Tetrahedron. Vol. 26, pp. 5437 to 5446. Pergamon Press 1970. Printed in Great Britain

A STEREOSPECIFIC SYNTHESIS OF 2-ISOPROPYLIDENE-*cis,cis*-4,8-DIMETHYL-6-KETO-*cis*-DECAHYDROAZULENE[1]

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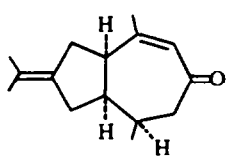
(*Received in USA* 30 *July* 1970; *Received in the UK for publication* 11 *August* 1970)

Abstract—A stereospecific synthesis of 2-isopropylidene-*cis,cis*-4,8-dimethyl-6-keto-*cis*-decahydroazulene (3) has been accomplished. Each of the 19 synthetic steps proceeds in good to excellent yields and the overall route permits a facile synthetic entry to carbocyclic systems of this type.

AT ITS inception the specific purpose of this research was to develop a total synthesis of β-vetivone, a sesquiterpene isolated from the essential oil of vetiver. The accepted structure for β-vetivone was as formulated in **1**.[3] However, in 1967 conclusive evidence was presented to show that structure **1** was incorrect[4] and it was reformulated as **2**.[5] Support for this reformulation was immediately forthcoming by the total synthesis of **2**.[5,6]



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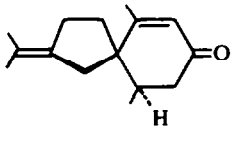

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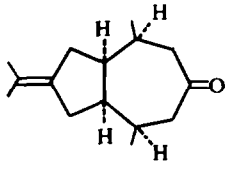

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Our synthetic efforts have led to a stereospecific synthesis of **3**. A comparison of the properties and IR spectrum of **3** with those of the ketone obtained by hydrogenation of β-vetivone from the natural source allowed us to deduce at about the same time as Marshall *et al.*[3,4] that the structure **1** was incorrect for β-vetivone.

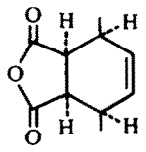
The scope of this manuscript will be to delineate a total stereospecific synthesis of the perhydroazulene structure **3**. Only a stereoselective route has been reported to the desisopropylidene analog of **3**, a route of limited stereochemical control.[4]

Synthetic route

The anhydride **4** with the stereochemical centers definitely established[7] was chosen as the starting compound for the synthetic objective. The development of the 5-membered ring was effected from the anhydride linkage and the 7-membered ring from the 6-membered unsaturated ring. The stereochemical centers (all *cis*) were left intact during all transformations and the four stereochemical centers in **3** were obtained.

The anhydride **4**[8] was reduced to the diol **5** (R = OH, R′ = Me)[8] with LAH. This diol **5** (R = OH, R′ = Me) on reaction with methanesulfonyl chloride in pyridine led to the dimesylate **5** (R = OMs, R′ = Me) in 90–95% yields. From this

intermediate **5** (R = OMs, R′ = Me) the formation of the 5-membered ring was envisioned by formation of the dicyanide **5** (R = CN, R′ = Me) and subsequent conversion to **6** either by a Thorpe–Ziegler cyclization followed by acidic hydrolysis of this cyclized product or by conversion of **5** (R = CN, R′ = Me) to the diacid **5** (R = COOH, R′ = Me) followed by a classical barium hydroxide ring closure sequence.



