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Oxidative cyclisation of 3,4-dibenzyltetrahydrofurans using ruthenium tetra(trifluoroacetate)

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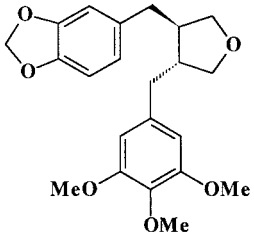
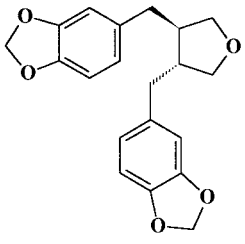
Abstract—A series of *trans*-3,4-dibenzyltetrahydrofurans has been synthesised and subjected to oxidative cyclisation using ruthenium tetra(trifluoroacetate), affording dibenzocyclooctadiene lignans belonging to the isostegane series, in high yields. Since no evidence was found for the formation of the corresponding stegane isomers it is assumed that the reactions proceed with complete diastereoselectivity.

1. Introduction

Tetrahydrofuran lignans are of interest due to their varied biological activity and their use in folk-medicine.[1] Several natural lignans, and analogues, possess potent anti-tumour activity. For example, burseran (**1**), and the cubebin derivative (**2**), function as spindle poisons since they interact with the tubulin–microtubule system by binding with tubulin to prevent the normal formation of the mitotic spindle.[2,3] The binding site, known as the *colchicine site*, has been shown to recognise a number of natural and unnatural products that contain two aromatic rings connected by a variety of structural elements, and is a potential lead in the design of new anti-tumour agents. In addition, tetrahydrofuran lignans exhibit platelet-activating factor antagonism and diuretic properties.[4,5]



(1)



(2)

The aim of the present work was to study the oxidative cyclisation of tetrahydrofuran lignans by ruthenium tetra-(trifluoroacetate).

2. Results and discussion

A convenient method for constructing the 3,4-dibenzyltetrahydrofuran framework is by reduction of a 2,3-dibenzylbutyrolactone to a 1,4-dibenzylbutanediol, followed by dehydration (Scheme 1).[6–11]

The dibenzylbutyrolactones (**3**–**8**), prepared using the previously reported conjugate addition methodology,[12,13] were reduced with $LiAlH_4$, affording the diols (**9**–**14**) in 57–72% yield (Scheme 2).

Evidence for the structures of **9**–**14** was provided by their ^1H and ^{13}C NMR spectra. A broad singlet, integrating to two protons, corresponding to H-2 and H-3, was observed in the ^1H NMR spectra, while the ^{13}C NMR spectra indicated that in each case a single diastereoisomer had been formed. Although the ^1H NMR spectra were not particularly complex, the coupling constant between H-2 and H-3 could not be measured. However, it was assumed that the *trans* (*threo*) configuration had been retained.

The dehydration of the dibenzylbutanediols (**9**–**14**) was carried out by refluxing with methanolic HCl,[8] yielding the tetrahydrofurans (**15**–**20**), including the hitherto unknown 'enterofuran' (**20**), in 64–83% yield (Scheme 3). Evidence for the structures of **15**–**20** came from analysis of their ^1H and ^{13}C NMR spectra. Once again the coupling constant between H-2 and H-3 could not be measured, but it was assumed that the stereochemistry was unchanged.

A few reports exist in the literature of both phenolic and non-phenolic coupling of 3,4-dibenzyltetrahydrofuran lignans. Thus, Pelter et al.[15] reported that treatment of the 3,4-dibenzyltetrahydrofuran (**2**) with DDQ in TFA afforded the dibenzocyclooctadiene (**21**), although in relatively low

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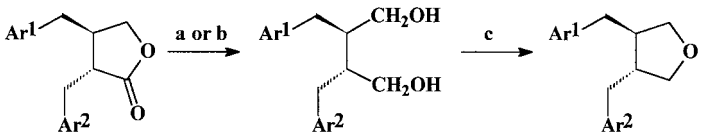


Scheme 1. *Reagents*: (a) $LiAlH_4$; (b) $BH_3{\cdot}SMe_2$; (c) HCl, $HClO_4$, $KHSO_4$ or TsCl/Pyr.

yield. When **2** was treated with DDQ in acetic acid two products were formed, the tetrahydrofuran (**22**) and the aryltetralin (**23**) (Scheme 4).

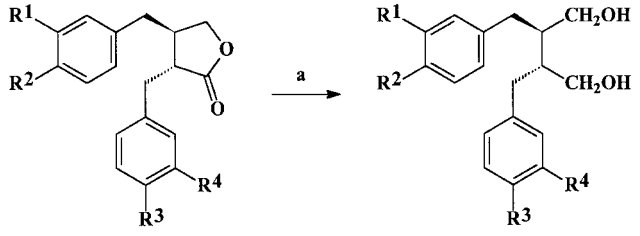
The use of thallium(III) has also been reported in the synthesis of dibenzocyclooctadiene lignans. Cambie et al.[10,16] have reported the use of this reagent for the oxidation of 3,4-dibenzyltetrahydrofurans. Hence, oxidative coupling of the non-phenolic dimethyl ether (**15**) with thallium(III) trifluoroacetate, generated in situ from thallium(III) oxide and TFA, gave the isostegane derivative (**24**). However, the monophenolic tetrahydrofuran (**16**) reacted with the same reagent to give a mixture of two monophenolic dibenzocyclooctadienes, the isostegane (**25**) and the stegane (**26**) in a 3:2 ratio (Scheme 5). The diastereoselectivity of oxidative coupling with thallium trifluoroacetate is believed to be the same as that for vanadium oxytrifluoride. Indeed, Schlessinger[17] suggested that oxidative coupling of yatein occurred via an intermediate spirodienone. The presence of a spirodienone intermediate is also believed to be involved when ruthenium(IV) dioxide in TFA–TFAA is employed as the coupling reagent.[18]

Although the thallium(III) procedure is very mild and efficient, the toxicity of thallium salts prevents its use on a large scale. The ruthenium reagent is an efficient alternative to thallium(III) in both phenolic and non-phenolic oxidative coupling. Hence, the coupling of tetrahydrofurans (**15**, **16**, **17** and **19**) was undertaken using this reagent.

Compound **15** was treated with ruthenium tetra(trifluoroacetate), generated in situ from two 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 86% yield (Scheme 6). It was evident from the ^1H spectrum that the aliphatic part of the molecule had been retained but that the aromatic region had been greatly simplified, showing only two singlets at 6.64 and 6.65 ppm, each integrating to two hydrogens. The ^{13}C NMR spectrum indicated that a single diastereoisomer had been formed and also suggested that the product had a very symmetrical structure, since only 11 signals were present, and this lead to the conclusion that oxidative coupling had taken place to give the dibenzocyclooctadiene (**24**). High resolution mass spectrometry confirmed the molecular formula as $C_{22}H_{26}O_5$.

