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Transformations of Lignans, Part IV.[1] Acid-catalysed Rearrangements of Gmelinol with BF_3-etherate and Study of a Product with a Unique Lignan Skeleton formed by Further Oxidation with DDQ

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Abstract: Reaction of gmelinol **1** with BF_3-etherate followed by treatment with various additives gave two isomeric products **2** and **5** formed by rearrangement of the 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octane skeleton. Compounds **2** and **5** on oxidation with DDQ in trifluoroacetic acid or benzene produced enantiomers **8** and **ent-8** respectively, which have a "distorted furofuran" skeleton. Compound **5** on reduction with triethylsilane and BF_3-etherate gave **13**, which is isomeric with di-*O*-methyl cycloolivil.

INTRODUCTION

The structural elucidation of natural products relies heavily on the use of physical methods such as NMR and mass spectrometry. As a result the chemical reactions of new natural products remain largely unexplored. In an effort to remedy this situation we have chosen to investigate the reactions of a series of lignans under oxidative and reductive conditions. In earlier papers[1a,1e,1f] we have shown that gmelinol **1** is converted by the action of triethylsilane and BF_3-etherate, or aluminium chloride, into the aryltetralin triol **16**, and by BF_3-etherate in *N,N*-dimethylaniline into the 2,4-bridged aryltetralin diol **2**, the stereochemistry of which was fully established, by rearrangement of the 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octane skeleton. We have also shown that gmelinol is converted into pyrone derivatives by the action of DDQ in benzene.[2]

We now report that BF_3-etherate in the presence of a variety of bases such as lithium aluminium hydride, $NaHCO_3$, triethylamine or sodium hydride converts **1** into the isomeric 2,4-bridged aryltetralin diols **2** and **5** in a 2:1 ratio. Furthermore, it has been observed that BF_3-etherate reacts readily with **1** in the presence of trifluoroacetic acid to produce **5** predominantly, while in the presence of *N,N*-dimethylaniline **2** is the major product.

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Compound **5** undergoes reduction by triethylsilane and BF_3-etherate to give a triol **13** which is isomeric with **11**[1f] and with di-*O*-methyl cycloolivil **18**. Compounds **2** and **5** on oxidation with DDQ in TFA or benzene produce enantiomers **8** and **ent-8** respectively, having a "distorted furofuran" skeleton, which is unprecedented in lignan chemistry. Treatment of either gmelinol **1** or neogmelinol **15** with DDQ under the same conditions did not yield **8** or **ent-8**. Compounds **8** and **ent-8**, and their derivatives **9** and **10**, and **ent-9** and **ent-10** respectively, are unusual in that they exhibit NMR spectra in which the aromatic protons and carbons associated with the pendant aryl ring can only be resolved at -60°C, indicating restricted rotation about the bond linking the aryl group to C-1. Compound **8** undergoes reduction with triethylsilane and BF_3-etherate to produce **2** and **11** in equal proportions.

RESULTS AND DISCUSSION

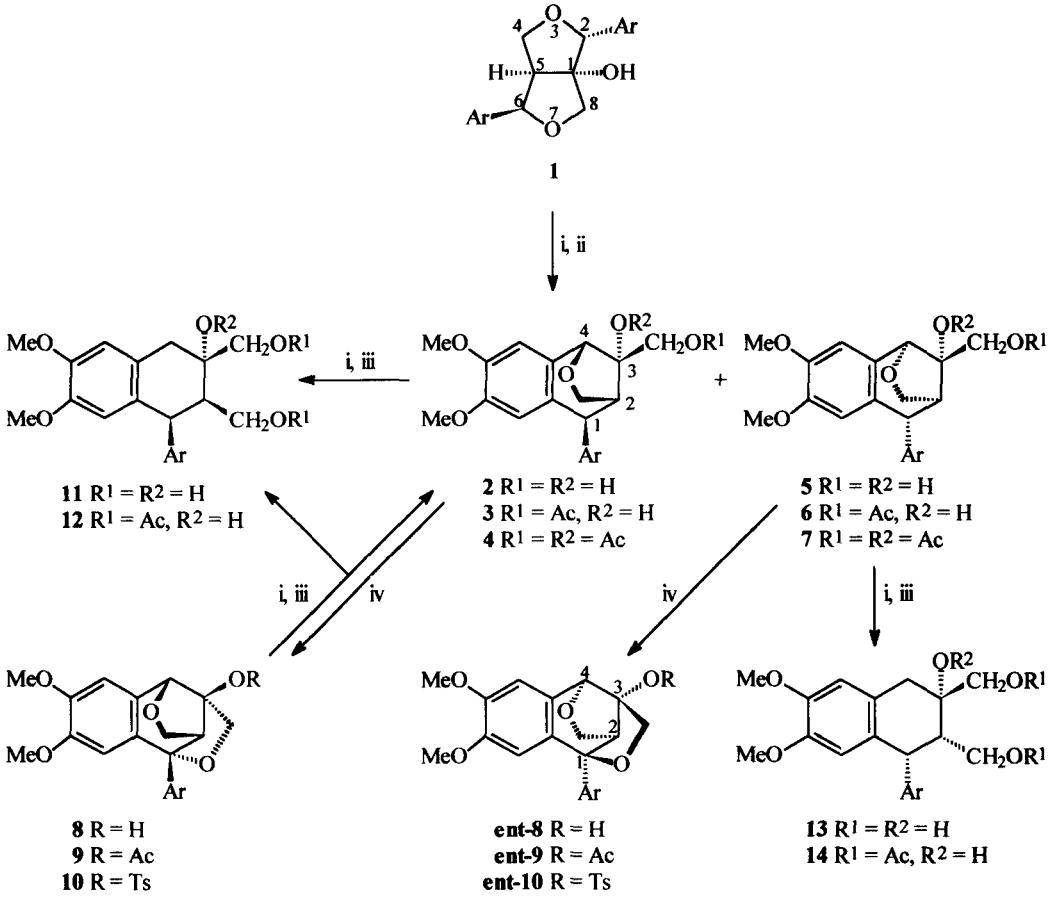
Treatment of **1** in dichloromethane with freshly distilled BF_3-etherate for 8 h followed by the addition of lithium aluminium hydride gave a mixture of two products in a 2:1 ratio (Scheme 1). The major product (60%) was identified as the 2,4-bridged aryltetralin diol **2** obtained earlier from gmelinol **1** by the action of BF_3-etherate and *N,N*-dimethylaniline.[1f] The minor product **5** (30%) was shown to be an isomer of **2** on the basis of its NMR and mass spectral data, and its structure was confirmed by X-ray analysis (see below). Reaction of gmelinol **1** with BF_3-etherate for 8 h, followed by treatment with $NaHCO_3$, triethylamine or sodium hydride, also produced **2** and **5** but in low yield. Later it was observed that when **1** was simply reacted with BF_3-etherate in TFA, **5** was obtained very readily as a major product (60%).

