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SYNTHETIC INTERMEDIATE POTENTIALLY USEFUL FOR THE SYNTHESIS OF DENDROBINE

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Abstract – Starting from thymol, a stereo-controlled synthesis of a *cis*-hydrindane derivative (**12**) possessing the desired stereochemistry at three asymmetric centres and functionalities for the synthesis of dendrobine (**1**) was carried out. In the final step of synthesizing **12**, abnormal ozonolysis of an allylic acetate system in **10** was employed, which could be effected under specific conditions.

DENDROBINE (**1**) a principal alkaloid obtained from *Dendrobium nobile* L. was shown by chemical and spectroscopic data to have the structure possessing the novel carbon skeleton and complex stereochemistry depicted in **1**.[1,2,3] Work on the synthesis of the tricyclic system of **1** has been recently reported.[4] We have been engaged in studies directed toward the synthesis of **1** and in the course of this work a facile stereo-controlled synthesis of a keto acid (**12**) a potentially useful intermediate for the synthesis of **1** was performed and is described here. An ingenious method of constructing a *cis*-hydrindane system *via* an intramolecular Michael condensation was reported by two groups and was employed in the present studies.[5,6]

As starting material, a butyric acid (**2**) was used,[7] which was prepared from thymol in three steps. The acid chloride of the butyric acid (**2**) was reacted with CH_2N_2. The resulting diazoketone was transformed by HI into a mixture of two compounds (**3** and the iodomethyl ketone), which was further treated with Zn in AcOH, affording the methyl ketone **3**. Treatment of **3** with ethylene glycol in the presence of acid gave the ketal **4** which was submitted to Birch reduction. Hydrolysis of the resulting enol ether, deketalization, and isomerization of the double bond were cleanly performed under the conditions specified in the experimental. The product showed one peak on GLC, indicating the formation of one diastereoisomer of a cyclohexenone derivative. The structure of the cyclohexenone (**5**) was secured by spectral data. When **5** was treated with t-BuOK in t-BuOH, a tricyclic ketol (**7**) was obtained in good yield. The structure of **7** was confirmed by spectral evidence: while the IR spectrum showed a strong band (saturated C=O) at 1701 cm^{-1} and a broad band (OH) at 3500 cm^{-1}, a singlet due to an angular Me group at δ 1·06 and a singlet (disappeared on addition of CF_3COOH) of an OH proton at δ 2·50 were observed in the NMR spectrum (*cf.* experimental). It should be noted that the Me signal at δ 2·08 arising from the MeCO group in **5** was not observed in the NMR spectrum of **7**. The formation of **7** is rationalized by the intramolecular Michael reaction of **5**, followed by an intramolecular aldol condensation. Acid-catalyzed cyclization of **5** was effected in ethanolic HCl under reflux for 3 hr, giving a mixture of two compounds (**6a**, **6b**) in approximately equal amounts: the IR spectrum of the mixture showed a saturated C=O band and the NMR spectrum revealed two singlets at δ 1·18 and 1·22 due to an angular Me group.

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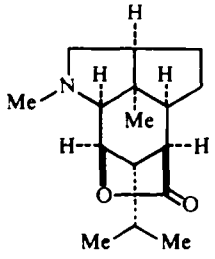

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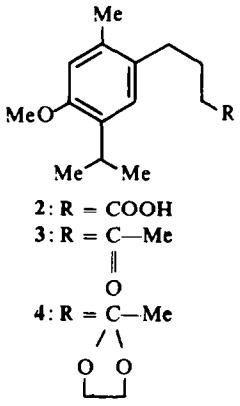

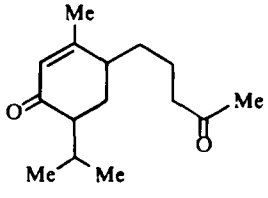

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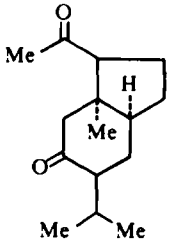

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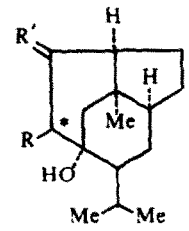
These two compounds were deduced to have a bicyclic structure as shown in **6**, and presumably would be stereoisomeric regarding the MeCO group. The mixture, without separation was treated with t-BuOK in t-BuOH to afford the tricyclic ketol (**7**).

