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REACTION OF GMELINOL WITH TRIETHYLSILANE AND BF_3-ETHERATE - REARRANGEMENT OF THE 2,6-DIARYL-3,7-DIOXABICYCLO[3.3.0]OCTANE SKELETON

By Andrew Pelter and Robert S. Ward,
(University College of Swansea, Singleton Park, Swansea, SA2 8PP, UK)
and
Reveru Venkateswarlu and C. Kamakshi,
(Andhra University Post-Graduate Centre, Nuzvid, 521 201, India).

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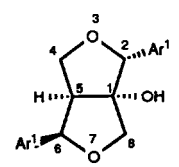
Summary. Reaction of gmelinol **1** with triethylsilane and BF_3-etherate gave two products, the major product **2** being an isomer of cycloolivil dimethyl ether, formed by reductive rearrangement of the 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octane skeleton. The minor product is a tetrahydrofuran **3** in which one of the aromatic rings has lost one of its methoxyl groups.

Treatment of gmelinol **1**[1] in dichloromethane solution with 1.5 equiv. BF_3-etherate followed by 4.5 equiv. triethylsilane gave two products along with recovered gmelinol. The major product (66%) was identified as the aryltetralin **2** and the minor product (3%) as the tetrahydrofuran **3**. Treatment of gmelinol with BF_3-etherate alone under the same conditions gave no reaction.

The gross structure of compound **2**, m.p. 165°, was established on the basis of its n.m.r. and mass spectra and this was confirmed by X-ray analysis, which also established the stereochemistry of C-1 relative to C-2. In the mass spectrum it gave a molecular ion at m/z 404 and a base peak at m/z 269 corresponding to the rearranged fragment ion **4** characteristic of such compounds.[2] Acetylation of **2** gave a diacetate **5**, m.p. 128°, which gave a molecular ion at m/z 488 and again had a base peak at m/z 269.



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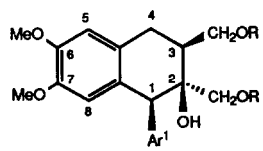
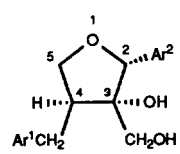


2 R = H
5 R = Ac



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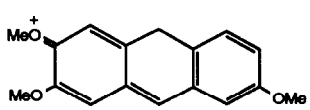
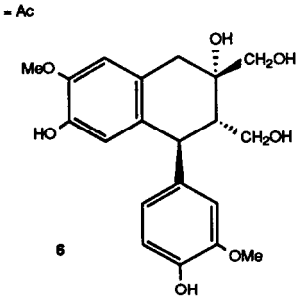
Ar^1 = 3,4-dimethoxyphenyl
Ar^2 = 3-methoxyphenyl



4 (m/z 269)



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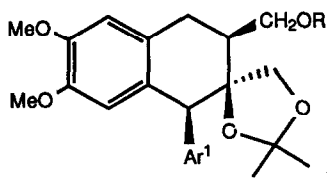
The 360 MHz ^{1}H n.m.r. spectra of **2** and its diacetate **5** are listed in Table 1 along with n.m.r. data for cycloolivil **6**.[3] H-1 appears as a singlet at δ4.22 in the spectra of both **2** and **5** indicating that C-2 is a quaternary centre and suggesting that the third (unacetylated) OH group is located at C-2. This is further confirmed by the observed coupling between H-3 and the adjacent CH_2 groups which can be removed by irradiating H-3 (see Table 1). The downfield shift of the signals due to the two CH_2OH groups on acetylation confirms that both of the primary alcohol groups have been acetylated, leaving only the tertiary OH group unreacted. The appearance of two of the aromatic protons as singlets is consistent with the location of the methoxy groups at C-6 and C-7. The ^{13}C n.m.r. spectra of **2** and **5** are recorded in Table 2.

Compound **2** reacted with acetone in the presence of p-toluene-sulphonic acid to give two isopropylidene derivatives which were assigned structures **7** and **8** on the basis of their ^{1}H and ^{13}C n.m.r. spectra (see Tables 1 and 2).

