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HASHISH[1]

SYNTHESIS OF (+)-Δ^4-TETRAHYDROCANNABINOL

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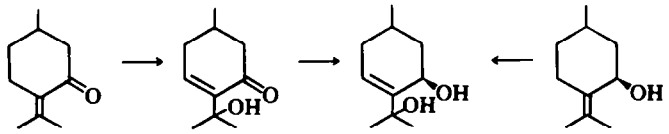
Abstract—Alkylation of olivetol with *p*-menth-4-en-3,8-diol (3) afforded Δ^4-tetrahydrocannabinol, an unknown isomer of the hashish active constituent Δ^1-THC, together with the "abnormal" isomer. The attack of olivetol onto the positions 3 and 5 and resp. 3 and 8 of (3) yielded derivatives of 2,6-methano-2H,1-benzoxocin-7-ol and new 2,3,4,4a-tetrahydroxanthenes.

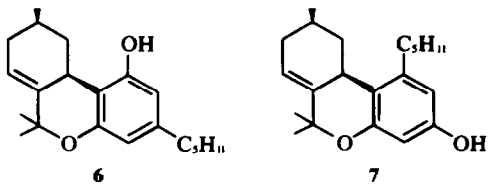
In a preceding paper[1] we have reported the synthesis of new cannabinoid derivatives by alkylation of resorcinols with *p*-menthen-3-ols in aqueous acid medium. Although the yields of the reaction were low, this method made possible for the first time the extensive use of the easily accessible *p*-menthen-3-ols as starting materials for the synthesis of hashish derivatives.[2] This paper concerns a new application of this general scheme, i.e. the synthesis of Δ^4-tetrahydrocannabinol (Δ^4-THC), the last unknown isomer among those of the active constituent Δ^1-THC with a double bond in a different position in the monoterpenoid moiety. All the other four isomers are synthetically accessible.[2a] For the synthesis of Δ^4-THC with the above said method, we needed *p*-mentha-4,8-dien-3-ol or an equivalent synthon. Recent work[3] has made *p*-menth-4-en-3,8-diol (3) readily available via photooxidation of pulegol (4) or of pulegone (1), followed by reduction.



1 2 3 4

The two allylic OH groups in (3) make this a convenient starting material as both the 3 and 8 positions are prone to yield a carbonium ion by protonation, and elimination of water. (Scheme 1) Thus (3) was reacted with olivetol in the presence of *p*-toluenesulfonic acid in benzene. There is no reason to use a particularly mild acidic medium, as acid-induced cyclization is required in this case.

The reaction gave a mixture of products (total yield 50%), from which, by careful chromatographic procedure, five compounds could be isolated and purified. Their structural assignment is based on spectroscopic data, especially on NMR analysis. The compounds (6) and (7), although rather different in polarity on TLC, exhibited very similar spectral features. Both are monohydroxy-derivatives, as they yield a monoacetate, and show a molecular peak at 314 *m/e* in the mass spectrum, consistent with the expected alkylation and dehydration. The presence of only one OH and of two singlet signals for the methyls at 1·2–1·5δ(Me_2–C–O) indicates that cyclization has occurred besides the attack on olivetol. The analysis of NMR spectra of (6) and (7) (Table 1) is consistent with the expected structure. The presence of only one olefinic proton, of a Me–CH Me group, and of a proton at *ca.* 3·6 δ (benzylic), rules out the other isomers with the double bond in a different position in the cyclohexene ring. Coupling constants are also in agreement with those expected on the basis of molecular models. The assignment of the respective formulae (6) and (7) is based on NMR and UV data. We have already observed[4] on a number of examples that it is possible to distinguish the so-called "normal" tricyclic cannabinoids (the natural ones) from the "abnormal" ones (isomers with the monoterpenoid unit attached to the position 4 of olivetol) on the basis of the specific solvent effect of benzene on the aromatic protons in NMR, and of the UV absorption maxima. The two aromatic protons of (6) are shifted apart going from CCl_4 (H_4, 6·11 and H_2, 5·94) to benzene (6·56 and 5·74) whereas for (7) they become closer (6·19 and 6·03 to 6·33 both). The UV absorption maxima of (6) (274 and 282 nm) are in the usual range for "normal" isomers, whereas they move to longer wavelength (282, 288) in (7). Moreover, the chemical shift of the H_{2eq} proton appears particularly indicative in this respect. It appears at lower field (3·05) in (6) than in (7) (2·01). This difference must be attributed to the effect of the proximity of the OH to the equatorial H_2, that does not happen in (7). This effect has been already observed in Δ^1-THC and in hexahydrocannabinol (HHC).[5]



