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BASE CATALYSED REARRANGEMENT OF A SPIRO OXY-COPE SYSTEM AND RELATED STUDIES

A NEW ENTRY INTO PERHYDROPHENALENE AND PERHYDROACENAPHTHYLENE SYSTEMS[1]

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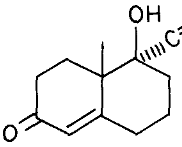
Abstract—The spirovinyl carbinol **5** when treated with methanolic potassium hydroxide was found to rearrange to perhydrophenalene- 1,4-dione **6** via an anionic oxy-Cope rearrangement followed by an intramolecular Michael addition. The epimeric mixture of ketol acetates **15a** and **15b** was also found to rearrange to 2- hydroxy-2-methyl perhydroacenaphthylene-1,3-dione **16** on treatment with base.

In earlier work, bicyclic compounds of the type **1** and **2** incorporating an oxy-Cope system conjugated with a carbonyl have been shown to undergo facile base catalysed rearrangements.[2-5]



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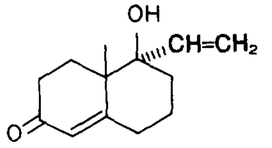

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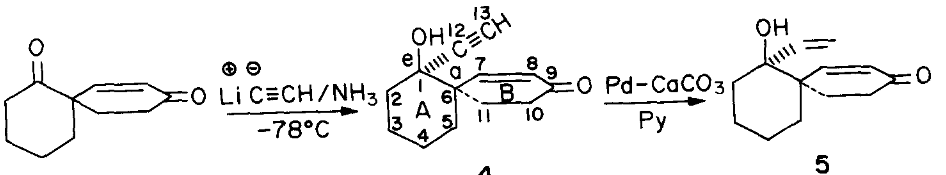
With a view to extend the scope of such rearrangements, it was of interest to incorporate such an oxy-Cope moiety in a spiro system and study its rearrangement. We report here the sysnthesis and base catalysed rearrangements of the spiro compound **5**, ketol acetates **15a** and **15b** and some related studies.

The spiro vinyl carbinol **5** was synthesised via the spirodione **3**[6] by the following reaction sequence:

like semicarbazide and 2,4-dinitrophenylhydrazine which are reported to react preferentially with the conjugated CO group.[6] This may be due to a combination of two factors: (i) the greater electrophilicity of the unconjugated CO group and (ii) the linear nature of the incoming nucleophile *viz.* the acetylide ion. The stereochemistry implied in structure **4** is based on the fact that addition of metal acetylides to 2,2-disubstituted cyclohexanones results in the formation of equatorial alcohols with the attacking reagent coming from the less hindered axial side.[7] With respect to ring A of **4**, the SP^2 C rather than SP^3 C is more likely to have an axial orientation.

Partial hydrogenation of the ethynyl carbinol **4** in the presence of Pd-$CaCO_3$ in pyridine furnished the vinyl carbinol **5** as a colourless viscous liquid. In the NMR spectrum the vinyl proton signals appeared as a multiplet between δ5.1–6.0 apart from the enone protons. The IR spectrum significantly showed the absence of acetylenic absorption. The structure of the vinyl carbinol **5** was further confirmed by mass spectral data and elemental analysis.

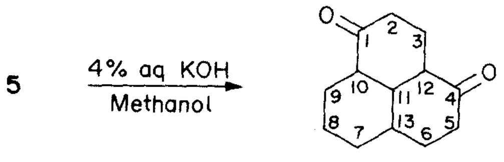


3 4 5

Addition of lithium acetylide in liquid ammonia at −78 to the spirodione **3** followed by workup gave the ethnyl carbinol **4** as a colourless crystalline solid. The IR (KBr) showed absorptions at 3300 (-OH), 3200 (C≡CH) and 1660 cm^{-1} (>C=O). The NMR spectrum displayed the AB quartet for the α- and β- protons of the enone moiety at δ6.0 and 7.1 (J = 9.5 Hz) respectively indicating that the addition of lithium acetylide took place at the saturated carbonyl. Elemental analysis coupled with mass spectrum indicated a molecular formula of $C_{13}H_{16}O_2$. All the above data and also ^{13}C NMR spectrum are consistent with the structure **4** assigned to the ethynyl carbinol.