The main difference between the ^{1}H n.m.r. spectra of the two compounds was that in one of them one of the methyl groups of the isopropylidene unit was shifted upfield by 0.7 p.p.m. suggesting that this group is shielded by the adjacent aryl group. Inspection of molecular models showed that this would be expected for the five-membered ketal **7** in which one of the methyl groups lies alongside the aryl group at C-1 and therefore gave an indication that the oxygen atom at C-2 was *cis* to the aryl group at C-1. Furthermore, acetylation of this compound yielded a monoacetate **9** in which a *double doublet* could be clearly seen having been shifted downfield to 4.53 p.p.m., and confirming the presence of a $CH\underline{CH_2}OAc$ group. Interestingly, the other isopropylidene derivative did not form an acetate on treatment with acetic anhydride and pyridine, indicating that the OH group is much more crowded as would be expected in **8**.

There were also significant differences in the ^{13}C n.m.r. spectra of **7** and **8**. In particular, the chemical shifts of C-2, one CH_2, and the quaternary carbon of the isopropylidene group differ appreciably in the spectra of the two compounds, consistent with the different ring sizes of the heterocyclic ring.



7 R = H

9 R = Ac

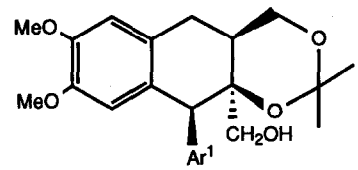


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Table 1. ^{1}H n.m.r. spectra*

	(2)	(5)	(6)[3] (in MeOD)	(7)	(8)	(9)
H-1	4.22 s	4.22 s	3.40-4.35 m	4.02 s	3.94 s	4.01 s
H-2	-	-	1.90-2.24 m	-	-	-
H-3	2.29 m	2.47 m	-	2.18 m	2.06 m	2.20 m
H-4	(2.61 dd (5, 16)^{o}	2.77 dd (5, 16)^{o}	2.60 d (17)	2.76 m	2.50 dd (4.7, 15.7)	2.85 dd (4.8, 16.2)
	(3.03 br.t (14.5)^{o}	3.04 br.t (14.3)^{o}	3.20 d (17)		2.75 t (14.3)	3.03 dd (11.1, 15.8)
2-CH_2	(3.40 d (11.5)$^{+}$	3.81 d (11.3)	)	)3.95 d (9.0)	3.20 d (12.0)	3.95 m
	(3.60 d (11.5)$^{+}$	3.96 d (11.3)	)3.4-4.35 m	)4.20 d (9.0)	3.7 m	4.16 d (9.0)
3-CH_2	(3.80 dd (2, 10.5)$^{o+}$	4.15 dd (6, 11.3)^{o}	)	)3.52 dd (6.0,11.6)	3.43 dd (3.5, 12.6)	3.95 m
	(3.95 dd (7.6, 10.6)$^{o+}$	4.39 dd (5.6, 11.3)^{o}	)	)3.86 m	3.8 m	4.53 dd (4,11)
	(2.87 br	-				
OH	(2.44 br	-		3.0 br	3.0 br	
	(2.01 s	1.79 s				
H-5	6.19 s	6.19 s	)	6.24 s	6.16 s	6.21 s
H-8	6.62 s	6.63 s	)	)	)	)
H-2'	6.73 d (2)	6.63 d (2)	)6.15-6.85 m	)6.60-6.80 m	)6.60-6.90 m	)6.6-6.8 m
H-5'	6.84 d (8)	6.83 d (8)	)	)	)	)
H-6'	6.77 dd (8, 2)	6.68 dd (8, 2)	)	)	)	)
	(3.89 s	3.88 s	3.73 s	3.60 s	3.54 s	3.57 s
OMe	(3.85 s	3.86 s	3.75 s	3.77 s	3.72 s	3.77 s
	(3.79 s	3.77 s		3.86 s	3.85 s	3.87 s
	(3.56 s	3.55 s		3.88 s	3.90 s	3.89 s
OAc	-	(2.05 s	-	-	-	2.08 s
		(2.10 s				
CMe_2	-	-	-	(0.77 s	1.33 s	0.61 s
				(1.47 s	1.35 s	1.42 s

*all spectra in $CDCl_3$ unless otherwise indicated. ^{o}reduced to doublet after irradiating H-3. $^{+}$sharpened after D_2O exchange.

