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Rearrangements of the 2,6-Diaryl-3,7-Dioxabicyclo[3.3.0] Octane Skeleton, Part III.[1] Reaction of Gmelinol with BF_3-Etherate and N,N-Dimethylaniline

By Robert S. Ward and Andrew Pelter
Chemistry Department, University of Wales Swansea, Singleton Park, Swansea SA2 8PP, UK

and Revuru Venkateswarlu, Chakicherla Kamakshi and Ayalasomayajula Lakshmi,
Department of Organic Chemistry, Andhra University, Visakhapatnam 530003, India

Abstract: Reaction of gmelinol **1** with BF_3-etherate and N,N-dimethylaniline gave a product **9** formed by rearrangement of the 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octane skeleton. Compound **9** on reduction with BF_3-etherate and triethylsilane produced **15** which is epimeric with di-O-methyl cycloolivil **18**.

INTRODUCTION

We have previously shown that BF_3-etherate and triethylsilane convert gmelinol **1** and paulownin **2** into aryltetralins **5** and **6** respectively, and that eudesmin **3** and sesamin **4** give aryltetralins **7** and **8** respectively, by reductive rearrangement of the 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octane skeleton.[1-3] We have also shown that lignans **1-4** undergo similar rearrangements using aluminium chloride and triethylsilane.[4] We have now shown that BF_3-etherate and N,N-dimethylaniline convert gmelinol **1** into a 2,4-bridged 1-aryltetralindiol **9**, which undergoes reduction by triethylsilane and BF_3-etherate to give the triol **15**, which is isomeric with **5** and with di-O-methylcycloolivil **18**.

RESULTS AND DISCUSSION

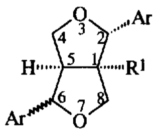
Treatment of gmelinol **1** in dichloromethane solution with freshly distilled BF_3-etherate for 1 hour followed by N,N-dimethylaniline for 14 hours gave a product, m.p. 179°C (64%), which was identified as the 2,4-bridged 1-aryltetralindiol **9**. Treatment of gmelinol **1** with BF_3-etherate alone under the same conditions gave no reaction, and on prolonged treatment for 3 hours gave a complex mixture which could not be separated.

The structure of **9** was established on the basis of its nmr and mass spectra and those of its derivatives and was confirmed by X-ray analysis (see below). The mass spectrum of **9** contained a base peak at *m/z* 402 corresponding to the molecular ion and a peak at *m/z* 269 corresponding to the rearranged ion **13** which is characteristic of the aryltetralin series.[5] Acetylation of **9** with acetic anhydride and pyridine gave a diacetate **10**, m.p. 175-6°C, which gave a molecular ion at *m/z* 486 and again showed the rearranged ion **13** at *m/z* 269. Compound **9** yielded a monoacetate **11**, m.p. 218°C, when refluxed with 50% aqueous acetic acid. Compound **11** gave a molecular ion at *m/z* 445 (M+1) as the base peak in its mass spectrum, and on further acetylation with acetic anhydride and pyridine yielded the diacetate **10** identical in all respects with the sample prepared by direct acetylation of **9**.

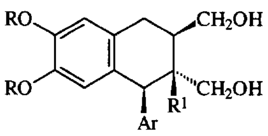
The ^1H nmr spectra of compounds **9-11** are listed in Table 1. A one-proton singlet at δ4.51 in the spectra of **9** and **11** which moves downfield to δ5.11 in **10** is assigned to H-4 and suggests that a tertiary hydroxyl group is present at C-3. A one-proton doublet (J=3.5) which occurs at δ4.79 in **9** and δ4.81 in **11** is assigned to H-1 and moves upfield to δ4.64 in **10** suggesting that this proton is on the same side of the ring as the tertiary hydroxyl group.

The presence of a primary hydroxyl in **9** is indicated by the fact that the CH_2 which appears as a multiplet at δ3.91 moves downfield and appears as a clear AB system in the spectra of **10** and **11**. The third unacetylated oxygen must be present as an ether attached to C-4 and to a second CH_2 group. The only remaining aliphatic proton (apart from the methoxyls) which occurs at δ2.39 is assigned to H-2 and is coupled both to H-1 and to the ether linked CH_2 group. It moves downfield to δ2.88 in the spectrum of the diacetate **10** which is consistent with its proximity to the tertiary OH at C-3.