Compound **5** produced a monoacetate **6**, when refluxed with 50% aqueous acetic acid, and a diacetate **7** with acetic anhydride and pyridine. The mass spectra of **5**, **6** and **7** showed base peaks at *m/z* 402, 444 and 486 respectively, corresponding to their molecular ions, and a peak at *m/z* 269 corresponding to the rearranged ion **19** which is characteristic of the aryltetralin series.[3]

A one proton singlet at δ 4.53 in the ^1H NMR spectra of **5** and **6**, which moves downfield to δ 5.23 in **7** is assigned to H-4 which undergoes a direct field effect due to acetylation of the adjacent OH group. This, together with the ^{13}C NMR spectra, is consistent with the presence of a tertiary hydroxyl group at C-3. A one proton singlet which also occurs at δ 4.53 in **5** and **6** is assigned to H-1 and comes at δ 4.64 as a doublet (J=3.9) in **7**.

The presence of a primary hydroxyl group in **5** is indicated by the fact that the methylene protons, which appear as multiplets at δ 3.83 and 3.91, move downfield to give doublets at δ 4.22 and 4.36 (J=11.8) in **6**, and at δ 4.49 and 4.79 (J=12.7) in **7**. It was deduced that the third unacetylated oxygen must be present as an ether,

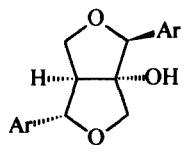
linking C-4 to the second CH_2 group attached to C-2. The remaining aliphatic proton, which occurs at δ 2.49, is assigned to H-2 and is coupled both to H-1 and to the ether-linked CH_2 group. It moves downfield to δ 2.89 in **6** and to δ 3.00 in **7**, which is consistent with its proximity to the tertiary hydroxyl at C-3.



Reagents : i, $BF_3.Et_2O$; ii, $LiAlH_4$; iii, Et_3SiH ; iv, DDQ in TFA or benzene

Scheme 1 (Ar = 3,4-dimethoxyphenyl)

In order to establish the configuration of the ether bridge linking C-2 and C-4, compound **5** was reduced by triethylsilane and BF_3-etherate to give triol **13**, which is isomeric with **11**[1f] and with di-*O*-methyl cycloolivil **18**. Indeed, comparison of the ^1H NMR spectra of **13** and cycloolivil **17**[4] (Table 5) clearly shows that while H-1 and H-2 are *trans* to one another in **17** (J=10.5), they are *cis* in **13** (J=5.1). This establishes structure **5** for the rearranged compound before hydrogenolysis.



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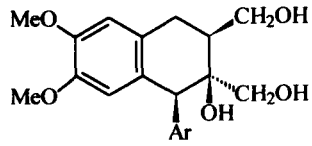

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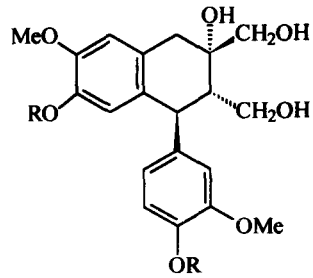
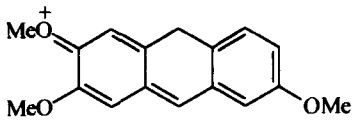


17 R = H
18 R = Me



19 *m/z* 269

The only significant differences in the ^{1}H NMR spectra of **2** and **5** are the presence of a doublet at δ 4.79 in **2**, which appears as a singlet at δ 4.53 in **5**, assigned to H-1, and a multiplet at δ 2.40 in **2**, which appears at δ 2.49 in **5**, assigned to H-2. These differences, coupled with the differences in the physical constants of **2** and **5** and their mono- and di-acetates, are considered to be due to the difference in stereochemistry of the ether bridge and C-1 in the two isomers, and this was confirmed by X-ray analysis of **5** (Figure 1). A possible mechanism for the formation of **5** from **1** is shown in Scheme 2. Thus, while the formation of **2** involves inversion of C-5 in gmelinol,[1f] the formation of **5** involves inversion at C-2.