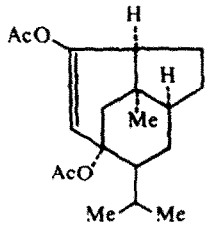
Various attempts* were made to remove the extra carbon marked with an asterisk in **7**. As one of the methods for this purpose, efforts were directed to the preparation of enol derivatives of **7**. Whereas enol ethers of **7** could not be prepared under a variety of conditions.† the diacetate (**10**) was obtained on treatment of **7** with isopropenyl acetate or Ac_2O·in the presence of *p*-toluenesulfonic acid. It is a general phenomenon that while abnormal ozonolyses involving rearrangements occur to a various extent in allylic alcohols and allylic ethers, ozonolyses of allylic acetates proceed in the normal manner without formation of abnormal products.[8,9] It is noteworthy that, contrary to this general phenomenon[8,9] the desired keto acid (**12**) resulting from rearrangement of the ozonide was obtained in the single step from **10** under the following condition. The diacetate (**10**) was ozonized in AcOH–AcOEt (v/v. 1:9) at 0° and the ozonide

* Some attempts examined were: (i) SeO_2 oxidation of **7** afforded a complex mixture. (ii) **7** with i-amyl nitrite under acidic conditions gave starting material. (iii) Bromination of **7** afforded an α-bromoketone (**8**), oxidation of which with DMSO did not take place. (iv) A diol **9** obtained by reduction with $NaBH_4$ or $LiAlH_4$ at elevated temperatures did not form a mesylate, useful for a fragmentation reaction. (v) Oxidation of **7** with $Pb(OAc)_4$ did not afford an α-acetoxy ketone derivative.

† The keto group in **7** seems to undergo addition reactions with great difficulty as exemplified by $NaBH_4$ reduction of **7** (*cf.* **9**), presumably owing to steric reasons. This property of the keto group in **7** would be responsible for the inability of forming the enol ether under the usual conditions, since the enol ether is formed from a ketone *via* the hemiketal or the ketal.



7: R = H; R′ = O
8: R = Br; R′ = O
9: R = H; R′ = H, OH



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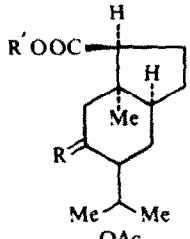
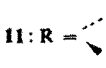
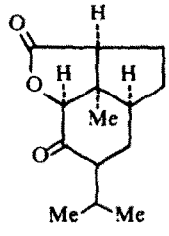


11: R =  : R′ = H
12: R = O; R′ = H



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decomposed with water at room temp, affording the keto acid **12**, $C_{14}H_{22}O_3$ [mass 238 (M^+)] (60%) together with a dicarboxylic acid (**11**) (16%), the normal ozonolysis product. The major product showed a strong band at 1720 cm^{-1} in the IR spectrum. a broad singlet (1H) of the carboxyl group at δ 8·2 and no signal corresponding to an acetate group in the NMR spectrum. which confirmed the structure as indicated in **12**. The structure of **11** was also secured by spectral data. The yield of the abnormal product **12** depends remarkably on the ozonolysis condition: e.g., ozonolysis of **10** in $CHCl_3$ at 0°. followed by treatment of the ozonide with Zn in ether–AcOH afforded **11** (~25%) as a major product together with **12** (10%). The keto acid **12** on treatment with pyridinium hydrobromide perbromide in THF gave a keto lactone (**13**). which showed two C=O bands at 1780 cm^{-1} (γ-lactone) and 1715 cm^{-1} (six-membered ring ketone). Formation of **13** confirms the stereochemistry of the carboxyl group as depicted in **12**. The configuration of the isopropyl group which is unknown in **12** could be controlled in the desired direction in the later stages of the synthesis.