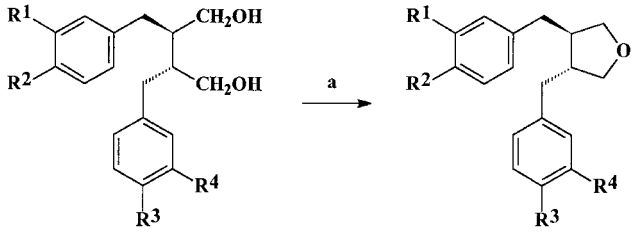
The stereochemistry about the biaryl bond was established from examination of the ^{13}C NMR spectrum. In the ^{13}C NMR spectrum of the isostegane lactone (**29**) the signals due to C-6 and C-7 occur at 46.8 and 50.0 ppm, respectively, whereas in the spectrum of the stegane isomer (**30**) they occur at 39.7 and 43.4 ppm (Fig. 1).[10] Chemical shifts of the corresponding signals due to C-6 and C-7 (49.0 ppm) in the spectrum of **25** were similar to those of **29** but were different from **30**. Definitive proof came from comparing the chemical shifts of C-6 and C-7 (41.6 ppm) for the stegane (**31**) and isostegane isomer (**24**) (Fig. 1).[10] The difference in values between the resonances of C-6 and C-7 was clearly evident and hence the diastereoselectivity of coupling was shown to afford the isostegane isomer.

The tetrahydrofuran (**16**) was treated with ruthenium tetra-(trifluoroacetate) at room temperature for 24 h, to afford compound **25** in 84% yield (Scheme 6). Analysis of the ^1H NMR spectrum showed that, as with compound **24**, the aliphatic region of the molecule had been retained and the aromatic region had been simplified, showing a broad three-proton singlet at δ 6.62 and a one-proton singlet at δ 6.73, consistent with a dibenzocyclooctadiene skeleton. High resolution mass spectrometry confirmed the molecular formula as $C_{21}H_{24}O_5$. The stereochemistry about the biaryl bond was established from comparison of the signals due to C-6 and C-7 (49.0) for compound **24** and the corresponding signals due to C-6 and C-7 (49.1 and 49.4, respectively) for compound **25**. As they were almost identical it was concluded that the biaryl stereochemistry was the same as



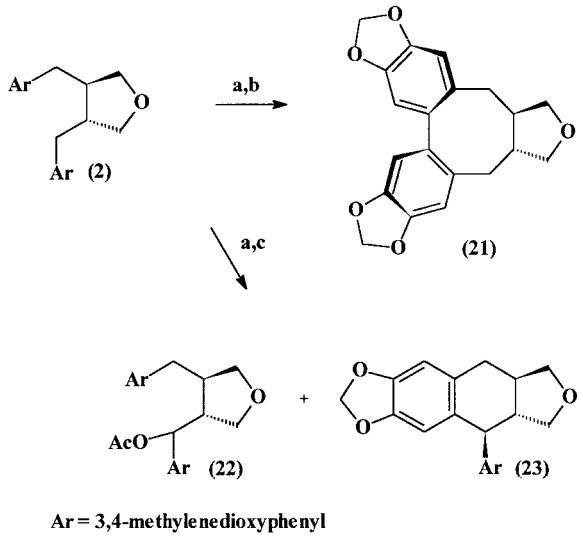
(3), (9) $R^1=R^2=R^3=R^4=OMe$
(4), (10) $R^1=R^2=R^4=OMe$; $R^3=OH$
(5), (11) $R^1=R^2=R^3=OMe$; $R^4=OH$
(6), (12) $R^1=R^2=OMe$; $R^3=OH$; $R^4=H$
(7), (13) $R^1=R^4=OMe$; $R^2=R^3=OH$
(8), (14) $R^1=R^4=OH$; $R^2=R^3=H$

Scheme 2. *Reagents*: (a) $LiAlH_4$/THF (57–68%).



(9), (15) $R^1=R^2=R^3=R^4=OMe$
(10), (16) $R^1=R^2=R^4=OMe$; $R^3=OH$
(11), (17) $R^1=R^2=R^3=OMe$; $R^4=OH$
(12), (18) $R^1=R^2=OMe$; $R^3=OH$; $R^4=H$
(13), (19) $R^1=R^4=OMe$; $R^2=R^3=OH$
(14), (20) $R^1=R^4=OH$; $R^2=R^3=H$

Scheme 3. *Reagents*: (a) MeOH/HCl (64–85%).



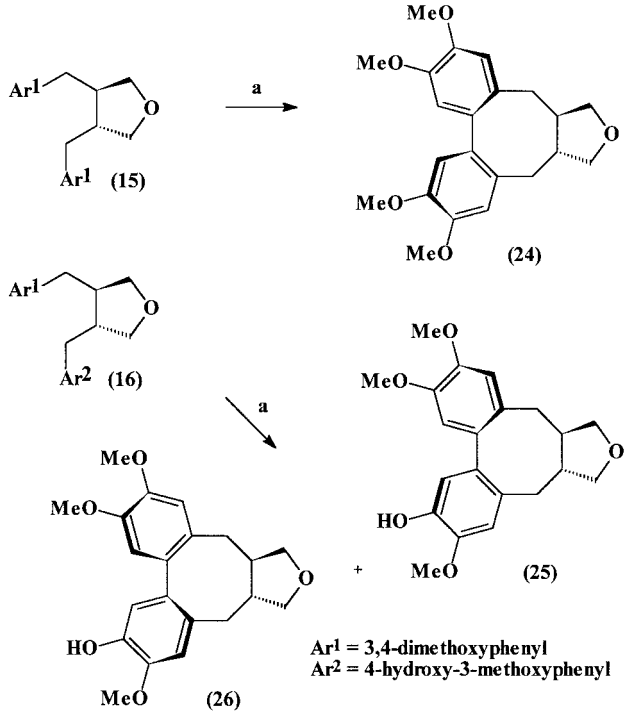
Scheme 4. *Reagents*: (a) DDQ; (b) TFA; (c) HOAc.

that for compound **24** and hence an isostegane structure had been formed in the reaction. The position of the phenolic moiety was established from examination of the ^{1}H NMR spectrum and from n.O.e experiments. As already mentioned, in the ^{1}H NMR spectrum of **25** one singlet is observed by itself at δ 6.73, downfield from the other three. It was therefore assumed that this proton is located next to the hydroxyl group. If it is assumed that the hydroxyl group is located at C-11, and that the singlet at 6.73 ppm is due to C-12, then one would not expect to observe an n.O.e between H-12 and H-8. In the n.O.e spectrum of **25** this is the case and hence the location of the hydroxyl group is confirmed.

