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Transformations of lignans. Part 11: Oxidation of diphyllin with hypervalent iodine reagents and reductive reactions of a resulting 1-methoxy-1-aryl-4-oxonaphthalene lactone

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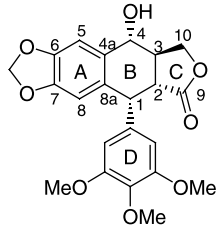
Abstract—Treatment of diphyllin **4** with phenyliodonium diacetate (PIDA) in methanol affords a 1-methoxy-1-aryl-4-oxonaphthalene lactone **6**. Reduction of **6** with lithium aluminium hydride yields, inter alia, 3,4-dihydrodiphyllin **13**, while reaction with sodium in ethanol yields **8** as a major product. These reactions illustrate that selective oxidation followed by reduction provides a facile route for the conversion of a 1-arylnaphthalene lactone to novel functionalised naphthalene and dihydronaphthalene derivatives. Of particular interest is that the oxidation indirectly activates the methylene position (C-10) of the γ-lactone, which may then potentially be substituted to give a new series of lignans. Reaction of **6** with hydroxylamine and benzyloxyamine also proceeds by way of initial attack at C-10.

1. Introduction

The anti-cancer properties of lignans such as podophyllotoxin **1** and its derivatives etoposide **2** and teniposide **3**, have prompted studies of their synthetic transformations[1,2] and biological activities.[3] Structure–activity relationship studies have revealed that di- and tetrahydronaphthalenes having a *trans*-lactone and a β-hydroxyl at C-4 have high therapeutic indices in tests for anti-neoplastic and anti-viral effects.[4] Although the conversion of di- and tetrahydronaphthalene lignans to naphthalene derivatives is facile,[5] the reduction of naphthalene lignans to the corresponding di- and tetrahydro derivatives is more difficult to accomplish.



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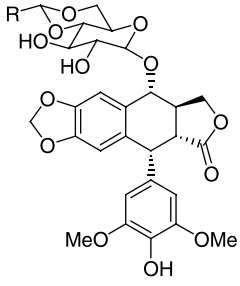
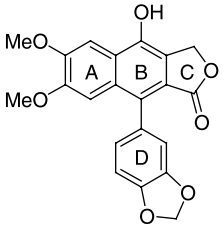


2 R = CH_3
3 R = 2-thienyl



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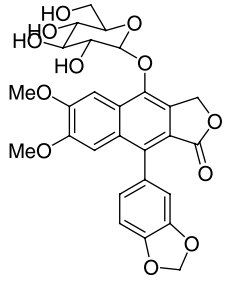

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Keywords: Lignans; Oxidative nucleophilic substitutions; Diphyllin; Synthesis; 3,4-Dihydrodiphyllin; Oxazinone; Benzyloxyoxime.
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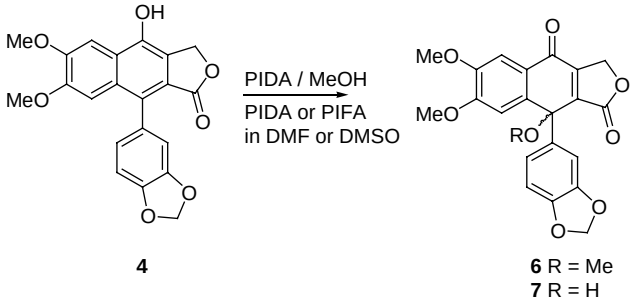
We have been studying the reactions of lignans in a bid to uncover novel chemistry that has been overlaid by the relative ease of structure establishment by modern physical methods.[6–14] A further general interest is the oxidation of phenols with hypervalent iodine compounds[15–17] and the possible mechanism of such reactions.[18] Drawing these interests together, we have previously reported the reactions of lignans of the dibenzylbutyrolactone series with phenyliodonium diacetate (PIDA) and phenyliodonium bis-trifluoroacetate (PIFA).[19,20] We have now used PIDA and PIFA to oxidise diphyllin **4**, a lignan isolated along with its glycoside cleistanthin **5** from *Cleistanthus collinus*,[21] and the result of that reaction and the transformations of the product are presented below.

2. Results and discussion

2.1. Oxidation of diphyllin 4 with PIDA or PIFA

Treatment of diphyllin **4** with 1 equiv of PIDA in dry methanol at room temperature for 1 h produced in 80% yield a yellow crystalline solid **6**, mp 230 °C, $C_{22}H_{18}O_8$ (Scheme 1). Its UV spectrum showed absorption maxima at 290 and 246 nm and its IR had peaks at 1740 (γ-lactone), 1702 (C=O) and 1600 cm^{-1}. In its ^1H NMR spectrum five aromatic proton signals were observed at δ 7.63s, 6.83s, 6.91d (J=1.9 Hz), 6.68d (J=8.3 Hz) and 6.81dd (J=1.9, 8.3 Hz), three of which exhibited the typical couplings of a 3,4-disubstituted pendant aryl group. Its ^1H NMR spectrum further showed an aliphatic methoxyl at δ 3.16 in addition to two aromatic methoxyls at δ 3.88 and 4.01. The ^{13}C NMR spectrum revealed the presence of a ketone carbonyl at δ 179.6 in addition to the lactone carbonyl at δ 168.8 and an aliphatic signal at δ 76.9, which could be assigned to a quaternary carbon (C-1) bearing a methoxyl substituent.



4 **6** R = Me **7** R = H

Scheme 1.

The presence of an aliphatic methoxyl and conjugated carbonyl in **6** can be explained by oxidation of the phenolic hydroxyl of diphyllin **4** followed by nucleophilic attack by methanol at C-1 (*para* to the phenolic group) to form the 1-methoxy-1-aryl-4-oxonaphthalene lactone **6** and this structure was confirmed by X-ray analysis (Fig. 1). This product was exactly as expected based upon our previous work and our calculations on the mechanism of the reaction.[18]

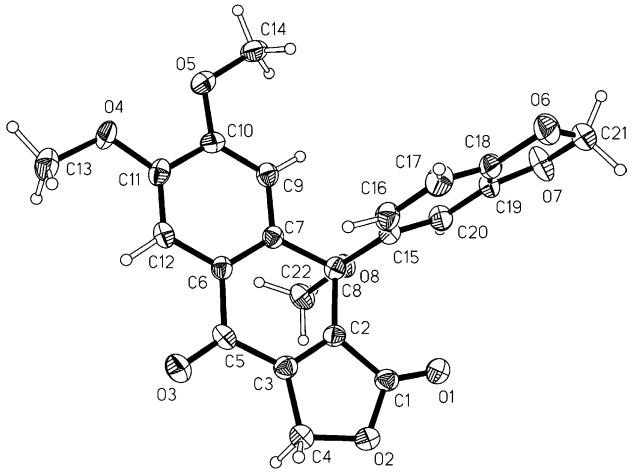
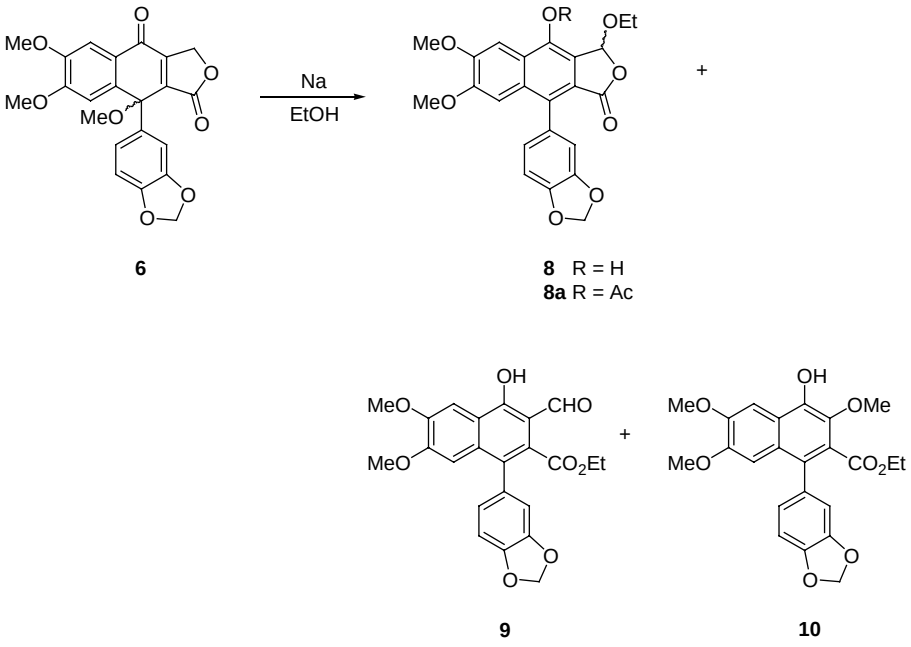


Figure 1. Structure of **6**.