Table 2. ^{13}C n.m.r. spectra*

	(2) (in DMSO)	(5)	(7)	(8)	(9)
C-1	50.32	51.58	52.47	52.46	52.44
C-2	73.06	71.57	83.32	71.32	81.96
C-3	39.90	38.62	45.42	45.38	43.21
C-4	28.52	28.79	29.72	27.79	29.96
CH_2	(62.93	65.24	64.82	62.56	66.06
CH_2	(61.50	65.03	71.69	67.05	70.37
C-5	(115.44	114.13	116.26	113.63	116.10
C-8	(114.21	113.46	113.72	113.19	113.53
C-2'	(111.44	111.26	110.95	111.04	110.61
C-5'	(110.62	110.77	110.37	109.66	110.04
C-6	(147.64	149.13	148.33 (x 2)	149.00	148.12 (x 2)
C-7	(147.28	148.60		148.18	
C-3'	(146.84	147.72	147.97	147.41	147.60
C-4'	(146.38	147.49	147.53	147.15	147.21
C-1'	133.91	131.96	133.70	133.03	133.32
C-8a	131.27	129.14	130.30	130.13	130.20
C-4a	128.88	127.74	128.32	127.64	128.04
C-6	124.00	123.47	124.92	124.15	124.98
OMe	(55.63	55.95		55.82	55.81
	(55.37	55.87		55.87	55.92
		(170.72			171.06
OAc	-	(170.15	-	-	21.06
		(20.88 (x 2)			
			(110.95	101.38	110.61
CMe_2	-	-	(27.05	25.09	27.00
			(26.55	24.49	26.14

*all spectra in $CDCl_3$ unless otherwise indicated.

The evidence presented above was adequate to establish the gross structure of the compound. It was further assumed on the basis of its formation from gmelinol that the two CH_2OH groups would almost certainly be *trans*. The only remaining uncertainty was therefore the relative configuration of the aryl group at C-1 and in order to settle this an X-ray analysis was carried out on the diacetate (Figure 1).[4] This clearly showed that the aryl group at C-1 was *cis* to the tertiary OH group, which would be consistent with a mechanism for the formation of **2** involving double inversion of configuration at C-2 of gmelinol (Scheme 1). It is interesting to note that cyclo-olivil dimethyl ether **12**, which is isomeric with **2**, can be prepared by acid catalysed cyclisation of one of the products **11** obtained by Na/NH_3 reduction of gmelinol (Scheme 2).[5,6]