The presence of a hydroxyl group at C-11 also resulted in a downfield shift of the signals of C-12 and C-12a (113.8 and 132.2, respectively) relative to those of C-1 and C-1a (116.7 and 132.7, respectively).

The tetrahydrofuran (**17**) was treated with ruthenium tetra-(trifluoroacetate) at room temperature for 24 h, to afford compound **27** in 87% yield (Scheme 6). Analysis of the ^{1}H NMR spectrum showed that, as with compounds **24** and **25**, the aliphatic region of the molecule had been retained and the aromatic region had been simplified, clearly showing four singlets at δ 6.62, 6.63, 6.64 and 6.70, consistent with a dibenzocyclooctadiene skeleton. High resolution mass spectrometry confirmed the molecular formula as $C_{21}H_{24}O_5$. Analysis of the ^{13}C NMR spectrum indicated that a single diastereoisomer had been formed, while the signals due to C-6 and C-7 (49.2 and 49.1) are consistent with the isostegane stereochemistry.

The position of the phenolic moiety was established by the same method as for compound **25**. A single proton was observed downfield from the other three at δ 6.70. Therefore, as in compound **25**, it was believed that this singlet was due to the proton situated next to the hydroxyl group. If this assumption is correct, and the hydroxyl group is located at C-10 and the proton resonating at δ 6.70 is located at C-9, then one would expect to observe an n.O.e between H-9 and H-8. From examination of the n.O.e spectrum of **27** it was



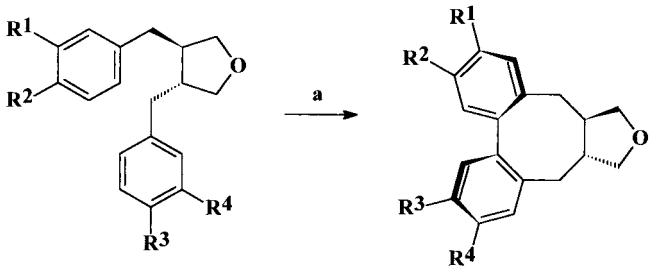
Scheme 5. *Reagents*: (a) Tl_2O_3, TFA, $BF_3{\cdot}Et_2O$.

evident that there was a clear n.O.e between the two protons, thus confirming the location of the hydroxyl group.

Having synthesised **24**, **25** and **27**, the oxidation of **19** was carried out under the same reaction conditions to afford the expected dibenzocyclooctadiene (**28**) in 90% yield (Scheme 6). Evidence for the structure of **28** was based on observations similar to those of the previous compounds. Two singlets were present in the ^{1}H NMR spectrum at 6.60 and 6.69 ppm, each integrating to two protons, while examination of the ^{13}C NMR spectrum indicated that a single diastereoisomer had been formed. It was also evident that the molecule was symmetrical as only 10 peaks were present in the carbon NMR spectrum. High resolution mass spectrometry confirmed the molecular formula as $C_{20}H_{22}O_5$.

The stereochemistry about the biaryl bond was assumed to be the same as the previous three oxidative cyclisation products **24**, **25** and **27**, since the reaction conditions were identical. The signals due to C-6 and C-7, both at 49.4 ppm, confirmed that compound **28** possessed an isostegane-type rather than a stegane-type structure. It was also assumed that the position of the hydroxyl groups were located at C-2 and C-11 since a zero n.O.e was observed between H-1 and H-5 and H-12 and H-8.

After the successful oxidations of **15**, **16**, **17** and **19**, the oxidation of enterofuran (**20**) was attempted using the same procedure. However, the corresponding dibenzocyclooctadiene could not be obtained in this reaction, and only inseparable, polar material was obtained. The attempted oxidative cyclisation of enterolactone (**8**) has been reported,[19] using a variety of reagents, but similar results have been obtained, and the corresponding dibenzocyclooctadiene could not be isolated. A possible hypothesis to explain the



Scheme 6. *Reagents*: (a) $RuO_2 \cdot 2H_2O$, TFA-TFAA, $BF_3 \cdot Et_2O$ (84–90%).

failure of the coupling of **8** and **20** is the lack of additional electron-donating substituents on the aromatic ring, which would be expected to activate the aromatic nucleus and facilitate radical-cation formation.

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-focussing 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.

TLC analysis was carried out on Merck 5785 Kiesegel $60F_{254}$ fluorescent plates. 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. THF was passed down an alumina column and distilled from sodium/benzophenone.

3.1. General procedure

3.1.1. Preparation of 2,3-bis-(3,4-dimethoxybenzyl)-1,4-butanediol (9). Compound **3**[12] (0.155 g, 0.402 mmol) was dissolved in dry THF (20 ml), under an argon atmosphere. To this stirred solution was carefully added $LiAlH_4$ (0.046 g, 1.206 mmol, 3 mol equiv.). Stirring was continued at room temperature for three days before being cooled to 0°C and quenched by the addition of damp THF, until no effervescence was observed. Water (20 ml) was then added and the product was extracted with EtOAc (3×40 ml). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated in vacuo to afford a gum. Purification via flash chromatography on silica and elution with CH_2Cl_2/EtOAc (10:90), followed by crystallisation from MeOH, afforded **9**

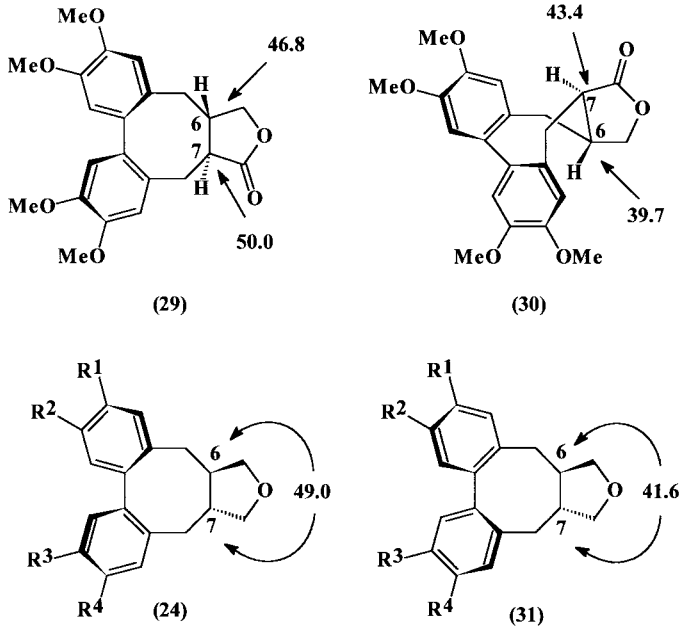


Figure 1.