The course of ethynylation of the diketone **3** is in contrast to its reactions with other nucleophilic reagents

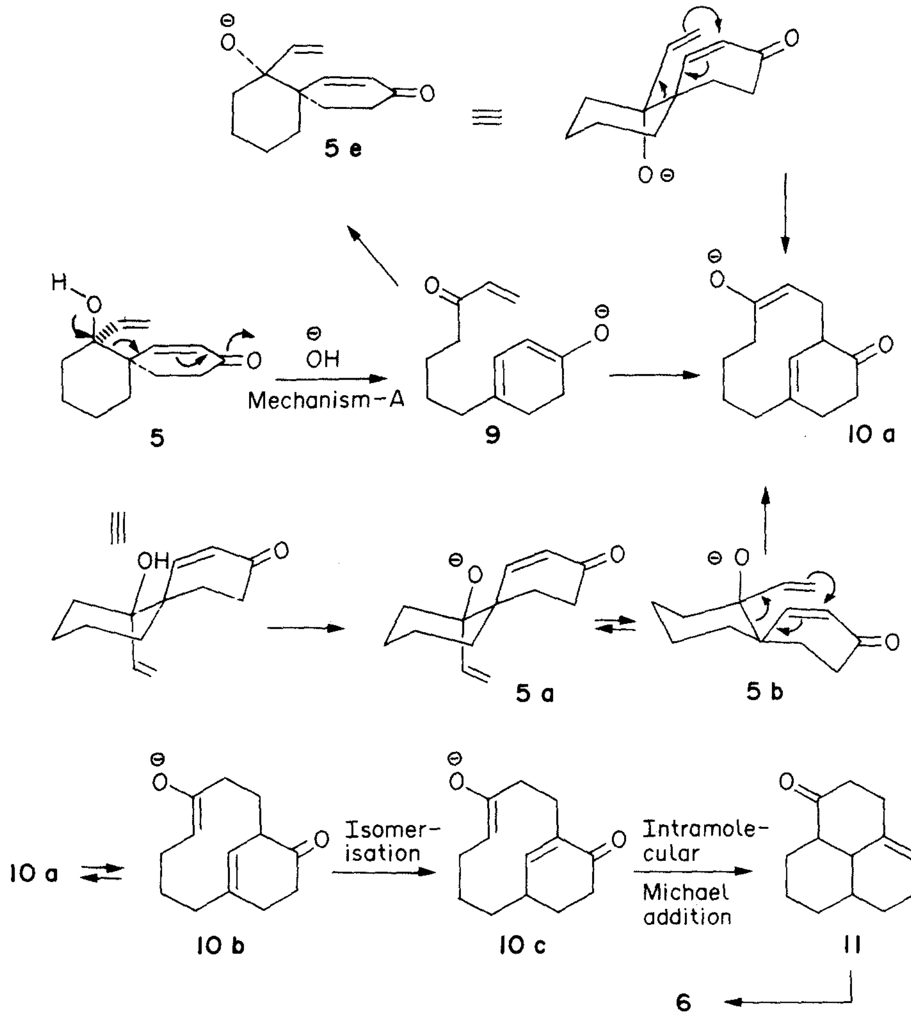
Refluxing the vinyl carbinol **5** with a catalytic amount of 4% aqueous potassium hydroxide furnished, after work up and purification, a colourless viscous liquid homogeneous on tlc and characterised as a disemicarbazone. The IR spectrum of the liquid product showed a strong absorption at 1700 cm^{-1} (>C=0). The ^1H NMR spectrum showed significantly the complete disappearance of all olefinic protons and the presence of two broad symmetric peaks between δ1.3 and 2.6 in the ratio of 4:5. Molecular weight (*m/e* 206) from mass spectrum and elemental analysis showed the compound to be isomeric with the starting vinyl carbinol **5**. The above data are best interpreted in favour of structure **6**-perhydrophenalene-1,4-dione—for the product.