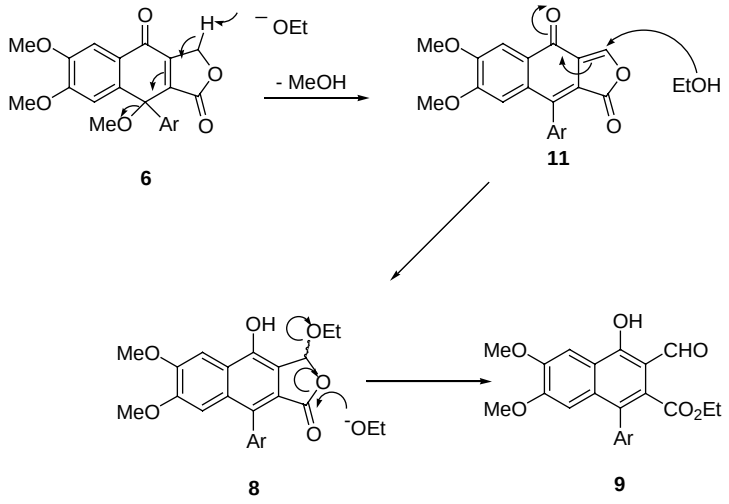
Treatment of diphyllin **4** with 1 equiv of PIDA or PIFA in DMF or DMSO at room temperature for 1 h, gave a pale yellow amorphous powder **7**, mp 210 °C, that had the molecular formula $C_{21}H_{16}O_8$. Compound **7** had almost identical spectral properties to **6** except for replacement of the methoxyl group at C-1 by a hydroxyl group.

2.2. Reaction of 6 with sodium in ethanol

Treatment of **6** with 1 equiv of sodium in ethanol gave a mixture of three compounds **8**, **9**, and **10** (Scheme 2). Compound **8** was obtained in 62% yield as a crystalline solid, mp 177 °C, $C_{23}H_{20}O_8$. Its ^1H NMR spectrum revealed two singlets at δ 6.48 and 6.45 besides the five aromatic protons. The singlet at δ 6.45 disappeared on D_2O exchange indicating the presence of a phenolic OH. The ^1H NMR spectrum also contained two one-proton multiplets at δ 4.03 and 3.90 and a double triplet for three protons at δ 1.37 (J=1.2, 7.0 Hz) indicating the presence of an OEt group. The one proton singlet at δ 6.48, which replaced the signals due to the lactone methylene in **6** suggested that an ethoxy group has been introduced at C-10, the lactone methylene position. The ^{13}C NMR spectrum of **8** lacked the carbonyl signal that in **6** showed at δ 179.6 as well as the quaternary carbon signal at δ 76.9, instead showing a pattern of carbon signals similar to that of diphyllin. Furthermore, the presence of a carbon signal at δ 99.1 in **8**, in place of the carbon signal of the lactone methylene at δ 67.9 in **6**, indicated that under nucleophilic conditions aromatisation and substitution into the γ-lactone at C-10 had both occurred to produce 10-ethoxydiphyllin **8** (Scheme 3). Compound **8** gave a monoacetate **8a**, mp 220 °C, having the molecular formula $C_{25}H_{24}O_9$. The fact that none of the other signals was affected by the introduction of the acetyl group confirms that the OH group is phenolic as in diphyllin **4**. The production of **8** can be explained (Scheme 3) by the production of key intermediate **11** by facile elimination followed by attack by ethanol on the β position (C-10) of the enone with concomitant aromatization. It is fascinating to note that by oxidation of ring B, the methylene position of the γ-lactone has been



Scheme 2.



Scheme 3.

activated to nucleophilic substitution. This route opens the way to the production, in good yields, of a wide variety of related compounds substituted at C-10 in the γ-lactone ring. It is noteworthy that there is no overall reduction in the process leading from **6** to **8**.

Compound **9** was obtained in 10% yield as orange crystals, mp 122 °C, and had molecular formula $C_{23}H_{20}O_8$. Its ^{1}H NMR spectrum showed characteristic signals for a strongly chelated phenolic hydroxyl group at δ 13.38s and an aldehyde at 9.95s, as well as a multiplet at δ 4.03 and triplet at 1.35 for the ethoxyl group. Its ^{13}C NMR spectrum showed a signal at δ 194.7 (CHO) and aliphatic carbons at δ 62.0 and 14.0 (OEt). Based upon the ^{1}H and ^{13}C NMR spectra, **9** was identified as ethyl 1-(3,4-methylenedioxyphenyl)-3-formyl-4-hydroxynaphthalene-2-carboxylate **9**. Its formation could be readily explained as arising from **8** by attack by ethanol (Scheme 3).

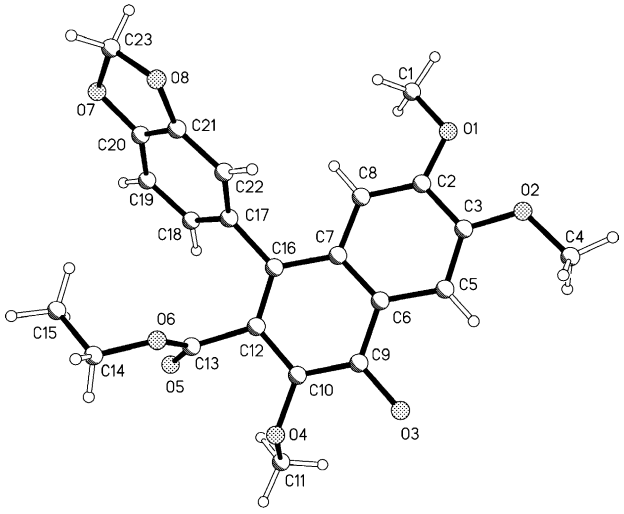
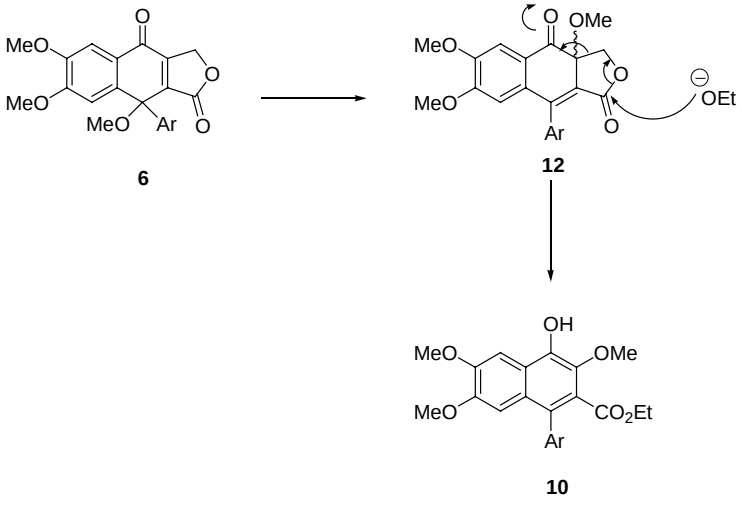


Figure 2. Structure of **10**.

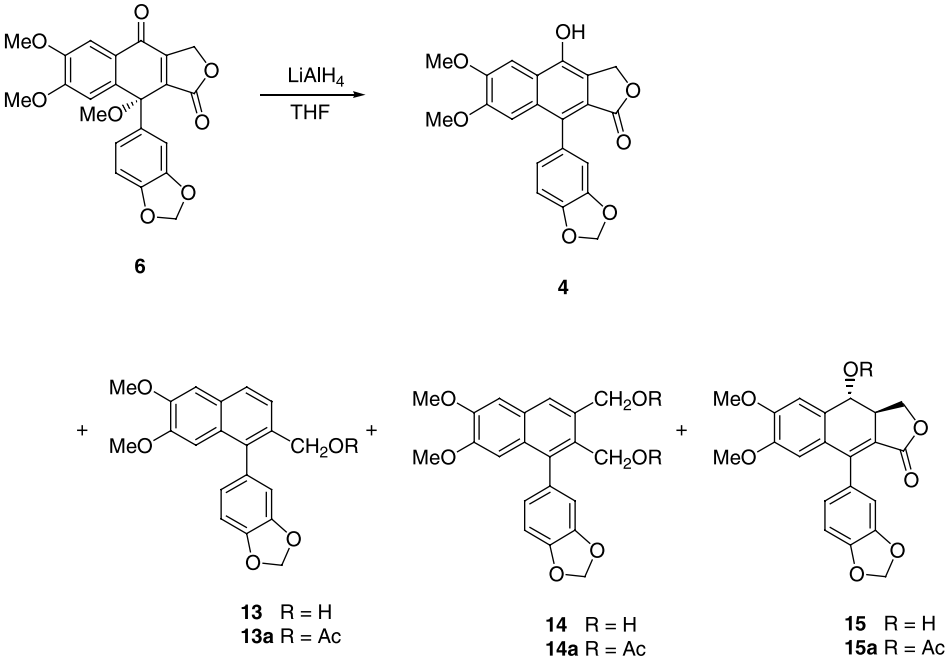
Compound **10** was obtained in 17% yield as a yellow amorphous powder, mp 150 °C, and had molecular formula $C_{23}H_{22}O_8$. Its ^{1}H NMR spectrum lacked signals for the lactone methylene in **6**, showing instead the presence of an extra aromatic methoxyl group, in addition to a triplet at δ 1.07 and a quartet at δ 4.12 due to an ethyl ester. Its ^{13}C NMR spectrum also showed the absence of the lactone methylene present in **6**, but showed signals for the extra methoxyl group at δ 62.8 and for the ethyl ester at δ 13.9 and 61.2. Thus based upon its spectral characteristics, the structure of this compound was assigned as ethyl 1-(3,4-methylenedioxyphenyl)-3-methoxy-4-hydroxy-naphthalene-2-carboxylate **10** and its structure was confirmed by X-ray analysis (Fig. 2). A possible mechanism for its formation involving allylic migration of methoxyl to C-3 to give intermediate **12**, followed by cleavage of the lactone by ethoxide and deformylation, is shown in Scheme 4.