as a white foam (0.089 g, 57%), mp 119–121°C (Lit.[7] 123–124°C); R_f [EtOAc] 0.18; IR (film): 3400 cm^{-1} (OH); δ_H (400 MHz $CDCl_3$) 6.68 (2H, d, J=8.1 Hz, H-5′,5″), 6.60 (2H, d, J=1.7 Hz, H-2′,2″), 6.58 (2H, m, H-6′,6″), 3.76 (6H, s, OMe), 3.74 (6H, s, OMe), 3.70 (2H, m, H-1a,4a), 3.44 (2H, dd, J=3.9, 11.3 Hz, H-1b,4b), 2.57–2.72 (4H, m, H-5a,5b,6a,6b), 1.96 (2H, br s, H-2,3),; δ_C (100.6 MHz, $CDCl_3$) 148.8 (C-3′,3″), 147.3 (C-4′,4″), 133.2 (C-1′,1″), 121.0 (C-6′,6″), 112.2 (C-5′,5″), 111.2 (C-2′,2″), 60.4 (C-1,4), 55.9 (2×OMe), 55.8 (2×OMe), 43.9 (C-2,3), 35.8 (C-5,6); *m/z*: (e.i.) 391 (21), 390 (M^+, 88), 372 (33), 281 (29), 151 (32%); (c.i.) 408 ($M+NH_4^+$, 100), 390 (18), 170 (71), 156 (57), 151 (43%) [Found: M^+ 390.2040; $C_{22}H_{30}O_6$ requires: 390.2042].

3.1.2. Preparation of 2-(4-hydroxy-3-methoxybenzyl)-3-(3,4-dimethoxybenzyl)-1,4-butanediol (10). The above experimental procedure was employed using as starting material the butyrolactone (**4**).[13] Purification via flash chromatography on silica and elution with CH_2Cl_2/EtOAc (10:90), followed by crystallisation from EtOAc/hexane, afforded **10** as a white solid (0.129 g, 62%), mp 115–116°C (Lit.[16] 109.5–111.5°C); R_f [EtOAc] 0.16; IR (film): 3525 (OH), 3400 cm^{-1} (OH); δ_H (400 MHz $CDCl_3$) 6.72 (1H, d, J=8.1 Hz, H-5′), 6.68 (1H, d, J=7.9 Hz, H-5″), 6.60 (1H, dd, J=1.7, 8.1 Hz, H-6′), 6.56 (1H, m, H-6″), 6.56 (1H, m, H-2″), 6.53 (1H, d, J=1.7 Hz, H-2′), 3.77 (2H, m, H-1a,4a), 3.77 (3H, s, OMe), 3.74 (3H, s, OMe), 3.73 (3H, s, OMe), 3.46 (2H, dd, J=4.2, 11.3 Hz, H-1b,4b), 2.55–2.72 (4H, m, H-5a,5b,6a,6b), 1.97 (2H, br s, H-2,3); δ_C (100.6 MHz, $CDCl_3$) 148.8 (C-3′), 147.2 (C-3″), 146.5 (C-4′), 143.8 (C-4″), 133.2 (C-1′), 132.4 (C-1″), 121.6 (C-6′), 121.0 (C-6″), 114.2 (C-5′), 112.1 (C-5″), 111.4 (C-2′), 111.1 (C-2″), 60.6 (C-1), 60.4 (C-4), 55.9 (OMe), 55.8 (2×OMe), 43.9 (C-2), 43.8 (C-3), 35.9 (C-5), 35.8 (C-6); *m/z*: (e.i.) 377 (21), 376 (M^+, 100), 358 (18), 151 (32), 137 (28%); (c.i.) 394 ($M+NH_4^+$, 100), 376 (33), 170 (24), 156 (23), 151 (21%) [Found: M^+ 376.1882; $C_{21}H_{28}O_6$ requires: 376.1886].

3.1.3. Preparation of 2-(3-hydroxy-4-methoxybenzyl)-3-(3,4-dimethoxybenzyl)-1,4-butanediol (11). The above experimental procedure was employed using as starting material the butyrolactone (**5**).[13] Purification via flash chromatography on silica and elution with CH_2Cl_2/EtOAc (10:90), followed by crystallisation from MeOH, afforded **11** as a white foam (0.389 g, 68%), mp 92–94°C [Found: C, 67.03; H, 7.50. $C_{21}H_{28}O_6$ requires: C, 67.00; H, 7.50%]; R_f [EtOAc] 0.15; IR (film): 3525 (OH), 3400 cm^{-1} (OH); δ_H (400 MHz $CDCl_3$) 6.68 (1H, d, J=8.1 Hz, H-5″), 6.66 (1H, d, J=8.2 Hz, H-5′), 6.66 (1H, d, J=2.0 Hz, H-2′), 6.62 (1H, dd, J=1.8, 8.1 Hz, H-6″), 6.59 (1H, d, J=1.8 Hz, H-2″), 6.53 (1H, dd, J=2.0, 8.2 Hz, H-6′), 3.77 (3H, s, OMe), 3.75 (3H, s, OMe), 3.74 (3H, s, OMe), 3.71 (2H, m, H-1a,4a), 3.43 (2H, dd, J=2.9, 11.3 Hz, H-1b,4b), 2.51–2.72 (4H, m, H-5a,5b,6a,6b), 1.97 (2H, br s, H-2,3); δ_C (100.6 MHz, $CDCl_3$) 148.8 (C-3′), 145.5 (C-3″), 147.2 (C-4′), 145.0 (C-4″), 133.8 (C-1′), 133.2 (C-1″), 121.0 (C-6′), 120.4 (C-6″), 115.3 (C-5′), 112.1 (C-5″), 111.1 (C-2′), 110.8 (C-2″), 60.4 (C-1), 60.2 (C-4), 56.0 (OMe), 55.9 (OMe), 55.8 (OMe), 44.1 (C-2,3), 35.7 (C-5), 35.5 (C-6); *m/z*: (e.i.) 377 (14), 376 (M^+, 50), 224 (83), 188 (90), 177 (100); (c.i.) 394 ($M+NH_4^+$, 100), 376 (23), 358 (32), 170 (28), 156 (27%) [Found: M^+ 376.1891; $C_{21}H_{28}O_6$ requires: 376.1886].