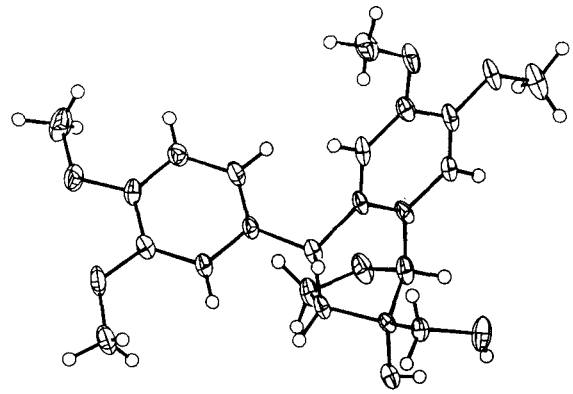
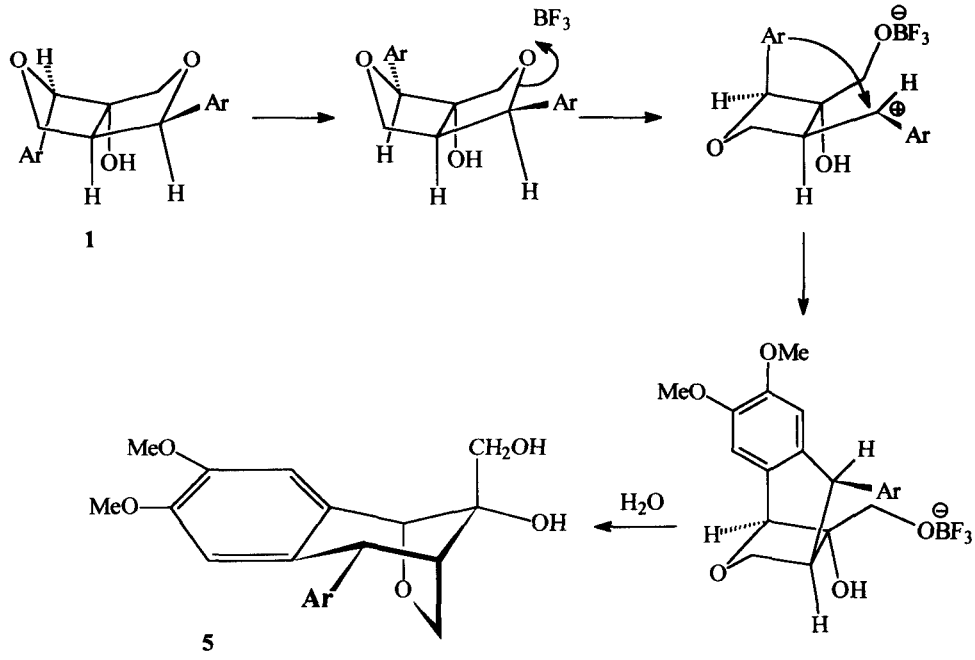


Figure 1. X-ray structure of 5

Treatment of **2** with DDQ in TFA or benzene for 3 h at room temperature produced a new compound **8**, whilst treatment of **5** with the same reagents gave the enantiomer **ent-8**. The mass spectra of **8** and **ent-8** showed a base peak at *m/z* 400 which is two mass units less than **2** and **5** indicating that dehydrogenation has



Scheme 2

and monotosylates **10** and **ent-10** with p-toluenesulfonyl chloride in pyridine,respectively. A one proton singlet at δ 4.81 in the ^{1}H NMR spectrum of **8** which moves downfield to δ 5.26 in **9** and 5.45 in **10** is assigned to H-4 which undergoes a direct field effect due to acetylation or tosylation of the adjacent OH group. This, together with the ^{13}C NMR spectra, is consistent with the presence of a tertiary hydroxyl group at C-3. The one proton doublet at δ 4.79 in **2**, and the singlet at δ 4.53 in **5**, which were assigned to H-1, are absent from the spectra of **8** and **ent-8**. This suggests that loss of H-1 is involved in the formation of **8** and **ent-8**. This observation is also supported by the fact that C-1, which comes at δ 46.8 in **2** and at δ 49.2 in **5**, is replaced by a quaternary signal at δ 90.0 in **8** and **ent-8**. Full interpretation of the ^{1}H and ^{13}C NMR spectra of **8** and **ent-8** and their derivatives **9** and **ent-9** and **10** and **ent-10** was hindered by the fact that the aromatic protons and carbons associated with the pendant aryl ring could only be resolved at -60°C indicating restricted rotation about the bond linking the aryl group to C-1.[5] Analysis of the NMR spectra of **8** and **ent-8** eventually led to the conclusion that a second ether bridge is present. In order to establish the configuration of the ether bridge linking C-3 and C-1, compound **8** was reduced with triethylsilane and BF_3-etherate which gave a mixture of **2** and **11**[1f] in equal proportions. This showed that no fundamental change in the carbon skeleton had occurred in the transformation of **2** into **8**. The structure of **8** was confirmed by X-ray crystallography (Figure 2).

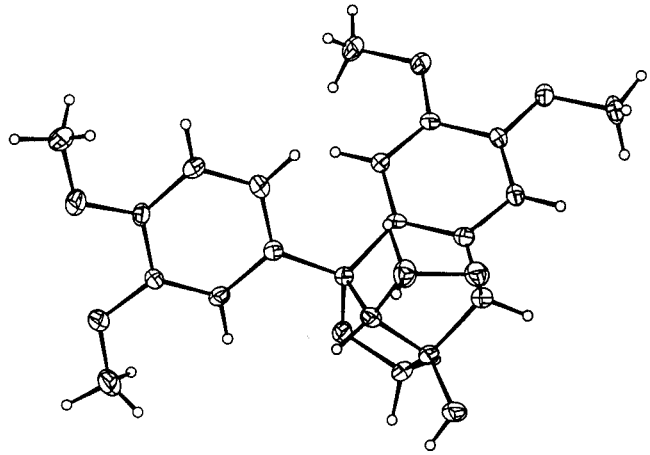
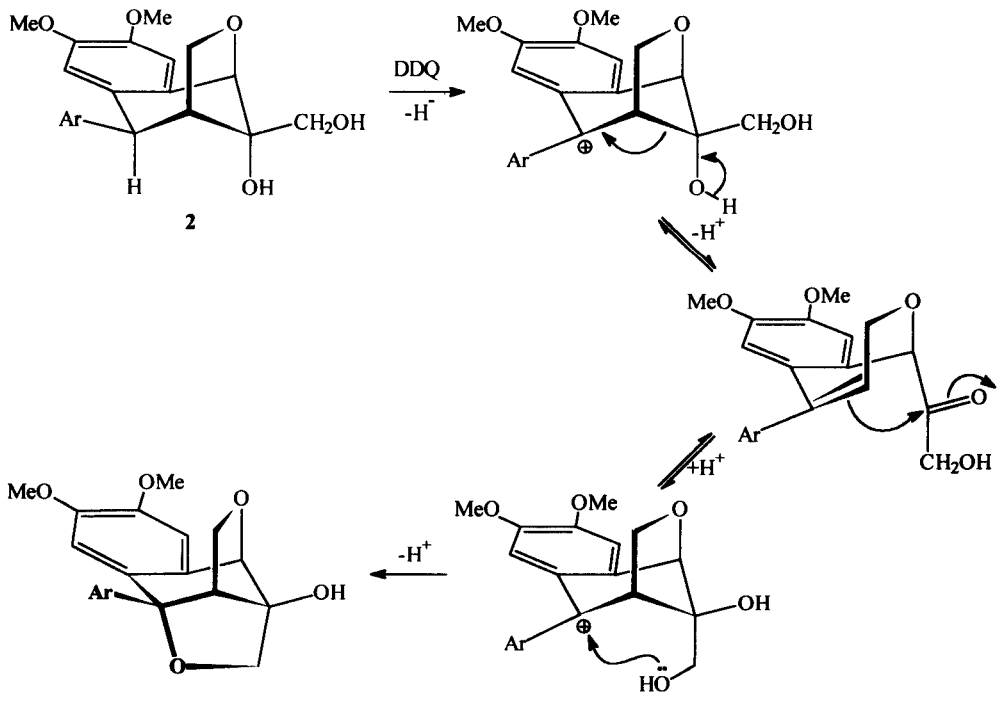