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In order to confirm the structure of (6) and to establish its stereochemistry, this compound was hydrogenated and the reduced compound was compared with those (9 and 10) obtained by reduction of Δ^3-THC (8), prepared through a known procedure.[6] NMR spectrum of (10) shows a proton at 3·00 δ, as a 5-line signal of width 22·5 Hz, which must be attributed to the proton H_3. The analysis of the system (three Js of 11·5, 4·5 and 6·0) requires the proton to be axial, in order to have two ax-eq and one ax-ax couplings. The ring junction must thus be *cis*. In the isomer (9), the signal assignable to proton 3 has

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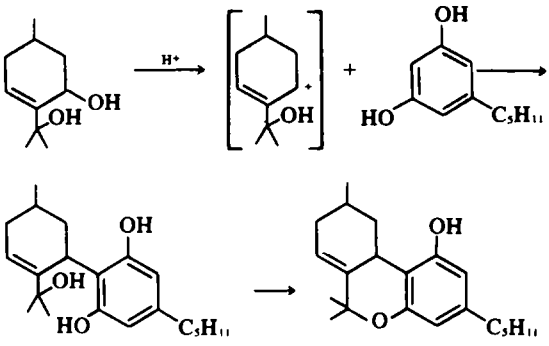
Table 1. NMR data (C_6D_6) for **6–10**

	δ_{2eq}	δ^{a}_{2ax}	δ_3(width)	$J_{H_3-H_{2eq}}$	$J_{H_3-H_{2ax}}$
6	3·05	1·0	3·72	4	10
7	2·1	0·8	3·54	3·5	11·5
9	3·4	1·1	3·27 (q)	3	5
10	~2·4	1·3	3·00 (22·5)	4·5 or 6·0	11·5
11			2·75 (22)		

[a]From decoupling experiments.

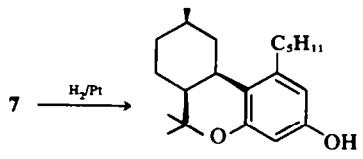
a width of *ca.* 9 Hz, suggesting an equatorial orientation of H_3 (three small couplings) on a *cis* ring junction.† Compounds (**9**) and (**10**) must thus differ for the relative orientation of the Me group on C-1. In each of the two compounds, the Me could be either axial or equatorial. Examination of Dreiding models shows clearly that in both compounds (1,3 *cis* or 1,3-*trans* arrangement) the most stable conformation is the one where the Me group is disposed equatorially. This observation allows us to assign 1,3-*cis* configuration (Me-eq, H_3-eq) to the isomer (**10**), and 1,3-*trans* (Me-eq, H_3-Ax) to the isomer (**9**). The chemical shift of the methyl group on C-1 of (**10**) in the ^{13}C NMR spectrum (22·4 ppm, $CDCl_3$) confirms its equatorial orientation.[7] Since reduction of (**6**) gave a compound identical with (**10**), the configuration of (**6**) is also established. This would also explain the fact that (**10**) is



Scheme 1.

obtained selectively with respect to *trans*-HHC, since hydrogenation takes place from the less hindered side, (opposite to the aromatic ring). Although the "abnormal" isomer of (**8**) was not available, the close similarity between the benzylic proton of (**11**) (width 22 Hz, 5 lines), obtained by similar reduction of (**7**), with H_3 of (**10**), prompts us to draw the same conclusion, i.e. that a 1,3-*cis* orientation must compete also to compound (**11**) and (**7**). Since (**6**) and (**7**) have been obtained from (+)-pulegone, the formulae (**6**), (**7**), (**9**) and (**10**) also represent the absolute configuration of these compounds.

