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AN ALTERNATE ROUTE TO A QUASSIN SYNTHON

COMPARISON OF 1,3-DIAXIAL AND PERI STERIC INTERFERENCES IN HYDRIDE REDUCTIONS

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Abstract—It is shown that in so far as hydride reductions are concerned the following order of steric hindrance can be stated: two 1,3-diaxial > peri > one 1,3-diaxial. An alternate route is described to quassin synthon 2 from Diels–Alder adduct 1 in eleven steps.

In 1980 quassin[1] **4** was synthesized from decalone **2**[2] prepared from the Wieland–Mischer ketone **3** in eleven steps.[3] Since the known[4] Diels–Alder adduct **1** already contains all the required C atoms, we undertook its conversion to decalone **2**. Another incentive towards this work is that the 5- and 8a-Me groups in adduct **1** are present in a *trans* relative position as defined by the Diels–Alder transition state,[5] whereas the same feature starting from the Wieland–Mischer ketone **3** had to be especially elaborated.

While several steps of this conversion were routine applications of known procedures, others revealed some novel aspects of decalin stereochemistry, which we wish to communicate here.

The main chemical changes to be carried out were the following:

(1) Transposition of the keto group from C4 to C3.
(2) Introduction of the $\Delta^{1,2}$ double bond.
(3) Inversion at C8.

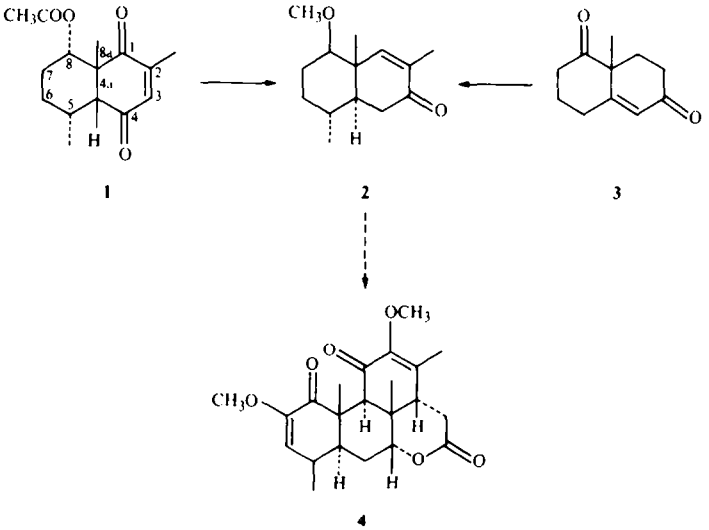
In order to achieve the first task we intended to introduce a $\Delta^{4,4a}$ double bond by the dehydration of the hydroxyketones **6** and **8** previously prepared by the selective reduction of the known diketones **5** and **7** respectively (eqns 1 and 2) which in turn were derived from adduct **1**.[6]

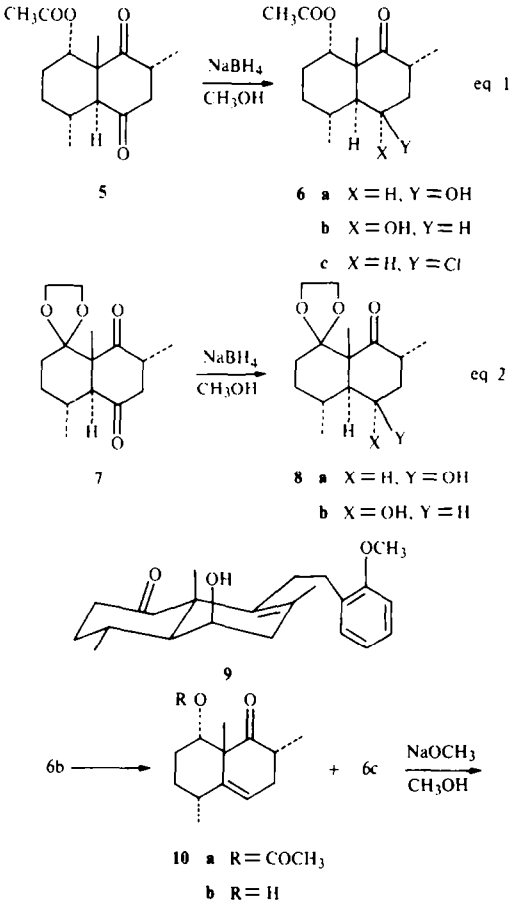
The stereochemistry of the OH in these hydroxyketones was previously assigned[6] the β-axial position, i.e. **6a** and **8a** in agreement with abundant experience in the steroid field,[7] and also due to the fact that in compound **9** the 4-OH was proved to be β-axial by X-ray crystallography.[8] The precursor of the latter compound **9**, was hydroxyketone **8b**, in which the OH will be shown to have the 4-OH in the α-equatorial position. Therefore an epimerization of this OH must have taken place in one of the steps leading to alcohol **9**, very probably in a prolonged treatment with formic acid at 90°.[6]

In an apparent contradistinction to steroid experience, evidence will be presented in the sequel necessitating the reassignment of the OH in both hydroxyketones from the axial to the equatorial position (**6a** → **6b**, **8a** → **8b**).

Chemical evidence for the equatorial assignment of OH in hydroxyketone **6b** was encountered when its treatment with $POCl_3$/pyridine gave the chlorosubstituted acetate **6c** (characterized in terms of chloroalcohol **13**) and olefin **10a**. Since the latter two compounds

†On leave from: Chinoin Pharmaceutical and Chemical Works Ltd., Budapest, Hungary.