6

^{13}C NMR spectrum also lends ample support for the structure **6** and showed the following peaks (δ values in ppm): 212.2 and 210.84 (s, C_1 and C_4); 49.74 and 48.08 (d, C_{10} and C_{12}); 46.24 and 40.93 (t, C_2 and C_5); 38.81 and 35.87 (d, C_{11} and C_{13}) and other carbons at 30.14; 26.74; 25.49; 25.35 and 19.71 as triplets.

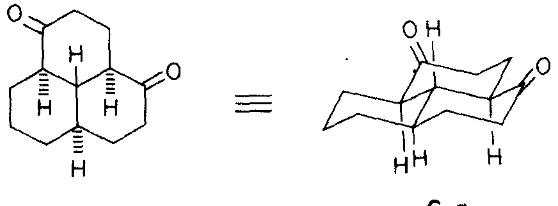
The formation of compound **6** can be rationalised as in Scheme 1:



Scheme 1.

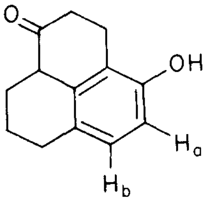
Either a fragmentation—recombination mechanism (Mechanism A) or a concerted oxy-Cope mechanism may be envisaged. Mechanism A involves a retroaldol (**5**→**9**) reaction, equilibration of the anion formed (**10a**⇄**10b**→**10c**), an intramolecular Michael addition (**10C**→**11**) and finally protonation to give **6**. A concerted oxy-Cope reaction is unlikely to take place in species **5a** which has the two vinyl moieties in the unfavourable 1,2-diaxial geometry. A flip over of ring A will give species **5b** with the two vinyl moieties in *trans* diequatorial geometry; a concerted oxy-Cope reaction can occur now to give species **10a** which can lead to compound **6** as in mechanism A. Alternatively, the retroaldol product **9** can undergo an internal 1,2-carbonyl addition to give species **5e** which is epimeric with **5a** and in which the vinyl moieties have a favourable cis geometry for a concerted oxy-Cope reaction to occur leading to **10a** and then to **6** as pictured earlier. The latter mechanism is similar to the one suggested by Heathcock and Tice for an analogous case.[8]

Since the rearrangement is being carried out under equilibrating conditions, the dione **6** may be expected to take up the most stable conformation *viz.* the all *trans* conformation **6a**.



6 6 a

With a view to get chemical evidence for the structure of compound **6**, attempts were made to dehydrogenate it. Only partial dehydrogenation to the phenol **7** resulted by refluxing compound **6** in *p*-cymene in the presence of Pd-C. Compound **7** had IR absorptions at 3600 (OH), 1700 (>C=O) and 1600 cm^{-1} (aromatic) and NMR proton signals at δ 1.3–2.5 (m, 10H, methylenes), 6.9 (d, 1H, H_a) and 7.1 (d, 1H, H_b). Attempts at further dehydrogenation of **7** gave essentially a mixture of starting material and a closely moving compound (tlc) believed to be the phenol **8**.



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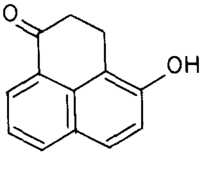
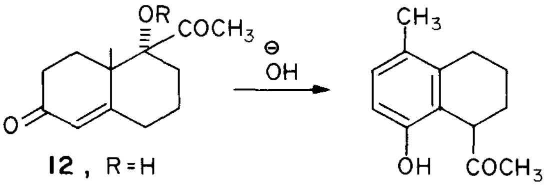


8

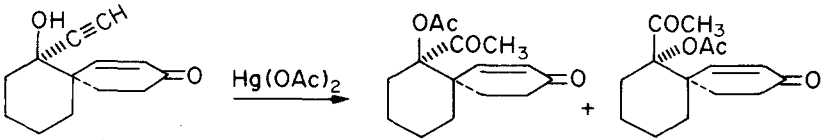
Base catalysed rearrangement of epimeric spiro ketol acetates **15a** *and* **15b**