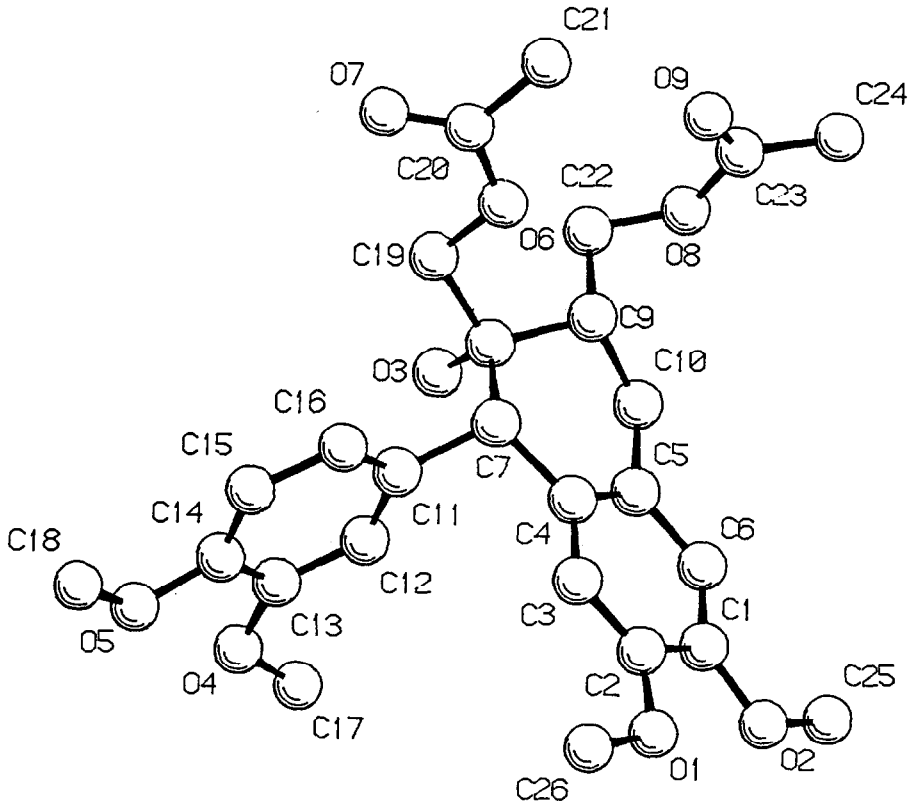
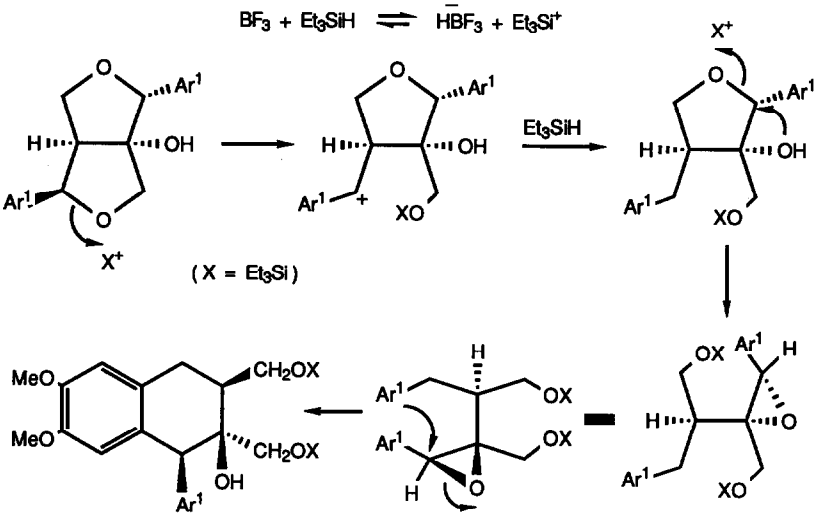
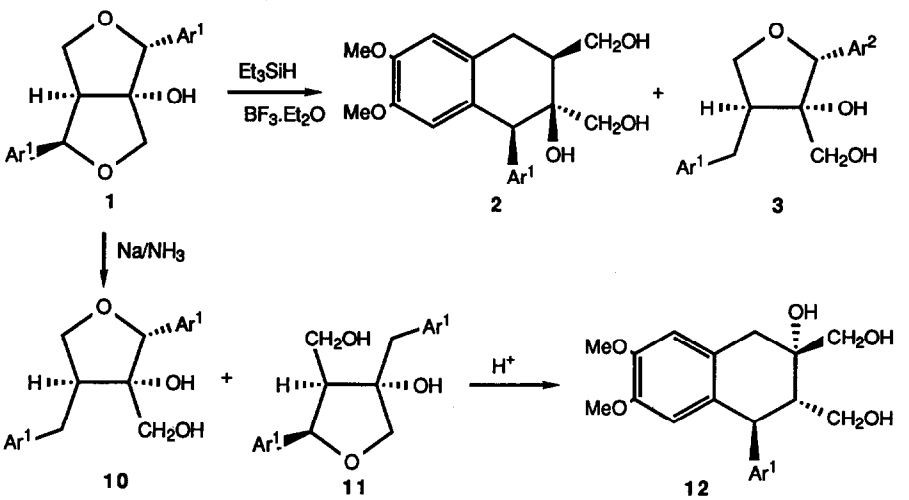


Figure 1. X-ray crystal structure of diacetate **5**.