Thus. the stereo-controlled synthesis of a *cis*-hydrindane system (**12**) containing the correct stereochemistry at three asymmetric centers and functionalities for the synthesis of **1** was achieved.

EXPERIMENTAL

M.ps are uncorrected. UV spectra were determined in MeOH on a Perkin–Elmer Model 202. IR spectra were recorded on a JASCO Model IR-S. NMR spectra were recorded on a JNMC-60H; only prominent peaks are cited; chemical shifts are in ppm from TMS as internal standard (δ); Mass spectra were obtained on a Hitachi RMU-6D mass spectrometer equipped with an all glass inlet system (ionization energy of 70 eV). GLC analyses were performed on a Hitachi K-52 on columns packed with 5% SE-30 on Chromosorb

W at 230°. TLC was carried out on silica gel GF_{254} (Merck) and column chromatography on silicic acid (100 mesh. Mallinckrodt). Organic solutions were dried over anhydrous Na_2SO_4 and evaporated by rotary evaporator.

5-(2'-Methyl-4'-methoxy-5'-isopropyl)pentan-2-one (**3**). To a solution of 7·0 g of γ-(2-methyl-4-methoxy-5-isopropylphenyl)butyric acid (**2**)[7] in dry C_6H_6 (35 ml) was added 11·5 g of oxalyl chloride and the mixture kept at room temp overnight. On removal of solvent a residue was obtained. which was taken up in C_6H_6 (35 ml). This solution was gradually added to CH_2N_2 (*ca.* 4·5 g) in ether at 0°. After 2 hr the solution was evaporated and the remaining oily diazoketone dissolved in $CHCl_3$. shaken with 55% HI for 10 min and evaporated. giving an oily residue. This was treated with 5·6 g of powdered Zn in AcOH (250 ml). diluted with water (500 ml) and filtered. The filtrate was extracted with C_6H_6 repeatedly and the combined extracts washed with water. $NaHCO_3$ aq. and water. Removal of C_6H_6 afforded 7·5 g of crude **3**. which was distilled. giving 5·6 g (81%) of pure **3**. (GLC analysis showed one peak). b.p. 146–148°/3 mm; IR (CCl_4) 1715 cm^{-1}; NMR (CCl_4) 1·17 (6H. d. J = 6·8 Hz. Me_2CH–). 2·03 (3H. s. Me-CO-). 2·24 (3H. s. aromatic Me). 3·77 (3H. s. MeO-). 6·49 (1H. s. aromatic H). 6·78 (1H. s. aromatic H); mass 248 (M^+). (Found: C. 77·42; H. 9·94. $C_{16}H_{24}O_2$ requires: C. 77·37; H. 9·74%).

2-Ethylenedioxy-5-(2'-methyl-4'-methoxy-5'-isopropylphenyl)pentane (**4**). A mixture of the methyl ketone **3** (6·0 g). *p*-TsOH (0·24 g), and freshly distilled ethylene glycol (15 ml) in C_6H_6 (360 ml) was refluxed for 5 hr in a system equipped with a water-separator. The mixture was cooled. washed with 5% NaOH aq and water. Removal of solvent gave crude **4**. which was distilled. giving 5·4 g (77%) of pure ketal **4** (GLC analysis showed one peak). b.p. 149–151°/2 mm; NMR (CCl_4) 1·17 (6H. d. J = 7·0 Hz. Me_2CH–). 122 (3H. s. Me—C(O–)(O–)—). 2·23 (3H. s. aromatic Me). 3·75 (3H. s. MeO-). 3·82 (4H. s. —OCH_2CH_2O—). 6·48 (1H. s. aromatic H). 6·82 (1H. s. aromatic H); mass 292 (M^+). (Found: C. 74·24; H. 9·77. $C_{18}H_{28}O_3$ requires: C. 73·93; H. 9·65%).