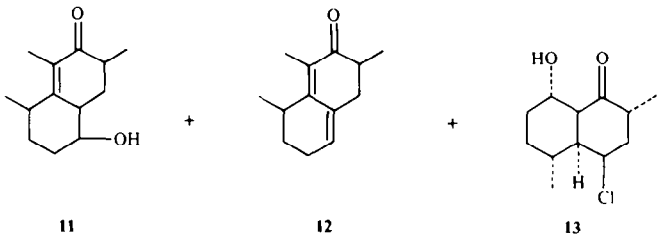


various complications arise. Thus cholestan-4α-ol when treated with $POCl_3$/pyridine gave cholestan-4α-yl dihydrogen phosphate,[11] a 7β-hydroxy-steroid with the same reagent furnished a chloro-substituted product,[15] cholestan-6α-ol with PCl_5 led to the formation of 6α-chlorocholestane exclusively according to an earlier report[12] but a more modern analysis reported the presence of cholest-5-ene and also of 6β-chlorocholestane.[13] The pyrolysis of 6α-cholestanyltrimethylammonium hydroxide led to the formation of 6α-dimethylaminocholectane.[14] Consequently it was concluded that the OH in **6b** should be assigned equatorial rather than the previously assigned axial position.[6]

The coupling constants derived from the high resolution PMR of equatorial alcohol **6b** were not those expected for a normal decalin system, but indicated a distorted geometry (J(3-He, 4-Ha) = 9.5 Hz; J(3-Ha, 4-Ha) = 6.8 Hz). This distortion might be the consequence of alleviating an $A^{1,3}$ steric repulsion[32] existing between the 5α-Me and 4α-OH groups. It was therefore necessary to obtain the epimeric axial alcohol **6a** too, so that its PMR spectrum could similarly be examined.

It was found that when the original, equatorial alcohol **6b** was dissolved in $POCl_3$ at 0° and poured on ice-water a 4:1 mixture of **6a** and **6b** respectively was formed from which the axial alcohol **6a** could be isolated in pure crystalline form. The PMR of axial alcohol **6a** furnished a set of coupling constants which were consistent with the expected values: J(3-He, 4-He) = 3.2 Hz, J(3-Ha, 4-He) = 2.8 Hz and J(4-He, 4a-Ha) = 3.1 Hz.

On the other hand, the chemical shift of the CHOH proton in equatorial alcohol **6b** was found at a lower field (δ = 4.57) than in the axial alcohol **6a** (δ = 4.37) which is contrary to the expectation since an axial



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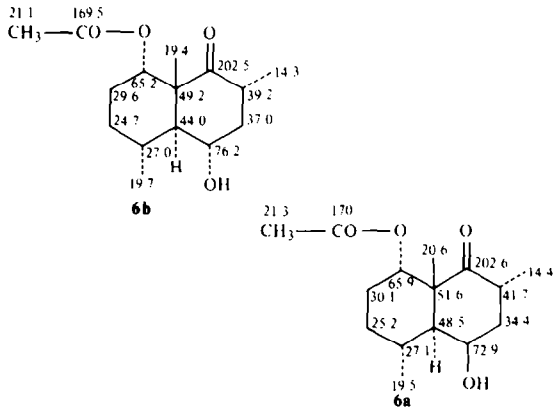
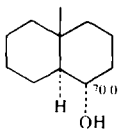
could not be separated by chromatography, their mixture was methanolyzed leading to the isolation of hydroxyketone **11**, unsaturated ketone **12** and the crystalline chloro-alcohol **13**. The formation of hydroxyketone **11** is explained by a retroaldol ring opening of hydroxyketone **10b**, followed by migration of the double bond and recondensation at C4. Hydroxyketone **11** is obviously the precursor of unsaturated ketone **12**.

The fact that alcohol **6b**, on treatment with $POCl_3$/pyridine predominantly led to substitution instead of smooth elimination to **10a** was in itself clear evidence for the equatorial position of OH in this compound. Since it is known that when the elements of H_2O to be eliminated are in an anti coplanar position as in the axial 6β-hydroxy-steroids, the Δ^5-steroids readily form with $POCl_3$/pyridine,[9] with PCl_5[10] or in a Hoffman elimination,[14] but when such a geometry cannot be attained,





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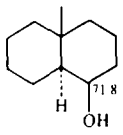

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proton generally resonates at a higher field than an equatorial one.[26] However, exceptions to the rule were also noted in the literature.[27]

The C^{13} spectra of alcohols **6b** and **6a** also exhibited some unusual features. The assignment of C signals was based on multiplicities and substituent effects in decalins[28] and decalols[29,30] as indicated below. ^{13}C NMR ($CDCl_3$/TMS int) δ[ppm]. It is known[29] that the α-deshielding effect of an equatorial OH group is generally larger than that of an axial OH unless the axial OH is syn-axial with the 8a-Me group as in decalol **21**. In the latter case the normally expected values are reversed and the equatorial decalol **20** resonates at a higher field.

It is suggested that a similar deshielding 1,3-interaction exists between the 5α-Me and 4α-OH groups in equatorial alcohol **6b** which deshields the C atom at position 4 thus reestablishing the normally expected trend.

The Cl atom in chloro-alcohol **13** and also, by implication, in chloro-acetate **10a** is also assigned axial because of the absence of two large diaxial coupling constants (>11 Hz) amongst the following data: J(3-He, 4-He) = 0.8 Hz, J(3-Ha, 4-He) = 5.9 Hz and J(4-He, 4a-Ha) = 7.7 Hz. The axial position of the Cl atom in compound **13** is corroborated by the presence of a peak at 700 cm^{-1} in its IR spectrum, characteristic of an axial Cl, and also by the absence of peaks in the 745–780 cm^{-1} region, indicative of an equatorial Cl.[12,19] The closest well-documented analogy to this inversion is the conversion of cholestan-6α-yl-tosylate to 6β-dimethylamino-cholestane.[14]

It is now necessary to discuss the reason why the equatorial alcohol **6b** rather than the axial alcohol **6a** forms during the reduction of diketone **5** by $NaBH_4$. As is well known in steroids the usual β-axial attack at the 6-keto[16]—as well as at the 4-keto[17]—group, is prevented because the approaching hydride ion must traverse a reaction coordinate along which a 1,3-diaxial intertaction with the 19-Me group is encountered.