2.3. Reduction of 4-oxo-lactone 6 with lithium aluminium hydride

When compound **6** was treated with 2 equiv of lithium aluminium hydride in THF, it yielded a mixture of four products, one of which was readily identified as diphyllin **4** (15%) by comparison with an authentic sample. Compounds **13** (14%) and **14** (15%) were identified as 1-(3,4-methylenedioxyphenyl)-2-hydroxymethylnaphthalene and 1-(3,4-methylenedioxyphenyl)-2,3-bis(hydroxy-



Scheme 4.



Scheme 5.

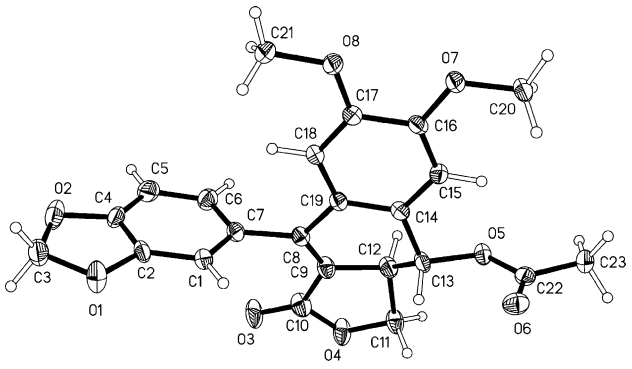


Figure 3. Structure of **15a**.

methyl)naphthalene, respectively. Compound **15** was identified as 3,4-dihydrodiphyllin (Scheme 5). The formation of **13** and **14** could be explained by reduction of **6** followed by aromatisation, dehydration and deformylation, steps that are well known in the chemistry of 1-aryltetralin lignans.[5]

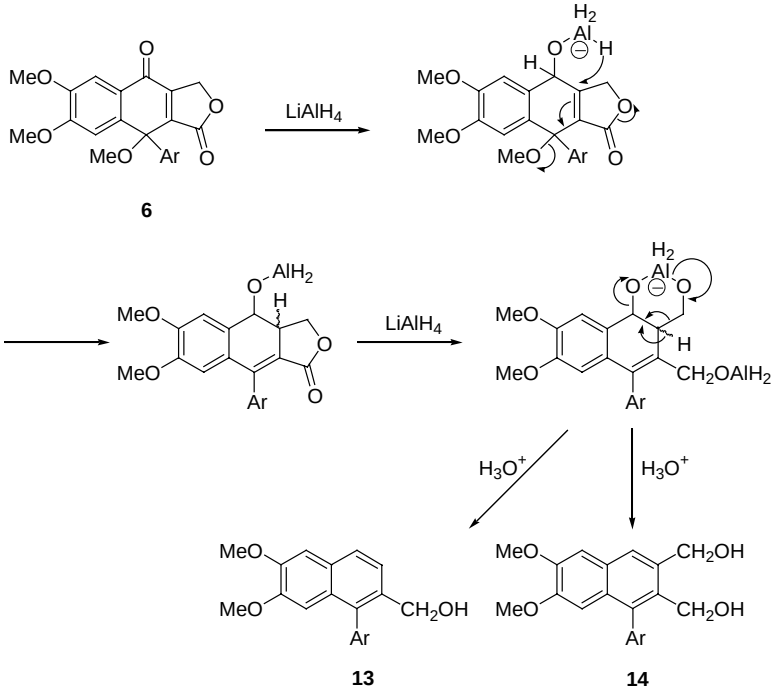
Compound **15** (32%) was obtained as a colourless solid, mp 238 °C, $C_{21}H_{18}O_7$. Its UV spectrum showed absorption maxima at 350, 265 and 235 nm and its IR spectrum contained bands at 3340 (OH), 1746 (γ-lactone), and 1602 (conj. C=C) cm^{-1}. Its ^1H NMR spectrum showed five aromatic protons at δ 7.47d (J= 0.7 Hz), 7.01d (J=8.0 Hz), 6.90m, 6.80s, 6.65s, three of which showed coupling consistent with the presence of a pendant 3,4-disubstituted aryl ring. Among the aliphatic protons the two protons of the lactone methylene appeared as two triplets at δ 4.80 (J=8.9 Hz) and 4.35 (J=8.9 Hz), and a multiplet at δ 3.46–3.54 is assigned to H-3. Compound **15** gave a monoacetate **15a** as a colourless solid, mp 152 °C. The ^1H NMR spectrum of **15** showed an aliphatic proton at δ 5.04dd (J=6.8, 13.8 Hz), which moved downfield to δ 6.16d (J=13.0 Hz) in the ^1H NMR spectrum of its acetate, **15a**, and is assigned to H-4. The trans relationship between H_3–H_4 is based on the observed large coupling constant ($J_{3,4}$=6.8 Hz).[22] The ^{13}C NMR spectrum of **15** showed two olefinic carbon signals at δ 119.8 and 128.5, assigned to C-1 and C-2, a lactone carbonyl at δ 167.0 and the lactone methylene at δ 70.6. The carbon signal at δ 73.3 is assigned to C-4, where hydroxyl is present. Thus based upon the ^1H and ^{13}C NMR spectra of **15** and its acetate **15a**, the structure was assigned as 3,4-dihydrodiphyllin **15** and this was confirmed by X-ray analysis of **15a** (Fig. 3). Possible mechanisms for the formation of compounds **13**, **14** and **15** from **6** are shown in Schemes 6 and 7.

It is interesting to note that the 3,4-dihydrodiphyllin **15** has neither been previously reported as a natural compound nor produced by synthesis.

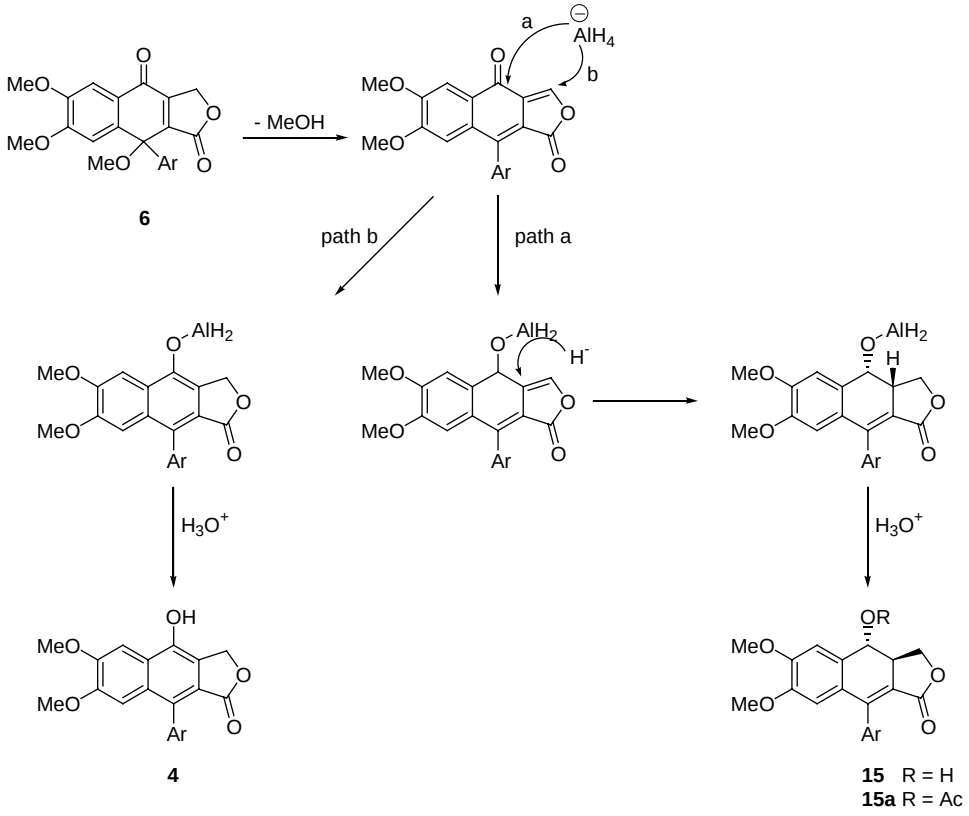
2.4. Reactions of 6 with hydroxylamine and with benzyloxyamine

Having noted that isoxazolone derivatives of lignans had been produced,[23] we attempted to introduce nitrogen at C-4 of the 4-oxolactone **6**. However, when **6** was reacted with either hydroxylamine or benzyloxyamine, nitrogen is introduced at C-10 and not at either the ketone or lactone carbonyl of **6**.