3-Methyl-4-(4'-oxopentyl)-6-isopropyl-2-cyclohexenone (**5**). To a solution of the ketal **4** (2·2 g) in anhyd THF (36 ml). anhyd t-BuOH (58 ml). and liquid NH_3 (145 ml). Li (4·35 g) was added in several portions over a period of 30 min with stirring. The dark blue mixture was kept at *ca.* −40° for 15 hr and allowed to stand at room temp. After evaporation of NH_3. water was added carefully. and the mixture concentrated *in vacuo*. The resulting aqueous mixture was extracted with C_6H_6 repeatedly and the combined extracts washed with water. The residue obtained on removal of solvent was dissolved in 0·2 N ethanolic HCl (EtOH-water. 1:1) (50 ml). refluxed for 1 hr (refluxing for longer time caused partial cyclization of **5**). cooled. and diluted with water. The resulting mixture was extracted with C_6H_6 several times. and the combined solutions washed with aqueous $NaHCO_3$ and water. On removal of solvent a yellow oil was obtained. Distillation of the oil gave 1·32 g (74%) of the cyclohexenone **5**. which showed a single peak on GLC analysis. b.p. 180–182°/4 mm; IR (CCl_4) 1716. 1670. 1626 cm^{-1}; NMR (CCl_4) 0·79 (3H. d. J = 6·7 Hz. Me of the isopropyl group). 0·93 (3H. d. J = 6·7 Hz. Me of the isopropyl group). 1·93 (3H. d. J = 1·5 Hz. vinyl Me). 2·08 (3H. s. Me–CO–). 5·63 (1H. d. J = 1·5 Hz. vinyl H); mass 236 (M^+).

Tricyclic ketol (**7**). A solution of 3·0 g of **5** in t-BuOH (50 ml) containing t-BuOK (0·29 g) was stirred at 30° for 40 hr. acidified with dil HCl. and diluted with water. The mixture was extracted with C_6H_6 repeatedly and the combined extracts washed with water. On removal of solvent a yellow oil was obtained. and chromatographed on silicic acid with $CHCl_3$. giving 1·43 g (48%) of crystals (**7**). sufficiently pure for next step. Pure **7** was obtained by recrystallization from ligroin. m.p. 81–83°; UV 279 nm (ε 30); IR (CCl_4) 3500. 1701 cm^{-1}; NMR (CCl_4) 0·80 (3H. d. J = 7 Hz. Me of the isopropyl group). 0·96 (3H. d. J = 7 Hz. Me of the isopropyl group). 1·06 (3H. s. tert. Me). 2·50 (1H. s. OH. disappeared on addition of CF_3COOH); mass 236 (M^+). (Found: C. 76·44; H. 10·49. $C_{15}H_{24}O_2$ requires: C. 76·22; H. 10·24%).

Cyclization of **5** *under acidic conditions.* A solution of *ca.* 2 g of **5** in 50 ml of 2N HCl (water-EtOH. 1:1) was refluxed for 3 hr. concentrated *in vacuo*. and extracted with C_6H_6 several times. The combined extracts were washed with water. $NaHCO_3$ aq. water. and dried. Evaporation of solvent afforded an oil. consisting of two compounds (**6a. 6b**): IR (CCl_4) 1715 cm^{-1}; NMR (CCl_4) ~0·9 (complex pattern. Me_2CH-). 1·18 and 1·22 (s. each. tert.Me; intensity of each singlet approximately same). 2·10 (3H. s. Me–CO–). The mixture was treated with t-BuOK in t-BuOH as described in the cyclization of **5** to **7**. giving crystals of **7**.