†*Trans* ring junction must be ruled out also by comparison of the spectrum with that of the known *trans*-HHC.[5]



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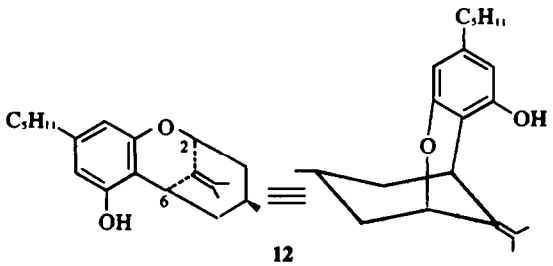
Another compound was isolated from the reaction mixture, to which the structure (**12**) could be attributed. A small amount of the isomer (**13**) was obtained as a mixture



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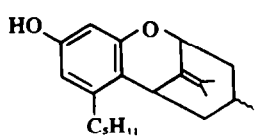

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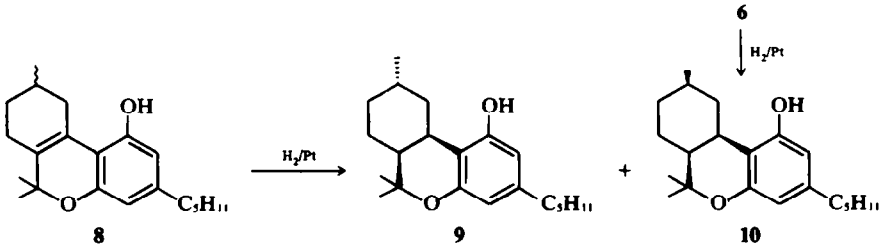
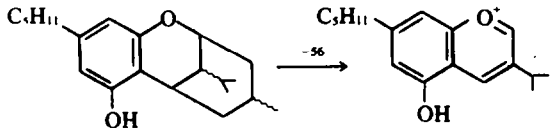
with (**7**), and could be identified in the NMR spectrum of the mixture. The structure of (**12**), which clearly comes from the attack of olivetol on the usual position 3 of the terpene (**3**) and by cyclization onto the allylic position 5, or *vice versa*, is consistent with the mass, UV and NMR spectra. Particularly, the NMR shows two singlets for the Me groups on a double bond (1·51 and 1·00) and two signals with small couplings (equatorial orientation) for H_6 (benzylic and allylic, 4·33) and H_2 (adjacent to C–O, 5·23). These data are unambiguously in favour of the structure (**12**). That (**12**) is the "normal" isomer, appears again from the NMR (aromatic protons shift by benzene) and UV



8 **9** **10**

spectra.[4] These data gave no clues for the assignment of the configuration of the methyl group in position 1. However, the chemical shift of this methyl in the ^{13}C NMR spectrum of (**12**) is consistent with an equatorial orientation (22 ppm, $CDCl_3$).[7] It follows that the aromatic and Me substituents have a 1,3-*trans* orientation on the monoterpene moiety. Hydrogenation of (**12**) yielded the corresponding dihydroderivative (**14**), in the NMR of which the Me groups (doublets, J = 6) the benzylic proton and H_2 (no more allylic) have shifted to higher field. The mass spectrum of (**14**) is consistent with the assigned structure, as it shows a new peak at 260 *m/e* besides the usual M, M-15, M-43, that corresponds to the loss of the ring C to give a stable benzopyrylium ion.



