 H, dd, *J* 2.7, 8.3 Hz, H-10), 6.63 (1 H, d, *J* 2.7 Hz, H-12), 6.61 (1 H, s, H-4), 6.60 (1 H, s, H-1), 5.23 (1 H, s, OH), 4.33 (1 H, dd, *J* 6.7, 8.5 Hz, H-13a), 3.86 (3 H, s, OMe), 3.79 (3 H, s, OMe), 3.72 (1 H, dd, *J* 8.5, 11.3 Hz, H-13b), 3.15 (1 H, d, *J* 13.6 Hz, H-8a), 2.60 (1 H, d, *J* 13.2 Hz, H-5a), 2.34 (1 H, dd, *J* 9.8, 13.2 Hz, H-5b), 2.24 (1 H, dd, *J* 9.3, 13.6 Hz, H-8b), 2.13 (1 H, m, H-6), 2.05 (1 H, dd, *J* 9.3, 13.3 Hz, H-7); δ_C (100.6 MHz, $CDCl_3$) 176.6 (C-14), 152.8 (C-11), 148.8 (C-3), 147.2 (C-2), 142.4 (C-8a), 132.3 (C-12a), 131.7 (C-4a), 130.5 (C-1a), 130.4 (C-9), 117.6 (C-10), 115.3 (C-12), 114.0 (C-4), 112.0 (C-1), 70.0 (C-13), 56.0 (2×OMe), 50.4 (C-7), 46.8 (C-6), 34.2 (C-5), 31.5 (C-8); *m/z*: (EI) 341 (21), 340 (M$^+$, 100), 255 (26), 181 (25), 165 (33), 152 (29%); (CI) 358 (M+NH$_4^+$, 100), 342 (15), 328 (12), 116 (34%); [Found: (M+NH$_4$)$^+$ 358.1654, $C_{20}H_{20}O_5$ requires 358.1654].

3.5. Preparation of *trans*-2-hydroxy-6-(hydroxymethyl)-3,10,11-trimethoxydibenzo[1a,4a:8a,12a]cyclooctadiene-7-carboxylic acid lactone (23) using ruthenium tetra(trifluoroacetate)

The above experimental procedure was employed using as starting material the dibenzylbutyrolactone (**20**)[15] (0.109 g, 0.293 mmol). Purification via flash chromatography on silica and elution with CH_2Cl_2/EtOAc (98:2), followed by crystallisation from EtOAc, afforded (**23**) as a white solid (0.092 g, 85%), m.p. 232–234°C; IR (film): 3435 cm^{-1} (OH), 1770 cm^{-1} (γ-lactone); [Found: C, 67.41; H, 6.00. $C_{21}H_{22}O_6$ requires C, 68.10; H, 5.99%]; δ_H (400 MHz, $CDCl_3$) 6.72 (1 H, s, H-9), 6.71 (1 H, s, H-1), 6.61 (1 H, s, H-12), 6.60 (1 H, s, H-4), 5.53 (1 H, s, OH), 4.33 (1 H, dd, *J* 6.7, 8.4 Hz, H-13a), 3.87 (3 H, s, OMe), 3.85 (3 H, s, OMe), 3.78 (3 H, s, OMe), 3.72 (1 H, dd, *J* 8.4, 11.0 Hz, H-13b), 3.09 (1 H, d, *J* 13.6 Hz, H-8a), 2.58 (1 H, d, *J* 13.3 Hz, H-5a), 2.33 (1 H, dd, *J* 9.6, 13.3 Hz, H-5b), 2.26 (1 H, dd, *J* 9.1, 13.6 Hz, H-8b), 2.16 (1 H, m, H-6), 2.09 (1 H, dd, *J* 9.1, 13.2 Hz, H-7); δ_C (100.6 MHz, $CDCl_3$) 176.8 (C-14), 147.1 (C-3,11), 146.3 (C-10), 143.9 (C-2), 133.3 (C-12a), 132.2 (C-8a), 131.7 (C-4a), 130.4 (C-1a), 117.3 (C-1), 114.0 (C-9), 111.3 (C-4,12), 70.1 (C-13), 56.1 (OMe), 56.0 (2×OMe), 50.1 (C-7), 47.1 (C-6), 34.3 (C-5), 32.1 (C-8); *m/z*: (EI) 371 (22), 370 (M$^+$, 100), 271 (9), 165 (11), 149 (14%); (CI) 388 (M+NH$_4^+$, 100), 358 (9), 279 (19), 170 (15), 152 (21), 116 (35%); [Found: (M+NH$_4$)$^+$ 388.1765, $C_{21}H_{22}O_6$ requires 388.1760].