Figure 2. X-ray structure of 8

The formation of **ent-8** from **5** presumably involves hydride abstraction by DDQ from C-1. In contrast the formation of **8** from **2** implies that inversion of configuration must occur at the quaternary carbon (C-3), not only under acidic conditions (TFA), but also when the reaction is carried out in benzene. A possible mechanism to account for this is shown in Scheme 3. The fact that neither **1** nor **15** produce **8** or **ent-8**, even in trace



2 **8** **Scheme 3**

amounts, on treatment with DDQ in TFA or benzene, indicates that **2** and **5** are obligatory intermediates on the pathway leading to **8** and **ent-8** respectively.

In conclusion, the acid-catalysed rearrangement of gmelinol reveals that cleavage of the 3,7-dioxabicyclo[3.3.0]octane skeleton can be accompanied by epimerisation at C-5 or C-2 (leading to **2** and **5** respectively), and that DDQ oxidation of these diastereomeric products produces enantiomers **8** and **ent-8** which are novel compounds with a distorted furofuran skeleton.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded on Bruker AC400 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 quadropole 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 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 spectrometer. Dichloromethane was purified by passing it down an alumina column and 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. Optical rotation measurements were obtained using a Rudolph Autopol III instrument.

Crystal structure determinations

Crystals of **5** and **8** suitable for structure determination were mounted on glass fibres using the oil drop technique, ready for data collection at 150K. Data were collected on a FAST TV Area detector diffractometer following previously described procedures.[6] The structures were solved *via* heavy atom methods (SHELX-S)[7] and then refined by full matrix least-squares on all F_O^2 data (SHELX-93).[8] Non-hydrogen atoms were treated anisotropically, whilst hydrogen atoms were placed in idealised positions, (C-H = 0.96 Å, with U_{iso} tied to U_{eq} of the parent atoms). Full details of the data collection, structure refinement, atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre and allocated deposition numbers 12790 and 12791 respectively.

Preparation of 2 and 5

To a solution of gmelinol **1** (0.5 g, 1.24 mmol) in dry CH_2Cl_2 (20 ml) cooled to 0°C, was added freshly distilled BF_3-etherate (1 ml, 7.98 mmol), and the solution was stirred for 8 h at 0°C. Lithium aluminium hydride

Table - 1 : ^{1}H NMR spectra of 2-7

	2	3	4	5	6	7
H-1	4.79 d (3.6)	4.81 d (3.8)	4.64 d (3.4)	4.53 s	4.52 s	4.64 d (3.9)
H-2	2.40 m	2.40 m	2.88 m	2.49 m	2.89 m	3.00 m
H-4	4.51 br.s	4.51 br.s	5.11 br.s	4.53 s	4.52 s	5.23 s
H-5	6.69 s	6.69 s	6.61 s	6.61 s	6.60 s	6.61 s
H-8	6.76 s	6.77 s	6.72 s	6.72 s	6.71 s	6.74 s
H-2'	6.73 d (1.8)	6.74 d (1.9)	6.72 d (1.7)	6.81 d (8.1)	6.66 d (1.6)	6.69 d (1.8)
H-5'	6.83 d (8.2)	6.85 d (8.3)	6.85 d (8.3)	6.71 m	6.85 d (8.3)	6.85 d (8.3)
H-6'	6.77 m	6.79 dd (1.9,8.3)	7.78 dd (1.7,8.3)	6.72 s	6.73 dd (1.6,8.3)	6.76 dd (1.8,8.3)
CH_2	3.82 m	4.42 d (11.7)	4.58 d (12.4)	3.83 m	4.22 d (11.8)	4.49 d (12.7)
	3.91 m	4.48 d (11.7)	4.78 d (12.4)	3.91 m	4.36 d (11.8)	4.79 d (12.7)
CH_2	3.67 m	3.92 m	3.67 m	3.40 m	3.92 m	3.90 m
	3.96 br.d (1			3.98 m		
OMe	3.72 s	3.73 s	3.71 s	3.70 s	3.71 s	3.71 s
OMe	3.82 s	3.82 s	3.83 s	3.80 s	3.81 s	3.81 s
OMe	3.88 s	3.89 s	3.90 s	3.88 s	3.89 s	3.89 s
OMe	3.90 s	3.92 s	3.91 s	3.88 s	3.91 s	3.91 s
OH	2.65 s	2.64 s	--	2.58 m	2.61 d (3.1)	--
OAc	--	2.20 s	1.82 s, 2.16 s	--	2.16 s	2.11 s, 2.14 s