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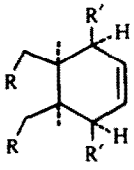

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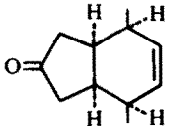

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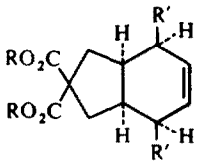
The reaction of the unsubstituted system **5** (R = OMs, R′ = H) with sodium cyanide in ethanol[9] or dimethylsulfoxide[10] as solvent readily led to good yields of the dicyanide **5** (R = CN, R′ = H). However, similar reaction conditions and longer heating times for the attempted conversion of **5** (R = OMs, R′ = Me) to the dicyanide **5** (R = CN, R′ = Me) were unsuccessful. Evidence for the incorporation of some cyanide in the molecule was obtained by IR analysis of the reaction products but absorptions for the sulphonate group were present and along with some unreacted **5** (R = OMs, R′ = Me) the mixture probably contained some of the monocyanide. One must attribute this resistance to didisplacement to a steric hindrance exerted by the ring Me groups in **5** (R = OMs, R′ = Me). These groups would exert a steric barrier to the approach of the attacking nucleophile (CN^-) and also a barrier to departure of the methanesulphonate group.

Despite the failures to obtain the dicyanide **5** (R = CN, R′ = Me), the reaction of the dimesylate **5** (R = OMs, R′ = Me) with the sodium salt of diethyl malonate in 1,2-dimethoxyethane or 1,2-dimethoxyethane-dimethylsulfoxide mixtures led to 80–90% yields of the diester **7** (R = Et, R′ = Me). Even after 117 hr of refluxing



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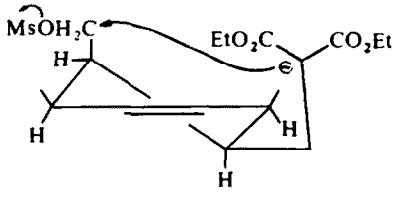

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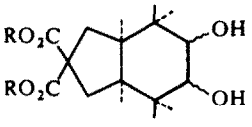

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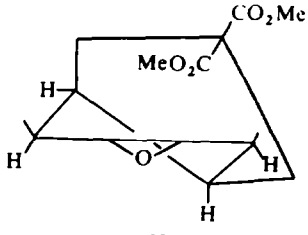
some unchanged **5** (R = OMs, R′ = Me) could be isolated from this reaction. The analogous reaction of **5** (R = OMs, R′ = H) to **7** (R = Et, R′ = H) also proceeded in good yield but with shorter reflux times than that necessary for **5** (R = OMs, R′ = Me). A similar ring formation reaction has been reported in the reaction of the ditosylate of *trans*-1,2-dimethanolcyclohex-4-ene with the anion of diethylmalonate in ethanol-benzene with added sodium iodide.[9c]

One notes that the system **5** (R = OMs, R′ = Me) yielded no isolatable dicyanide but that the 5-membered ring could be formed in an excellent yield from the anion of

diethylmalonate. In this latter case the anion of the monodisplacement product **8** is favorably positioned for an intramolecular S_N2 displacement of the second mesylate grouping to lead to **7** (R = Et, R′ = Me). However, in the case of the cyanide displacements the introduction of the second nitrile group is apparently sterically hindered.

The diester **7** (R = Et, R′ = Me) was saponified to the diacid **7** (R = H, R′ = Me) and then converted into the solid dimethyl ester **7** (R = CH_3, R′ = Me) by treatment with diazomethane. The NMR spectrum of this ester showed a doublet centered at δ 1·05 (J = 7 Hz) for the $C\underline{H}_3$— protons on the ring, singlets at 3·70 (3H) and 3·75 (3H) for the stereochemically different $C\underline{H}_3O$—C(=O)— protons and a singlet at 5·65 for the protons on the double bond.

The reaction of **7** (R = Me, R′ = Me) with formic acid, hydrogen peroxide,[11] followed by treatment with methanol, sodium methoxide, yielded a diol mixture **9** (R = Me) in yields of 70–80%. It was possible to isolate two crystalline diols from this reaction of m.p. 69–70° and 89–90° by repeated crystallization. These diols analyzed the same, exhibited different IR spectra and yielded the same dialdehyde **11** on oxidative cleavage. Therefore these isomers differ in the relative stereochemistry of the —OH groups and are perhaps the *cis*- and *trans*-diols. It seems likely that the *endo*-like carbomethoxy group is exerting an effect on the opening of the expected transiently formed epoxide in this reaction.