A comparable peri steric hindrance must be exhibited by the 5-Me group against an equatorially attacking hydride ion at C4 in diketone **5**, and therefore, an axial attack will still be preferred on stereoelectronic grounds, leading to the equatorial alcohol **6b**.

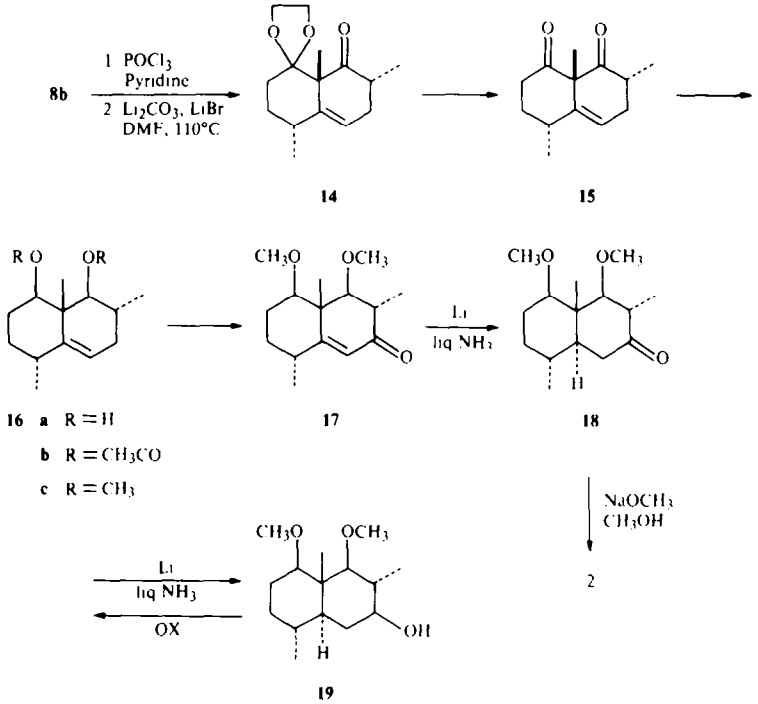
That such a peri interaction indeed exists is also corroborated by the C^{13} spectra of alcohols **6a** and **6b**.

However the hydride reduction of 4,4-dimethyl-6-keto-steroids[18] furnishes the 6β-alcohols, proving that two 1,3-diaxial interferences exert a stronger steric hindrance than one peri interaction. Hence it should be concluded that in so far as hydride reductions are concerned the following order of steric hindrance can be stated: two 1,3-diaxial > peri > one 1,3-diaxial.

According to the author's knowledge, for the last inequality no example has been encountered in steroid or terpene chemistry.

The stereochemistry of the ketonalcohol obtained by $NaBH_4$ reduction of diketone **7** must also be assigned as represented by **8b** rather than **8a**[6] because when treated with $POCl_3$/pyridine a mixture of olefin **14** and the corresponding chloro-decalin (no formula is presented for the latter)formed, as evidenced by NMR and analysis for Cl. In order to complete the elimination the mixture was then treated with Li_2CO_3, LiCl in DMF furnishing an excellent yield of the crystalline olefin-ketal **14** (Scheme 1).

After hydrolysis, diketone **15** was obtained which was then reduced to the pure diequatorial diol **16a** with LiAl(O-t.-Bu)$_3$ H in THF. Other complex hydrides such as



Scheme 1.

$NaBH_4$, $LiBH_4$ and $LiAlH_4$ all led to mixtures containing various stereoisomers of diol **16a**. It would appear that the latter three hydrides might have formed some complexes with the intermediate hydroxy-ketones which then led to the other stereoisomers, whereas with LiAl(O-t.-Bu)$_3$ H such complex-formation is precluded because the reagent is already a trialcoholate.

In the PMR spectrum of diacetate **16b** the two diaxial coupling constants (8 Hz and 10 Hz for 1-Ha and 8-Ha respectively) were readily discernable. The corresponding signals were obscured in dimethylether 16c prepared with Me_3I/NaH.[20]

The allylic oxidation to unsaturated ketone **17** was carried out in good yield by the 3,5-dimethyl-pyrazol-chromium trioxide complex.[21] The *trans*-fused ketone **18** was then obtained by reduction with Li/liq.NH_3.[22] As usual some overreduction to alcohol **19** occurred[23] which was reoxidized by pyridinium dichromate.[24] The base-catalyzed elimination of β-methoxy-ketone **18** led to the *trans*-fused ketone **2** in excellent yield and was found to be identical with a sample kindly provided by Prof. P. A. Grieco.

It is to be noted that during the reduction with Li/liq.NH_3 followed by the addition of NH_4Cl no Elcb elimination[25] took place. This is probably due to the lower temperature of liquid ammonia as contrasted to the elimination **18**→**2** which was carried out at room temperature.

Our seven step sequence (Scheme 1) provides an alternate route to synthon **2** from *trans* diketone **7** in a yield of 45%. The latter compound **7** in turn was prepared from adduct **1** in four steps.[6]

The conversion to ketone **2** described above, together with Grieco's synthesis,[2] represents a route to quassin in which all the C–C bonds involved were formed by the Diels–Alder reaction.

It is to be mentioned that Mandell *et al.* have made a so far unsuccessful attempt to incorporate all the C atoms of quassin by a single Diels–Alder reaction.[31]

EXPERIMENTAL

All m.ps were taken on a Fisher–Johns m.p. apparatus and are uncorrected. The elemental analyses were carried out by Dr. C. Daessle, Montreal, P.Q. and Canadian Micro Analytical Service Ltd., Vancouver. The IR spectra were recorded on a Beckman Spectrophotometer IR 4230, the UV spectra on a Varian Cary 210 Spectrophotometer. For the NMR spectra a Varian Associates T60 spectrophotometer and a Nicolet 220NB were used. The mass spectra were obtained with a Hitachi–Perkin–Elmer model RMS-4 spectrometer, using electrons of 70 eV energy. The ^{13}C NMR spectra were recorded on a Nicolet 360 MHz narrow bore NMR spectrophotometer.