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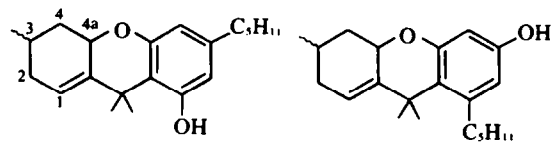
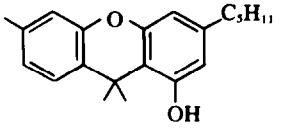
The last couple of compounds which were isolated as crystalline solids from the reaction mixture were the isomeric (**15**) and (**16**). These two compounds are very similar in their spectroscopic properties. Their mass spectra are not characteristic, and again the most significant structural hints come from NMR spectra. These show the methyls as singlets around 1·5–1·7 δ, whereas two protons appear at low field, both with small couplings, at 4·35 and 5·75 in (**15**) and 4·27 and 5·65 in (**16**). They must be attributed to CH–O–R and to a –CH= group.



15 16

These data rule out all of the possible isomers with tetrahydrocannabinol structure. Sulfur dehydrogenation of (**15**) gave (**17**), whose spectral properties, certainly different from those of cannabinol, are consistent with a xanthene backbone (UV spectrum[8]), so supporting, together with the other data, the structures of 2,3,4,4a-tetrahydroxanthene derivatives for (**15**) and (**16**).† Both (**15**) and (**16**) give a monoacetate and are reduced to dihydroderivatives with PtO_2 in methanol. Each of them gives a couple of dihydroderivatives. In the NMR spectra of these compounds the olefinic proton has disappeared and the H_{4a} hydrogen is now around 4·0 δ as a not-resolved signal (width *ca.* 9 Hz) for (**18**) and (**20**), or as a 6-line signal (width *ca.* 25 Hz) for (**19**) and (**21**). We



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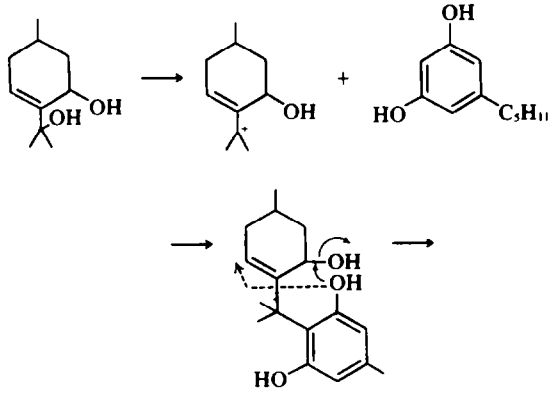
suppose that the compounds with the large H_{4a} signal (**19** and **21**) have a *trans* ring junction (two large and one small coupling for H_{4a}) and the others have a *cis* ring junction (H_{4a} equatorial with three small couplings). These results are in very good agreement with the conclusions reached by Moreau *et al.*[9] for unsubstituted hexahydroxanthenes.

They too assign the large signal for H_{4a} to the isomer with the *trans* junction and *vice versa*. Also the difference in the chemical shift of H_{4a} in the pairs (**18–20**) and (**19–21**) (4·3 against 3·8 in CCl_4) is consistent with the data of the French authors, who have attributed the higher shielding to the purely axial proton in the *trans* junction. There are no unambiguous data concerning the orientation of the methyl group on position 1 of the four isomers, so that the configuration of this group remains unassigned also for (**15**) and (**16**).

The formation of (**15**) and (**16**) in the reaction between (**3**) and (**5**) is understandable if one supposes that the carbonium ion formed by protonation of (**3**) at C-8 attacks olivetol and then the OH can substitute on the position 3 (or on the corresponding allylic position 5).



Scheme 2.