When **6** was treated with 2 equiv of hydroxylamine hydrochloride in the presence of Na_2CO_3 or triethylamine

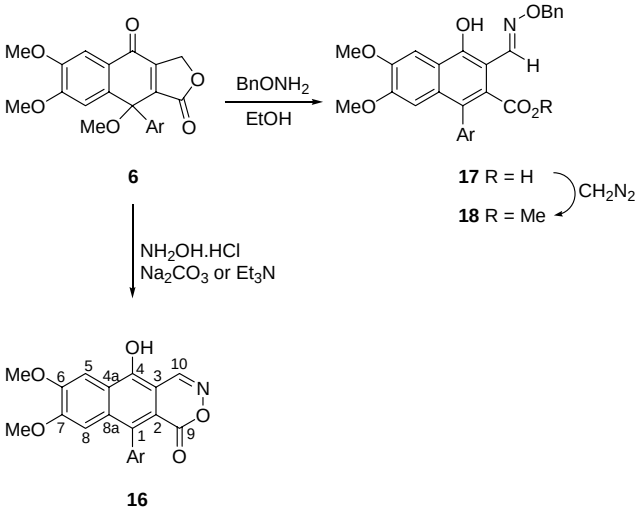


Scheme 6.



Scheme 7.

in ethanol, an amorphous solid, mp 195 °C **16** (40%) was obtained. This had molecular formula $C_{21}H_{15}O_7N$ and its IR spectrum showed bands at 3467 (OH), 1708 (C═O), 1645 (C═N), and 1617 (arom. C═C) cm^{-1}. Its ^1H NMR spectrum showed five aromatic protons at δ 7.65s, 6.88s, 6.86d ($J=1.2$ Hz), 6.83dd ($J=7.9$, 1.4 Hz) and 6.94d ($J=7.9$ Hz) of which three showed couplings consistent with the presence of a 3,4-disubstituted pendant aryl ring. Further, a highly deshielded proton was observed as a singlet at δ 8.40, which may be due to the imine proton at C-10. Its ^{13}C NMR spectrum showed a lactone carbonyl at δ 169.6 and a signal at δ 153.70, which is assigned to an imino carbon (C═N–O) and on this basis the oxazinone structure **16** was assigned (Scheme 8). In order to prove that nucleophilic attack on **6** by hydroxylamine took place at C-10, compound **6** was treated with 1 equiv of benzyloxyamine hydrochloride and gave the expected benzyloximinocarboxylic acid **17** as a crystalline solid, mp 264 °C, $C_{28}H_{23}O_8N$.



Scheme 8.

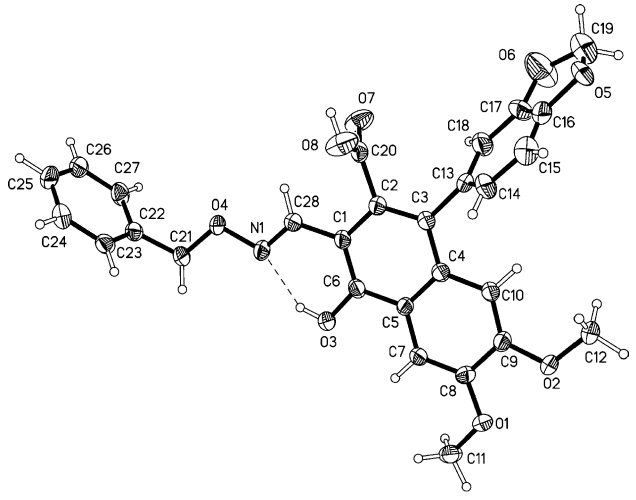
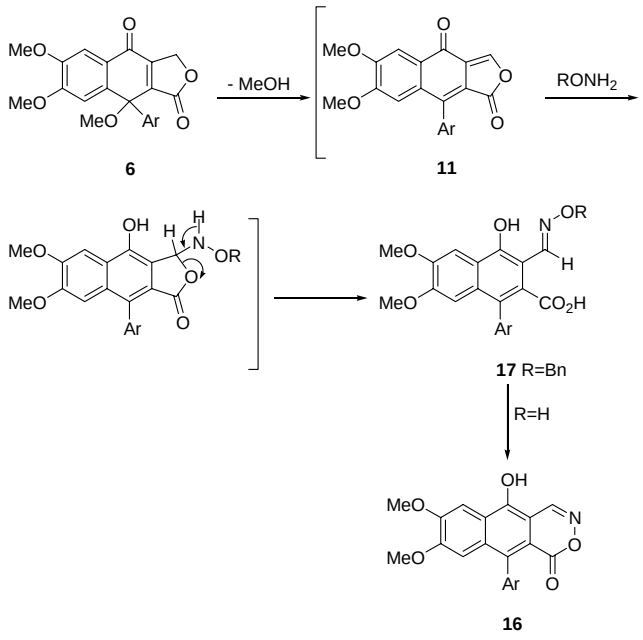


Figure 4. Structure of **17**.



Scheme 9.

Its ^{1}H NMR spectrum showed an acidic proton as a broad singlet at δ 11.4 for the –COOH and another highly deshielded proton as a singlet at δ 8.54 for the imino proton (H–C═N–O). The benzyloxy methylene was observed as a singlet at δ 5.2. Its ^{13}C NMR spectrum showed signals at δ 170.5 for the carboxylic acid, an imino carbon at δ 150.6, and a signal due to a benzyloxymethylene group at δ 77.26. Based upon its NMR spectra structure **17** was assigned. The presence of a carboxyl group in **17** was confirmed by the production of its methyl ester **18**. The X-ray structure of **17** is shown in Figure 4. Possible pathways for the formation of **16** and **17** are shown in Scheme 9. Once more attack on **6** occurs at C-10 through the intermediacy of the elimination product **11**.

3. Conclusion

Oxidation of diphyllin **4** by PIDA and PIFA proceeds, as expected, on the aromatic ring bearing a free phenolic group, which is dearomatised selectively to yield 1-methoxy- or 1-hydroxy-1-aryl-4-oxonaphthalene lactones **6** and **7**. The 4-oxolactone **6** can be converted to a number of unusual products caused by elimination and attack at C-10, in the lactone ring. On reduction of **6** the production of, previously unknown, dihydrophyllin **15** was observed.

4. Experimental

4.1. General procedure

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 400 instrument at 400 and 100 MHz, respectively. All spectra used tetramethylsilane as internal standard and were run in $CDCl_3$. Mass spectra were recorded either on a VG 12-250 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. Infra-red spectra were recorded either as a Nujol mull or as films on NaCl plates using a Perkin-Elmer Fourier transform 1725X spectrophotometer. Dichloromethane was purified by passing it down on alumina column followed by distillation over calcium hydride. Silica gel-G was used for column chromatography and for TLC. Melting points were recorded on an Electrothermal 9100 melting point apparatus and are uncorrected.

Crystal structure data for (**6**), (**10**), (**15a**) and (**17**) are given in Table 1. Cell dimensions and intensity data were recorded at 150 K, using either a Bruker Nonius KappaCCD or an Enraf Nonius FAST equipped with a rotating anode; standard procedures were followed. Crystallographic data (excluding structure factors) for the structures in this paper

Table 1. Crystal data for **6**, **10**, **15a** and **17**

Compound	**6**	**10**	**15a**	**17**
Formula	$C_{22}H_{18}O_8$	$C_{23}H_{22}O_8$	$C_{23}H_{20}O_8$	$C_{28}H_{23}NO_8$
Crystal	Yellow prism	Yellow needle	Colourless block	Colourless plate
M	410.36	426.40	424.39	501.47
Crystal system	Monoclinic	Monoclinic	Monoclinic	Triclinic
Space group	$P2_1/c$	$P2_1/n$	$P2_1/c$	$P\bar{1}$
a (Å)	11.9852(5)	11.349(2)	11.2554(8)	9.0768(18)
b (Å)	14.3476(10)	18.540(4)	24.3001(14)	10.020(2)
c (Å)	11.1874(6)	20.056(4)	7.6694(4)	16.638(3)
α (°)	90	90	90	94.50(3)
β (°)	110.07(3)	104.39(3)	109.076(3)	90.86(3)
γ (°)	90	90	90	114.68(3)
U (Å^3)	1806.95(18)	4087.8(14)	1982.4(2)	1368.8(5)
Z	4	8	4	2
Density (g cm^{-3})	1.508	1.382	1.422	1.217
μ (Mo Kα) (mm)	0.116	0.105	0.108	0.090
Reflections coll.	12,467	41,975	13,049	10,124
Indep. refs./R_{int}	3526/0.0984	9342/0.1623	3448/0.1402	4173/0.0674
Parameters/restraints	344/0	568/18	281/0	354/0
$R1$ ($F>4\sigma$)	0.0455	0.1893	0.0737	0.0769
$wR2$ (all data)	0.0950	0.4769	0.2228	0.1648

have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 276028 (**6**) 217955 (**10**), 217992 (**15a**), 223292 (**17**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 IEZ, UK (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