8α - acetoxy - 4α - hydroxy - 2α,5α,8aβ - trimethyl - 3,4,4aα,5,6,7,8,8a - octahydronaphthalen - 1(2H) - one **6b**

The preparation of this compound was previously reported but the stereochemistry of the 4-OH group was erroneously assigned[6] as β. This must now be corrected to α on the basis of chemical and spectroscopic evidence (Discussion). Here only the high resolution PNMR spectrum is recorded.

PNMR ($CDCl_3$, 220 MHz)δ 1.05(d, 3, J = 6.5 Hz, 2-CH_3), 1.08(d, 3, J = 5.8 Hz, 5-CH_3), 1.19(s, 3, 8a-CH_3), 1.26(m, 1, 6-H_a), 1.49(td, 1, 3-H_a), 1.56(d, 1, OH), 1.58(m, 1, 6-H_e), 1.72(m, 1, 7-H_a), 1.86(m, 1, 7-H_e), 1.90–2.00(m, 2, 4a-H_a, 5-H_a), 1.93(s, 3, CH_3CO), 2.37(m, 1, 2-H_a), 2.49(ddd, 1, 3-H_e), 4.57(m, 1, 4-H_a), 5.10(t, 1, 8-H_e). J(3-H_e, 2-H_a) = 5.1 Hz; J(3-H_e, 4-H_a) = 9.5 Hz; J(3-H_e, 3-H_a) = 14.3 Hz; J(3-H_a, 2-H_a) = 14.3 Hz; J(3-H_a, 4-H_a) = 6.8 Hz; J(4-H_a, OH) = 3.6 Hz; J(8-H_e, 7-H_e) = J(8-H_e, 7-H_a) = 2.7 Hz.

Effect of irradiation. 2.37(m, 1, 2-H_a) $\xrightarrow[\text{at } 1.05]{\text{irradiation}}$ 2.37 (dd, 1, J = 5.1 Hz and J = 14.3 Hz are present). This signal can not be due to 5-H_a because that would be more complicated than dd. It is however compatible with the 2-H_a assignment.

1.05(d, 3, J = 6.5 Hz, 2-CH_3) $\xrightarrow[\text{at } \delta 2.37]{\text{irradiation}}$ 1.05(s, 3, 2-CH_3).

1.08(d, 3, J = 5.8 Hz, 5-CH_3) $\xrightarrow[\text{at } \delta 1.90]{\text{irradiation}}$ 1.08(s, 3, 5-CH_3).

1.26(M, 1, 6-H_a) $\xrightarrow[\text{at } \delta 1.90]{\text{irradiation}}$ 1.26 (narrower signal, therefore it must be due to 6-H_a).

4.57(m, 1, 4-H_a) $\xrightarrow[\text{at } \delta 1.90]{\text{irradiation}}$ 4.57 (simplification of signal, therefore **4a** proton lies here covered).

2.49(ddd, 1; J(3-H_e, 2-H_a) = 5, 1 Hz, J(3-He, 3-H_a) = 14.3 Hz, J(3-H_e, 4-H_a) = 9.5 Hz; 3-H_e) $\xrightarrow[\text{at } \delta 4.57]{\text{irradiation}}$.

2.49(dd, 1, J = 9.5 Hz disappears, J = 5.1 Hz and J = 14.3 Hz are still present).

1.49(td, 1; J(3-H_a, 4-H_a) = 6.8 Hz, J(3-H_e, 3-H_a) = 14.3, J(3-H_a, 2-H_a) = 14.3 Hz; 3-H_a) $\xrightarrow[\text{at } \delta 1.49]{\text{irradiation}}$ 1.49-t, 1; J = 6.8 Hz disappears, J = 14.3 Hz is still present).

Thus the unusual conclusion is drawn J(3-H_e, 4H_a) = 9.5 Hz and J(3-H_a, 4H_a) = 6.8 Hz which must be a reflection of distorted conformation.

8α - Acetoxy - 4β - hydroxy - 2α,5α,8aβ - trimethyl - 3,4,4aα,5,6,7,8,8a - octahydronaphthalen - 1(2H) - one **6a**

The isomerization of **6b** *to* **6a**. To a chilled, magnetically stirred soln of **6b** (1.00 g) in dry CH_2Cl_2 (10 ml) $POCl_3$ (1.0 ml) diluted with CH_2Cl_2 (3 ml) was dropped in 5 min. The 3-necked flask was equipped with a condenser/$CaCl_2$ and kept under a stream of dry N_2. After stirring for 14 hr at room temp the soln was poured on crushed ice (10 g) and extracted with CH_2Cl_2 (3 × 5 ml). The combined organic phase was washed with 10% $NaHCO_3$ (5 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The crystalline product (0.95 g, 95%) was examined by TLC (silicagel, benzene/ether/4/1). Two closely moving components showed up, which were separated by preparative TLC. The minor component (0.15 g, R_f = 0.60) was identified as the starting material (the equatorial **6b**) and the major component (0.60 g, R_f = 0.50) must be assigned as the axial **6a**.

The latter was recrystallized (EtOH/H_2O/1/1, m.p. 143–144°) to prepare an analytical sample from which the spectra were also recorded.