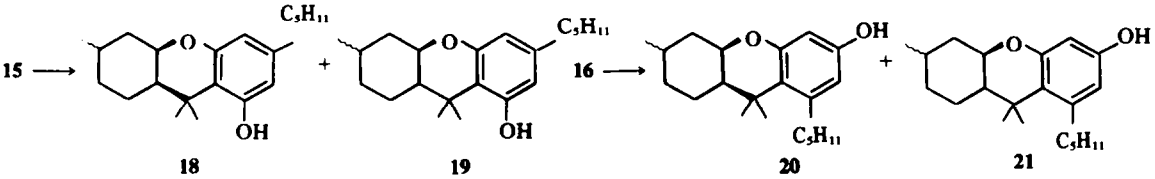
The biological activity of the compounds reported here has not yet been tested.

EXPERIMENTAL

All m.ps are uncorrected. UV spectra were measured in 95% EtOH solns, NMR spectra (values in δ, J in Hz, TMS as internal standard, benzene-d_6 as solvent unless otherwise indicated), with Varian XL-15-100 spectrometer, Mass spectra with a Hitachi RMU6D instrument at 70 eV (80 A), samples being directly introduced in the ion source at 250°. Chromatographies were performed with silica gel 0·05–0·02 mm Merck for columns, and Merck HF_{254} for TLC.

p-Menth-4-en-3,8-diol was prepared by hematoporphyrin-sensitized photooxidation of pulegone and $NaBH_4$ reduction as it was described in the literature.[3]

4·1 g of olivetol and 3·5 g of *p*-menth-4-en-3,8-diol in 200 ml benzene were added with 750 mg of *p*-toluenesulfonic acid and left at room temp. for 2 days. Taking up with water separation and evaporation of the solvent gave a mixture, which was chromatographed on a column of silica gel with hexane containing increasing percentage of benzene. The chromatography was monitored with TLC using hexane/benzene 1/1 as eluent, spraying the



18 19 20 21

plates with $FeCl_3$ solution. The fractions were eventually mixed and purified by preparative TLC with the same eluent. The following products were thus isolated:

(a) Compound **15** (0·65 g), m.p. 105–106°C (petrolether),

†Again the assignment of the respective structure ("normal" or "abnormal") is based on the effect of benzene on the aromatic protons and on UV absorption.[4]

Found(: C, 79·86; H, 9·70, $C_{21}H_{30}O_2$ requires: C, 80·21, H, 9·62%. $[\alpha]_D^{20}$ = +3·70° (*c* = 0·35 MeOH). UV: 232 sh, 275, 282 (5300, 5300), NMR: 0·83 (Me–CH_2 s), 0·85 (Me–CH d), 1·66 and 1·74 (Me_2–C s), 1–2·3 (11 H), 2·37 (CH_2–Ph t) 4·35 (H_{4a} m width = 10), 5·75 (H_1 m width = 10 Hz), 5·65 and 6·60 (2 H aromatic J = 2), 4·35 OH M.S.: 314,299,257,242,200... Acetylation gave the monoacetate, oily, NMR: 0·81 (Me–CH_2 s), 0·83 (Me–CH d), 1·43 and 1·54 (Me_2–C s), 1·89 (Ac), 4·20 (H_{4a} width 10 Hz), 5·63 (H_1 m width 10 Hz), 6·60 and 6·76 (H_5 and H_7, J = 2).

(b) Compound **6** (0·85 g), a viscous oil, UV 234 sh, 274, 282, (2500, 2500), $[\alpha]_D^{20}$ = +65·2° (*c* = 0·32 MeOH)†, M.S. 314, 299, 271, 257, 243, NMR: 0·85 (Me–CH_2 t), 0·93 (Me–CH d), 1·24 and 1·52 (Me_2–C s), 1·0–2·2 (3 CH_2, m), 2·40 (CH_2–Ph, t), 3·05 (H_{2eq}, ddd J 12, 2·5, 4), 1·0 (H_{2ax}), 3·72 (H_3 m), 5·60 (H_5, ddd J 6·9, 2·5, 2·5) 5·74 and 6·56 (2 H aromatic), 4·26 (OH). Monoacetate, M.S.: 356, 341, 314, 299, 271....