The ketol **12** and its acetate **13** have been shown to rearrange to the napthol **14** in previous studies.[9]



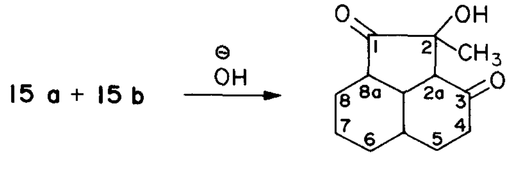
12, R=H
13, R=COCH3
14

It was of interest, therefore, to hydrate the ethnyl carbinol **4** and study the behaviour of the product of hydration, in the presence of base. The carbinol **4** was readily hydrated to give, after chromatographic purification, a colourless viscous liquid in 60–70% yield; this liquid though homogeneous on tlc, was a mixture of the epimeric ketol acetates **15a** and **15b** as evidenced by the presence of overlapping doublets at δ 6.0 and 7.2 for the enone protons in the NMR spectrum.



4 15 a 15 b

Refluxing this epimeric mixture of ketol acetates with methanolic potassium hydroxide furnished a colourless crystalline solid in 27% yield with a molecular formula $C_{13}H_{18}O_3$ as shown by mass spectrum and analysis. The IR spectrum displayed absorptions at 3420 (OH), 1735 (cyclopentanone CO) and 1700 cm^{-1} for another CO group. In the NMR spectrum, the characteristic AB quartet for the enone protons present in the carbinol **4** was significantly absent. Instead, the NMR spectrum showed absorptions at δ 1.2 (s, 3H, tertiary Me) and 1.4–2.5 (m, 15H, methylenes). These data are best interpreted in favour of structure **16** for the product.

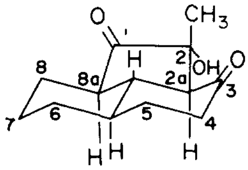


16

The formation of product **16** can be accounted for as given in Scheme 2.

The intermediate **16a** formed by fragmentation can give rise to **16b** by an internal aldol condensation; a subsequent intramolecular Michael addition leads to the perhydronaphthylene derivative **16**.

The fact that the tertiary -OH in product **16** survived the base treatment indicates an unfavourable geometrical disposition of the OH and the H at C-2a for an E_2 elimination and also the inherent strain involved in the ring system with the *endo* double bond. Furthermore, the OH and C_{2a}-C_3 bond must be *trans* dipseudo equatorial as in **17**; if they were diaxial, a retroaldol fragmentation of **16** might have resulted. Since the reaction was done under equilibrating conditions, the all *trans* conformation **17** may be written down for the product **16**.



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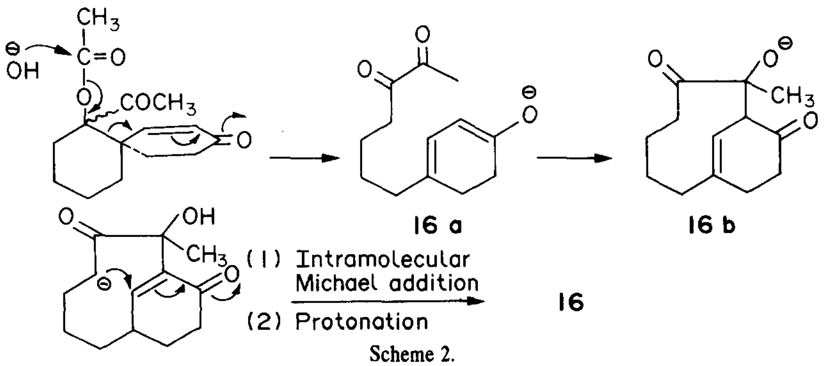
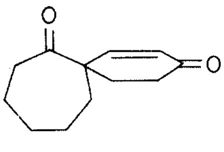
In an extension of the above studies, it was of interest to undertake the ethynylation of the known spirodiones[6] **18** and **19**.



Scheme 2.