IR ($CHCl_3$), 3610; 3500; 3000; 2920; 1710; 1455; 1370; 1230; 995 cm^{-1}. Mass spectrum (70 eV) *m/e* (relative intensity): 268 (8, parent peak), 225(8), 208(32), 141(35), 123(44), 109(100). PNMR ($CDCl_3$, 220 MHz)δ, 1.02(d, 6, J = 6.5 Hz, 2-, 5-CH_3), 1.35(s, 3, 8a-CH_3), 1.51(d, 1, OH), 1.61(td, 1, 3-H_a), 1.76(dd, 1, 4a-H_a), 1.99(s, 3, CH_3CO), 2.18(ddd, 1, 3-H_e), 3.10(m, 1, 2-H_a), 4.36(m, 1, 4-H_e), 5.13(t, 1, 8-H_e).

J(3-H_e, 2-H_a) = 5.7 Hz; J(3-H_e, 4-H_e) = 3.2 Hz; J(3-H_e, 3-H_a) = 14.0 Hz; J(3-H_a, 2-H_a) = 14.0 Hz; J(3-H_a, 2-H_a) = 2.8 Hz; J(4-H_e, 4a-H_a) = 3.1 Hz; J(4a-H_a, 5-H_a) = 13.4 Hz; J(4-H_e, OH) = 1.7 Hz; J(8-H_e, 7-H_e) = J(8-H_e, 7-H_a) = 2.8 Hz.

Effect of irradiation. 2.18(ddd, 1, J(3-H_e, 2-H_a) = 5.7 Hz, J(3-H_e, 4-H_e) = 3.2 Hz, J(3-He, 3-H_a) = 14.0 Hz, 3-H_e) $\xrightarrow[\text{at } \delta \sim 4.36]{\text{irradiation}}$ 2.18 (dd, 1; J = 3.2 Hz disappears, J = 5.7 Hz and J = 14.0 Hz are still present). 1.76 (dd, 1, J(4a-H_a, 5H_a) = 13.4 Hz, J(4-H_e, 4a-H_a) = 3.1 Hz, 4a-H_a) $\xrightarrow[\text{at } \delta = 4.36]{\text{irradiation}}$ 1.76 (d, 1, J = 3.1 Hz disappears, J = 13.4 Hz is still present).

1.61(td, 1, J(3-H_3, 3-H_a) = J(3-H_a, 2-H_a) = 14 Hz, J(3-H_a, 4-H_e) = 2.8 Hz, 3-H_a) $\xrightarrow[\text{at } \delta \sim 4.36]{\text{irradiation}}$ 1.61 t, 1, J = 2.8 disappears, J = 14 Hz is still present).

The coupling constants for isomer **6a** agree with the expected values.

Found: C, 67.19; H, 8.98. Calc. for $C_{15}H_{24}O_4$: C, 67.14; H, 9.01%).

Reaction of 8α - *acetoxy* - 4α - *hydroxy* - 2α,5α,8aβ - *trimethyl* - 3,4,4aα,5,6,7,8,8a - *octahydronaphthalen* - 1(2H) - *one* **6b** *with* $POCl_3$ *in pyridine and methanolysis of the resulting mixture*

(i) *Reaction.* To a soln of **6b** (2.00 g, 3, 73 mmol) in anhyd pyridine (5 ml), $POCl_3$ (1 ml) was dropped while cooling with ice-water, and stirring magnetically. The mixture was stirred at room temp for 14 hr then it was poured on crushed ice (10 g). After extraction with $CHCl_3$ (4 × 5 ml) the combined extracts were washed with 10% H_2SO_4 (2 × 10 ml) in the presence of ice (10 g), then with 10% $NaHCO_3$ (10 ml). After drying ($MgSO_4$) and concentration *in vacuo*, an oil (1.86 g) was obtained consisting of two components barely distinguishable by TLC (silicagel, benzene). According to NMR and subsequent chemical evidence the mixture contains **6c** (57%) and **10a** (43%). NMR ($CDCl_3$, 60 MHz) δ identifiable peaks

(a) Chloro compound **6c**: 1.98(s, 3, CH_3CO), 4.30(m, 1, 4-H), 5.20(t, 1, 8-H)

(b) Olefin **10a**: 1.95(s, 3, CH_3CO), 4.92(t, 1, J = 3 Hz8-H), 5.75(m, 1, olefinic proton).

(ii) *Methanolysis.* To the mixture of **6c** and **10a** obtained above (1.86 g) a soln of NaOMe (prepared from 0.5 g Na and 20 ml/MeOH) was added. The soln was allowed to stand for 14 hr. After dilution with water (20 ml) it was extracted with ether (4 × 10 ml). The combined ether extracts were washed with water (10 ml), dried ($MgSO_4$) and concentrated *in vacuo*, furnishing a slightly yellow oil consisting of three components according to TLC (silicagel, benzene/MeOH/4/1), which were separated by preparative TLC using the same solvent mixture.

(a) To the oily component of $R_f = 0.40$ (microdistilled at 130°/0.01 mmHg, 420 mg) structure 11 is assigned: 5 - hydroxy - 1,3,8 - trimethyl - 4,4a,5,6,7,8 - hexahydronaphthalen - 2(3H) - one on the basis of the following spectroscopic properties:

IR ($CHCl_3$) 3620, 3470, 2980, 2940, 2880, 1690, 1615, 1450, 1380, 1040, 995 cm^{-1}; UV_{max} (96% C_2H_5OH) 248 nm (ε = 10.043); NMR ($CDCl_3$, 60 MHz) δ1.13(d, 6, J = 7 Hz, CH_3, CH_3), 1.80 (s, 3, olefinic Me); Mass spectrum (70 eV) *m/e* (relative intensity) 208(23, parent peak), 152(100), 138(18), 137(14), 123(20). Found: C, 75.00; H, 9.65. Calc for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68%).

(b) To the crystalline chloroalcohol of $R_f = 0.55$ (670 mg, recrystallized from $EtOH/H_2O$/1/1, m.p. 112–114°) structure **13** is assigned: 4β - chloro - 8α - hydroxy - 2α,5α,8aβ - trimethyl - 3,4,4aα,5,6,7,8,8a - octahydronaphthalen - 1(2H) - one.