Table - 2 : ^{13}C NMR spectra of 2-7

	2	3	4	5	6	7
C-6	147.7	148.0 x 2	147.7	147.8	148.0	148.0
C-7	148.0	148.9 x 2	147.9	147.9	148.2	148.1
C-3'	148.9	--	148.9	148.8	149.0	148.9
C-4'	149.1	--	--	149.1	149.4	149.4
C-4a	129.4	128.9	128.8	127.6	127.2	127.4
C-8a	129.5	129.4	128.9	130.9	130.7	130.4
C-1'	135.2	135.0	134.8	134.9	134.7	134.3
C-6'	121.7	121.8	121.9	121.6	121.7	121.9
C-5	111.2	111.2	111.2	110.9	110.9	111.0
C-8	112.1	112.0	111.6	111.0	111.2	111.1
C-2'	112.7	112.5	111.9	112.4	112.6	112.3
C-5'	112.7	112.7	112.8	112.6	112.6	112.6
C-1	46.8	46.7	46.8	49.2	49.7	48.4
C-2	45.7	46.1	44.9	48.9	49.1	47.6
C-3	79.3	78.5	77.1	81.7	79.9	87.9
C-4	77.7	78.1	84.0	81.6	81.9	79.1
CH_2	65.4	66.4	62.9	62.7	65.3	61.1
CH_2	66.4	67.6	64.8	66.8	66.7	66.7
OMe	55.9	55.9	55.5	55.8	55.9	55.9
	56.0	56.0	55.9	55.9	56.0	55.9
	56.0	56.0	56.0	56.0	56.0	56.0
			56.0			
OAc	--	21.0	20.88, 21.0	--	20.9	20.8, 22.0
		171.9	169.8, 170.7		171.1	170.5, 176.6

Table 3 : ^{1}H NMR spectra of 8-10

	8	9	10
H-2	2.92 d (6.2)	3.08 d (6.2)	3.19 d (6.2)
H-4	4.81 s	5.26 s	5.45 s
H-5	6.49 s	6.51 s	6.50 s
H-8	6.85 s	6.86 s	6.86 s
H-2' ⎫ H-5' ⎬ H-6' ⎭	6.90 br	6.90 br	6.90 br
2-CH_2	3.72 d (9.4)	4.05 d (10.4)	3.95 d (10.3)
	4.10 d (9.4)	4.12 d (10.4)	4.56 d (10.3)
3-CH_2	3.72 d (10.0)	3.78 d (9.8)	3.72 d (10.0)
	4.10 dd (6.2, 10.6)	4.09 dd (6.2, 9.8)	3.99 dd (6.2, 10.0)
OMe	3.67 s	3.67 s	3.67 s
	3.92 s	3.92 s	3.92 s
	3.95 s	3.93 s	3.93 s
	3.95 s	3.93 s	3.93 s
OH	2.34	--	--
OAc	--	2.16 s	--
OTs	--	--	7.37 d (8.1)
			7.88 d (8.1)
			2.47 s

(0.5 g, 13.15 mmol) was added and the mixture stirred for 2 h at 0°C. Ethyl acetate (10 ml) was then added and the mixture stirred for ½ h before being poured onto ice-water and extracted with CH_2Cl_2 (3 x 30 ml). The combined organic extracts were washed successively with dil. HCl (3 x 20 ml) and brine (3 x 20 ml), then dried ($MgSO_4$) and filtered. After removal of the solvent under reduced pressure a dark brown residue was obtained. Column chromatography (eluent EtOAc-CH_2Cl_2 3:7) of the residue gave a major product (0.34 g) and a minor product (0.24 g). When the major product was recrystallised from methanol, **2** separated out as colourless flakes, m.p. 178-9°C (lit. 179°C)[1f] (0.3 g, 60%). $[\alpha]_D^{25}$ –17.18 (c 0.22, $CHCl_3$). *m/z* (EI) 402 (M^+, 100%), 384 (10), 341 (22), 325 (32), 315 (29), 269 (10), 205 (20), 177 (60) and 151 (40). *m/z* (CI) 420 ($M+NH_4^+$, 100%), 403 ($M+H^+$, 20) and 390 (17). Found : M^+ 402.1679. $C_{22}H_{26}O_7$ requires 402.1679. ν_{max} (KBr) 3400 (OH), 2936 (CH), 1608, 1515, 1465 cm^{-1}. When the minor product was recrystallised from methanol, **5** separated out as colourless crystals, m.p. 148°C (0.15 g, 30%). $[\alpha]_D^{25}$ +16.68 (c 0.46, $CHCl_3$). *m/z* (CI) 402 (5%), 341 (5), 269 (10), 205(10), 149 (100). Found : M^+ 402.1679. $C_{22}H_{26}O_7$ requires 402.1679. ν_{max} (KBr) 3570 (OH), 2934 (CH), 1617, 1450 cm^{-1}. For ^{1}H and ^{13}C NMR spectra see Tables 1 and 2.

Reaction of gmelinol 1 with BF_3-etherate and $NaHCO_3$, Et_3N or sodium hydride:

To a solution of gmelinol **1** (0.5 g, 1.24 mmol) in dry CH_2Cl_2 (20 ml) was added BF_3-etherate (1 ml, 7.98

Table 4 : ^{13}C NMR spectra of 8-10

	8	9	10
C-6	147.8	147.9	148.0
C-7	148.4	148.9	148.6
C-3'	148.8	149.0	149.1
C-4'	149.2	149.2	149.5
C-4a	126.5	127.1	126.4
C-8	127.9	129.3	126.8
C-1'	132.4	131.9	131.3
C-6'	117.9	118.2	118.3
C-5	110.0	110.0	110.0
C-8	110.0	110.1	110.2
C-2'	109.2	109.3	109.2
C-5'	108.1	107.9	107.9
C-1	90.0	93.0	98.7
C-2	60.6	58.7	59.7
C-3	88.9	88.5	88.6
C-4	85.0	82.4	82.8
CH_2	63.3	63.2	63.1
CH_2	67.3	67.6	67.1
OMe	56.0	56.2	55.9
	56.0	56.1	56.0
	56.1	56.0	56.1
	56.2	56.0	56.2
OAc	--	21.5	--
		171.6	
OTs	--	--	133.7, 130.2, 127.6
			145.8, 22.2

mmol) and the solution stirred for 8 h at 0°C. Then $NaHCO_3$ (1 g) or Et_3N (1 ml) or sodium hydride (1 g, free from paraffin wax) was added and the solution stirred for 2 h. The reaction mixture was poured onto ice-water and worked up as described above. After removal of the solvent under reduced pressure a dark brown residue (0.40 g) was obtained which on column chromatography (eluent EtOAc-CH_2Cl_2 3:7) gave **2** and **5** in low yields (10 and 5% respectively using $NaHCO_3$ and Et_3N, and 20 and 10% using NaH).