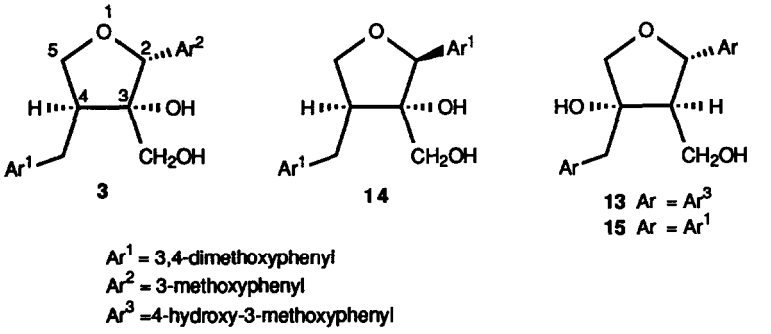


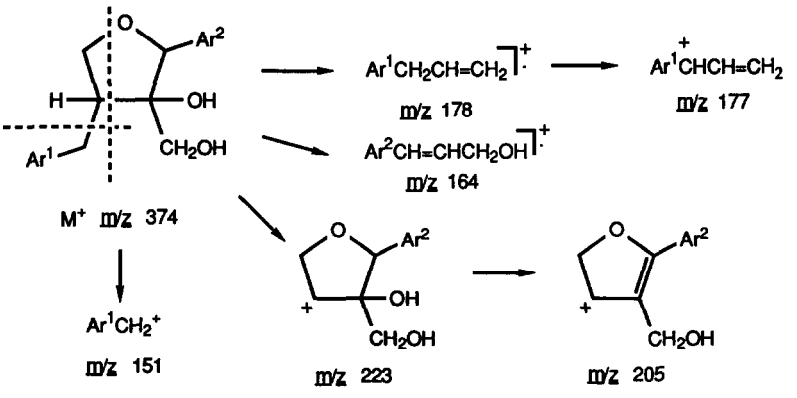
Scheme 1



Scheme 2

The structure of the minor product isolated from the reaction of gmelinol with triethylsilane and BF_3-etherate was readily established by analysis of its n.m.r. and mass spectra. The mass spectrum gave a series of ions at m/z 374, 223, 205, 178, 177, 164 and 151 (see Scheme 3) characteristic of compounds belonging to the tetrahydrofuran and furofuran series,[7,8] and suggesting that the basic gmelinol structure had been largely retained. The ^1H n.m.r. spectrum contained a singlet at δ4.95 due to H-2 and multiplets due to the CH_2O- and CH_2OH groups resembling very closely the spectrum of dihydroneogmelinol **14** and showing significant differences from that of dihydrogmelinol **11** and olivil dimethyl ether **15** (Table 3). Surprisingly, the spectrum only indicated the presence of three OMe groups and this was further supported by the ^{13}C n.m.r. spectrum (Table 4) which confirmed the presence of one 3,4-dimethoxyphenyl and one 3-methoxyphenyl group. On the basis of the mass spectral fragmentation pattern (see Scheme 3) these could be identified as Ar^1 and Ar^2 respectively in structure **3**. The ^{13}C n.m.r. data listed in Table 4 can be directly compared with those of gmelinol **1**[8] and olivil **13**.[9] Thus C-2 occurs at a similar position in all three spectra while the chemical shift of C-3 in **3** is very similar to that of C-4 in **13**, as would be expected since both carry a tertiary OH group. Similarly, C-5 in **3** has an almost identical chemical shift to C-4 in gmelinol **1**, confirming that the upper tetrahydrofuran ring has been retained.





Scheme 3

Table 3. ^{1}H n.m.r. spectra of tetrahydrofuran derivatives

	(3)	(14)	(15)	(11)
H-2	4.95 s	4.75 s	4.75 d (8)	5.56 d (6)
H-5	(3.6-4.0 m (4.22 dd (6,8)	3.83 t (8.5) 4.08 t (8.5)	3.70 d (9) 3.95 d (9)	3.56 d (6) 4.28 d (9)
H-3	-	-	2.5 m	2.3 m
H-4	2.5 m	2.8 m	-	-
CH_2OH	(3.6-4.0 m (3.1 br.d (10)	3.70 d (12) 3.48 br.d (12)	3.9 m	3.65 m 3.55 br.d
CH_2Ar	(2.5 m (3.6-4.0 m	2.43 dd (11,13) 2.98 dd (4,13)	2.96 d (14) 3.10 d (14)	3.03 d (13.7) 3.11 d (13.7)
OH	2.0 br.	3.1 br.	2.2 br.	2.0 br.
OMe	((3.85 s (3.91 s (x 2) (	3.87 s 3.88 s 3.89 s 3.90 s	3.87 s 3.88 s 3.89 s 3.90 s	3.90 s
arom.	6.7-7.0 m + 7.3 m	6.7-7.0 m	6.8-7.0 m	6.8-7.0 m