IR ($CHCl_3$) 3600, 3500, 2930, 2870, 1695, 1490, 1205, 990, 700 cm^{-1}. Found: C, 63.73; H, 8.63; Cl, 14.52. Calc for $C_{13}H_{21}O_2Cl$: C, 63.70; H, 8.65; Cl, 14.48%.)

Mass spectrum (70 eV) *m/e* (relative intensity) 244(5, parent peak), 208(37), 161(34), 159(100), 152(58), 123(78).

PNMR ($CDCl_3$, 220 Mz)δ. 0.98(s, 3, 8a-CH_3), 1.14(d, 3, J = 6.6 Hz, 2-CH_3), 1.17(d, 3, J = 6.6 Hz, 5-CH_3), 2.18(ddd, 1, 3-H_e), 2.30(ddd,1,3-H_a), 2.39(dd, 1, 4a-H_a), 2.73(m, 1, 2-H_a), 4.18(t, 1, 8-H_e), 4.22(ddd, 1, 4-H_e).

J(3-H_e, 2-H_a) = 4.7 Hz; J(3-H_e, 4-H_e) = 0.8 Hz; J(3-H_e, 3-H_a) = 15.6 Hz; J(3-H_a, 2-H_a) = 13.7 Hz; J(3-H_a, 4-H_e) = 5.9 Hz; J(4-H_e, 4a-H_a) = 7.7 Hz; J(4a-H_a, 5-H_a) = 11.1 Hz; J(8-H_e, 7H_e) = J(8-H_e, 7-H_a) = 2.9 Hz.

Effect of irradiation. 2.18(ddd, 1; J(3-H_e, 4-H_e) = 0.8 Hz, J(3-H_e, 2-H_e) = 4.7 Hz, J(3-H_e, 3-H_a) = 15.6 Hz; 3-H_e) $\xrightarrow[\text{at } \delta = 4.22]{\text{irradiation}}$ 2.18(dd, 1, J = 0.8 Hz disappears, J = 4.7 Hz and J = 15.6 Hz are still present). 2.30(ddd, 1; J(3-H_a, 4-H_e) = 5.9 Hz, J(3-H_a, 2-H_a) = 13.7 Hz, J(3-H_e, 3-H_a) = 15.6 Hz; 3-H_a) $\xrightarrow[\text{at } \delta = 4.22]{\text{irradiation}}$ 2.30(dd, 1; J = 5.9 Hz disappears, J = 13.7 Hz and H = 15.6 Hz are still present). 2.39(dd, 1; J(4-H_e, 4a-H_a) = 7.7 Hz, J(4a-H_a, 5-H_a) = 11.1 Hz, 4a-H_a) $\xrightarrow[\text{at } \delta = 4.22]{\text{irradiation}}$ 2.39(d, 1, J = 7.7 Hz disappears, J = 11.1 Hz is still present) 1.14(d, 3, 8a-CH_3, J = 6.6 Hz, 2-CH_3) $\xrightarrow{2.73}$ 1.14 (S, 3).

(c) To the unsaturated ketone with $R_f = 0.70$ (100 mg, oil, micro-distilled at 98–100°/0.01 mmHg) structure **12** is assigned: 1,3,8 - trimethyl - 4,6,7,8 - tetrahydro - naphthalen - 2(3H) - one.

IR ($CHCl_3$) 3000, 2960, 2930, 2870, 1690, 1625, 1580, 1440, 1230 cm^{-1}; uv_{max} (96% C_2H_5OH) 295 nm (ε = 8410); NMR ($CDCl_3$, 60 MHz) δ1.07(d, 3, J = 7 Hz, CH_3), 1.22(d, 3, J = 7 Hz, CH_3), 1.88(s, 3, olefinic methyl), 5.97(m, 1, olefinic proton); Mass spectrum (70 eV) *m/e* (relative intensity) 190(100, parent peak), 175(44), 162(69), 161(31), 147(72), 119(39), 105(55). (Found: C, 82.10; H, 9.49. Calc for $C_{13}H_{18}O$: C, 82.06; H, 9.53%).

2α,5α,8aβ - *Trimethyl* - 2,3,5,6 - *tetrahydronaphthalen* - 1, 8(7H,8aH) *dione* - 8 - *ethyleneketal* **14**

To a soln of **8b**[6] (30.00 g, 0.111 mol) in dry pyridine (150 ml) $POCl_3$ (30 ml) was dropped at 0–5° in 2 hr while stirring. The mixture was stirred overnight at room temp then it was poured on a mixture of crushed ice (300 g) and 10% H_2SO_4 (50 ml). After extracting with $CHCl_3$ (4 × 150 ml) the organic phase was washed in succession with 10% H_2SO_4 (100 ml) and water (100 ml). The dried ($MgSO_4$) solution was concentrated to an oil (28.69 g) *in vacuo* and subjected to the conditions below to complete the elimination.

The oily residue, dissolved in DMF (150 ml), was stirred and heated at 80–100° for 2 hr in the presence of Li_2CO_3 (3.00 g) and LiBr (30.00 g) under N_2. The cool mixture was poured on water (400 ml) and extracted with benzene (4 × 150 ml). After drying ($MgSO_4$), the benzene was evaporated *in vacuo*, furnishing a crystalline product (26.7 g, 95.4%). The TLC homogeneous crystals (silicagel, benzene) were used without purification for the next step (**14**→**15**). After two recrystallizations from $EtOH/H_2O$/3/1, the product melted at 66–68°. Its composition was determined in terms of **16a**. IR ($CHCl_3$), 3000, 2960, 2930, 2880, 1705, 1456, 1146, 1069, 1010, 972 cm^{-1}; NMR ($CDCl_3$), 60 Mz)δ, 1.02(d, 3, J = 6 Hz, CH_3), 1.07(d, 3, J = 6 Hz, CH_3), 1.33(S, 3, 8a-CH_3), 2.93(M, 1, 2-proton), 3.77(M, 4, O - CH_2 - CH_2 - O), 5.58(m, 1, olefinic proton); Mass spectrum (70 eV) *m/e* (relative intensity), 250(100, M^+), 206(8), 180(12), 149(22), 135(16), 121(29).