Reaction of gmelinol 1 with BF_3-etherate in TFA :

To a solution of gmelinol **1** (0.5 g, 1.24 mmol) in TFA (5 ml) was added BF_3-etherate (0.5 ml) and the solution stirred for approx. 5 min. The reaction mixture was then poured onto crushed-ice and extracted with dichloromethane (3 x 20 ml). The combined dichloromethane extracts were washed successively with aq. $NaHCO_3$ (3 x 20 ml) and brine (3 x 20 ml), then dried ($MgSO_4$) and filtered. After removal of the solvent under reduced pressure, a brown residue (0.48 g) was obtained. Column chromatography (eluent : EtOAc-CH_2Cl_2 3:7)

Table 5 : ^{1}H NMR spectra of aryltetralins

	11	12	13	14	17[4]
H-1	4.67 d (5.7)	4.75 d (5.6)	4.31d (5.1)	4.31d (5.7)	4.01d (10.5)
H-2	2.23 m	2.42 m	2.17 m	2.40 m	1.90-2.12 m
H-4a	2.63 d (17.5)	2.76 d (17.1)	2.81 d (16.9)	2.82 d (16.8)	2.60 d (16.7)
H-4b	2.97 d (17.5)	3.00 d (17.1)	2.95 d (16.5)	2.92 d (16.8)	3.21 d (16.7)
H-5	6.56 s	6.58 s	6.57 s	6.59 s	6.20 s
H-8	6.59 s	6.61 s	6.59 s	6.74 s	6.61 s
H-2'	6.80 d (1.7)	6.76 d (1.8)	6.79 d (3.0)	6.68 d (1.9)	6.68 d (1.9)
H-5'	6.84 d (8.1)	6.86 d (8.3)	6.81d (8.2)	6.80 d (8.0)	6.75 d (7.8)
H-6'	6.78 s	6.81 dd (1.8, 8.3)	6.72 dd (2.7,8.1)	6.76 dd (2.4,8.3)	6.66 dd (1.9,7.8)
2-CH_2	3.36 m	3.83 m	3.35 m	4.36 dd (3.9,11.75)	3.46 dd (2.5,12.0)
				4.27 t (4.8)	3.77 dd (4.1,12.0)
3-CH_2	3.60 m	4.07 dd (4.8, 12.1)	3.68 dd	4.15 dd (6.4,11.6)	3.54 d (11.3)
		4.27 s	(5.4,11.8)	3.80 m	3.76 d (11.3)
OMe	3.64 s	3.65 s	3.63 s	3.65 s	
	3.80 s	3.82 s	3.81 s	3.77 s	3.76 s
	3.84 s	3.87 s	3.87 s	3.88 s	3.79 s
	3.88 s	3.90 s	3.89 s	3.88 s	
OH	3.00 s	1.79 s	3.10 s	1.69 br.s	
OAc	--	2.15 s	--	2.10 s	
				2.18 s	

of the residue gave **2** (0.05 g, 10%), **5** (0.30 g, 60%), and starting material (0.1 g).

Preparation of monoacetate 6 :

Compound **5** (0.1 g, 0.25 mmol) was dissolved in 50% aqueous acetic acid (10 ml) and heated at 100°C for 24 h. The mixture was cooled and water (20 ml) was added and the mixture was extracted with dichloromethane (3 x 10 ml). The combined dichloromethane extracts were washed successively with saturated aq.$NaHCO_3$ (3 x 10 ml) and brine (3 x 10 ml), then dried ($MgSO_4$) and filtered. After removal of the solvent under reduced pressure a pale brown residue (0.1 g) was obtained. Column chromatography (eluent CH_2Cl_2-EtOAc 4:1) of the residue yielded a colourless gum (0.08 g, 72%) which crystallised from methanol to give colourless crystals of the monoacetate **6**, m.p. 215°C *m/z* (CI) 462 ($M+NH_4^+$, 10%), 444 (35), 427 (85), 402 (20), 385 (55), 367 (40), 269 (10), 247 (100). For ^{1}H and ^{13}C NMR spectra see Tables 1 and 2. Found : M^+ 444.1785. $C_{24}H_{28}O_8$ requires 444.1784. Found : $M+NH_4^+$ 462.2127. $C_{24}H_{32}O_8N$ requires 462.2127. ν_{max} (KBr) 3490 (OH), 2937 (CH), 1740 (Ac), 1515 cm^{-1}.

Preparation of diacetate 7 :

Compound **5** (0.1 g, 0.25 mmol) was dissolved in dry pyridine (2 ml) and treated with acetic anhydride (2

Table 6 : ^{13}C NMR spectra of aryltetralins

	11	12	13	14	17[4]
C-6	147.1	147.3	147.6	147.6	149.2
C-7	147.7	147.8	148.0	147.8	147.6
C-3'	148.8	147.8	148.1	148.0	146.2
C-4'	--	148.7	148.9	148.7	145.5
C-4a	126.0	125.0	125.8	126.4	126.6
C-8 a	128.3	128.1	126.4	127.5	138.4
C-1'	134.9	134.1	133.6	134.5	133.7
C-6'	122.1	122.5	121.7	122.2	123.7
C-5	111.1	111.0	111.2	111.0	117.4
C-8	111.8	111.7	111.5	111.4	116.2
C-2'	112.1	112.2	112.3	112.6	114.3
C-5'	113.3	113.3	112.6	113.1	113.3
C-1	48.6	44.8	45.4	46.5	45.0
C-2	44.3	44.0	40.1	44.4	47.9
C-3	73.9	72.4	76.0	72.1	74.9
C-4	35.2	29.7	35.5	37.2	40.1
CH_2	60.9	62.5	62.3	62.3	69.5
CH_2	68.8	70.2	66.6	69.4	61.0
OMe	55.8	55.9	55.8	55.8	58.6
	55.9	56.0	55.9	55.9	56.6
	55.9		56.0		
OAc	--	20.7	--	20.5	
		170.6		170.6	
		20.9		20.8	
		171.1		171.2	