Bromination of the tricyclic ketol **7**. To a solution of the ketol **7** (50 mg) in AcOH (5 ml) was added dropwise a solution of Br_2 (*ca.* 50 mg) in AcOH (6·5 ml), kept at room temp for 15 min, cooled at 0°, and diluted with EtOH. The mixture was evaporated and the residue was taken up in C_6H_6. The solution was washed with $NaHCO_3$ aq and water. On removal of solvent a brown residue was obtained. chromatographed on silicic acid to give 52 mg (78%) of oily bromoketone **8**; UV 297 nm; IR (CCl_4) 3560. 1705 cm^{-1}; NMR

(CCl_4) 0·81 (3H. d. J = 7 Hz. Me of the isopropyl group). 0·98 (3H. d. J = 7 Hz. Me of the isopropyl group). 1·06 (3H. s. tert.Me). 2·12 (1H. s. OH). 4·51 (1H. d. J = 2·0 Hz. –CO–CHBr–); mass 316 and 314 (M^+).

Reduction of **7** *with complex metal hydrides.* (a) A mixture of **7** (70 mg) and $NaBH_4$ (40 mg) in EtOH (15 ml) was kept at 45–55° for 9 hr with stirring. evaporated. diluted with water. and extracted with C_6H_6 several times. The combined extracts were washed with water. On evaporation of solvent there remained 53 mg (76%) of crystals (**9**). Recrystallization from ligroin gave pure **9**. m.p. 95–98°; IR ($CHCl_3$) 3500–3200 cm^{-1} (broad); mass 238 (M^+). (Found: C. 75·53; H. 11·44. $C_{15}H_{26}O_2$ requires: C. 75·58; H. 11·00%).

(b) A mixture of **7** (50 mg) and $LiAlH_4$ (30 mg) in dry ether (10 ml) was kept at room temp with stirring for 9 hr. then AcOEt was added slowly. The mixture was diluted with water and extracted with ether repeatedly. The extracts were washed with water and evaporated. giving 42 mg (84%) of crystals **9**.

Acetylation of the tricyclic ketol **7**. A mixture of the ketol **7** (90 mg). camphorsulphonic acid (60 mg). and Ac_2O (8 ml) was kept at 102–105° for 15 hr. The brown mixture was added with solid AcOK (60 mg) and evaporated. giving a residue. which was taken up in a mixture of $CHCl_3$ (10 ml) and $NaHCO_3$ aq (10 ml). The aqueous phase was further extracted with two 10 ml portions of $CHCl_3$. The combined extracts were washed with water and a saturated NaCl aq. dried. and evaporated. giving 110 mg of brown oil. Chromatography of the residue over silicic acid (5·5 g) using $CHCl_3$ afforded 105 mg (92%) of colorless liquid **10**. sufficiently pure for the next step; IR (CCl_4) 1760. 1740. 1672 cm^{-1}; NMR (CCl_4) 0·75 (3H. d. J = 7·0 Hz. Me of the isopropyl group). 0·88 (3H. d. J = 7·0 Hz. Me of the isopropyl group). 1·00 (3H. s. tert.Me). 1·95 (3H. s. AcO). 2·08 (3H. s. AcO). 5·20 (1H. br. s. vinyl H); mass 320 (M^+).