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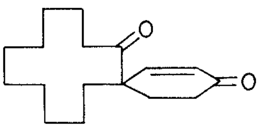
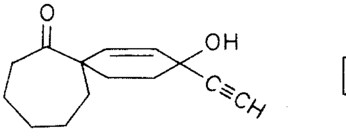


19

The products of reaction with lithium acetylide in liquid ammonia in both cases *viz.* **18** and **19** turned out to be the carbinols **20** and **21** respectively, arising from the reaction at the conjugated cogroup in contrast to the course of ethynylation of the spirodione **3**.



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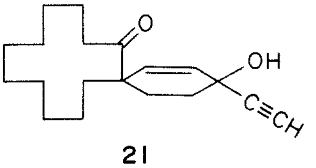

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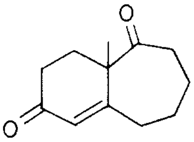

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The behaviour of diketones **18** and **19** is consistent with the observations of Dave and Whitehurst who also reported that the enone carbonyl in these diketones was more reactive towards some selected nucleophiles than the unconjugated CO group. Similar observations have also been reported from our laboratory[10] and elsewhere[11] on the addition of some nucleophiles including lithium acetylide to bicyclic diketone **22**. One plausible explanation for the reduced reactivity of the saturated carbonyl group in these diones is that medium sized ring ketones suffer from no torsional strain, but have transannular strain. Because of the latter effect, a CO group finds itself in a state of steric compression such that normal CO reactivities are diminished.

EXPERIMENTAL

All m.ps. and b.ps. are uncorrected. IR spectra were recorded on a Beckmann IR-20 instrument. ^{1}H and ^{13}C NMR spectra were taken using Varian EM-390, Perkin-Elmer R-32 and Varian XL-100 spectrometers with CCl_4 and $CDCl_3$ as solvents. The chemical shifts are given in ppm downfield from the internal TMS. Mass spectra were recorded using Varian Mat CH-7 mass spectrometer. TLC was run over glass plates coated with silica gel -G(ACME) of 0.25 mm thickness and visualised with iodine. $MgSO_4$ was used as the drying agent.

The spirodiones **3**, **18**, and **19** were prepared essentially by the procedure reported by Whitehurst *et al*[6]. The reported yield of spirodiones **3** and **18** is only 35% based on 2-hydroxymethylene cyclohexanone. The yield could be improved to 50% by cyclising the crude Michael adduct from methyl vinyl ketone and 2-hydroxymethylene-cyclohexanone without purifying it by distillation.

General method for ethynylation of spirodiones **3**, **18**, *and* **19**. Li metal (0.56 g, 0.08 g atom) was added to liquid ammonia (distilled over Na) while dry acetylene gas was passed through the soln. After the formation of lithium acetylide was complete, the soln was cooled to −80° and spirodione (0.04 mole) in dry ether (100 ml) was added dropwise during 20 min with vigorous stirring. After stirring for 1 hr the mixture was quenched with solid NH_4Cl (5g). After completely evaporating ammonia, water (20 ml) was added to the residue and was extracted with $CHCl_3$ (2 × 75 ml). The combined $CHCl_3$ extracts were washed with sat NaCl aq and dried. Removal of the solvent by distillation under reduced pressure and chromatography of the residue over a column of silica gel (1:4 EtOAc-petrol) furnished the carbinols. The carbinol **4** was obtained as a colourless crystalline solid, m.p. 124–125, yield: 50%; ^{1}H NMR ($CDCl_3$/TMS): δ1.4 − 2.2 (m, 12H, methylenes); 2.6 (s, 1H, C≡CH); 3.0 (br s, 1H, -OH); 6.0 (d, 1H, J = 9.5 Hz, -CH≡C$\underline{\text{H}}$-CO-) and 7.1 (d, 1H, J = 9.5 Hz, -C$\underline{\text{H}}$≡CO-); IR (KBr); 3300 (tertiary OH), 3200 (-C≡CH) and 1660 cm^{-1} (α, β-unsaturated ketone); UV (EtOH); λ_{max} 232 nm (ϵ = 7,136); ^{13}C NMR ($CDCl_3$/TMS); δ210.5(s, C_9), 157.32 (d, C_7), 130.28 (d, C_8), 86.4 (s, C_1), 75.6 (d, C_{13}), 73.36 (s, C_{12}), 43.8 (s, C_6) and other carbons at 35.38, 33.9, 31.92, 25.72, 22.54, and 20.78 as triplets. $C_{13}H_{16}O_2$ requires C = 76.44, H = 7.9; Found: C = 76.6, H = 8.1%; *m/e* at 204. The ethynyl carbinol **20** was obtained as a viscous syrupy liquid, yield 1.5g (30%); NMR ($CDCl_3$/TMS): δ1.5 − 2.2 (m, 14H, methylenes); 2.5 (s, 1H, -C≡CH); 3.8 (br s, 1H OH); 5.7 (d, 1H, J = 10 Hz, -CH=C$\underline{\text{H}}$-C$\lfloor$-) and 5.8 (d, 1H, J = 10 Hz, -C$\underline{\text{H}}$=CH-C-); IR ($CHCl_3$): 3600 (tertiary OH), 3300 (-C≡CH) and 1700 cm^{-1} (>C=0); $C_{14}H_{18}O_2$ requires: C = 77.06, H = 8.25; Found: C = 77.4, H = 8.50%; *m/e* at 218.