3.1.4. Preparation of 2-(4-hydroxybenzyl)-3-(3,4-dimethoxybenzyl)-1,4-butanediol (12). The above experimental procedure was employed using as starting material the butyrolactone (**6**).[13] Purification via flash chromatography on silica and elution with CH_2Cl_2/EtOAc (10:90) afforded **12** as a gum (0.117 g, 65%); R_f [EtOAc] 0.17; IR (film): 3281 cm^{-1} (OH); δ_H (400 MHz $CDCl_3$) 6.91 (2H, d, J=8.4 Hz, H-2″,6″), 6.70 (1H, d, J=8.2 Hz, H-5′), 6.65 (2H, d, J=8.4 Hz, H-3″,5″), 6.62 (1H, dd, J=1.8, 8.2 Hz, H-6′), 6.56 (1H, d, J=1.8 Hz, H-2′), 3.79 (3H, s, OMe), 3.75 (3H, s, OMe), 3.72 (2H, m, H-1a,4a), 3.46 (2H, m, H-1b,4b), 2.54–2.72 (4H, m, H-5a,5b,6a,6b), 1.98 (2H, br s, H-2,3); δ_C (100.6 MHz, $CDCl_3$) 154.4 (C-4″), 148.8 (C-3′), 147.2 (C-4′), 133.2 (C-1′), 132.0 (C-1″), 130.0 (C-2″,6″), 121.1 (C-6′), 115.3 (C-3″,5″), 112.2 (C-5′), 111.2 (C-2′), 60.4 (C-1), 60.2 (C-4), 55.9 (OMe), 55.8 (OMe), 44.1 (C-2,3), 35.7 (C-5), 35.2 (C-6); *m/z*: (e.i.) 346 (M^+, 11), 151 (100), 107 (59), 121 (17%); (c.i.) 364 ($M+NH_4^+$, 100), 346 (52), 326 (21), 154 (16), 124 (19%) [Found: M^+ 346.1781; $C_{21}H_{28}O_6$ requires: 346.1780].

3.1.5. Preparation of 2,3-bis(4-hydroxy-3-methoxybenzyl)-1,4-butanediol (13) (secoisolariciresinol). The above experimental procedure was employed using as starting material the butyrolactone (**7**).[20] Purification via flash chromatography on silica and elution with CH_2Cl_2/EtOAc (10:90), followed by crystallisation from EtOAc/hexane, afforded **13** as a white solid (0.129 g, 62%), mp 114–115°C (Lit.[7] 113.5°C); R_f [EtOAc] 0.15; IR (film): 3436 cm^{-1} (OH); δ_H (400 MHz $CDCl_3$) 6.72 (2H, d, J=8.0 Hz, H-5′,5″), 6.54 (2H, dd, J=1.8, 8.0 Hz, H-6′,6″), 6.51 (2H, d, J=1.8 Hz, H-2′,2″), 3.72 (6H, s, OMe), 3.75 (2H, m, H-1a,4a), 3.47 (2H, dd, J=4.4, 11.4 Hz, H-1b,4b), 2.54–2.69 (4H, m, H-5a,5b,6a,6b), 1.78 (2H, br s, H-2,3); δ_C (100.6 MHz, $CDCl_3$) 146.5 (C-3′,3″), 143.8 (C-4′,4″), 132.4 (C-1′,1″), 121.6 (C-6′,6″), 114.1 (C-5′,5″), 111.4 (C-2′,2″), 60.7 (C-1,4), 55.8 (OMe), 55.7 (OMe), 43.8 (C-2,3), 35.9 (C-5,6); *m/z*: (e.i.) 363 (16), 362 (M^+, 83), 360 (59), 344 (30), 177 (83), 137 (35%); (c.i.) 380 ($M+NH_4^+$, 100), 362 (29), 360 (27), 156 (36%) [Found: M^+ 362.1738; $C_{20}H_{26}O_6$ requires: 362.1729].

3.1.6. Preparation of 2,3-bis(3-hydroxybenzyl)-1,4-butanediol (14) (enterodiol). The above experimental procedure was employed using as starting material the butyrolactone (**8**).[14] Purification via flash chromatography on silica and elution with EtOAc/hexane (50:50), followed by crystallisation from EtOAc, and a little CH_2Cl_2, afforded **14** as a white solid (0.129 g, 62%), mp 165–167°C (Lit.[21] 171–173°C); R_f [(EtOAc/hexane (50:50)] 0.10; IR (film): 3410 (OH), 3400 cm^{-1} (OH); δ_H (400 MHz $CDCl_3$) 6.48–6.97 (8H, m, H-2′,2″,4′,4″,5′,5″,6′,6″), 3.52 (2H, dd, J=3.8, 11.2 Hz, H-1a,4a), 3.42 (2H, dd, J=5.2, 11.2 Hz, H-1b,4b), 2.53–2.56 (4H, m, H-5a,5b,6a,6b), 1.91 (2H, br s, H-2,3); δ_C (100.6 MHz, $CDCl_3$) 157.1 (C-3′,3″), 142.7 (C-1′,1″), 129.0 (C-5′,5″), 120.2 (C-6′,6″), 115.8 (C-2′,2″), 112.5 (C-4′,4″), 60.3 (C-1,4), 43.3 (C-2,3), 35.0 (C-5,6); *m/z*: (e.i.) 302 (M^+, 11), 284 (13), 121 (100), 105 (41%); (c.i.) 320 ($M+NH_4^+$, 81), 302 (27), 107 (83), 98 (100%) [Found: $(M+NH_4)^+$ 320.1863; $C_{18}H_{22}O_4$ requires: 320.1862].