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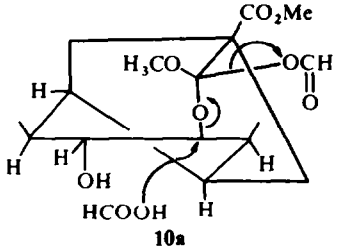
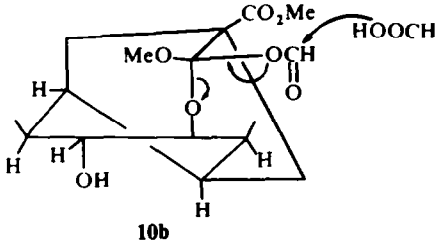


10a



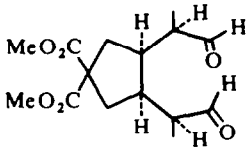
10b

Examination of Dreiding models seems to indicate a preferential attack of the double bond by the peracid to form the α-epoxide 10.[12] It is possible that the endo-carbomethoxy group participates in the opening of the epoxide via an intermediate such as **10a** which could open by attack of formic acid in the manner indicated to yield the formate ester of the α-*cis* diol. The *trans*-diol could result from a normal competitive epoxide ring opening process (attack of formic acid appears to be somewhat hindered from the backside of the C—O bond being broken) or collapse of intermediate **10a** as indicated in **10b**. On the basis of the available evidence no definite assignments can be made as to the stereochemistry of the two diols isolated.*

* The problem of stereochemistry is currently under investigation.

However, since the stereochemical question had no bearing on the success of the next synthetic step the isomer mixture was utilized. The oxidative cleavage of crude **9** (R = Me) with aqueous sodium meta periodate at 0° led to the dialdehyde **11** in excellent yield. The dialdehyde **11** showed strong carbonyl absorption at 5·80 μ (broad band) and at 3·67 μ (aldehyde proton). This reaction was also performed in heavy water to ascertain whether any epimerization of the protons adjacent to the aldehyde groups had occurred. IR analysis of the reaction product showed no detectable incorporation of deuterium. This suggests that enolization is slow and that no epimerization of the Me groups has occurred.

The reduction of the crude dialdehyde **11** to the diol **12** (R = OH) was effected in 80–90% yields by reaction with sodium borohydride in methanol at 0°. The IR spectrum of **12** (R = OH) showed a broad OH band at 3·02 μ and ester absorption at 5·76 μ. This diol on reaction with excess *p*-toluenesulfonyl chloride in pyridine led to a 90% yield of the ditosylate **12** (R = OTs). Reaction of **12** (R = OTs) with excess sodium cyanide in dimethyl sulfoxide as solvent at room temperature for 6 days led to the dicyanide **12** (R = CN) in 90% yield. In this displacement reaction it was found that if the dimethylsulfoxide was heated, the formation of the monoester dicyanide **13** resulted from a competing decarbomethoxylation reaction. This reaction was further exploited on simple esters and represents a new synthetic route for the formation of monoesters from geminal diesters.[13]



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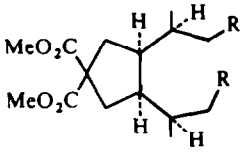

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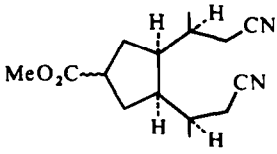

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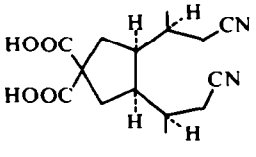
The reaction of **12** (R = CN) with aqueous sodium hydroxide at room temperature for 25 hr led to 90–95% yields of the diacid **14**. The decarboxylation of **14** in refluxing pyridine led to **16** in an excellent yield. An isomer mixture was obtained and no attempt was made to separate these isomers. The IR spectrum for this acid mixture exhibited a band at 5·85 μ for the carboxyl CO and a band at 4·42 μ for the cyanide group.