2α,5α,8aβ - *Trimethyl* - 2,3,5,6 - *tetrahydronaphthalen* - 1,8(7H,8aH) - *dione* **15**

A soln of **14** (10.00 g, 39.95 mmol) in diethyl ether (100 ml), water (20 ml) and 38% HCl (20 ml) was stirred with a magnetic stirrer at room temp for 14 hr. The organic phase was separated and the water phase was extracted with ether (20 × 20 ml). The combined organic phase was washed in succession with water (50 ml), 10% $NaHCO_3$ aq (20 ml) and with water (20 ml) again. After drying ($MgSO_4$) and evaporation *in vacuo*, a crystalline, TLC homogeneous (silicagel), benzene/ether/4/1) was obtained (7.53 g, 91.4%) which was used without further purification for the preparation of **16a**. Recrystallized twice from $EtOH/H_2O$/3/1) m.p. 55–57°. IR ($CHCl_3$), 2965, 2930, 1722, 1695, 1660, 1452, 1005 cm^{-1}; NMR ($CDCl_3$, 60 MHz), 1.10(d, 3, J = 6 Hz, CH_3), 1.17(d, 3, J = 6 Hz, CH_3), 1.53(s, 3, 9a-CH_3), 5.73(m, 1, olefinic proton); Mass spectrum (70 eV) (relative intensity), 206 (100, parent peak), 191(33), 164(68), 149(45), 136(48).

2α,5α,8aβ - *Trimethyl* - 1,2,3,5,6,7,8,8a - *octahydronaphthalen* - 1β,8β - *diol* **16a**

To a soln of Li-Al-(tri-t-butoxy)-hydride (14.79 g, 58.17 m mol) in dry THF (50 ml) a soln of **15** (4.00 g, 19.39 mmol) in dry THF (50 ml) was dropped in 30 min while stirring at 0–5° under an atmosphere of dry N_2. After stirring at room temp for 14 hr the mixture was hydrolyzed with water (20 ml) while cooling with ice. The suspension was diluted with diethylether (400 ml) and filtered through celite with the help of a 20-cm Buchner funnel. The filtrate was washed with water (100 ml) and dried ($MgSO_4$). After evaporation *in vacuo* a crystalline residue was obtained (3.40 g, 83.4%, m.p. 141–142°). IR ($CHCl_3$), 3400, 2985, 2955, 2870, 1452, 1043, 1015 cm^{-1}; NMR ($CDCl_3$, 60 MzH)δ, 0.93(d, 3, J = 6 Hz, CH_3), 1.03(d, 3, J = 6 Hz, CH_3), 1.28(s, 3, 8a-CH_3), 3.35, (dd, 1, J = 11 Hz, 5 Hz, 1-proton), 3.93(d, 1, J = 5 Hz, 1-OH), 4.00(ddd, 1, J = 10 Hz, 6 Hz, 2 Hz, 8-proton), 4.65(d, 1, J = 2 Hz, 8-OH, 5.30(m, 1, olefinic proton); mass spectrum (70 eV) *m/e* (relative intensity), 220(0, M^+), 192(32), 159(100), 135(77), 133(53); 132(37). (Found: C, 74.27; H, 10.60. Calc for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54%.)

2α,5α,8β - *Trimethyl* - 1,2,3,5,6,7,8,8a - *octahydronaphthalen* - 1β,8β - *diol diacetate* **16b**

A soln of **16a** (1.00 g, 4.75 mmol) in pyridine (5 ml) and Ac_2O (5 ml) was allowed to stand for 14 hr. The mixture was poured on a mixture of ice (20 g) and 10% H_2SO_4 (20 ml) and extracted with $CHCl_3$ (4 × 10 ml). The combined $CHCl_3$ extracts were washed in succession with 10% H_2SO_4 (2 × 10 ml), 10% $NaHCO_3$ (10 ml) and water (10 ml). After drying ($MgSO_4$) and evaporation *in vacuo* a colorless TLC homogeneous (silicagel, benzene) oil was obtained (1.22 g, 87.2%) which was examined spectroscopically. IR ($CHCl_3$), 2950, 1720, 1362, 1250, 1030 cm^{-1}; NMR ($CDCl_3$, 60 MHz)δ, 0.93(d, 3, J = 6 Hz, CH_3), 1.00(d, 3, J = 6 Hz, CH_3), 1.23(s, 3, 8a-CH_3), 2.03(s, 3, CH_3CO), 2.05(s, 3, CH_3CO), 4.90(d, 1, J = 8 Hz, 1-proton), 5.13(dd, 1, J = 10 Hz, 6 Hz, 8-proton), 5.43(m, 1, olefinic proton).

2α,5α,8aβ, Trimethyl - 1,2,3,5,6,7,8,8a - octahydronaphthalen - 1β,8β - diol - 1,8 - dimethyl ether **16c**