4.1.1. Reaction of diphyllin 4 with PIDA in methanol: isolation of 1-methoxy-1-(3,4-methylenedioxyphenyl)-4-oxo-6,7-dimethoxynaphthalene-2,3-lactone 6. To a solution of diphyllin (**4**) (0.20 g, 0.52 mmol) in dry methanol (10 ml) was added PIDA (0.16 g, 0.50 mmol) and the mixture stirred at room temperature for 1 h. The reaction was quenched with aq $NaHCO_3$ and the mixture was poured into ice-water and extracted with EtOAc (3×20 ml). The combined EtOAc extracts were washed with brine (3× 20 ml), then dried ($MgSO_4$) and filtered. Removal of the solvent under reduced pressure gave a yellow residue (0.2 g). Column chromatography on silica gel-G (eluent: hexane/EtOAc, 8:2) yielded (**6**) as a yellow powder (0.16 g, 78%) which crystallised from methanol to give yellow crystals, mp 230 °C; *m/z* (EI) 410 (M^+, 5%), 395 (70), 380 (44), 351 (33), 321 (40), 293 (100), 265 (20), 163 (46); λ_{max} ($CHCl_3$) 290 (1.12), 246 (1.80) nm; ν_{max} (Nujol) 1740 (γ-lactone), 1702 (C═O), 1600 (arom.) and 940 (OCH_2-O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.63 (1H, s, H-5), 6.91 (1H, d, J=1.9 Hz, H-2′), 6.83 (1H, s, H-8), 6.81 (1H, dd, J=1.9, 8.3 Hz, H-6′), 6.68 (1H, d, J=8.3 Hz, H-5′), 5.93 (1H, d, J=1.3 Hz, OC*H*$_2$O), 5.92 (1H, d, J=1.3 Hz, OC*H*$_2$O), 5.15 (1H, d, J=18.1 Hz, H-10), 5.10 (1H, d, J=18.1 Hz, H-10), 4.01 (3H, s, ArOMe), 3.88 (3H, s, ArOMe), 3.16 (3H, s, ROMe); δ_C (100 MHz, $CDCl_3$) 179.6 (C-4), 168.8 (C-9), 155.3 (C-2), 153.5 (C-3), 149.8 (C-8a), 147.7 (C-6), 147.5 (C-7), 141.9 (C-3′), 141.2 (C-4′), 133.5 (C-1′), 126.1 (C-4a), 120.2 (C-6′), 109.6 (C-5), 108.1 (C-8), 107.3 (C-2′), 107.1 (C-5′), 101.3 (O*C*H$_2$O), 76.9 (C-1), 67.9 (C-10), 56.5 and 56.3 (ArOMe), 52.7 (ROMe); Found: M^+410.1004, $C_{22}H_{18}O_8$ requires 410.1002.

4.1.2. Reaction of 4 with PIDA or PIFA in DMSO: isolation of 1-hydroxy-1-(3,4-methylenedioxyphenyl)-4-oxo-6,7-dimethoxynaphthalene-2,3-lactone 7. To a solution of diphyllin **4** (0.2 g, 0.52 mmol) in DMSO (10 ml) was added PIDA (0.116 g, 0.50 mmol) [or diphyllin (0.3 g, 0.78 mmol) and PIFA (0.4 g, 0.93 mmol)] and the reaction was stirred at room temperature for 1 h. The mixture was quenched with aq $NaHCO_3$ and worked up as described in experiment (Section 4.1.1). Column chromatography of the residue on silica gel-G (eluent: hexane/EtOAc, 8:2) yielded **7** as a yellow powder (0.14 g, 71%), mp 210 °C; *m/z* (EI) 396 (M^+, 10%), 378 (15), 351 (60), 322 (30), 247 (80), 219 (60); λ_{max} ($CHCl_3$) 240 (1.82), 280 (1.18) nm; ν_{max} (Nujol) 3468 (OH), 1740 (γ-lactone), 1692 (C═O) and 927 (OCH_2O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.53 (1H, s, H-5), 6.92 (1H, s, H-8), 6.87 (1H, dd, J=1.9, 8.2 Hz, H-6′), 6.78 (1H, d, J=1.9 Hz, H-2′), 6.74 (1H, d, J=8.2 Hz, H-5′), 5.94 (1H, d, J=1.3 Hz, OC*H*$_2$O), 5.93 (1H, d, J=1.3 Hz, OC*H*$_2$O), 5.20 (1H, d, J=18.0 Hz, H-10), 5.12 (1H, d, J=18.0 Hz, H-10), 3.97 (3H, s, ArOMe), 3.95 (1H, s, ROH), 3.89 (3H, s, ArOMe); δ_C (100 MHz, $CDCl_3$) 179.5 (C-4), 170.5 (C-9), 154.9 (C-2), 149.9 (C-3), 149.4 (C-8a), 148.2 (C-6), 147.6 (C-7), 142.5 (C-3′), 142.2 (C-4′), 134.2 (C-1′), 123.4 (C-4a), 118.6 (C-6′), 109.3 (C-5), 108.5 (C-8), 107.2 (C-2′), 105.8 (C-5′), 101.4 (O*C*H$_2$O), 70.9 (C-1), 68.5 (C-10), 56.3 and 56.2 (ArOMe); Found: $[M+NH_4]^+$414.1187, $C_{21}H_{20}NO_8$ requires 414.1189; Found: $[M+H]^+$397.0917, $C_{21}H_{17}O_8$ requires 397.0923.

4.1.3. Reaction of 6 with sodium and ethanol: isolation of 10-ethoxydiphyllin 8, ethyl 1-aryl-3-formyl-4-hydroxynaphthalene-2-carboxylate 9, and ethyl 1-(3,4-methylenedioxyphenyl)-3-methoxy-4-hydroxynaphthalene-2-carboxylate 10. To a solution of **6** (0.6 g, 1.5 mmol) in ethanol (20 ml) was added sodium (0.033 g, 1.5 mmol) and the mixture stirred for 2 h, and then quenched with aq NH_4Cl solution. After removal of the ethanol under reduced pressure the reaction mixture was poured into crushed ice and extracted with EtOAc (3×20 ml). The combined EtOAc extracts were washed with brine (3×20 ml), then dried ($MgSO_4$) and filtered. Removal of the solvent under reduced pressure gave a brown residue (0.6 g). Column chromatography on silica gel (eluent: hexane/EtOAc, 9:1) yielded 10-ethoxydiphyllin **8** (0.37 g, 58%) as a pale yellow gum, which was crystallised from methanol, mp 177 °C; λ_{max} ($CHCl_3$) 285 (3.2), 246 (1.7), 202 (0.8) nm; *m/z* (EI) 424 (M^+, 20%), 379 (30%), 378 (100), 350 (10), 322 (80), 307 (35), 264 (20), 163 (60), 150 (90); ν_{max} (KBr) 3368 (broad OH), 1721 (C═O), 1617 (arom.) and 947 (OCH_2-O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.61 (1H, s, H-5), 7.06 (1H, d, J=0.8 Hz, H-8), 6.93 (1H, d, J=8.1 Hz, H-5′), 6.85 (1H, d, J=1.5 Hz, H-2′), 6.80 (1H, dd, J=1.5, 8.1 Hz, H-6′), 6.48 (1H, s, H-10), 6.45 (1H, s, O*H*), 6.07 (1H, s, OCH_2O), 6.00 (1H, s, OCH_2O), 4.07 (3H, s, ArOMe), 4.03 (1H, m, OC*H*$_2$CH$_3$), 3.90 (1H, m, OC*H*$_2$CH$_3$), 3.82 (3H, s, ArOMe), 1.37 (3H, dt, J=1.2, 7.0 Hz, OCH_2CH_3); δ_C (100 MHz, $CDCl_3$) 167.9 (C-9), 151.2 (C-6), 150.7 (C-7), 147.5 (C-4′), 147.4 (C-3′), 145.7 (C-4), 132.2 (C-4a), 131.5 (C-8a), 128.4 (C-1′), 128.3 (C-2), 128.0 (C-3), 123.8 (C-6′), 119.4 (C-1), 111.0 (C-5), 108.2 (C-8), 108.2 (C-2′), 106.2 (C-5′), 101.2 (O*C*H$_2$O), 99.1 (C-10), 65.3 (O*C*H$_2$CH$_3$), 56.1 and 55.8 (OMe), 15.2 (OCH_2CH_3); Found: M^+424.1152, $C_{23}H_{20}O_8$ requires 424.1158. Compound **9** (0.06 g, 9%) crystallised from methanol as orange coloured crystals, mp 122 °C; λ_{max} ($CHCl_3$) 280 (3.1), 266 (2.9) nm; *m/z* (EI) 424 (M^+, 100%), 422 (30), 394 (100), 378 (20), 322 (40); ν_{max} (KBr) 1729 (CO), 1602 (arom.), 931 (OCH_2O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 9.96 (1H, s, H-9), 7.74 (1H, s, H-5), 6.92 (1H, dd, J=1.6, 7.9 Hz, H-6′), 6.84 (1H, d, J=1.6 Hz, H-2′), 6.82 (1H, s, O*H*), 6.78 (1H, s, H-8), 6.78 (1H, d, J=7.9 Hz, H-5′), 6.04 (1H, d, J=1.2 Hz, OCH_2O), 6.03 (1H, d, J=1.2 Hz, OCH_2O), 4.13 (2H, q, J=7.1 Hz, OC*H*$_2$CH$_3$), 4.06 (3H, s, ArOMe), 4.05 (3H, s, ArOMe), 1.37 (3H, t, J=7.1 Hz, OCH_2CH_3); δ_C (100 MHz, $CDCl_3$) 194.7 (C-10), 167.6 (C-9), 152.4 (C-6), 150.0 (C-7), 149.7 (C-4), 147.5 (C-4′), 147.2 (C-3′), 133.0 (C-3), 132.9 (C-2), 130.7 (C-8a), 129.7 (C-1′), 129.0 (C-4a), 124.4 (C-6′), 119.8 (C-1), 110.9 (C-5), 108.3 (C-8), 106.1 (C-2′), 103.0 (C-5′), 101.2 (OCH_2O), 61.6 (O*C*H$_2$CH$_3$), 56.2 and 55.9 (OMe), 13.9 (OCH_2CH_3); Found: M^+424.1153, $C_{23}H_{20}O_8$ requires 424.1158. Compound **10** (0.11 g, 17%) was obtained from methanol as yellow amorphous powder mp 150 °C; λ_{max} 290 (4.1), 279 (3.5), 226 (1.2) nm; *m/z* (EI) 426 (M^+, 100%), 380 (50), 365 (80), 350 (20), 337 (70); ν_{max} (KBr) 3436 (chelated OH), 1727, 1653 (C═O), 1617 (arom.) and 924 (OCH_2O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.47 (1H, s, H-5), 6.81 (1H, dd, J=1.6, 7.9 Hz, H-6′), 6.86 (1H, d, J=1.6 Hz,