The next step in the synthetic sequence involved the formation of the 7-membered ring from intermediate **15**.



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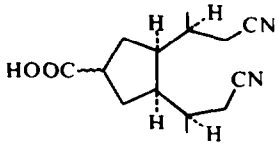

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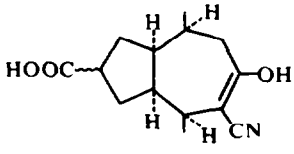

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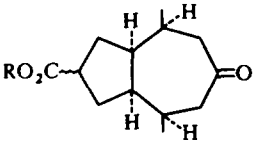
The cyclization was accomplished in 70–80% yields by refluxing **15** with excess potassium t-butoxide in benzene.[14] Hydrolysis of the crude reaction product with hydrochloric acid yielded **16**. Compound **16** showed infrared absorption at 4·50 μ

for the conjugated nitrile, 5·87 μ for the carboxyl group and 6·12 μ for the enolic double bond.

The hydrolysis of **16** was fairly difficult but could be accomplished in about a 50% yield by heating **16** with aqueous phosphoric acid at 150–175° for about 1 hr. This led to the keto acid **17** (R = H), which showed absorption in the infrared at



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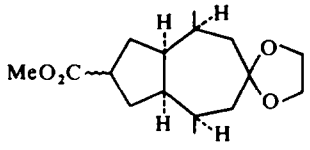

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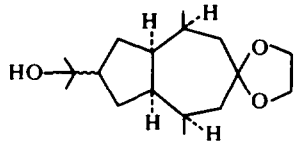

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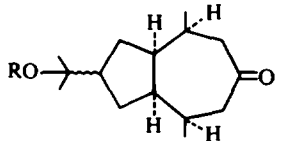
5·85 μ (shoulder) and 5·90 μ. The keto acid **17** (R = H) was converted into the methyl ester **17** (R = Me) by reaction with an ethereal solution of diazomethane in 80–90% yield. The NMR spectrum of **17** (R = Me) showed a doublet at δ 0·98 (6H, J = 6 Hz) for the Me protons and a singlet at δ 3·73 (3H) for the Me protons of the ester group. The IR showed an ester CO grouping at 5·78 μ and the ring CO at 5·90 μ.

With the basic ring skeleton now complete, the incorporation of the isopropylidene grouping remained. The reaction of **17** (R = Me) with ethylene glycol in benzene as solvent in the presence of *p*-toluenesulfonic acid led to a 80–90% yield of the ethylene ketal **18**. The IR spectrum of **18** showed a single CO absorption at 5·76 μ for the ester group. The NMR spectrum of **18** exhibited a doublet at δ 0·95 (6H, J = 6·5 Hz) for the Me protons, a singlet at 3·73 (3H) for the Me protons of the ester, and a singlet at 3·97 (4H) for the protons of the ethyleneketal.

Reaction of **18** with methylmagnesium iodide led to **19** which was not further



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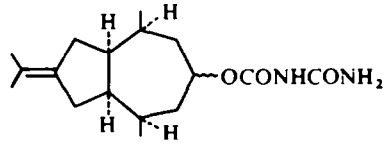

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purified and showed IR absorption at 2·90 μ for the OH group. The crude **19** was hydrolyzed to **20** in a 70% yield by reaction with dilute hydrochloric acid at room temperature. The ring carbonyl of **20** appeared at 5·92 μ in the IR spectrum. The NMR spectrum showed a doublet centered at δ 0·99 (6H, J = 6·5 Hz) for the Me protons on the 7-membered ring, a singlet at 1·30 (6H) for the Me groups on the carbon holding the OH group. Reaction of **20** (R = H) with acetic anhydride yielded the acetate **20** (R = Ac). The IR spectrum of **20** (R = Ac) showed ester absorption at 5·78 μ and ketone absorption at 5·90 μ. In the NMR, a doublet appeared at δ 1·00 (6H) for the Me groups on the ring, a singlet at 1·54 (6H) for the Me groups on the carbon bearing the OH group, a singlet at 2·02 (3H) for the acetate group proton and a broad peak at δ 2·45 (4H) for the protons α to the CO group.