3.1.7. Preparation of 2,3-bis(3,4-dimethoxybenzyl)tetrahydrofuran (15). Compound **9** (0.129 g, 0.331 mmol) was dissolved in MeOH (30 ml). HCl (12 M) (10 drops) was added and the reaction mixture was refluxed overnight. The solvent was removed and water (30 ml) was added to the residue. The product was extracted with EtOAc (3×40 ml) and the combined organic extracts were washed with aqueous $NaHCO_3$ (2×30 ml) and water (2×30 ml), dried ($MgSO_4$), filtered and evaporated in vacuo to afford an off-white solid. Purification via flash chromatography and elution with CH_2Cl_2/EtOAc (90:10), followed by crystallisation from MeOH, afforded **15** as a white solid (0.102 g, 83%), mp 113–115°C (Lit.[6] 118–119°C); R_f [EtOAc] 0.75; δ_H (400 MHz $CDCl_3$) 6.68 (2H, d, J=8.1 Hz, H-5′,5″), 6.55 (2H, dd, J=1.9, 8.1 Hz, H-6′,6″), 6.51 (2H, d, J=1.9 Hz, H-2′,2″), 3.77 (6H, s, OMe), 3.76 (6H, s, OMe), 3.83 (2H, dd, J=6.6, 8.7 Hz, H-1a,4a), 3.45 (2H, dd, J=6.0, 8.7 Hz, H-1b,4b), 2.46 (2H, dd, J=8.3, 13.7 Hz, H-5a,6a), 2.55 (2H, dd, J=6.1, 13.7 Hz, H-5b,6b), 2.11 (2H, m, H-2,3); δ_C (100.6 MHz, $CDCl_3$) 148.8 (C-3′,3″), 147.4 (C-4′,4″), 133.0 (C-1′,1″), 120.5 (C-6′,6″), 111.9 (C-5′,5″), 111.1 (C-2′,2″), 73.3 (C-1,4), 55.9 (2×OMe), 55.8 (2×OMe), 46.6 (C-2,3), 39.0 (C-5,6); *m/z*: (e.i.) 373 (6), 372 (M^+, 26), 152 (55), 151 (100%); (c.i.) 390 ($M+NH_4^+$, 100), 372 (6), 360 (9), 151 (13%) [Found: $(M+NH_4)^+$ 390.2280; $C_{22}H_{28}O_5$ requires: 390.2278].

3.1.8. Preparation of 2-(4-hydroxy-3-methoxybenzyl)-3-(3,4-dimethoxybenzyl)tetrahydrofuran (16). The above experimental procedure was employed using as starting material the butanediol (**10**). Purification via flash chromatography on silica and elution with CH_2Cl_2/EtOAc (90:10), followed by crystallisation from MeOH, afforded **16** as a white solid (0.113 g, 78%), mp 66–67°C (Lit.[16] 61–63°C); R_f [EtOAc] 0.69; IR (film): 3440 (OH); δ_H (400 MHz $CDCl_3$) 6.71 (1H, d, J=8.0 Hz, H-5′), 6.67 (1H, d, J=8.1 Hz, H-5″), 6.53 (1H, dd, J=1.8, 8.0 Hz, H-6′), 6.51 (1H, dd, J=1.7, 8.1 Hz, H-6″), 6.48 (1H, d, J=1.8 Hz, H-2′), 6.45 (1H, d, J=1.7 Hz, H-2″), 3.84 (2H, m, H-1a,4a), 3.75 (3H, s, OMe), 3.72 (3H, s, OMe), 3.70 (3H, s, OMe), 3.46 (2H, m, H-1b,4b), 2.41-2.56 (4H, m, H-5a,5b,6a,6b), 2.10 (2H, m, H-2,3); δ_C (100.6 MHz, $CDCl_3$) 148.8 (C-3′), 147.4 (C-3″), 146.5 (C-4′), 144.0 (C-4″), 133.0 (C-1′), 132.2 (C-1″), 121.3 (C-6′), 120.5 (C-6″), 114.3 (C-5′), 111.9 (C-5″), 111.2 (C-2′), 111.1 (C-2″), 73.3 (C-1,4), 55.9 (2×OMe), 55.8 (OMe), 46.6 (C-2), 46.4 (C-3), 39.1 (C-5), 39.0 (C-6); *m/z*: (e.i.) 359 (8), 358 (M^+, 42), 151 (100), 137 (83%); (c.i.) 376 ($M+NH_4^+$, 100), 358 (6), 346 (6), 151 (8%) [Found: $(M+NH_4)^+$ 376.2124; $C_{21}H_{26}O_5$ requires: 376.2132].

3.1.9. Preparation of 2-(3-hydroxy-4-methoxybenzyl)-3-(3,4-dimethoxybenzyl)tetrahydrofuran (17). The above experimental procedure was employed using as starting material the butanediol (**11**). Purification via flash chromatography on silica and elution with CH_2Cl_2/EtOAc (90:10), followed by crystallisation from MeOH, afforded **17** as a white solid (0.180 g, 77%), mp 83–85°C [Found: C, 70.04; H, 7.30. $C_{21}H_{26}O_5$ requires: C, 70.37; H, 7.31%]; R_f [EtOAc] 0.67; IR (film): 3421 cm^{-1} (OH); δ_H (400 MHz $CDCl_3$) 6.69 (1H, d, J=8.1 Hz, H-5′), 6.65 (1H, d, J=8.2 Hz, H-5″), 6.61 (1H, d, J=2.1 Hz, H-2′), 6.57 (1H, dd, J=1.9, 8.2 Hz, H-6″), 6.51 (1H, d, J=1.9 Hz, H-2″), 6.49 (1H, dd, J=2.1, 8.1 Hz, H-6′), 3.84 (2H, m, H-1a,4a), 3.79 (3H, s, OMe), 3.78 (3H, s, OMe), 3.76 (3H, s, OMe), 3.44 (2H, m, H-1b,4b), 2.40–2.58 (4H, m, H-5a,5b,6a,6b), 2.10 (2H, m, H-2,3); δ_C (100.6 MHz, $CDCl_3$) 148.8 (C-3′), 147.4 (C-3″), 145.4 (C-4′), 144.9 (C-4″), 133.7 (C-1′), 133.0 (C-1″), 120.5 (C-6′), 120.0 (C-6″), 114.9 (C-5′), 111.8 (C-5″), 111.1 (C-2′), 110.5 (C-2″), 73.4 (C-1,4), 55.9 (2×OMe), 55.8 (OMe), 46.6 (C-2), 46.5 (C-3), 39.0 (C-5), 38.7 (C-6); *m/z*: (e.i.) 359 (6), 358 (M^+, 26), 151 (100), 137 (96), 121 (37%); (c.i.) 376 ($M+NH_4^+$, 100), 346 (12), 358 (6), 162 (13), 151 (12%) [Found: $(M+NH_4)^+$ 376.1778; $C_{21}H_{26}O_5$ requires: 376.1780].