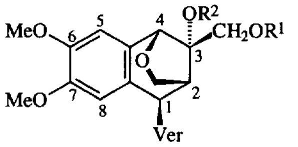
On the basis of the ^1H nmr data the gross structure **14** was established and this was consistent with the ^{13}C nmr spectra (Table 2). In addition compound **9** reacted with acetone in the presence of acid to give an isopropylidene derivative **12** m.p. 165°C, which confirmed the vicinal glycol system present.



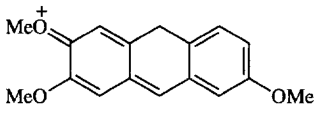
1 Ar = Ver, R^1 = OH
2 Ar = Pip, R^1 = OH
3 Ar = Ver, R^1 = H
4 Ar = Pip, R^1 = H



5 Ar = Ver, R = CH_3, R^1 = OH
6 Ar = Pip, R,R = CH_2, R^1 = OH
7 Ar = Ver, R = CH_3, R^1 = H
8 Ar = Pip, R,R = CH_2, R^1 = H



9 $R^1 = R^2$ = H
10 $R^1 = R^2 = COCH_3$
11 $R^1 = COCH_3$, R^2 = H
12 R^1,R^2 = CMe_2

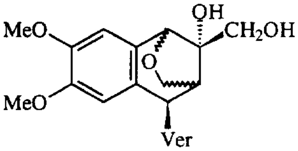


13 *m/z* 269

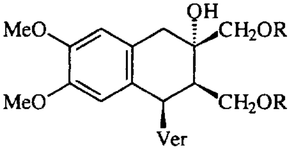
Ver = 3,4-dimethoxyphenyl
Pip = 3,4-methylenedioxyphenyl

In order to establish the configuration of the ether bridge linking C-2 and C-4 the compound was reduced using triethylsilane and BF_3-etherate to give the triol **15** which is isomeric with **5** and with di-O-methyl cycloolivil **18**. Indeed comparision of the ^{1}H nmr spectra of **15** and cycloolivil **17**[6] (Table 3) clearly showed that while H-1 and H-2 are *trans* to one another in **17** (J = 10.5) they are *cis* in **15** (J = 5.5). This establishes the structure **9** for the rearranged compound before hydrogenolysis and this was subsequently confirmed by X-ray crystallography of **10** (Figure 1).[7] The ^{13}C nmr spectra of **15-17** are listed in Table 4.

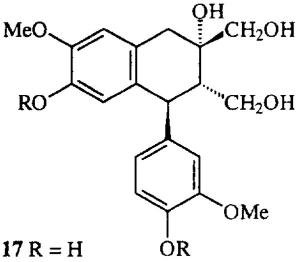
The structure of compound **9** is surprising in that its formation must involve inversion of configuration at C-5 of gmelinol (C-2 in **9**). A possible mechanism to explain the formation of **9** is shown in Scheme 1. The formation of a bridged structure such as **9** from a 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octane is unprecedented in lignan chemistry. The only compounds in the literature having similar structures are **19** and **20** which have been prepared from podophyllotoxin and picropodophyllin respectively by LAH reduction followed by treatment with acid.[9,10] Although the role of the N,N-dimethylaniline is not clear, the combination of $AlCl_3$ and N,N-dimethylaniline has been previously used for the deprotection of benzyl and allyl ethers.[11]



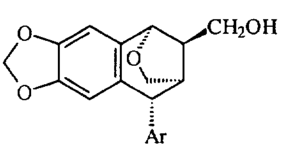
14



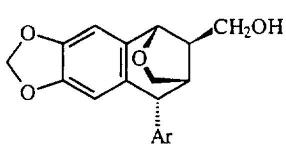
15 R = H
16 R = $COCH_3$



17 R = H
18 R = Me



19



20

(Ar = 3,4,5-trimethoxyphenyl)