* all spectra run in $CDCl_3$

Table 4 ^{13}C n.m.r. spectra of (1), (3) and (13).*

	(1)[8]		(3)	(13)[9] (in DMSO)
C-2	87.80	C-2	84.18	83.1
C-1	91.80	C-3	82.56	60.4
C-5	60.15	C-4	49.97	80.4
C-4	71.80	C-5	71.43	76.1
C-8	74.81	CH_2OH	64.19	58.8
C-6	85.81	CH_2Ar	34.01	38.8
C-1'	127.83	C-1'	139.03	129.1
C-2'	109.88	C-2'	112.84	111.1
C-3'	148.97	C-3'	159.92	146.8
C-4'	149.48	C-4'	113.75	144.6
C-5'	111.22	C-5'	129.04	114.7
C-6'	119.05	C-6'	119.29	122.4
C-1"	133.16	C-1"	132.40	134.4
C-2"	110.08	C-2"	111.50	111.1
C-3"	149.35	C-3"	147.67	147.2
C-4"	149.55	C-4"	149.13	145.4
C-5"	111.54	C-5"	112.15	114.7
C-6"	119.05	C-6"	120.78	119.0
OMe	56.01	OMe	(55.26 (55.93 (x 2)	55.6

* all spectra run in $CDCl_3$ unless otherwise indicated.

Experimental

^{1}H and ^{13}C n.m.r. spectra were recorded on Varian HA-100 and XL-100 instruments with high field ^{1}H n.m.r. spectra being recorded on Bruker 250 and 360-MHz instruments. Mass spectra were recorded on a VG 12-253 quadrupole instrument and on a double focussing VG ZAB-E instrument. Dichloromethane was purified by passage through an alumina column and distillation over calcium hydride. Silica gel G was used for tlc. Melting points are uncorrected.

Reaction of gmelinol 1 with BF_3-etherate and triethylsilane: Isolation of compound 2.

To a solution of gmelinol **(1)** (1.5g, 3.73 mmoles) in dry CH_2Cl_2 (18 ml) cooled to 0^{o}, was added BF_3-etherate (0.85 g, 5.99 mmoles) and stirred for 1½h. Triethylsilane (3ml) was then added and the mixture left stirring at room temperature overnight. After a period of 14 h, tlc of the reaction mixture showed 8 close running spots. Sodium bicarbonate solution (10 ml) was added and the mixture stirred for 2h. The reaction mixture was poured onto crushed ice and extracted with ethyl acetate (3 x 30 ml). The organic layer was washed with sodium bicarbonate solution (3 x 20 ml), brine (3 x 20 ml) and dried ($MgSO_4$). After removal of the solvent, a pale yellow residue (1.38g) was obtained. When this residue was dissolved in chloroform and benzene added, compound **2** separated as a colourless solid. This was crystallised from THF and benzene to give an amorphous powder, m.p. 165^{o} (1g, 66%) m/z 404.1838 (34%, M^{+}) 386(10), 325(21), 287(28), 269(100), 235(15), 165(32) and 151(72). For ^{1}H and ^{13}C n.m.r. spectra see Tables 1 and 2.

Reaction of gmelinol 1 with BF_3-etherate :

To a solution of gmelinol **1** (0.45g, 1.12 mmoles) in dry CH_2Cl_2 (15 ml) cooled to 0^{o} was added BF_3-etherate (0.22g, 1.55 mmoles) and the solution stirred at 0^{o} for 1h and left stirring at room temperature overnight. After a period of 14h, sodium bicarbonate solution (10 ml) was added and the reaction worked up as described above to give a brown residue (0.43g). It was identified as the starting material by comparison with authentic gmelinol **1**.