ml) and the mixture heated under reflux for 3 h. The reaction mixture was then poured onto crushed ice and extracted with dichloromethane (3 x 20 ml). The combined extracts were washed successively with dil. HCl (3 x 20 ml) and brine (3 x 20 ml), then dried ($MgSO_4$) and filtered. After removal of the solvent a pale brown gum (0.1 g) was obtained which was purified by column chromatography (eluent CH_2Cl_2-EtOAc 9:1) to give a pale amorphous powder (0.08 g, 66%). When a small portion of the powder was recrystallised from benzene, diacetate **7** separated out as colourless crystals, m.p. 169°C. *m/z* (EI) 486 (M^+, 20%), 396 (10), 366 (15), 337 (100) and 269 (8). *m/z* (CI) 504 ($M+NH_4^+$, 100%) and 487 ($M+H^+$, 38). For ^1H and ^{13}C NMR spectra see Tables 1 and 2. Found : $M+H^+$ 487.1968. $C_{26}H_{31}O_9$ requires 487.1968. ν_{max} (KBr) 3474 (OH), 2935 (CH), 1745 (Ac), 1515 cm^{-1}.

Preparation of di-*O*-methyl isocycloolivil 13 :

Compound **5** (0.2 g, 0.5 mmol) dissolved in dry CH_2Cl_2 was treated with freshly distilled BF_3-etherate

(0.23 g, 1.6 mmol) at 0°C and the solution stirred at room temperature for 1 h. Triethylsilane (0.5 ml) was then added and the solution left stirring at room temperature overnight. Aq.$NaHCO_3$ (10 ml) was then added and the mixture stirred for ½ h. The reaction mixture was then poured onto ice-water and extracted with chloroform (3 x 20 ml). The combined extracts were washed successively with aq.$NaHCO_3$ (3 x 10 ml) and brine (3 x 10 ml), then dried ($MgSO_4$) and filtered. After removal of the solvent under reduced pressure a pale brown residue (0.2 g) was obtained. Column chromatography (eluent : $CHCl_3$-EtOAc 9:1) of the residue yielded di-*O*-methyl isocycloolivil **13** as a colourless gum (0.15 g 75%). *m/z*(EI) 404(M^+, 60%), 387(20), 386(25), 369(50), 338(40), 337(55) and 325(100). For ^1H and ^{13}C NMR spectra see Tables 3 and 4. Found : M^+ 404.1801. $C_{22}H_{28}O_7$ requires 404.1835. ν_{max}(Nujol) 3400(OH), 2932(CH), 1608, 1512 cm^{-1}.

Preparation of di-*O*-methyl isocycloolivil diacetate 14 :

Compound **13** (0.1 g, 0.25 mmol) dissolved in dry pyridine was treated with acetic anhydride (2 ml) and the reaction mixture left standing at room temperature for 3 h. After completion of the reaction, the mixture was poured onto crushed ice and extracted with ethyl acetate (3 x 10 ml). The combined ethyl acetate extracts were washed successively with dil. HCl (3 x 10 ml) and brine (3x10 ml), then dried ($MgSO_4$) and filtered. After removal of the solvent under reduced pressure a pale brown residue (0.1 g) was obtained. Column chromatography (eluent CH_2Cl_2-EtOAc 9:1) yielded the diacetate **14** (0.08 g, 66%) as a colourless gum. *m/z*(EI) 488(M^+, 25%), 444(5), 410(20), 397(18), 350(50), 337(85), 319(100), 305(20), 269(70). For ^1H and ^{13}C NMR spectra see Tables 3 and 4. Found : M^+ 488.2015. $C_{26}H_{32}O_9$ requires 488.2046. ν_{max}(Nujol) 3500(OH), 2931(CH), 1740(Ac), 1515 cm^{-1}.

Oxidation of 2 with DDQ and isolation of 8 :

To a solution of compound **2** (0.5 g, 1.24 mmol) in TFA (10 ml) was added DDQ (0.5 g, 2.2 mmol) and the mixture was stirred at room temperature for 2 h. After completion of the reaction, the mixture was poured onto ice-water and extracted with dichloromethane (3 x 50 ml). The combined dichloromethane extracts were washed successively with aqueous sodium metabisulphite (3 x 30 ml), aq.$NaHCO_3$ (3 x 30 ml) and brine (3 x 30 ml), then dried ($MgSO_4$) and filtered. After removal of the solvent under reduced pressure a brown residue (0.48 g) was obtained. Column chromatography (eluent $CHCl_3$-EtOAc 95:5) of the residue gave a pale yellow gum (0.45 g, 90%). The gum was crystallised from chloroform-ether and then recrystallised from benzene-ether to give orange crystals of **8** (0.32 g, 64%) m.p. 148°C. $[\alpha]_D^{25}$ +1.54 (c 4.59, $CHCl_3$) *m/z*(CI) 400(M^+, 100%),

341(65), 328(10), 311(20), 203(10), 193(18), 165(30), 151(15). ν_{max}(KBr) 3500(OH), 2935(CH), 1628 and 1495 cm^{-1}. For ^{1}H and ^{13}C NMR spectra see Tables 3 & 4. Found : M^{+} 400.1522. $C_{22}H_{24}O_7$ requires 400.1522.

When **8** was crystallised from ethyl acetate-ether and then recrystallised from methanol, some yellow and orange coloured crystals separated out. When these crystals were separated by hand picking and then recrystallised separately from methanol, yellow crystals, m.p. 122°C and orange crystals, m.p. 122°C were obtained. The NMR spectra and X-ray structures of both sets of crystals were identical and contained one molecule of methanol per unit cell.