Ozonolysis of the diacetate **10**. (a) Ozone was passed through a solution of 120 mg of **10** in 12 ml of AcOH–AcOEt (v/v, 1 :9) at 0° for 3 hr. After excess ozone was removed by passing N_2 rapidly into the solution. water (8 ml) was added. The mixture was vigorously stirred at room temp for 15 hr and concentrated *in vacuo*. affording a colourless oil. which was taken up in AcOEt (15 ml). The AcOEt solution was extracted with three 8 ml portions of saturated $NaHCO_3$ aq. The combined extracts were acidified with dil HCl. to which solid NaCl was added. The aqueous solution was shaken with three 10 ml portions of AcOEt and the combined AcOEt extracts washed with saturated NaCl aq. Removal of solvent gave 90 mg of a colourless oil. which showed two spots on TLC with $CHCl_3$. The oily residue was chromatographed on silicic acid (4·5 g); fractions eluted with $CHCl_3$–AcOEt (5 :1) gave 57 mg (60%) of crystals (**12**) and fractions eluted with $CHCl_3$–AcOEt (5 :2) afforded 20 mg (16%) of crude crystals (**11**).

11: m.p. 171–173° (dec.) [recrystallization from AcOEt–petroleum ether (b.p. 30–60°)]; IR ($CHCl_3$) 1735. 1715 cm^{-1} (shoulder); NMR (acetone-d_6) 0·76 (3H. d. J = 7·0 Hz. Me of the isopropyl group). 0·99 (3H. d. J = 7·0 Hz. Me of the isopropyl group). 1·35 (3H. s. tert. Me). 2·00 (3H. s. AcO). *ca.* 9 (2H. br.s. two COOH). (Found: C. 62·26; H. 8·04. $C_{17}H_{24}O_6$ requires: C. 62·56; H. 8·03%).

12: m.p. 114–115° (recrystallization from ligroin); IR (CCl_4) 1720 cm^{-1} (broad. strong); NMR ($CDCl_3$) 0·80 (3H. d. J = 7·5 Hz. Me of the isopropyl group). 0·93 (3H. d. J = 7.5 Hz. Me of the isopropyl group). 1·20 (3H. s. tert.Me). *ca.* 8·2 (1H. br.s. COOH); mass 238 (M^+). (Found: C. 70·24; H. 9·19. $C_{14}H_{22}O_3$ requires: C. 70·55; H. 9·31%).

(b) Through a solution of 230 mg of crude **10** in $CHCl_3$ (10 ml) ozone was passed for 1 hr at 0°. Removal of solvent gave an oily residue. which was dissolved in AcOH (2 ml) and ether (1 ml). Zn powder (200 mg) was added to the solution. and the mixture stirred at room temp overnight and filtered. The filtrate was concentrated. diluted with water. and repeatedly extracted with AcOEt. The combined extracts were shaken with $NaHCO_3$ aq several times. washed with water. dried. and evaporated. giving 66 mg of oily residue (a keto acetate resulting from hydrolysis of the enol acetate moiety of **10**). The combined $NaHCO_3$ solutions were acidified with 10% HCl and the mixture extracted repeatedly with AcOEt. The AcOEt solutions were washed with water and dried. Removal of solvent gave a solid (90 mg). which was washed with C_6H_6–petroleum ether (b.p. 30–60°) affording 20 mg of **11**. The residue obtained by treating the mother liquor with CH_2N_2 was chromatographed on silicic acid using $CHCl_3$; early fractions afforded 14 mg of the methyl ester of **12**. GLC analysis of which showed one peak. and from later fractions 20 mg of the dimethyl ester of **11** was obtained. Since the keto acetate (66 mg) was recovered. the yields of **11** and **12** actually obtained from **10** were 25% and 10% respectively.

Formation of the keto lactone **13**. Pyridinium hydrobromide perbromide (12 mg) was added to a solution of the keto acid **12** (~2 mg) in dry THF (0·3 ml). The solution was stirred at room temp for 20 min. added with several drops of acetone. and evaporated. giving a residue. which was taken up in $CHCl_3$–dil HCl. The organic layer which separated was washed with $NaHCO_3$ aq and saturated NaCl aq. dried. and evaporated. affording a colourless residue (**13**). which showed one spot on TLC with $CHCl_3$–AcOEt (4 :1) and a single peak on GLC analysis: IR ($CHCl_3$) 1780. 1715 cm^{-1}; mass 236 (M^+).

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