Preparation of Compound 3

To a solution of gmelinol **1** (0,9g 2.24 mmoles) in dry CH_2Cl_2 (20 ml) cooled to 0^{o} was added BF_3-etherate (0.44g, 3.1 mmoles) and the solution stirred for 1 hr. Triethyl silane (2ml) was then added and the mixture left stirring at room temperature overnight. After a period of 14 hrs. and after work up as described above, a gum (0.85g) was obtained which resisted crystallisation from benzene, chloroform and methanol. Preparative chromatography of the residue over silicagel-G (eluent chloroform-methanol 95:5) yielded compound **(3)** (25 mg) as a gum, along with unreacted gmelinol **1** (250 mg) and compound **2** (350 mg). Data for compound **3** m/z 374.1728 (46%,M^{+}), 223.0970 (5), 205.0848 (24), 178.0980 (7), 177.0921 (19), 164.0839 (21), 152.0778 (22) and 151.0768 (100). For ^{1}H and ^{13}C n.m.r. spectra see Tables 3 and 4.

Preparation of Acetate 5.

Compound **2** (0.36g), dissolved in dry pyridine (6 ml), was treated with acetic anhydride (6 ml) at 0^{o} and the solution left standing at room temperature for ½h. The reaction mixture was poured onto crushed ice and extracted with chloroform (3 x 30 ml). The organic layer was washed with dilute HCl (3 x 20 ml), brine (3 x 20 ml) and dried ($MgSO_4$). After removal of the organic solvent a pale brown gum (0.38 g) was obtained. A small portion of the crude residue was purified by preparative tlc (eluent benzene-ethyl acetate 3:2) to give 50 mg of the acetate **5**. When the remaining portion of the crude acetate was left standing for a very long period, crystals of the acetate **5** separated out. The acetate was recrystallised from methanol to give colourless crystals, m.p. 120^{o}. m/z 488.2048 (52%,M^{+}), 470(8), 410(13), 368(13), 351(17), 300(13), 299(13), 287(20%), 269(100%), 165(20) and 151(30%). For ^{1}H and ^{13}C n.m.r. spectra see Tables 1 and 2.

Preparation of O-Isopropylidene derivatives 7 and 8.

Compound **2** (200 mg) in pure acetone (15 ml) was treated with a few crystals of p-toluenesulphonic acid and left at room temperature overnight. After a period of 14h, two new spots were observed on tlc (Rf 0.73 and 0.50, benzene-ethyl acetate 1:1), in addition to that of compound **2** (Rf 0.15). There was no further progress, even when the reaction was set aside for another 6 hrs. Therefore, 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 (20 ml) and extracted with chloroform (3 x 20 ml). After work up, a pale brown residue (190 mg) was obtained. The residue was separated by preparative chromatography over Silicagel-G. (Benzene-ethyl acetate 1:1) into O-isopropylidene derivative **7**, m/z 444.2139 (76%,M^{+}), 386(11), 355(12), 341(13), 337(13), 328(15), 300(31), 269(100), and 151(32); and O-isopropylidene derivative **8**, m/z 444.2139 (100% M^{+}), 428(13), 386(7), 355(15), 338(5), 299(26), 287(33), 269(55%), 151(30%). For ^{1}H and ^{13}C n.m.r. spectra see Tables 1 and 2.

Acetylation of O-isopropylidene derivative 7 : Isolation of acetate 9.

Isopropylidene derivative **7** (40 mg) in dry pyridine (1 ml) was treated with acetic anhydride (1 ml) at 0^{o} and allowed to stand at room temperature for 1 hr. The reaction mixture was poured onto crushed ice (20 ml) and extracted with chloroform (3 x 20 ml). The organic layer was washed with 1% HCl (3 x 10 ml), brine (3 x 10 ml) and dried ($MgSO_4$). After removal of the organic solvent a pale brown gum (40 mg) was obtained which was purified by preparative chromatography on silicagel-G, (CH_2Cl_2-ethyl acetate 9:1) to give the O-isopropylidene derivative acetate **9** (35 mg) m/z 486 (5%,M^{+}), 368(3), 300(9), 269(54), 151(26). For ^{1}H and ^{13}C n.m.r. spectra see Tables 1 and 2.

Attempted acetylation of O-isopropylidene derivative 8.

O-isopropylidene derivative **8**, (80mg) in dry pyridine (1.5 ml) was treated with acetic anhydride (1.5 ml) at 0^{o} and allowed to stand at room temperature for more than 14 hrs. Tlc showed no progress in the reaction even when it was heated for 1 h

over a water bath. After work up as described above a pale brown residue (70 mg) was obtained and was identified by tlc as the starting material.

Acknowledgement.

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