3.6. Preparation of *trans*-3-hydroxy-6-(hydroxymethyl)-2,10,11-trimethoxydibenzo[1a,4a: 8a,12a]cyclooctadiene-7-carboxylic acid lactone (24) using ruthenium tetra(trifluoroacetate)

The above experimental procedure was employed using as starting material the dibenzylbutyrolactone (**21**)[15] (0.128 g, 0.344 mmol). Purification via flash chromatography on silica and elution with CH_2Cl_2/EtOAc (98:2), followed by crystallisation from EtOAc, afforded (**24**) a white gum (0.103 g, 81%); IR (film): 3438 cm^{-1} (OH), 1770 cm^{-1} (γ-lactone); δ_H (400 MHz, $CDCl_3$) 6.73 (1 H, s, H-9), 6.70 (1 H, s, H-4), 6.62 (1 H, s, H-12), 6.61 (1 H, s, H-1), 5.56 (1 H, s, OH), 4.31 (1 H, dd, *J* 6.7, 8.5 Hz, H-13a), 3.85 (3 H, s, OMe), 3.81 (3 H, s, OMe), 3.80 (3 H, s, OMe), 3.71 (1 H, dd, *J* 8.5, 11.0 Hz, H-13b), 3.09 (1 H, d, *J* 13.4 Hz, H-8a), 2.56 (1 H, d, *J* 13.2 Hz, H-5a), 2.29 (1 H, dd, *J* 9.5, 13.2 Hz, H-5b), 2.26 (1 H, dd, *J* 9.3, 13.4 Hz, H-8b), 2.16 (1 H, m, H-6), 2.06 (1 H, dd, *J* 9.3, 13.2 Hz, H-7); δ_C (100.6 MHz, $CDCl_3$) 176.8 (C-14), 148.9 (C-2), 147.2 (C-3), 145.3 (C-11), 144.9 (C-10), 132.5 (C-12a), 132.1 (C-8a), 131.9 (C-4a), 131.7 (C-1a), 114.9 (C-9), 114.1 (C-4), 113.4 (C-12), 111.7 (C-1), 70.1 (C-13), 56.1 (3× OMe), 50.1 (C-7), 47.0 (C-6), 33.9 (C-5), 32.1 (C-8); *m/z*: (EI) 371 (21), 370 (M$^+$, 100), 207 (12), 165 (16), 152 (16 %); (CI) 388 (M+NH$_4^+$, 100), 372 (10), 279 (11), 152 (15), 116 (27%); [Found: (M+NH$_4$)$^+$ 388.1761, $C_{21}H_{22}O_6$ requires 388.1760].

3.7. Preparation of *trans*-3,11-dihydroxy-6-(hydroxymethyl)-2,10-dimethoxydibenzo[1a,4a: 8a,12a]cyclooctadiene-7-carboxylic acid lactone (25) using ruthenium tetra(trifluoroacetate)