3.1.10. Preparation of 2-(4-hydroxybenzyl)-3-(3,4-dimethoxybenzyl)tetrahydrofuran (18). The above experimental procedure was employed using as starting material the butanediol (**12**). Purification via flash chromatography on silica and elution with CH_2Cl_2/EtOAc (90:10) afforded **18** as a gum (0.174 g, 85%); R_f [EtOAc] 0.68; IR (film): 3421 (OH); δ_H (400 MHz $CDCl_3$) 6.86 (2H, d, J=8.3 Hz, H-2″,6″), 6.69 (1H, d, J=8.1 Hz, H-5′), 6.64 (2H, d, J=8.3 Hz, H-3″,5″), 6.56 (1H, dd, J=1.8, 8.1 Hz, H-6′), 6.49 (1H, d, J=1.8 Hz, H-2′), 3.79 (3H, s, OMe), 3.76 (3H, s, OMe), 3.84 (2H, m, H-1a,4a), 3.46 (2H, m, H-1b,4b), 2.41–2.57 (4H, m, H-5a,5b,6a,6b), 2.11 (2H, m, H-2,3); δ_C (100.6 MHz, $CDCl_3$) 154.0 (C-4″), 146.7 (C-3′), 145.1 (C-4′), 133.0 (C-1′), 132.4 (C-1″), 129.8 (C-2″,6″), 120.6 (C-6′), 115.2 (C-3″,5″), 111.9 (C-5′), 111.2 (C-2′), 73.3 (C-1,4), 55.9 (OMe), 55.8 (OMe), 46.5 (C-2,3), 39.0 (C-5), 38.5 (C-6); *m/z*: (e.i.) 329 (6), 328 (M^+, 27), 151 (86), 121 (19), 107 (100%); (c.i.) 346 ($M+NH_4^+$, 100), 221 (23), 151 (36), 124 (32%) [Found: M^+ 328.4081; $C_{20}H_{24}O_4$ requires: 328.4080].

3.1.11. Preparation of 2,3-bis(4-hydroxy-3-methoxybenzyl)tetrahydrofuran (19). The above experimental procedure was employed using as starting material the butanediol (**13**). Purification via flash chromatography on silica and elution with CH_2Cl_2/EtOAc (90:10), followed by crystallisation from MeOH, afforded **19** as a white solid (0.148 g, 83%), mp 130–133°C (Lit.[22] 112–114°C); R_f [EtOAc] 0.70; IR (film): 3550 cm^{-1} (OH); δ_H (400 MHz $CDCl_3$) 6.72 (2H, d, J=8.0 Hz, H-5′,5″), 6.51 (2H, dd, J=1.8, 8.0 Hz, H-6′,6″), 6.43 (2H, d, J=1.8 Hz, H-2′,2″), 3.75 (6H, s, OMe), 3.85 (2H, dd, J=6.6, 8.7 Hz, H-1a,4a), 3.46 (2H, dd, J=5.7, 8.7 Hz, H-1b,4b), 2.44 (2H, dd, J=7.9, 13.7 Hz, H-5a,6a), 2.50 (2H, dd, J=7.0, 13.7 Hz, H-5b,6b), 2.10 (2H, m, H-2,3); δ_C (100.6 MHz, $CDCl_3$) 146.4 (C-3′,3″), 143.9 (C-4′,4″), 132.3 (C-1′,1″), 121.3 (C-6′,6″), 114.1 (C-5′,5″), 111.1 (C-2′,2″), 73.3 (C-1,4), 55.8 (2×OMe), 46.4 (C-2,3), 39.2 (C-5,6); *m/z*: (e.i.) 345 (13), 344 (M^+, 45), 137 (100), 122 (25), 94 (19%); (c.i.) 362 ($M+NH_4^+$, 100), 240 (7), 224 (18), 207 (20), 137 (12%) [Found: $(M+NH_4)^+$ 362.1967; $C_{20}H_{24}O_5$ requires: 362.1969].

3.1.12. Preparation of 2,3-bis(3-hydroxybenzyl)tetrahydrofuran (20) (enterofuran). The above experimental procedure was employed using as starting material the butanediol (**14**). Purification via flash chromatography on silica and elution with CH_2Cl_2/EtOAc (50:50), followed by crystallisation from MeOH, afforded **20** as a white solid (0.072 g, 64%), mp 130–133°C; R_f [CH_2Cl_2/EtOAc (50:50)] 0.53; IR (film): 3145 cm^{-1} (OH); δ_H (400 MHz

$CDCl_3$) 6.49–7.06 (8H, m, H-2′,2″,4′,4″,5′,5″,6′,6″), 3.84 (2H, dd, J=6.7, 8.5 Hz, H-1a,4a), 3.45 (2H, dd, J=6.2, 8.5 Hz, H-1b,4b), 2.43 (2H, dd, J=7.9, 13.5 Hz, H-5a,6a), 2.51 (2H, dd, J=5.9, 13.5 Hz, H-5b,6b), 2.12 (2H, m, H-2,3); δ_C (100.6 MHz, $CDCl_3$) 155.7 (C-3′,3″), 142.0 (C-1′,1″), 129.6 (C-5′,5″), 120.9 (C-6′,6″), 115.7 (C-2′,2″), 113.2 (C-4′,4″), 73.3 (C-1,4), 46.1 (C-2,3), 39.1 (C-5,6); *m/z*: (e.i.) 285 (19), 284 (M^+, 65), 266 (12), 177 (80), 133 (85), 107 (100%); (c.i.) 302 ($M+NH_4^+$, 100), 286 (26), 196 (29), 177 (16), 108 (13%) [Found: $(M+NH_4)^+$ 302.1754; $C_{18}H_{20}O_3$ requires: 302.1756].

3.1.13. Preparation of compound 24. To a stirred solution of $RuO_2{\cdot}2H_2O$ (42 mg, 0.320 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 **15** (0.061 g, 0.160 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 solution of $NaHCO_3$. 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 (4×30 ml). The combined organic extracts were washed with brine (2×30 ml), water (2×30 ml), dried ($MgSO_4$), filtered and evaporated in vacuo to afford an off-white solid. Purification via flash chromatography on silica and elution with CH_2Cl_2, followed by crystallisation from CH_2Cl_2/hexane, afforded **24** as a white solid (0.051 g, 86%), mp 150–152°C (Lit.[10] 148–149°C); R_f [5 ml CH_2Cl_2 and 5 drops EtOAc] 0.18; δ_H (400 MHz $CDCl_3$) 6.65 (2H, s, H-4,9), 6.64 (2H, s, H-1,12), 4.01 (2H, t, J=7.5 Hz, H-13a,14a), 3.87 (6H, s, 2×OMe), 3.81 (6H, s, 2×OMe), 3.36 (2H, dd, J=7.5, 11.1 Hz, H-13b,14b), 2.52 (2H, d, J=13.1 Hz, H-5a,8a), 2.20 (2H, dd, J=9.4, 13.1 Hz, H-5b,8b), 1.80 (2H, m, H-6,7); δ_C (100.6 MHz, $CDCl_3$) 147.7 (C-2,11), 145.9 (C-3,10), 132.8 (C-1a,12a), 132.2 (C-4a,8a), 113.7 (C-4,9), 111.9 (C-1,12), 72.8 (C-13,14), 55.9 (4×OMe), 49.0 (C-6,7), 32.6 (C-5,8); *m/z*: (e.i.) 371 (24), 370 (M^+, 100), 270 (14), 165 (17), 151 (22), 139 (15%); (c.i.) 388 ($M+NH_4^+$, 100), 370 (18), 358 (17), 152 (7%) [Found: $(M+NH_4)^+$ 388.2121; $C_{22}H_{26}O_5$ requires: 388.2124].