H-2′), 6.12 (1H, s, O*H*), 6.88 (1H, s, H-8), 6.88 (1H, d, J=7.9 Hz, H-5′), 6.05 (1H, d, J=1.3 Hz, OCH_2O), 6.01 (1H, d, J=1.3 Hz, OCH_2O), 4.12 (2H, q, J=7.1 Hz, OCH_2CH_3), 4.04 (3H, s, ArOMe), 3.93 (3H, s, ArOMe), 3.77 (3H, s, ArOMe), 1.07 (3H, t, J=7.1 Hz, OCH_2CH_3); δ_C (100 MHz, $CDCl_3$) 167.5 (C-9), 149.9 (C-6), 149.5 (C-7), 142.1 (C-4), 147.0 (C-4′), 147.3 (C-3′), 137.1 (C-3), 125.7 (C-2), 131.5 (C-8a), 125.8 (C-1′), 128.5 (C-4a), 123.9 (C-6′), 120.3 (C-1), 111.0 (C-5), 108.1 (C-8), 105.4 (C-2′), 100.4 (C-5′), 101.1 (OCH_2O), 62.8 (OMe), 61.2 (OCH_2CH_3), 56.0 and 55.7 (OMe), 13.9 (OCH_2CH_3); Found: M^+426.1312, $C_{23}H_{22}O_8$ requires 426.1315.

4.1.4. Preparation of 4-*O*-acetyl-10-ethoxydiphyllin 8a. To a solution of **8** (0.1 g, 0.21 mmol) in dry pyridine (2 ml) was added acetic anhydride (2 ml) and the mixture was heated under reflux for 1 h on an oil bath. The reaction mixture was then poured onto crushed ice and extracted with EtOAc (3×20 ml). The combined EtOAc extracts were washed successively with dil HCl (2×20 ml) and brine (3×20 ml), then dried ($MgSO_4$) and filtered. Removal of the solvent under reduced pressure gave a light brown residue (0.1 g). Column chromatography on silica gel-G (eluent: hexane/EtOAc, 4:1) yielded **8a**, (0.08 g, 80%) as a gum, which crystallised from methanol to give colourless plates, mp 220 °C; *m/z* (EI) 466 (M^+, 25%), 424 (10), 378 (90), 350 (10), 322 (45), 307 (15); λ_{max} 279 (3.0), 270 (2.9), 245 (1.2) nm; ν_{max} 1721, 1653 (C=O), 1617 (arom.) and 924 (OCH_2O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.25 (1H, s, H-5), 7.09 (1H, d, J=0.9 Hz, H-8), 6.96 (1H, d, J=7.9 Hz, H-5′), 6.85 (1H, d, J=1.5 Hz, H-2′), 6.82 (1H, dd, J=1.5, 7.9 Hz, H-6′), 6.38 (1H, s, H-10), 6.09 (1H, d, J=1.1 Hz, OCH_2O), 6.05 (1H, d, J=1.1 Hz, OCH_2O), 4.05 (3H, s, ArOMe), 3.94 (1H, m, OCH_2CH_3), 3.81 (1H, m, OCH_2CH_3), 3.81 (3H, s, ArOMe), 2.53 (3H, s, OAc), 1.31 (3H, t, J=7.0 Hz, OCH_2CH_3); δ_C (100 MHz, $CDCl_3$) 167.9 (C-9), 166.7 ($OCOCH_3$), 152.2 (C-6), 150.8 (C-7), 147.7 (C-3′), 147.6 (C-4′), 139.7 (C-4), 131.7 (C-4a), 131.7 (C-8a), 127.9 (C-3), 127.1 (C-1′), 126.2 (C-2), 123.6 (C-6′), 120.0 (C-1), 110.7 (C-5), 110.4 (C-8), 108.3 (C-2′), 106.4 (C-5′), 101.3 (OCH_2O), 99.8 (C-10), 65.1 (OCH_2CH_3), 56.0 and 55.9 (OMe), 20.8 ($OCOCH_3$), 15.1 (OCH_2CH_3); Found: M^+466.1259, $C_{25}H_{22}O_9$ requires 466.1264.

4.1.5. Reaction of 6 with lithium aluminium hydride: isolation of 2-(hydroxymethyl)-1-(3,4-methylenedioxyphenyl)naphthalene 13, 2,3-bis-(hydroxymethyl)-1-(3,4-methylenedioxy phenyl)naphthalene 14, diphyllin 4, and 3,4-dihydrodiphyllin 15. To solution of **6** (0.6 g, 0.14 mmol) in dry THF (10 ml) at −80 °C, was added $LiAlH_4$ (0.11 g, 0.28 mmol) and the mixture stirred for 0.5 h and then brought to room temperature. The excess $LiAlH_4$ was decomposed with EtOAc (10 ml), then poured into crushed ice and extracted with EtOAc (3×20 ml). The combined EtOAc extracts were washed with brine (3×20 ml), then dried ($MgSO_4$) and filtered. Removal of the solvent under reduced pressure gave a light brown residue (0.6 g). Column chromatography on silica gel (eluent: hexane/EtOAc, 3:2) yielded **13** (0.09, 14%) as a gum, λ_{max} 286, 270, 262 nm; ν_{max} ($CHCl_3$) 3443 (OH), 1623 (arom.) and 933 (OCH_2O) cm^{-1}; *m/z* (EI) 338 (M^+, 100%), 322 (25), 309 (15), 289 (40), 263.1 (20), 205 (25), 176 (45); δ_H (400 MHz, $CDCl_3$) 7.70 (1H, dd, J=1.6, 7.9 Hz, H-6′), 7.66 (1H, d, J=8.4 Hz, H-4), 7.47 (1H, d, J=8.4 Hz, H-3), 7.08 (1H, s, H-5), 6.76 (1H, d, J=7.9 Hz, H-5′), 6.74 (1H, d, J=1.6 Hz, H-2′), 6.73 (1H, s, H-8), 6.08 (1H, d, J=1.2 Hz, OCH_2O), 6.04 (1H, d, J=1.2 Hz, OCH_2O), 4.50 (1H, s, H-9), 3.99 (3H, s, ArOMe), 3.75 (3H, s, ArOMe), 3.13 (1H, s, OH); δ_C (100 MHz, $CDCl_3$) 150.0 (C-3′), 149.6 (C-6), 149.5 (C-7), 147.9 (C-4′), 136.4 (C-4a), 134.5 (C-8a), 132.3 (C-1′), 128.6 (C-2), 126.2 (C-4), 124.4 (C-3), 123.5 (C-1), 123.3 (C-6′), 110.5 (C-5), 108.5 (C-8), 106.2 (C-2′), 105.2 (C-5′), 101.0 (OCH_2O), 63.5 (C-9), 55.6 and 55.4 (OMe); Found: M^+338.1143, $C_{20}H_{18}O_5$ requires 338.1149. Compound **14** (0.09, 15%) crystallised from methanol as a white crystalline solid, mp 218 °C; λ_{max} 289, 270, 265 nm; ν_{max} ($CHCl_3$) 333 (OH), 1622 (arom.) and 932 (OCH_2O) cm^{-1}; *m/z* (EI) 368 (M^+, 100%), 350 (85), 321 (35), 291 (31), 277 (20), 189 (40), 176 (35); δ_H (400 MHz, $CDCl_3$) 7.70 (1H, s, H-4), 7.13 (1H, s, H-5), 6.95 (1H, d, J=7.8 Hz, H-5′), 6.83 (1H, d, J=1.7 Hz, H-2′), 6.82 (1H, s, H-8), 6.77 (1H, dd, J=1.7, 7.8 Hz, H-6′), 6.10 (1H, d, J=1.4 Hz, OCH_2O), 6.05 (1H, d, J=1.4 Hz, OCH_2O), 4.91 (1H, s, H-9), 4.63 (1H, s, H-10), 4.01 (3H, s, ArOMe), 3.76 (3H, s, ArOMe), 3.13 (1H, s, OH); δ_C (100 MHz, $CDCl_3$) 149.7 (C-6), 149.6 (C-7), 147.6 (C-3′), 146.9 (C-4′), 138.8 (C-2), 135.6 (C-4a), 133.2 (C-8a), 132.4 (C-3), 128.8 (C-4), 128.6 (C-1′), 127.4 (C-1), 124.0 (C-6′), 108.3 (C-5), 106.2 (C-8), 104.5 (C-2′), 103.8 (C-5′), 99.4 (OCH_2O), 61.0 (C-10), 57.2 (C-9), 53.0 and 52.7 (OMe); Found: $[M+Na]^+$391.1157, $C_{21}H_{20}O_6$ requires 391.1152. Diphyllin **4** (0.09, 15%) was obtained from methanol as a pale yellow solid, mp 290 °C; λ_{max} ($CHCl_3$) 350, 265, 235 nm; ν_{max} (Nujol) 3200 (OH), 1730 (γ-lactone), 1610 (arom.) and 930 (OCH_2O) cm^{-1}; *m/z* (EI) 380 (M^+, 100%); δ_H (400 MHz, $CDCl_3$) 7.46 (1H, s, H-5), 7.12 (1H, s, H-8), 6.97 (1H, d, J=7.1 Hz, H-5′), 6.86 (1H, s, H-2′), 6.72 (1H, d, J=7.1 Hz, H-6′), 6.08 (1H, s, OCH_2O), 4.09 (3H, s, ArOMe), 3.83 (3H, s, ArOMe); δ_C (100 MHz, $CDCl_3$) 169.6 (C-9), 150.6 (C-4′), 149.8 (C-3′), 146.7 (C-6), 146.7 (C-7), 145.0 (C-4), 129.7 (C-4a), 129.7 (C-8a), 129.0 (C-1′), 123.7 (C-6′), 123.5 (C-3), 121.7 (C-2), 118.8 (C-1), 110.0 (C-8), 107.7 (C-5′), 105.8 (C-2′), 101.0 (OCH_2O), 100.8 (C-5), 66.6 (C-10), 55.6 and 55.2 (OMe). Compound **15** (0.18, 32%) was obtained from methanol as colourless solid, mp 238 °C; λ_{max} 350, 265, and 235 nm; ν_{max} ($CHCl_3$) 3340 (OH), 1746 (γ-lactone), 1602 (arom.) and 930 (OCH_2O) cm^{-1}; *m/z* (EI) 382 (M^+, 10%), 354 (100), 335 (10), 319 (10), 305 (20), 277 (30), 176 (30), 162.9 (60); δ_H (400 MHz, $CDCl_3$) 7.47 (1H, d, J=0.7 Hz, H-5), 7.01 (1H, d, J=8.0 Hz, H-6′), 6.90 (1H, m, H-5′), 6.80 (1H, s, H-2′), 6.65 (1H, s, H-8), 6.18 (1H, d, J=1.5 Hz, OCH_2O), 6.16 (1H, d, J=1.5 Hz, OCH_2O), 5.10 (1H, d, J=6.8 Hz, OH), 5.04 (1H, dd, J=6.8, 13.8 Hz, H-4), 4.80 (1H, t, J=8.9 Hz, H-10), 4.35 (1H, t, J=8.9 Hz, H-10), 4.00 (3H, s, ArOMe), 3.71 (3H, s, ArOMe), 3.46–3.54 (1H, m, H-3); δ_C (100 MHz, $CDCl_3$) 167.0 (C-9), 152.1 (C-6), 148.8 (C-7), 148.6 (C-3′), 147.9 (C-4′), 146.9 (C-4a), 135.9 (C-8a), 128.9 (C-1′), 128.5 (C-2), 119.8 (C-1), 113.8 (C-6′), 108.5 (C-5), 108.2 (C-8), 108.2 (C-5′), 108.2 (C-2′), 102.1 (OCH_2O), 73.3 (C-4), 70.6 (C-10), 56.2 and 56.1 (OMe), 44.1 (C-3); Found: $[M+H]^+$383.1134, $C_{21}H_{19}O_7$ requires 383.1131.