The above experimental procedure was employed using as starting material the dibenzylbutyrolactone (**22**)[15] (0.127 g, 0.355 mmol). Purification via flash chromatography on silica and elution with CH_2Cl_2/EtOAc (98:2), followed by crystallisation from EtOAc, afforded (**25**) as white crystals (0.110 g, 87%), m.p. 208–211°C; IR (film): 3431 cm^{-1} (OH), 1781 cm^{-1} (γ-lactone); δ_H (400 MHz, $CDCl_3$) 6.71 (1 H, s, H-9), 6.70 (1 H, s, H-12), 6.67 (1 H, s, H-4), 6.57 (1 H, s, H-1), 5.60 (2 H, br.s, OH), 4.30 (1 H, dd, *J* 6.6, 8.5 Hz, H-13a), 3.85 (3 H, s, OMe), 3.78 (3 H, s, OMe), 3.70 (1 H, dd, *J* 8.5, 11.0 Hz, H-13b), 3.08 (1 H, d, *J* 13.6 Hz, H-8a), 2.54 (1 H, d, *J* 13.1 Hz, H-5a), 2.28 (1 H, dd, *J* 9.6, 13.1 Hz, H-5b), 2.23 (1 H, dd, *J* 9.2, 13.6 Hz, H-8b), 2.15 (1 H, m, H-6), 2.05 (1 H, dd, *J* 9.2, 13.2 Hz, H-7); δ_C (100.6 MHz, $CDCl_3$) 176.9 (C-14), 146.4 (C-11), 145.3 (C-2), 144.9 (C-10), 143.7 (C-3), 133.4 (C-12a), 131.7 (C-8a), 131.6 (C-4a), 131.5 (C-1a), 117.0 (C-12), 114.9 (C-4), 113.7 (C-9), 111.2 (C-1), 70.2 (C-13), 56.1 (OMe), 56.0 (OMe), 50.3 (C-7), 46.9 (C-6), 33.9 (C-5), 32.2 (C-8); *m/z*: (EI) 357 (21), 356 (M^+, 100), 271 (9), 257 (11), 152 (10%); (CI) 374 ($M+NH_4^+$, 57), 222 (11), 154 (26), 116 (72%); [Found: $(M+NH_4)^+$ 374.1596, $C_{20}H_{20}O_5$ requires 374.1604].

3.8. Preparation of *trans*-6-(hydroxymethyl)-10,11,12-trimethoxy-2,3-methylenedioxy-dibenzo[1a,4a:8a,12a] cyclooctadiene-7-carboxylic acid lactone (7) using ruthenium tetra(trifluoroacetate)

The above experimental procedure was employed using as starting material the dibenzylbutyrolactone (**5**)[5] (0.083 g, 0.209 mmol). Purification via flash chromatography on silica and elution with CH_2Cl_2/EtOAc (98:2), followed by crystallisation from EtOAc/hexane, afforded (**7**) as a white foam (0.049 g, 59%), m.p. 169–171°C (Lit.[6] 172–172.5°C); IR (film): 1777 cm^{-1} (γ-lactone); δ_H (400 MHz, $CDCl_3$) 6.63 (1 H, s, H-9), 6.56 (1 H, s, H-1), 6.55 (1 H, s, H-4), 5.93 (1 H, d, *J* 1.4 Hz, OCH_2O), 5.91 (1 H, d, *J* 1.4 Hz, OCH_2O), 4.35 (1 H, dd, *J* 6.6, 8.4 Hz, H-13a), 3.83 (6 H, s, 2×OMe), 3.82 (3 H, s, OMe), 3.70 (1 H, dd, *J* 8.4, 11.0 Hz, H-13b), 3.05 (1 H, d, *J* 13.2 Hz, H-8a), 2.57 (1 H, d, *J* 13.1 Hz, H-5a), 2.32 (1 H, dd, *J* 9.6, 13.1 Hz, H-5b), 2.22 (1 H, dd, *J* 9.1, 13.2 Hz, H-8b), 2.12 (1 H, m, H-6), 2.03 (1 H, dd, *J* 8.8, 13.2 Hz, H-7); δ_C (100.6 MHz, $CDCl_3$) 176.2 (C-14), 153.1 (C-10), 151.6 (C-12), 147.4 (C-3), 145.6 (C-2), 140.6 (C-11), 135.7 (C-4a), 130.9 (C-1a), 128.8 (C-12a), 126.5 (C-8a), 113.0 (C-9), 111.7 (C-1), 108.4 (C-4), 103.1 (OCH_2O), 72.6 (C-13), 56.0 (3×OMe), 50.1 (C-7), 46.8 (C-6), 34.2 (C-5), 31.9 (C-8); *m/z*: (EI) 398 (M^+, 100), 383 (8), 181 (15), 152 (7%); (CI) 416 ($M+NH_4^+$, 26), 391 (87), 296 (19), 279 (100), 152 (24), 136 (53%); [Found: $(M+NH_4)^+$ 416.1705, $C_{22}H_{22}O_7$ requires 416.1709].