The acetate **20** (R = Ac) by treatment with boron trifluoride etherate yielded mainly **3** along with a small amount of the methylene isomer. At this stage it was possible to make a comparison of synthetic **3** with the compound previously formulated as **3** from the natural source.

Optically inactive dihydro-6,7-β-vetivol had been prepared from β-vetivone by hydrogenation using Raney nickel.[2a] Dihydro-6,7-β-vetivol was regenerated from the allophanate derivative,* previously formulated as **21**[2a] by hydrolysis with aqueous methanolic sodium hydroxide and exhibited a m.p. of 108–109° (lit m.p. 108·5–109°). Oxidation of this alcohol with chromium trioxide-pyridine yielded dihydro-6,7-β-vetivone which had been formulated as **2**.[2a] A comparison of the IR spectrum of this ketone derived from natural β-vetivone and synthetic **2** clearly indicated the complete dissimilarity of the compounds. In particular, the CO stretching frequency of synthetic **3** exhibited absorption at 5·88 μ (7-membered ring ketone) while the material derived from the natural source showed CO absorption at 5·80 μ (6-membered ring ketone). Thus, structure **3** does not represent the structure of this ketone derived from β-vetivone.

Although the synthesis of the natural product was not successfully accomplished, the synthetic route developed is adaptable to the synthesis of other stereoisomers of this type system and the route represents a fairly easy scheme to compounds of the general carbon skeleton of **3**.

EXPERIMENTAL

cis,cis-3,6-*Dimethyl*-cis,cis-1,2-*dihydroxymethylcyclohex*-4-*ene* (**5**, R = OH, R′ = CH_3). The anhydride **4**[8] (100 g, 0·56 mole) in 400 ml dry 1,2-dimethoxyethane was added over a 4 hr period to LAH (25 g, 0·66 mole) in 500 ml 1,2-dimethoxyethane. The mixture was stirred for 10 hr, refluxed for 4 hr, cooled, and 200 ml water was added dropwise. An additional 100 ml 1,2-dimethoxyethane was added, the mixture was refluxed for 1 hr, cooled, and filtered. The filtrate was concentrated under water pump pressure and the diol **5** (R = OH, R′ = CH_3) distilled at 130–137° (0·3 mm). The diol solidified in the receiver, wt 78 g (83%), and was crystallized from ether at − 20° to yield 70 g (74%), m.p. 77–78° (lit.[8] 78–78·2°).

cis,cis-3,6-*Dimethylcyclohex*-4-*ene*-cis,cis-1,2-*dihydroxymethanol dimesylate* (**5**, R = OMs, R′ = CH_3). A soln of diol **5** (R = OH, R′ = Me) (32 g, 0·18 mole) in 150 ml pyridine was added over a 6 hr period to a cold soln of methanesulfonyl chloride (86 g, 0·76 mole) in 100 ml pyridine. The mixture was kept at − 20° overnight, poured into ice water, and the solid was filtered and dried, wt 54 g (90%), m.p. 66–68°. Crystallization from EtOAc-light petroleum yielded an analytical sample, m.p. 67–68°; IR (KBr) 7·45 μ and 8·53 μ (—SO_2—). (Found: C, 45·46; H, 6·89; S, 19·67. $C_{12}H_{22}S_2O_6$ requires: C, 45·25; H, 6·80; S, 19·89%).