4.1.6. Acetylation of 13. To a solution of **13** (0.01 g, 0.029 mmol) in dry pyridine (2 ml) was added acetic anhydride (2 ml) and the mixture was stirred at room temperature for 3 h. The reaction mixture was then poured

into crushed ice and extracted with EtOAc (3×20 ml). The combined EtOAc extracts were washed successively with dil HCl (2×20 ml) and brine (3×20 ml), then dried ($MgSO_4$) and filtered. Removal of solvent under reduced pressure gave light brown residue (0.1 g). Column chromatography on silica gel-G (eluent: hexane/EtOAc, 4:1) yielded **13a** (0.08 g, 80%) as a colourless gum, λ_{max} ($CHCl_3$) 289, 260, 252 nm; *m/z* (EI) 380 (M^+, 100%), 338 (5), 320 (20), 289 (35), 263 (15), 176 (30); δ_H (400 MHz, $CDCl_3$) 7.66 (1H, d, J=8.4 Hz, H-4), 7.33 (1H, d, J=8.4 Hz, H-3), 7.07 (1H, s, H-5), 6.86 (1H, d, J=7.9 Hz, H-5′), 6.72 (1H, d, J=1.7 Hz, H-2′), 6.72 (1H, s, H-8), 6.67 (1H, dd, J=1.7, 7.9 Hz, H-6′), 6.08 (1H, d, J=1.2 Hz, OCH_2O), 6.04 (1H, d, J=1.2 Hz, OCH_2O), 4.94 (1H, s, H-9), 4.00 (3H, s, ArOMe), 3.75 (3H, s, ArOMe), 2.05 (3H, s, OAc); δ_C (100 MHz, $CDCl_3$) 169.0 ($OCOCH_3$), 149.6 (C-3′), 149.6 (C-6), 149.5 (C-7), 149.5 (C-4′), 137.9 (C-4a), 137.9 (C-8a), 129.2 (C-1′), 128.6 (C-2), 126.2 (C-4), 124.9 (C-3), 123.4 (C-1), 123.4 (C-6′), 110.6 (C-5), 108.3 (C-8), 106.2 (C-2′), 105.4 (C-5′), 101.1 (OCH_2O), 65.0 (C-9), 55.9 and 55.7 (OMe), 21.4 ($OCOCH_3$); Found: $[M+NH_4]^+$398.1599, $C_{22}H_{20}O_6$ requires 398.1598.

4.1.7. Acetylation of 14. To a solution of **14** (0.1 g, 0.27 mmol) in dry pyridine (2 ml) was added acetic acid anhydride (2 ml) and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was then poured into crushed ice and extracted with EtOAc (3×20 ml). The combined EtOAc extracts were washed successively with dil HCl (2×20 ml) and brine (3×20 ml) then dried ($MgSO_4$) and filtered. Removal of the solvent under reduced pressure gave a light brown residue (0.1 g). Column chromatography on silica gel-G (eluent: hexane/EtOAc, 3:2) yielded **14a** (0.08, 80%) as a gum, λ_{max} $CHCl_3$ 290, 286, 270 nm; *m/z* (EI) 452 (40%), 392 (40), 350 (67), 332 (100), 319 (35), 289 (40), 189 (65); δ_H (400 MHz, $CDCl_3$) 7.79 (1H, s, H-4), 7.16 (1H, s, H-5), 6.93 (1H, d, J=7.9 Hz, H-5′), 6.77 (1H, dd, J=1.7, 7.9 Hz, H-6′), 6.74 (1H, s, H-8), 6.73 (1H, d, J=1.7 Hz, H-2′), 6.10 (1H, d, J=1.4 Hz, OCH_2O), 6.06 (1H, d, J=1.4 Hz, OCH_2O), 5.33 (1H, d, J=3.4 Hz, H-9), 5.05 (1H, dd, J=3.4, 12.1 Hz, H-10), 4.02 (3H, s, ArOMe), 3.76 (3H, s, ArOMe), 2.13 (3H, s, OAc), 2.04 (3H, s, OAc); δ_C (100 MHz, $CDCl_3$) 170.3 and 170.0 ($OCOCH_3$), 150.2 (C-6), 150.0 (C-7), 147.7 (C-4′), 147.1 (C-3′), 140.4 (C-2), 131.9 (C-4a), 130.9 (C-8a), 129.2 (C-1′), 128.8 (C-3), 128.0 (C-1), 127.9 (C-4), 123.3 (C-6′), 110.9 (C-5), 108.1 (C-8), 106.2 (C-2′), 105.7 (C-5′), 101.2 (OCH_2O), 64.8 (C-10), 62.0 (C-9), 55.8 and 55.6 (OMe), 21.5 and 20.9 ($OCOCH_3$); Found: $[M+NH_4]^+$470.1810, $C_{23}H_{28}NO_8$ requires 470.1815.