3.9. Preparation of *cis*-6-(hydroxymethyl)-2,3,10,11-tetramethoxydibenzo[1a,4a:8a,12a]cyclooctadiene-7-carboxylic acid lactone (31) and *cis*-6-(hydroxymethyl)-2,3,10,11-tetramethoxydibenzo-[1a,4a:8a,12a] cyclooctadiene-7-carboxylic acid lactone (34) using ruthenium tetra(trifluoroacetate)

The above experimental procedure was employed using as starting material the dibenzylbutyrolactone (**28**)[15] (0.097 g, 0.252 mmol). Purification via flash chromatography on silica and elution with CH_2Cl_2/EtOAc (95:5) afforded a mixture of the two isomers (**31**) and (**34**), in a 1.6:1 ratio, as a gum (0.088 g, 91%); IR (film): 1778 cm^{-1} (γ-lactone); δ_H (400 MHz, $CDCl_3$) major isomer: 7.17 (1 H, s), 6.73 (1 H, s), 6.71 (1 H, s), 6.63 (1 H, s), 4.37 (1 H, m, H-13a), 3.99 (1 H, d, *J* 9.1 Hz, H-13b), 3.86 (3 H, s, OMe), 3.85 (3 H, s, OMe), 3.83 (3 H, s, OMe), 3.82 (3 H, s, OMe), 2.41-3.10 (6 H, m); minor isomer: 6.83 (1 H, s), 6.73 (1 H, s), 6.69 (1 H, s), 6.48 (1 H, s), 4.37 (1 H, m, H-13a), 4.08 (1 H, dd, *J* 8.8, 11.8 Hz, H-13b), 3.86 (3 H, s, OMe), 3.85 (3 H, s, OMe), 3.82 (3 H, s, OMe), 3.79 (3 H, s, OMe), 2.41-3.10 (6 H, m); δ_C (100.6 MHz, $CDCl_3$) major isomer: 177.3 (C-14), 148.7 (C-2), 147.5 (C-3,10), 147.4 (C-11), 130.2 (C-1a), 129.7 (C-4a), 128.5 (C-8a), 127.6 (C-12a), 115.9 (C-1), 111.6 (C-4,9), 111.4 (C-12), 73.1 (C-13), 56.1 (2×OMe), 56.0 (2×OMe), 42.5 (C-6), 40.2 (C-7), 35.6 (C-8), 28.9 (C-5); minor isomer: 179.4 (C-14), 149.0 (C-2), 148.2 (C-3), 147.8 (C-10,11), 133.6 (C-1a), 133.1 (C-4a,8a), 133.0 (C-12a), 113.6 (C-1), 112.5 (C-4), 111.8 (C-9,12), 69.4 (C-13), 56.2 (2×OMe), 55.9 (2×OMe), 44.5 (C-7), 37.2 (C-6), 30.3 (C-8), 30.0 (C-5); *m/z*: (EI) 385 (22), 384 (M^+, 100), 226 (8), 165 (8), 152 (8%); (CI) 402 ($M+NH_4^+$, 100), 384 (6), 372 (5%); [Found: $(M+NH_4)^+$ 402.1922, $C_{22}H_{24}O_6$ requires 402.1917].

3.10. Preparation of *cis*-10-hydroxy-6-(hydroxymethyl)-2,3,11-trimethoxydibenzo[1a,4a:8a,12a]cyclooctadiene-7-carboxylic acid lactone (32) and *cis*-10-hydroxy-6-(hydroxymethyl)-2,3,11-trimethoxydibenzo [1a,4a:8a,12a]cyclooctadiene-7-carboxylic acid lactone (35) using ruthenium tetra(trifluoroacetate)