cis,cis-2,5-*Dimethyl*-cis-*bicyclo*[4.3.0]*non*-3-*ene*-8,8-*dicarboxylic acid* (**7**, R = H, R′ = Me). Diethyl malonate (86 g, 0·54 mole) was added dropwise to a suspension of NaH (22·0 g of 58·6% in mineral oil, 0·54 mole) in 360 ml 1,2-dimethoxyethane under N_2. The dimesylate **5** (R = OMs, R′ = Me) (55·0 g, 0·17 mole) in 200 ml 1,2-dimethoxyethane and 80 ml DMSO was added and the mixture was refluxed for 117 hr. The salt was filtered and the filtrate was concentrated. Water was added, the mixture was extracted with pentane (5.5 g of unreacted **5** (R = OMs, R′ = Me) was recovered), and the pentane extracts were dried over Na_2SO_4. Evaporation of the pentane yielded 68 g crude **7** (R = Et, R′ = CH_3) (mineral oil still present).

To the oil was added a soln of KOH (50 g, 0·89 mole) in 200 ml water and 300 ml MeOH. The mixture was refluxed for 15 hr and the solvents removed in vacuum. About 300 ml water was added and the mixture was extracted with pentane. The aqueous layer was concd to 150 ml and acidified with conc HCl. The mixture was cooled and filtered to yield 30·4 g (84%) **7** (R = H, R′ = Me), m.p. 193–195°; IR (KBr 3,45 and 3·80 μ (broad), 5·85 μ (broad COOH); NMR (CD_3COCD_3, external TMS) δ 0·58 and 0·67 (d, —C<u>H</u>$_3$, J = 7 Hz) and 5·25 (s, <u>H</u>—C=C—<u>H</u>). The analytical sample was crystallized from acetone–water, m.p. 194–196°. (Found: C, 65,47; H, 7·61. $C_{13}H_{18}O_4$ requires: C, 65·17; H, 7·48%).

cis-*bicyclo*[4.3.0]*non*-3-*ene*-8,8-*dicarboxylic acid* (**7**, R = H, R′ = H). Diethyl malonate (40 g, 0·25 mole) was added dropwise to a suspension of NaH (8·4 g of a 58·6% dispersion, 0·20 mole) in 200 ml 1,2-dimethoxyethane. The soln was refluxed for 50 hr and the salts were filtered off. The filtrate was concentrated under reduced pressure (4 g of the starting dimesylate separated). Distillation of the residue gave 7·3 g, b.p.

* Professor Naves (Givaudan Corp.) kindly supplied us with this sample and we wish to extend our thanks to him.

105–118° (0·2 mm) of **7** (R = Et, R′ = H). This was saponified by refluxing with a KOH (4·2 g) soln in 50 ml EtOH and 10 ml water. After 24 hr the solvents were partially removed and the aq residue on acidification with 85% H_3PO_4 yielded 4·0 g (87%) diacid. The diacid was recrystallized from hot water, m.p. 170–171° (dec); IR (KBr) 5·89 μ (COOH). (Found: C, 63·10; H, 6·95. $C_{11}H_{14}O_4$ requires: C, 62·91; H, 6·62%).

Dimethyl-cis,cis-2,5-*dimethyl*-cis-*bicyclo*[4.3.0]*non*-3-*ene*-8,8-dicarboxylate (**7**, R = Me, R′ = Me). An ethereal soln of diazomethane was added dropwise to **7** (R = H, R′ = Me) (12 g, 0·054 mole) in ether which was being cooled in an ice bath. The soln was concentrated and cooled overnight (− 20°). Filtration yielded 12 g (83%) crystals, m.p. 59–60°; IR (KBr) 5·76 μ (CO_2Me); NMR ($CDCl_3$, external TMS) δ 1·05 (d, 6H, J = 7 Hz, CH_3—CH—), 1·2–2·6 (8H Envelope), 3·70 (s, 3H), 3·75 (s, 3H), and 5·65 (s, 2H—C=C—H). (Found: C, 67·43; H, 8·11. $C_{15}H_{22}O_4$ requires: C, 67·64; H, 8·33%).