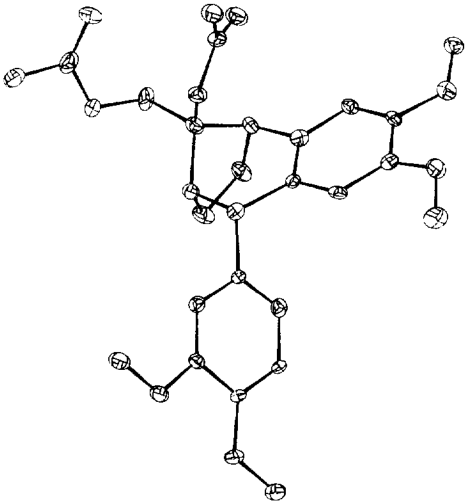
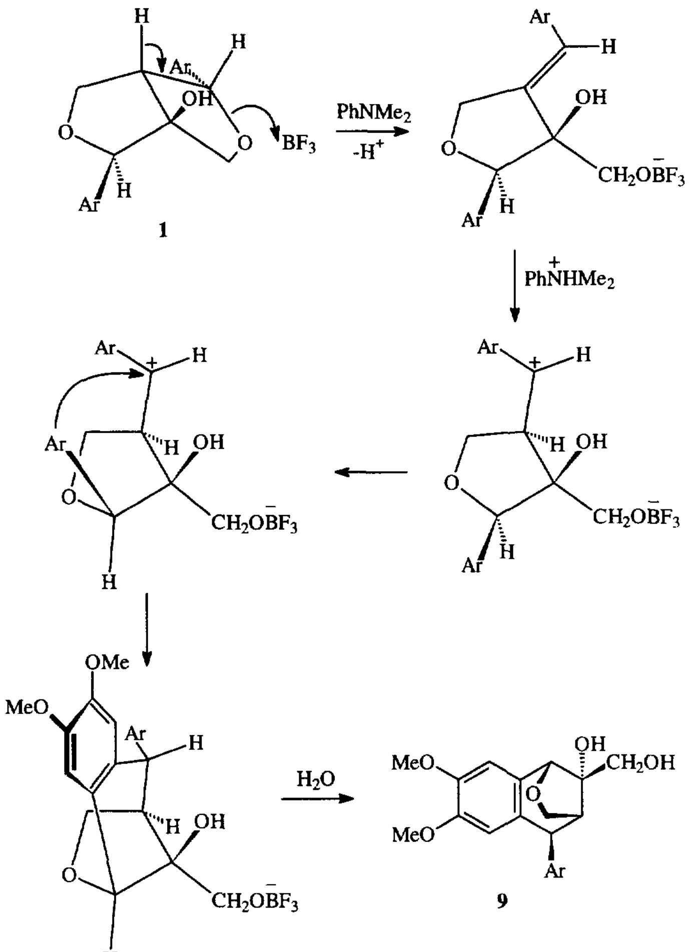


Figure 1



Scheme 1

(Ar =3,4-dimethoxyphenyl)

EXPERIMENTAL

^1H and ^{13}C nmr spectra were recorded on a Bruker AC400 instrument at 400 and 100 MHz respectively. Mass spectra were recorded on a VG 12-253 low resolution quadrupole instrument and on a double focusing VG ZAB-E high resolution instrument. Infrared spectra were recorded on a Perkin Elmer Fourier transform 1725X spectrometer. Dichloromethane was purified by passing down an alumina column and distillation over calcium hydride. Silica gel G was used for tlc. Melting points are uncorrected.

Table 1: ^{1}H nmr spectra#

	9	**10**	**11**	**12**
arom	6.69 - 6.84 m [5H]	6.61 - 6.85 m [5H]	6.68 - 6.85 m [5H]	6.65 - 6.85 m [5H]
H-1	4.79 br.d (3.4)	4.64 d (3.4)	4.81 d (3.8)	4.81 d (3.6)
H-4	4.51 br.s	5.11 br.s	4.51 s	4.34 s
H-2	2.39 m	2.88 m	2.40 m	2.37 m
CH_2OR^1	3.91 m [3H]	(4.78 d (12.4)	4.48 d (11.7)	4.22 d (8.7)
		(4.58 d (12.4)	4.42 d (11.7)	4.00 d (8.7)
CH_2O	3.66 dd (5.5, 9.6)	3.67 m [2H]	3.92 m [2H]	3.63 m [2H]
OH	2.73 br.s [2H]	---	2.64 s [1H]	---
	3.89 s	3.91 s	3.92 s	3.91 s
OMe	3.88 s	3.90 s	3.89 s	3.89 s
	3.81 s	3.83 s	3.82 s	3.81 s
	3.71 s	3.71 s	3.73 s	3.71 s
OAc	---	2.16 s	2.20 s	---
	---	1.82 s	---	---
CMe_2	---	---	---	1.52 s
	---	---	---	1.37 s

#All spectra are in $CDCl_3$ unless otherwise indicated.