The above experimental procedure was employed using as starting material the dibenzylbutyrolactone (**29**)[15] (0.134 g, 0.360 mmol). Purification via flash chromatography on silica and elution with CH_2Cl_2/EtOAc (95:5) afforded a mixture of the two isomers (**32**) and (**35**), in a 1:1 ratio, as a gum (0.108 g, 81%); IR (film): 3440 cm^{-1} (OH), 1774 cm^{-1} (γ-lactone); δ_H (400 MHz, $CDCl_3$) 7.20 (1 H, s), 6.90 (1 H, s), 6.73 (2 H, s), 6.70 (1 H, s), 6.66 (1 H, s), 6.62 (1 H, s), 6.48 (1 H, s), 5.68 (1 H, br.s, OH), 5.54 (1 H, br.s, OH), 4.36 (2 H, m, H-13), 4.06 (1 H, m, H-13), 3.99 (1 H, d, *J* 9.2 Hz, H-13), 3.85 (3 H, s, OMe), 3.84 (6 H, s, OMe), 3.83 (6 H, s, OMe), 3.80 (3 H, s, OMe), 2.40–3.08 (12 H, m); δ_C (100.6 MHz, $CDCl_3$) 179.3, 177.3 (C-14), 148.7, 148.2 (C-2), 147.8, 147.4 (C-3), 145.6, 145.4 (C-10), 145.2, 144.6 (C-11), 133.8, 133.3 (C-1a), 132.9, 132.6 (C-4a), 130.5, 130.3 (C-8a), 129.2, 127.7 (C-12a), 119.0, 114.9 (C-1), 113.6, 112.6 (C-4), 111.8, 111.7 (C-9), 111.1, 110.9 (C-12), 73.1, 69.3 (C-13), 56.2, 56.1, 56.1, 56.0, 56.0, 56.0 (OMe), 44.4, 40.2 (C-7), 42.4, 37.2 (C-6), 35.6, 30.3 (C-8), 30.0, 28.9 (C-5); *m/z*: (EI) 371 (19), 370 (M^+, 90), 211 (12), 165 (13%); (CI) 388 ($M+NH_4^+$, 100), 358 (9), 152 (13), 124 (17%); [Found: $(M+NH_4)^+$ 388.1758, $C_{21}H_{22}O_6$ requires 388.1760].

3.11. Preparation of *cis*-11-hydroxy-6-(hydroxymethyl)-2,3-dimethoxydibenzo[1a,4a:8a,12a]cyclooctadiene-7-carboxylic acid lactone (33) and *cis*-11-hydroxy-6-(hydroxymethyl)-2,3-dimethoxydibenzo[1a,4a:8a,12a] cyclooctadiene-7-carboxylic acid lactone (36) using ruthenium tetra(trifluoroacetate)

The above experimental procedure was employed using as starting material the dibenzylbutyrolactone (**30**)[15] 0.113 g, 0.331 mmol). Purification via flash chromatography on silica and elution with CH_2Cl_2/EtOAc (95:5) afforded a mixture of the two isomers (**33**) and (**36**), in a 1:1 ratio, as a gum (0.090 g, 80%); IR (film): 3410 cm^{-1} (OH), 1745 cm^{-1} (γ-lactone); δ_H (400 MHz, $CDCl_3$) 7.10 (1 H, d, *J* 8.3 Hz, H-9), 7.00 (1 H, d, *J* 8.4 Hz, H-9), 6.79 (1 H, dd, *J* 2.7, 8.3 Hz, H-10), 6.75 (1 H, dd, *J* 3.0, 8.4 Hz, H-10), 6.71 (1 H, d, *J* 3.0 Hz, H-12), 6.68 (1 H, d, *J* 2.7 Hz, H-12), 6.66

(1 H, s), 6.65 (2 H, s), 6.60 (1 H, s), 5.33 (2 H, br.s, OH), 4.37 (2 H, m, H-13), 4.09 (1 H, m, H-13), 4.01 (1 H, d, *J* 9.3 Hz, H-13), 3.86 (3 H, s, OMe), 3.84 (3 H, s, OMe), 3.81 (3 H, s, OMe), 3.79 (3 H, s, OMe), 2.42–3.15 (12 H, m); δ_C (100.6 MHz, $CDCl_3$) 179.5, 177.5 (C-14), 154.5, 154.3 (C-11), 148.8, 147.5 (C-3), 145.6, 142.3 (C-2), 134.3, 133.1 (C-1a), 130.9, 130.5 (C-4a), 130.4, 129.9 (C-8a), 129.6, 128.2 (C-12a), 117.6 115.6 (C-1), 115.5, 115.2 (C-4), 114.3, 113.6 (C-9), 112.5, 112.0 (C-12), 73.3, 69.4 (C-13), 56.2, 56.0, 55.9 (4×OMe), 44.9, 40.2 (C-7), 42.7, 37.1 (C-6), 35.6, 30.0 (C-8), 29.7, 28.5 (C-5); *m/z*: (EI) 341 (19), 340 (M^+, 100), 255 (13), 181 (11), 165 (9%); (CI) 358 (100), 342 (20), 328 (13), 152 (11), 116 (45%); [Found: M^+ 340.1307, $C_{20}H_{20}O_5$ requires 340.1311].

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