3.1.14. Preparation of compound 25. The above experimental procedure was employed using as starting material the tetrahydrofuran (**16**). Purification via flash chromatography on silica and elution with CH_2Cl_2, followed by crystallisation from acetone, afforded **25** as white crystals (0.084 g, 84%), mp 188–189°C (Lit.[16] 188.5–189.5°C); R_f [5 ml CH_2Cl_2 and 5 drops EtOAc] 0.20]; IR (film): 3450 cm^{-1} (OH); δ_H (400 MHz $CDCl_3$) 6.73 (1H, s, H-12), 6.62 (3H, br s, H-1,4,9), 4.00 (2H, m, H-13a,14a), 3.88 (3H, s, OMe), 3.86 (3H, s, OMe), 3.78 (3H, s, OMe), 3.36 (2H, dd, J=7.6, 11.1 Hz, H-13b,14b), 2.51 (2H, dd, J=3.8, 13.2 Hz, H-5a,8a), 2.20 (2H, m, H-5b,8b), 1.80 (2H, m, H-6,7); δ_C (100.6 MHz, $CDCl_3$) 148.4 (C-3), 146.2 (C-2), 145.3 (C-11), 143.4 (C-10), 133.3 (C-4a), 132.7 (C-1a), 132.6 (C-8a), 132.2 (C-12a), 116.7 (C-12), 113.8 (C-9), 112.0 (C-4), 111.2 (C-1), 72.9 (C-13,14), 56.0 (2×OMe), 55.9 (OMe), 49.4 (C-6), 49.1 (C-7), 32.8 (C-5,8); *m/z*: (e.i.) 357 (19), 356 (M^+, 59), 281 (23), 207 (100), 191 (20), 149 (23%); (c.i.) 374 ($M+NH_4^+$, 100), 358 (12), 344 (8) 279 (38%) [Found: $(M+NH_4)^+$ 374.1963; $C_{21}H_{24}O_5$ requires: 374.1967].

3.1.15. Preparation of compound 27. The above experimental procedure was employed using as starting material the tetrahydrofuran (**17**). Purification via flash chromatography on silica and elution with CH_2Cl_2, followed by crystallisation from acetone, afforded **27** as a gum (0.084 g, 84%); R_f [5 ml CH_2Cl_2 and 5 drops EtOAc] 0.21]; IR (film): 3450 cm^{-1} (OH); δ_H (400 MHz $CDCl_3$) 6.70 (1H, s, H-9), 6.64 (1H, s, H-12), 6.63 (1H, s, H-4), 6.62 (1H, s, H-1), 3.98 (2H, dd, J=7.4, 14.8 Hz, H-13a,14a), 3.85 (3H, s, OMe), 3.80 (3H, s, OMe), 3.79 (3H, s, OMe), 3.33 (2H, m, H-13b,14b), 2.50 (2H, d, J=13.4 Hz, H-5a,8a), 2.15 (2H, m, H-5b,8b), 1.78 (2H, m, H-6,7); δ_C (100.6 MHz, $CDCl_3$) 148.5 (C-3), 146.9 (C-2), 145.2 (C-11), 144.6 (C-10), 133.8 (C-4a), 133.0 (C-8a), 132.5 (C-1a), 131.9 (C-12a), 115.1 (C-4), 113.9 (C-1), 113.1 (C-9), 112.0 (C-12), 72.9 (C-13,14), 56.0 (2×OMe), 55.9 (OMe), 49.2 (C-7), 49.1 (C-6), 32.8 (C-8), 32.6 (C-5); *m/z*: (e.i.) 357 (23), 356 (M^+, 100), 255 (14), 152 (17), 115 (19%); (c.i.) 374 ($M+NH_4^+$, 100), 358 (14), 344 (10), 240 (7%) [Found: $(M+NH_4)^+$ 374.1967; $C_{21}H_{24}O_5$ requires: 374.1967].

3.1.16. Preparation of compound 28. The above experimental procedure was employed using as starting material the tetrahydrofuran (**19**). Purification via flash chromatography on silica and elution with CH_2Cl_2, followed by crystallisation from acetone, afforded **28** as white crystals (0.103 g, 90%), mp 191–193°C [Found: C, 70.05; H, 6.55. $C_{20}H_{22}O_5$ requires: C, 70.16; H, 6.48%]; R_f [5 ml CH_2Cl_2 and 5 drops EtOAc] 0.18; IR (film): 3440 cm^{-1} (OH); δ_H (400 MHz, $CDCl_3$) 6.69 (2H, s, H-1,12), 6.60 (2H, s, H-4,9), 3.99 (2H, t, J=7.4 Hz, H-13a,14a), 3.86 (6H, s, 2×OMe), 3.34 (2H, dd, J=7.4, 11.2 Hz, H-13b,14b), 2.48 (2H, d, J=13.2 Hz, H-5a,8a), 2.18 (2H, dd, J=9.4, 13.2 Hz, H-5b,8b), 1.78 (2H, m, H-6,7); δ_C (100.6 MHz, $CDCl_3$) 146.1 (C-3,10), 143.4 (C-2,11), 133.1 (C-1a,12a), 132.3 (C-4a,8a), 116.7 (C-1,12), 111.2 (C-4,9), 73.0 (C-13,14), 56.0 (2×OMe), 49.4 (C-6,7), 32.7 (C-5,8); *m/z*: (e.i.) 343 (13), 342 (M^+, 58), 281 (17), 207 (39%); (c.i.) 360 ($M+NH_4^+$, 100), 342 (10), 279 (37), 296 (8), 234 (19), 152 (23%) [Found: $(M+NH_4)^+$ 360.1812; $C_{20}H_{22}O_5$ requires: 360.1811].

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