Oxidation of 5 with DDQ and isolation of ent-8 :

To a solution of **5** (0.2 g, 0.5 mmol) in TFA (5 ml), was added DDQ (0.15 g) and the reaction mixture was stirred at room temperature for 2 h. After completion of the reaction, the mixture was worked-up as described above. Column chromatography (eluent $CHCl_3$-EtOAc 95:5) of the residue yielded a pale yellow gum (0.18 g, 90%), which on crystallisation from benzene-ether and recrystallisation from ethyl acetate-ether yielded orange crystals of **ent-8**, m.p. 136°C, the NMR and mass spectra of which were identical with those of **8**. $[\alpha]_D^{25}$ –1.11 (c 2.7, $CHCl_3$). Recrystallisation from methanol gave a sample having m.p. 118°C.

Reaction of gmelinol 1 with DDQ in TFA :

To a solution of gmelinol **1** (0.1 g, 0.25 mmol) in TFA (2 ml) was added DDQ (0.1 g, 0.44 mmol) and the mixture stirred at room temperature for 3 h. Aq.$NaHCO_3$ (2 ml) was added and the solution stirred for 15 min, then poured onto ice-water and worked-up as described above to give a brown residue (0.1 g), which was identified as gmelinol by comparison with an authentic sample, and contained no trace of **8** or **ent-8**.

Reaction of neogmelinol 15 with DDQ in TFA :

To a solution of neogmelinol (0.1 g, 0.25 mmol) in TFA (2 ml) was added DDQ (0.1 g, 0.44 mmol) and the mixture stirred at room temperature for 3 h. Aq.$NaHCO_3$ (2 ml) was added and the mixture stirred for 15 min, then poured onto ice-water and worked-up as described above to give a brown residue (0.1 g), which was identified as neogmelinol by comparison with an authentic sample, and contained no trace of **8** or **ent-8**.

Preparation of acetate 9

Compound **8** (0.2 g, 0.5 mmol) dissolved in dry pyridine (4 ml) was treated with acetic anhydride (4 ml) and the mixture was refluxed for 3 h. The reaction mixture was poured onto crushed ice and extracted with ethyl

acetate (3 x 20 ml). The combined extracts were washed successively with dil. HCl (3 x 10 ml) and brine (3 x 10 ml), then dried ($MgSO_4$) and filtered. After removal of the solvent under reduced pressure a pale yellow residue (0.18 g) was obtained. Column chromatography (eluent CH_2Cl_2-EtOAc 95:5) of the residue followed by recrystallisation gave the acetate **9** as colourless crystals (0.16 g, 72%), m.p. 162°C. $[\alpha]_D^{25}$ +20.16 (c 2.38, $CHCl_3$) *m/z* (CI) 442 (M^+, 100%), 400 (10), 383 (55), 353 (10), 245 (10), 165 (20), 151(20). For ^1H and ^{13}C NMR spectra see Tables 5 and 6. Found : M^+ 442.1628. $C_{24}H_{26}O_8$ requires 442.1628. ν_{max} (Nujol) 2935 (CH), 1745 (Ac), 1608 and 1515 cm^{-1}.

Preparation of acetate ent-9

Treatment of **ent-8** with acetic anhydride and pyridine as described above gave **ent-9**, m.p. 163°C, the NMR and mass spectra of which were identical to those of **9**. $[\alpha]_D^{25}$ –9.80 (c 0.285, $CHCl_3$)

Preparation of tosylate 10 :

Compound **8** (0.2 g, 0.5 mmol) dissolved in dry pyridine (4 ml) was treated with p-toluenesulfonyl chloride (0.3 g) and the mixture refluxed for 3 h. After completion of the reaction, the mixture was poured onto crushed ice and extracted with $CHCl_3$ (3 x 20 ml). The combined chloroform extracts were washed successively with dil. HCl (3 x 10 ml) and brine (3 x 10 ml), then dried ($MgSO_4$) and filtered. After evaporation of the solvent under reduced pressure a pale brown residue (0.2 g) was obtained. Column chromatography (eluent CH_2Cl_2-EtOAc 9:1) of the residue yielded a pale brown residue (0.18 g, 65%). When a small portion of the residue was crystallised from benzene-ether and then recrystallised from acetone, colourless crystals of **10**, m.p. 220-222°C separated out. $[\alpha]_D^{25}$ +19.23 (c 1.30, $CHCl_3$). *m/z* (CI) 555 ($M+H^+$, 65%), 554 (30), 400 (10), 383 (80), 369 (5), 341 (25), 314 (30), 261 (20), 165 (70), 151 (50). For ^1H and ^{13}C NMR spectra data see Tables 5 and 6. Found : M^+ 554.1611. $C_{29}H_{30}SO_9$ requires 554.1611.

Preparation of tosylate ent-10

Treatment of **ent-8** with p-toluenesulfonyl chloride and pyridine as described above gave **ent-10**, m.p. 222-224°C, the NMR and mass spectra of which were identical to those of **10**. $[\alpha]_D^{25}$ –36.75 (c 1.60, $CHCl_3$).

Reduction of 8 with triethylsilane and BF_3-etherate :

To a solution of **8** (0.4 g, 1 mmol) in dry CH_2Cl_2 (20 ml), cooled to 0°C was added freshly distilled BF_3-etherate (0.5 ml) and the solution stirred for 1 h. Triethylsilane (0.5 ml) was added and the mixture left stirring

at room temperature overnight. Aq.$NaHCO_3$ (10 ml) was then added and the mixture stirred for ½ hr. The reaction mixture was poured onto crushed ice and extracted with ethyl acetate (3 x 30 ml). The combined ethyl acetate extracts were washed successively with aq.$NaHCO_3$ (3 x 20 ml) and brine (3 x 20 ml), then dried ($MgSO_4$) and filtered. After removal of the solvent under reduced pressure a pale brown residue (0.4 g) was obtained. Column chromatography (eluent CH_2Cl_2-EtOAc 9:1) yielded one fraction (0.18 g) which on crystallisation from methanol yielded compound **2** as a colourless powder (0.15 g, 37%), m.p. 178-9°C and another fraction (0.15 g, 37%), which on crystallisation from methanol yielded compound **11** as a powder (0.1 g, 25%) m.p. 148°C, which was identical with the compound previously reported.[1f]

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