The ethynyl carbinol **21** was obtained, after crystallisation (1:9 EtOAc-petrol), as a colourless crystalline solid; m.p. 105–107° yield 2.2 g (35%); NMR (CCl_4/TMS): δ1.1 − 2.4 (m, 24H, methylenes); 2.5 (s, 1H, -C≡C$\underline{\text{H}}$), 5.7 (d, 1H, J = 10 Hz, CH=C$\underline{\text{H}}$- C -) and 5.8 (d, 1H, J = 10 Hz, C$\underline{\text{H}}$=CH- C -); IR ($CHCl_3$); 3590 (br, -OH), 3300 (-C≡CH) and 1700 cm^{-1} (>C = 0); $C_{19}H_{28}O_2$ requires: C = 79.12, H = 9.79; Found: C = 79.36, H = 10.0%; *m/e* at 288.

Hydrogenation of ethynyl carbinol **4**. A solution of **4**(1g) in dry pyridine (5 ml) was hydrogenated over Pd-$CaCO_3$ (100 mg) at 25 psi of H-pressure for 20 min. The catalyst was filtered off and the solvent removed by distillation under reduced pressure. The residue was diluted with ether (50 ml) and successively washed with ice-cold 1% HCl, water and dried. Removal of the solvent under reduced pressure and purification of the residue by chromatography over silica gel (1:4 ethylacetate- petrol) gave analytically pure **5**, yield = 0.9 g (90%). NMR ($CDCl_3$/TMS): δ1.3–2.5 (m, 13H, methylenes and OH), 5.1–6.0 (m, 3H, $CH=CH_2$), 6.0 (d, 1H, J = 9.5 Hz, CH=C$\underline{\text{H}}$-CO) and 7.1 (d, 1H, J = 9.5 Hz, C$\underline{\text{H}}$=CH-CO); IR ($CHCl_3$): 3600 (-OH) and 1660 cm^{-1} (α,β-unsaturated ketone); UV (EtOH): λ_{max} 233.6 nm (ϵ = 6,900); $C_{13}H_{18}O_2$ requires: C = 75.69, H = 8.8; Found: C = 75.40, H = 8.95%; *m/e* at 206.