4.1.8. Acetylation of 15: isolation of 3,4-dihydrodiphyllin acetate 15a. To a solution of **15** (0.1 g, 0.26 mmol) in dry pyridine (2 ml) was added acetic anhydride (2 ml) was added acetic anhydride (2 ml) and the reaction mixture was poured into crushed ice and extracted with EtOAc (3×20 ml). The combined EtOAc extracts were washed successively with dil HCl (3×20 ml) and brine (3×20 ml), then dried ($MgSO_4$) and filtered. Removal of the solvent under reduced pressure gave a light yellow residue (0.1 g). Column chromatography on silica gel (eluent: CH_2Cl_2/EtOAc, 8:2) yielded **15a** (0.08 g, 80%) as colourless gum, which crystallised from benzene as a colourless crystalline solid, mp 152 °C; λ_{max} 1746 (γ-lactone), 1602 (arom.), 930 (OCH_2O) cm^{-1}; *m/z* (EI) 425 ($M+H^+$, 25%), 386 (10), 365 (100), 335 (10), 323 (15); δ_H (400 MHz, $CDCl_3$) 6.85 (1H, d, J=7.8 Hz, H-2′), 6.74–6.84 (1H, m, H-6′), 6.74–6.84 (1H, m, H-5′), 6.72 (1H, s, H-5), 6.53 (1H, s, H-8), 6.16 (1H, d, J=13.0 Hz, H-4), 6.04 (1H, s, OCH_2O), 6.02 (1H, s, OCH_2O), 4.56 (1H, t, J=9.0 Hz, H-10), 4.27 (1H, t, J=9.0 Hz, H-10), 3.91 (3H, s, ArOMe), 3.67 (3H, s, ArOMe), 3.45–3.56 (1H, m, H-3), 2.29 (3H, s, OAc); δ_C (100 MHz, $CDCl_3$) 170.3 ($OCOCH_3$), 167.0 (C-9), 150.9 (C-6), 148.6 (C-7), 148.2 (C-4′), 147.3 (C-3′), 147.1 (C-4a), 128.5 (C-8a), 128.1 (C-1′), 126.9 (C-2), 124.0 (C-6′), 117.4 (C-1), 112.0 (C-5), 107.9 (C-5′), 107.8 (C-8), 107.3 (C-2′), 101.2 (OCH_2O), 74.6 (C-4), 67.1 (C-10), 55.8 and 53.4 (OMe), 41.6 (C-3), 20.8 ($OCOCH_3$); Found: $[M+H]^+$425.1235, $C_{23}H_{21}O_8$ requires 425.1236.

4.1.9. Reaction of 6 with benzyloxyamine hydrochloride: isolation of 17. To a solution of **6** (0.2 g, 0.48 mmol) in ethanol (20 ml) was added benzyloxyamine hydrochloride (0.077 g, 0.48 mmol) and Na_2CO_3 (50 mg) and the mixture was heated under reflux for 4 h. The reaction mixture was poured into cold water and extracted with EtOAc (3×20 ml). The combined extracts were washed with brine (3×20 ml), then dried ($MgSO_4$) and filtered. Removal of the solvent under reduced pressure gave a light brown residue (0.2 g). Column chromatography on silica gel yielded a gum, which crystallised from DMF and water to give **17** as a coloured crystalline solid, (0.16 g, 80%), mp 264 °C; λ_{max} 280, 275, 266 nm; ν_{max} ($CHCl_3$) 3446 (OH), 1742 (C=N–O and –CO–OH), 1610 (arom.) and 935 (OCH_2O) cm^{-1}; *m/z* (EI), 501 (M^+, 10%), 484 (15), 425 (90), 409 (80); δ_H (400 MHz, $CDCl_3$) 11.40 (1H, 3, CO_2H), 8.54 (1H, s, H-10), 7.68 (1H, s, H-5), 7.36–7.48 (5H, m, OCH_2Ph), 6.87 (1H, dd, J=1.5, 7.9 Hz, H-6′), 6.84 (1H, s, H-8), 6.82 (1H, d, J=7.9 Hz, H-5′), 6.81 (1H, d, J=1.5 Hz, H-2′), 6.06 (1H, d, J=1.4 Hz, OCH_2O), 6.03 (1H, d, J=1.4 Hz, OCH_2O), 5.20 (2H, s, OCH_2Ph), 4.06 (3H, s, ArOMe), 3.79 (3H, s, ArOMe), 3.74 (1H, s, OH); δ_C (100 MHz, $CDCl_3$) 170.5 (C-9), 153.7 (C-6), 151.3 (C-7), 150.6 (C-10), 149.9 (C-3′), 147.4 (C-4′), 147.1 (C-4), 136.5 (C-8a), 131.4 (C-1′), 136.8, 129.8, 128.8, and 128.6 (OCH_2Ph), 129.7 (C-4a), 127.9 (C-3), 123.9 (C-2), 123.9 (C-6′), 120.3 (C-1), 110.9 (C-5), 108.2 (C-8), 105.7 (C-5′), 102.0 (C-2′), 101.1 (OCH_2O), 77.3 (OCH_2Ph), 56.0 and 55.7 (OMe); Found: $[M+H]^+$502.1496, $C_{28}H_{23}NO_8$ requires 502.1496.

4.1.10. Reaction of 17 with diazomethane: isolation of benzyloxime ester 18. To a solution of benzyloxime **17** (0.1 g, 0.20 mmol) in ether was added an ethereal solution of diazomethane at −10 °C. The reaction mixture was left overnight. After evaporation of the solvent a light yellow residue (0.1 g) was obtained. Column chromatography on silica gel G (eluent: hexane/EtOAc, 4:1) yielded **18** as a gum (0.05 g, 50%) which was crystallised from methanol as colourless plates, mp 165 °C; λ_{max} 280, 275, 245 nm; ν_{max} ($CHCl_3$) 3428 (chelated OH), 1720, 1670 (C=O), 1615 (arom.) and 925 (OCH_2O) cm^{-1}; *m/z* (CI) 516 ($M+H^+$, 100%), 439 (25), 410 (25), 269 (10), 210 (15), 152 (20); δ_H (400 MHz, $CDCl_3$) 11.18 (1H, s, CO_2H), 8.30 (1H, s, H-10), 7.61 (1H, s, H-5), 7.25–7.40 (5H, m, OCH_2Ph), 6.83 (1H, dd, J=1.2, 6.9 Hz, H-6′), 6.78 (1H, s, H-8), 6.74 (1H, d, J=6.9 Hz, H-5′), 6.71 (1H, d, J=1.2 Hz, H-2′), 6.04 (1H, s, OCH_2O), 6.02 (1H, s, OCH_2O), 5.14 (2H, s, OCH_2Ph), 4.03 (3H, s, ArOMe), 3.77 (3H, s, ArOMe), 3.55 (3H, s, CO_2Me);

δ_C (100 MHz, $CDCl_3$) 168.8 (C-9), 153.8 (C-6), 151.4 (C-7), 150.4 (C-10), 149.9 (C-4′), 149.2 (C-3′), 147.0 (C-4), 141.4 (C-2), 136.5 (C-8a), 129.6 (C-1′), 129.5 (C-4a), 128.5, 128.5, and 128.3 (OCH_2Ph), 127.9 (C-3), 123.8 (C-6′), 120.5 (C-1), 110.9 (C-5), 108.0 (C-8), 105.4 (C-5′), 102.1 (C-2′), 101.0 (OCH_2O), 76.7 (OCH_2Ph), 55.7 and 55.5 (OMe), 51.8 (CO_2Me); Found: $[M+H]^+$516.1661, $C_{29}H_{25}NO_8$ requires 516.1658.

4.1.11. Reaction of 6 with hydroxylamine hydrochloride: isolation of oxazinone 16. To a solution of **6** (0.1 g, 0.24 mmol) in ethanol (20 ml) was added hydroxylamine hydrochloride (0.034 g, 0.48 mmol) and Na_2CO_3 (50 mg) and the mixture was refluxed for 4 h. The reaction mixture was filtered and the solvent was removed under reduced pressure to leave a brown residue (60 mg). Column chromatography on silica gel-G yielded oxazinone **16** as a gum, which was crystallised from methanol to give a light yellow powder, (40 mg, 40%), mp 195 °C; λ_{max} ($CHCl_3$) 3467 (OH), 1708 (C=O), 1617 (arom.), 1645 (C=N) and 940 (OCH_2O) cm^{-1}; *m/z* (EI) 393 (M^+, 10%), 385 (5), 348 (10), 320 (15), 307 (20), 247 (70), 249 (35), 150 (37); δ_H (400 MHz, $CDCl_3$) 8.40 (1H, s, H-10), 7.65 (1H, s, H-5), 6.94 (1H, d, $J=7.9$ Hz, H-5′), 6.88 (1H, s, H-8), 6.86 (1H, d, $J=1.4$ Hz, H-2′), 6.83 (1H, dd, $J=1.4$, 7.9 Hz, H-6′), 6.08 (1H, d, $J=1.0$ Hz, OCH_2O), 6.05 (1H, d, $J=1.0$ Hz, OCH_2O), 3.94 (3H, s, ArOMe), 3.84 (3H, s, ArOMe); δ_C (100 MHz, $CDCl_3$) 169.6 (C-9), 153.7 (C-6), 152.4 (C-7), 151.0 (C-3′), 150.8 (C-10), 148.3 (C-4′), 148.0 (C-4), 132.3 (C-4a), 131.2 (C-8a), 130.2 (C-1′), 127.7 (C-3), 124.9 (C-2), 124.9 (C-6′), 120.6 (C-1), 111.8 (C-5), 108.7 (C-8), 106.4 (C-5′), 102.4 (C-2′), 102.1 (OCH_2O), 55.9 and 55.6 (OMe); Found: $[M+H]^+$394.0922, $C_{21}H_{15}NO_7$ requires 394.0921.

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