Reaction of gmelinol **1** *with BF_3-etherate and N,N-dimethylaniline:*

To a solution of gmelinol **1** (0.5 g, 1.24 mmoles) in dry CH_2Cl_2 (20 ml) cooled to 0°C was added freshly distilled BF_3-etherate (0.7 ml, 6.6 mmoles) and the solution stirred for 1 h. Then freshly distilled N,N-dimethylaniline (0.5 ml 6.5 mmoles) was added and the mixture left stirring at room temperature overnight. After a period of 14 h, tlc of the reaction mixture showed predominantly one spot. Sodium bicarbonate solution (10 ml) was added and the mixture stirred for 1/2 h. 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 sodium bicarbonate solution (3 x 20 ml), and brine (3 x 20 ml)

Table 2: ^{13}C nmr spectra#

	9	**10**	**11**	**12**
C-6	149.12	148.91 (x 2)	148.93 (x 2)	148.87
C-7	148.90	147.91	148.01 (x 2)	147.76
C-3'	147.96	147.65		147.67
C-4'	147.75			
C-4a	135.19	134.76	135.03	135.48
C-8a	129.53	128.93	129.36	130.52
C-1'	129.46	128.77	128.92	129.20
C-6'	121.69	121.93	121.78	121.74
C-2'	112.73	112.80	112.73	112.61
C-5'	112.67	111.94	112.53	112.38
C-5	112.12	111.60	111.97	111.35
C-8	111.18	111.17	111.17	111.16
C-3	79.27	83.96	78.48	85.45
C-4	77.72	77.12	78.07	78.71
CH$_2$O	66.44	64.80	67.64	73.07
	65.44	62.89	66.43	66.27
OMe	55.99	56.01	56.02	55.98
	55.95	55.96	55.99	55.90
	55.90	55.89	55.91	
		55.54		
C-1	46.85	46.83	46.71	47.82
C-2	45.74	44.86	46.07	47.65
OAc	---	170.72	171.86	---
	---	169.78		---
	---	21.04	20.97	---
	---	20.88		---
Me$_2$C	---	---		110.08
	---	---		26.65
	---	---		26.54

#All spectra are in CDCl$_3$ unless otherwise indicated. All assignments are supported by DEPT spectra.

Table 3: ^{1}H nmr spectra#

	15	**16**	**17**^{7} **(CH_3OD)**
H-1	4.67 d (5.5)	4.75 d (5.6)	4.01 d (10.5)
H-2/3	2.24 m	2.42 m	1.90 - 2.12 m
H-4	2.64 d (17.2)	2.76 d (17.1)	2.60 d (16.7)
	2.97 d (17.2)	3.00 d (17.1)	3.21 d (16.7)
CH_2	3.37 dd (7.1, 11.6)	4.27 s	3.46 dd (2.5, 12.0)
	3.59 dd (7.0, 11.0)		3.77 dd (4.1, 12.0)
CH_2	3.81 m	3.78 - 3.88 m	3.54 d (11.3)
		4.07 dd (4.8, 12.1)	3.76 d (11.3)
H-5	6.56 s	6.58 s	6.20 s
H-8	6.59 s	6.61 s	6.61 s
H-2'		6.75 d (1.8)	6.68 d (1.9)
H-5'	6.78 - 6.85 m	6.86 d (8.3)	6.75 d (7.8)
H-6'		6.81 dd (1.8, 8.3)	6.66 dd (1.9, 7.8)
OMe	3.64 s	3.65 s	3.76 s
	3.80 s	3.82 s	3.79 s
	3.85 s	3.87 s	
	3.88 s	3.90 s	
OAc	---	1.79 s	
	---	2.15 s	