Rearrangement of compound **5** *to* **6**. Compound **5** (0.5 g) was refluxed with a catalytic amount of 4% KOHaq in MeOH (20 ml) for 2 hr. Solvent MeOH was removed under reduced pressure, water (5 ml) was added to the residue and extracted with $CHCl_3$ (2 × 20 ml). The organic layer was washed with water once and dried. Removal of solvent left a viscous liquid which on chromatographic separation over silica gel (1:4 EtOAc- petrol) gave **6** as a colourless, viscous liquid. This liquid solidified in the refrigerator but melted at room temp, yield: 0.25 g (50%); ^{1}H NMR ($CDCl_3$/TMS): δ1.3–2.6 (two broad multiplets in the ratio of 4:5); IR ($CHCl_3$): 1700 cm^{-1} (>C=0); $C_{13}H_{18}O_2$ requires C = 75.69, H = 8.81; Found: C = 75.35, H = 9.1%; *m/e* at 206. The bis semicarbazone melted at 180–182.° NMR spectrum of this could not be taken due to poor solubility. IR (KBr): 3410 (-NH), and 1670 cm^{-1} (>C=0): $C_{15}H_{24}N_6O_2$ requires: C = 56.25, H = 7.51, N = 26.25; Found: C = 56.60, H = 7.56, N = 26.1%.

Partial dehydrogenation of compound **6** *using* Pd-C. A mixture of **6** (0.2 g), 10% Pd-C (0.02 g) and *p*-cymene (15 ml) was refluxed for 24 hr and extracted with 3% NaOHaq (2 × 10 ml). The alkali extract was neutralised, extracted with ether (2 × 25 ml), organic layer washed with water and dried. Solvent ether was distilled off and the crude residue was purified by passing through a column of silica gel (1:1 petrol - ether) to get the pure **7** as a viscous liquid, homogeneous on TLC, yield = 80 mg (40%); NMR (CCl_4/TMS): δ1.3–2.5 (m, 10H, methylenes), 6.9 (d, 1H, H_a) and 7.1 (d, 1H, H_b); IR ($CHCl_3$): 3600 (-OH), 1700 (>C=0) and 1600 cm^{-1} (aromatic).

Hydration and rearrangement of ethynyl carbinol **4**. A mixture of **4** (2.0 g, 0.01 mole), mercuric acetate (6.1 g, 0.02 mole) and EtOAc (40 ml) containing 1 ml of water was stirred at room temp for 20 hr. The soln was saturated with H_2 and the precipitated mercuric sulphide was filtered off. The filtrate was successively washed with water, sat $NaHCO_3$aq, water and dried. Removal of solvent under reduced pressure and chromatography of the crude product over silica gel (2:3 EtOAc- petrol) gave the epimeric mixture of **15a** and **15b** as a colourless viscous liquid, homogeneous on tlc, yield = 1.8 g (70%); NMR ($CDCl_3$/TMS): δ2.1 (s, 3H, $-COCH_3$), 2.2 (s, 3H, $-OCOCH_3$), 6.0 (overlapping doublets, 1H, J = 10 Hz, –CH=C$\underline{H}$–CO), 7.2 (overlapping doublets, 1H, J = 10 Hz, –C$\underline{H}$=CH–CO); IR ($CHCl_3$): 1730 ($-OCOCH_3$), 1700 ($-COCH_3$) and 1660 cm^{-1} (α,β-unsaturated ketone); $C_{15}H_{20}O_4$ requires: C = 68.16, H = 7.63; Found: C = 68.51, H = 7.7%; *m/e* at 264.

A soln of **15a** and **15b** (1 g) and KOH pellets (1 g) and MeOH (30 ml) was refluxed for 4–5 hr. Solvent MeOH was removed under reduced pressure, cold water (10 ml) was added and extracted with $CACl_3$ (2 × 50 ml). The extract was washed with water, and dried. A solid was obtained on removal of the solvent. Crystallisation (ETOAc–petrol afforded colourless crystals of **16**, m.p. 136–138°, yield = 0.3 g (27%); NMR ($CDCl_3$/TMS): δ1.2 (s, 3H, tertiary CH_3), 1.4–2.5 (m, 15H, methylenes and OH); IR (KBr): 3420 (strong, -OH), 1735 (cyclopentanone carbonyl), 1700 cm^{-1} (>C–O); $C_{13}H_{18}O_3$ requires C = 70.27, H = 8.18; Found: C = 70.42, H = 8.37%; *m/e* at 222.

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