In a dry 100 ml 3-neck flask equipped with reflux condenser, drying tube ($CaCl_2$) and magnetic stirrer, NaH as 50% oil suspension (4.00 g, 83 mmol, Alfa Inorganics) was placed under N_2. After washing with dry pentane (3 × 5 ml), by removing the supernatant liquid with a dry pipet, the last traces of the solvent were driven away by a stream of N_2. Then dry THF (40 ml) and Bu_4NI (1.00 g) was added. To this suspension a soln of **16a** (4.00 g, 19.02 mmol) in dry THF (40 ml) was dropped. The suspension was stirred for 30 min then MeI (9.2g, 65 mmol) was dropped into it while cooling with ice-water for 10 min. After stirring at 0–5° for 30 min, the mixture was allowed to react for 14 hr, at room temp. After the addition of water (10 ml), the THF was removed *in vacuo*. The residue was suspended in pentane (50 ml) and filtered through celite. After separation of the phases, the water layer was extracted with pentane (2 × 10 ml) and the combined organic phase was washed with water (10 ml). After drying ($MgSO_4$), and concentration *in vacuo*, a colorless, TLC (silicagel, benzene) homogeneous oil (4.36 g, 96.2%) was obtained which was characterized in terms of unsaturated **2**. IR ($CHCl_3$), 2990, 2950, 2930, 2900, 2870, 1455, 1090 cm^{-1}; NMR ($CDCl_3$, 60 MHz)δ, 0.97(d, 3, J = 6 Hz, CH_3), 1.00(d, 3, J = 6 Hz, CH_3), 1.12(s, 3, 8a-CH_3), 3.10–3.70(2, 1- and 8-protons), 3.35 (s, 3, CH_3O), 3.42(s, 3, CH_3O), 5.27(m, 1, olefinic proton); Mass spectrum (70 eV) *m/e* (relative intensity): 238 (59, parent peak), 223(71), 181(50), 159(62), 135(100).

4β,5β - Dimethoxy - 3α,4aβ,8α - trimethyl - 4,4a,5,6,7,8 - hexahydronaphthalen - 2(3H) - one **17**

To a magnetically stirred suspension of chromic anhydride (dried over P_2O_5 for 24 hr, 12.59 g, 125.91 mmol) in dry CH_2Cl_2(100 ml) at −20°, 3,5-dimethyl-pyrazol (12.10 g, 125.91 mmol) was added in a single quantity with a sudden movement. The mixture was stirred at −20° for 15 min, then a soln of **16c** (2.50 g, 10.49 mmol) in 10 ml dry CH_2Cl_2 was dropped on it in 5 min. After stirring for 4 hr at −10-(−20)° 5 N NaOH (50 ml) was added and the stirring was continued at 0° for 1 hr. The soln was then extracted with ether (3 × 100 ml). The combined extracts were washed in succession with 10% H_2SO_4 (2 × 70 ml), 10% $NaHCO_3$ (70 ml) and water (70 ml). The dried ($MgSO_4$) soln was concentrated to 50 ml and passed through a short column of fluorosil (60 g). The nearly colorless soln was concentrated *in vacuo*, furnishing a TLC (silicagel, benzene) homogeneous oil (2.06 g, 77.8%) with the following spectroscopic properties. The product was used without further purification for the following steps. IR ($CHCl_3$), 2995, 2980, 1655, 1615, 1455, 1378, 1095 cm^{-1}; NMR ($CDCl_3$, 60 MHz)δ, 1.07(d, 3, J = 6 Hz, CH_3), 1.23(d, 3, J = 7 Hz, CH_3), 1.25(s, 3, 4a-CH_3), 2.82(dd, 1, J = 8 Hz, 2 Hz, 4-proton), 3.33(s, 6, CH_3O, CH_3O), 3.70(dd, 1, J = 11 Hz, 4 Hz, 5-proton), 5.70(d, 1 H, J = 2 Hz, olefinic proton); UV_{max}: (96% C_2H_5OH) 240.5 nm(ε = 12.050), 288 nm (ε = 1766); Mass spectrum (70 eV) *m/e* (relative intensity), 252 (78, parent peak), 220(85), 205(70), 165(65), 162(67), 149(60).

5β - Methoxy - 3,4aβ,8α - trimethyl - 4a,5,6,7,8,8a - hexahydronaphthalen - 2(1H) - one **2**

Liquid ammonia (200 ml) is condensed in a 500 ml 3-neck flask equipped with a dropping funnel and a dry ice condenser to which a drying tube containing sodalime was attached. A soln of **17** (2.00 g, 7.93 mmol) in diethyl ether (20 ml) was dropped in, then Li (1 g) was added in 6–8 pieces in 15 min while stirring magnetically and cooling with dry ice-acetone. The mixture was stirred for 15 min then after the addition of NH_4Cl (2 g) the ammonia was allowed to evaporate. To the residue, water (100 ml) was added and the product was extracted with $CHCl_3$ (4 × 50 ml). The combined extracts were washed with water (50 ml), dried ($MgSO_4$) and concentrated *in vacuo*.

To the residue dissolved in dry DMF (15 ml), pyridinium dichromate[24] (4.00 g, mmol) was added at room temp while stirring; the reaction was continued for 14 hr.

Then the mixture was diluted with water (25 ml) and extracted with benzene (4 × 10 ml). The combined extracts were washed with water (10 ml) dried ($MgSO_4$) and concentrated *in vacuo*.

The residue was dissolved in MeOH (10 ml) containing NaOMe (0.23 g) and allowed to stand at room temp for 14 hr. After diluting the mixture with water (20 ml), it was extracted with ether (4 × 10 ml). The combined ether extracts were washed with water (10 ml), dried ($MgSO_4$) and concentrated *in vacuo* (1.45 g, 82.2%, m.p. 37°C). The product was identical with a sample kindly provided by Prof. P. Grieco with respect to all spectroscopic properties recorded below: IR ($CHCl_3$), 2975, 2930, 1660, 1460, 1378, 1310, 1133, 1095 cm^{-1} UV_{max} (96% EtOH) 239 nm (ε = 8943); mass spectrum (70 eV) *m/e* (relative intensity), 222(34, parent peak), 175(15), 149(100), 123(30); NMR ($CDCl_3$, 60 MHz)δ, 0.87(d, 3, J = 7 Hz, 8α-CH_3) 1.03(s-3, 4aβ-CH_3), 1.75(d, 3, J = 1.5 Hz, 3-CH_3), 3.43(s, 3, CH_3O), 7.03(q, 1, J = 1.5, olefinic proton).

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