#All spectra are in $CDCl_3$ unless otherwise indicated.

and dried ($MgSO_4$). After removal of the solvent a pale yellow residue (0.48g) was obtained. When this residue was crystallised from methanol, compound **9** separated out as colourless flakes, m.p. 179° (0.32 g 64%). *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). For ^{1}H and ^{13}C nmr spectra see Tables 1 and 2. Found: M^+ 402.1679. $C_{22}H_{26}O_7$ requires 402.1679. ν_{max} (KBr) 3401 (OH), 2936 (CH), 1608, 1515, 1465cm^{-1}.

Reaction of gmelinol **1** *with BF_3-etherate:*

To a solution of gmelinol **1** (0.44 g, 1.1 mmoles) in dry CH_2Cl_2 (15 ml) cooled to 0° was added BF_3-etherate (0.2 g 1.2 mmoles) and the mixture stirred at 0° for 1 h. and at room temperature overnight. After a period of 14 h. sodium bicarbonate solution (10 ml) was added and the reaction mixture worked up as described

Table 4: ^{13}C nmr spectra#

	15	**16**	**17**[8] **(CH$_3$OD)**
C-6	148.8	148.7	149.2
C-7	147.7	147.8	147.6
C-3’	147.1	147.8	146.2
C-4’		147.3	145.5
C-1’	134.9	134.1	133.7
C-8a	128.3	128.1	138.4
C-4a	126.0	125.0	126.6
C-6’	122.1	122.5	123.7
C-5	113.3	113.3	117.4
C-8	112.1	112.2	116.2
C-2’	111.8	111.7	114.3
C-5’	111.1	111.0	113.3
C-1	48.6	44.8	45.0
C-2	73.9	72.4	74.9
C-3	44.3	44.0	47.9
C-4	29.7	29.7	40.1
CH$_2$O	68.8	70.2	69.5
CH$_2$O	60.9	62.5	61.0
	55.9	55.9	56.6
OMe	55.9	55.9	56.6
	55.8		
	53.4		
OAc		171.1	
		170.6	
		20.9	
		20.7	

#All spectra are in CDCl$_3$ unless otherwise indicated. All assignments are supported by DEPT spectra.

above to give a brown residue (0.43 g). It was identified as the starting material by comparison with authentic gmelinol **1**.

Preparation of diacetate **10***:*

Compound **9** (0.4 g) dissolved in dry pyridine (8 ml) was treated with acetic anhydride (8 ml) and the mixture left standing at room temperature overnight. 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 20 ml) and brine (3 x 20 ml) and dried ($MgSO_4$). After removal of the organic solvent a pale brown gum (0.4 g) was obtained. The crude residue was purified by column chromatography (eluent, CH_2Cl_2-EtOAc 9:1) to give a colourless residue (0.3 g). When a small portion was crystallised from methanol, colourless crystals of diacetate **10**, separated out, m.p. 175-6°. *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^+ 486.1890. $C_{26}H_{30}O_9$ requires 486.1890. ν_{max} (KBr) 3474 (OH), 2935 (CH), 1746 (Ac), 1515cm^{-1}.

Preparation of monoacetate **11***:*

Compound **9** (0.1 g) dissolved in 50% aqueous acetic acid (10 ml) was heated at 100° for 24 h. After cooling, water (20 ml) was added and the mixture extracted with chloroform (3 x 10 ml). The combined chloroform extracts were washed successively with saturated aqueous sodium bicarbonate solution (3 x 10 ml) and brine (3 x 10 ml) and dried ($MgSO_4$). After removal of the solvent 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 (80 mg), which was crystallised from ethanol to give colourless crystals of monoacetate **11** m.p. 218° *m/z* (CI) 462 ($M+NH_4^+$, 50%), 445 ($M+H^+$, 100), 402 (20), 385 (10) and 247 (10). For ^1H and ^{13}C nmr spectra see Tables 1 and 2. Found: $M+NH_4^+$ 462.2127. $C_{24}H_{32}O_8N$ requires 462.2127. ν_{max} (KBr) 3490 (OH), 2936 (CH), 1741 (Ac), 1515cm^{-1}.