(c) A mixture of **6** and **12** (0·43 g).

(d) Compound **12** (0·40 g), a viscous oil MS: 314, 299, 271, 257. UV 234 sh 272, 282, NMR: 0·7 (Me–CH d) 0·84 (Me–CH_2 t), 1·51 and 1·60 (Me_2C=C s), 1–2·3 (11 H), 2·42 (CH_2–Ph), 4·33 (H_6 width = 9 Hz), 5·23 (H_2 width = 9) 5·91 and 6·58 (2 H aromatic J = 2 Hz), 4·85 (OH). Monoacetate, MS: 356, 341, 313, 297, 271, 257...

(e) Compound **16** (30 mg), m.p. 99–100° (petrolether), MS: 314, 299, 257, 243, UV 230 sh, 282, 288 (2600, 2600), NMR: 0·82 (Me–CH_2 t), 0·96 (Me–CH d), 1·50 and 1·51 (Me_2–C s), 1–2·3 (11 H m), 2·7 (CH_2–Ph m), 4·27 (H_{4a} m width = 9) 5·65 (H_1 m width = 10), 6·26 and 6·28 (2 H aromatic), 3·7 (OH).

(f) Compound **7** (0·9 g), oily, MS: 314, 299, 271, 257, 243, UV: 230 sh, 282, 288 (2500, 2500), $[\alpha]_D^{20}$ = +20·2 (*c* = 0·27 MeOH), NMR: 0·86 (Me–CH_2, t), 0·88 (Me–CH, d), 1·24 and 1·51 (Me_2–C, s), 1–2·2 (3 CH_2, m), 2·55 (CH_2–Ph, m), 0·88 (H_{2ax}), 2·1 (H_{2eq}, m), 3·54 (H_3, ddddd J 11·5, 3·0, 3·5, 3·5, 3·5), 5·57 (H_5, m), 6·33 (2 arom. H), 4·57 (OH).

Hydrogenation experiments

(a) Hydrogenation of **6** (100 mg) in 20 ml MeOH with PtO_2 as a catalyst for 12 hr in a Parr apparatus gave a product from which, after prep TLC with benzene, **10** was obtained, as an oily product, MS: 316, 273, 260, 193; UV: 230 sh, 273, 281 (2900, 2900); NMR: 0·85 (Me–CH_2, t), 0·89 (Me–CH, d), 1·32 (Me_2–C, s), 1·0–2·0 (13 H), 2·44 (CH_2–Ph, t), 2·4 (H_2), 3·00 (H_{3ax} ddd J = 11·5, 6, 4·5) 5·86 and 6·60 (2 arom. H), 4·20 (OH).

(b) Similar hydrogenation of the acetate of **7** gave, after TLC purifn., **11** Ac, oily, MS: 356, 341, 313, 299, 271, 257, 243; UV: 283, 288 (2400, 2400); hydrolysis of (**11** Ac) gave (**11**), 9,10a - *cis* - 10a,6a - *cis* - 1 - pentyl - 6,6,9 - trimethyl - 6a,7,8,9,10,10a - hexahydro - 6H - dibenzo[b,d]pyran - 3 - ol, NMR: 0·83 (Me–CH_2, t), 0·85 (Me–CH, d), 1·30 and 1·34 (Me_2–C), 1·0–2·0 (14 H), 2·50 (CH_2–Ph, m), 2·75 (H_3, m, width 22 Hz), 6·30 (2 arom. H), 4·30 (OH).