Preparation of diacetate **10** *from monoacetate* **11***:*

Compound **11** (100 mg) dissolved in dry pyridine (2 ml) was treated with acetic anhydride (2 ml) and the mixture left standing at room temperature overnight. The reaction mixture was poured onto crushed ice and worked up as described for the preparation of **10**. The diacetate, m.p. 176°, so obtained was found to be identical with diacetate **10** in all aspects.

Preparation of isopropylidene derivative **12***:*

Compound **9** (100 mg) in freshly distilled acetone (10 ml) was treated with a few crystals of p-toluenesulphonic acid and left at room temperature overnight. The reaction mixture was made alkaline by addition of sodium methoxide solution and the acetone was removed under reduced pressure. The residue was treated with water (10 ml) and extracted with chloroform (3 x 10 ml). The combined chloroform extracts were washed with brine (3 x 10 ml) and dried ($MgSO_4$). After removal of the solvent a pale yellow residue was obtained. This was purified by column chromatography (eluent CH_2Cl_2 - EtOAc 4:1) to give isopropylidene derivative **12**, (80 mg) m.p 165° *m/z* (CI) 460 ($M+NH_4^+$, 10%), 443 ($M+H^+$, 100), 402 (10), 385 (25) 369 (20), 355 (20), 299 (10) and 225 (15). For ^1H and ^{13}C nmr spectra see Tables 1 and 2. Found: $M+H^+$ 443.2076 $C_{25}H_{31}O_7$ requires 443.2076. ν_{max} (KBr) 2936 (CH), 1608, 1515, 1465cm^{-1}.

Preparation of di-O-methyl epicycloolivil **15***:*

To a solution of **9** (200 mg, 0.5 mmoles) in dry CH_2Cl_2 (5 ml) was added freshly distilled BF_3 - etherate (0.23 g, 1.6 mmoles) and the solution stirred at room temperature for 1 h. Then triethylsilane (0.5 ml) was added and the solution left stirring at room temperature overnight. After a period of 14 h, sodium bicarbonate solution (10 ml) was added and the mixture stirred for 1/2 h, before being poured onto crushed ice and extracted with chloroform (3 x 20 ml). The combined chloroform extracts were washed successively with sodium bicarbonate solution (3 x 10 ml) and brine (3 x 10 ml) and dried ($MgSO_4$). After removal of the solvent a pale yellow residue (180 mg) was obtained. This residue was purified by column chromatography (eluent EtOAc - CH_2Cl_2 7:3) to give di-O-methyl epicycloolivil **15** as a colourless gum (110 mg 55%), *m/z* (EI) 404 (M^+, 60%), 387 (20), 386 (25), 369 (50), 338 (40), 337 (55) and 325 (100). *m/z* (CI) 404 (M^+, 25%), 387 (65) and 369 (100). For ^1H and ^{13}C nmr spectra see Tables 3 and 4. Found: M^+ 404.1835. $C_{22}H_{28}O_7$ requires 404.1835. ν_{max} (KBr) 3402 (OH), 2932 (CH), 1608, 1512cm^{-1}.

Preparation of di-O-methyl epicycloolivil diacetate **16***:*

Compound **15** (100 mg) dissolved in dry pyridine (2 ml) was treated with acetic anhydride (2 ml) and the solution left standing at room temperature overnight. The reaction 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 (3 x 10 ml) and dried ($MgSO_4$). After removal of organic solvent, a pale brown residue (100 mg) was obtained. This was purified by column chromatography (eluent CH_2Cl_2 - EtOAc 4:1) to give di-O-methyl epicycloolivil diacetate **16** (80 mg) as a colourless gum *m/z* (EI) 488 (M^+, 15%), 410 (25), 350 (45) 337 (100%), 319 (60), 305 (10) and 269 (10). *m/z* (CI) 506 ($M+NH_4^+$, 90%), 489 ($M+H^+$, 10), 471 (45) and 411 (100). For ^1H and ^{13}C nmr see Tables 3 and 4. Found: M^+ 488.2046. $C_{26}H_{32}O_9$ requires 488.2046. ν_{max} (KBr) 3500 (OH), 2931 (CH), 1740 (Ac), 1515cm^{-1}.

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