(c) Hydrogenation of Δ^3-THC, **8**[7] with PtO_2 in AcOH at room temp gave a mixture from which, by prep TLC with hexane-benzene, two compounds could be separated: (**10**), identical on TLC and by spectral comparison with the compound obtained by hydrogenation of **6**, oily, MS: 316, 273, 266, 193, 136, NMR: 0·84 (Me–CH_2, t), 0·94 (Me–CH, d), 1·08 and 1·26 (Me_2–C, s), 1–1·8 (12 H m), 1·1 (H_{2ax}), 2·40 (CH_2–Ph), 3·40 (H_{2eq}, m J = 13 Hz), 3·27 (width = 9 Hz), 5·67 and 6·52 (2 H aromatic J = 2), 4·20 (OH).

Hydrogenation of **12** with PtO_2 in MeOH overnight gave **14**, oily, MS: 316, 273, 260, 233, 217, 192... NMR: 0·68, 0·80 and 0·87 (3 Me–CH, d), 0·85 (Me–CH_2, t), 1–2·3 (13 H), 2·43 (CH_2–Ph, t), 3·46 (H_6 m width = 11) 4·55 (H_2 m width = 9), 5·99 and 6·55 (2 H aromatic J = 2), 5·10 (OH).

(e) Hydrogenation of **15** in AcOH with PtO_2 at 2 atm (room temp) gave a crude product, which was purified by TLC to give **18** as a glassy product, MS: 316, 301, 300, 290, 260, 231, 207, 193... UV 275, 283, NMR: 0·85 (Me–CH_2 t) 0·86 (Me–CH, d), 1·43 and 1·54 (Me_2–C, s), 1–2·3 (14 H), 2·38 (CH_2–Ph, t), 4·24 (H_{4a}, m width = 10 Hz) 5·62 and 6·56 (2 aromatic J = 2 Hz), 4·24 (OH). The product contains another compound, that from the NMR spectrum appears to be the stereoisomer **19**, 4a,9a - *trans* - 3,9,9 - trimethyl - 6 - pentyl - 8 - hydroxy - 1,2,3,4,4a,9a - hexahydroxanthene, NMR: 0·82 (Me–CH_2, d), 0·85 (Me–CH_2, t), 1·54 and 1·57 (Me_2–C, s), 1–2·3 (14 H), 2·38 (CH_2–Ph t), 3·86 (H_{4a} ddd J = 10, 10, 5) 5·62, 6·56 (2 H aromatic J = 2), 4·30 (OH).

(f) Hydrogenation of **16** in the same conditions gave two products which were separated by repeated preparative TLC (benzene-ether 9:1, then benzene, four runs) to give **20**, MS: 316, 309, 272, 259, 244, 230, 177, 165, 149, 136, 121, 97... UV 282, 288 NMR: 0·84 (Me–CH_2 t), 0·87 (Me–CH, d), 1·30 and 1·32 (Me_2–C, s), 1–2·3 (14 H m) 2·68 (CH_2–Ph, m), 4·26 (H_{4a} m, width = 9 Hz), 6·29 and 6·33 (2 H aromatic J = 2), 4·00 (OH), and **21** MS: 316, 301, 273, 260, 245, 219, 193, 175, 161, 149... NMR: 0·82 (Me–CH d), 0·85 (Me–CH_2, t), 1·20 and 1·34 (Me_2–C s), 1–2·3 (14 H m), 2·70 (CH_2–Ph, m), 3·85 (H_{4a} ddd J = 10, 10, 5), 6·29 and 6·33 (2H aromatic J = 2), 4·15 (OH).

Dehydrogenation of (**15**). Heating 10 mg of (**15**) with excess of sulphur at 240° for 20 min.[10], and extn with ether and purification by TLC gave (**17**), (mass: 310, 299, 296, 295, 238; UV: 251, 280, 289, NMR ($CDCl_3$): 0·90 (Me-chain), 1·77 (Me_2–C–9), 2·31 (Me–3), 2·50 (Aryl–CH_2), 6·21 and 6·46 (H_5 and H_7), 6·79 (H_4), 6·86 (H_2), 7·30 (H_1).

†Measured on a sample purified only by TLC.

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