Conversion of **7** (R = Me, R′ = Me) *to diols* **9** (R = Me). About 25 g of 31% H_2O_2 was added dropwise over a ½-hr period to **7** (R = Me, R′ = Me) (14·4 g, 0·054 mole) in 100 ml 90% formic acid. The mixture was stirred for 16 hr and concentrated. The residue was treated with 150 ml MeOH and 4·0 g NaOMe and the MeOH was removed under reduced pressure. Ether was added and the suspension was filtered. The filtrate was concentrated, taken up in a pentane–ether mixture, and filtered. Concentration of the filtrate, addition of pentane, and cooling gave 9·5 g, m.p. 78–88°; IR (KBr) 3·00 μ (OH) and 5·76 μ (CO_2Me). A second crop of crystals, m.p. 61–66° was collected on cooling the filtrate, wt 2·5 g—total wt 12·0 g (74%).

On repeated crystallization of fraction 1 a solid of m.p. 88–89° was obtained; IR (KBr) 3·00 μ (OH) and 5·76 μ (CO_2Me). (Found: C, 60·13; H, 8·24. $C_{15}H_{24}O_6$ requires: C, 59·98; H, 8·05%).

On repeated crystallization of fraction 2 a solid of m.p. 67–68° was obtained; IR (KBr) 3·02 μ (shoulder at 2·80 μ, OH), 5·70 and 5·78 (split peak). (Found: C, 59·98; H, 8·04. $C_{15}H_{24}O_6$ requires: 59·98; H, 8·05%).

Preparation of the dialdehyde **11**. Sodium metaperiodate (8·2 g, 0·040 mole) in 80 ml water was added over a 30-min period to 8·3 g (0·028 mole) **9** (R = Me) in 80 ml water which was being cooled in an ice bath. The mixture was stirred at the ice bath temp for 2½ hr, extracted with CH_2Cl_2, the extracts dried over Na_2SO_4, and the solvent was removed by water aspiration, wt 8·0 g, IR (neat) 5·80 μ (—CH=O) and 3·67μ (H—CO).

Reduction of dialdehyde **11** *to diol* **12** (R = OH). The crude **11** in 60 ml MeOH was added to $NaBH_4$ (1·2 g, 37 mmoles) in 60 ml MeOH at 0° over a 10-min period. On removal of solvent, addition of water, and cooling 7·2 g (84%) of **12** (R = OH) was obtained, m.p. 110–114°. Crystallization from Et_2O–CH_2Cl_2 gave 6·6 g (79%) of **12** (R = OH), m.p. 118–119°; IR (KBr) 3·02 μ (broad OH) and 5·76 μ (CO_2Me). (Found: C, 59·44; H, 8·75. $C_{15}H_{26}O_6$ requires: C, 59·58; H, 8·67%).

Conversion of diol **12** (R = OH) *to ditosylate* **12** (R = OTs). The diol **12** (R = OH) (8·7 g, 29 mmoles) in 65 ml pyridine was added over 3 hr to a cold soln of *p*-toluenesulfonyl chloride (23·0 g, 120 mmoles) in 100 ml pyridine. After being allowed to stand in the refrigerator for 24 hr the mixture was poured into one l ice water and the solid was filtered off, wt 16·4 g (93%). Recrystallization from MeOH yielded 16·1 g (91%) of **12** (R = OTs), m.p. 121–122°; IR (KBr) 5·78 μ with a shoulder at 5·70 μ (CO_2Me). (Found: C, 57·01; H, 6·40. $C_{29}H_{38}O_{10}S_2$ requires: C, 57·04; H, 6·27%).

Conversion of ditosylate **12** (R = OTs) *to dicyanide* **12** (R = CN). The ditosylate **12** (R = OTs) (16·4 g, 27 mmoles) and NaCN (3·0 g, 61 mmoles) in 190 ml DMSO were stirred under N_2 at room temp for 12 days. On removal of the DMSO, addition of water and cooling, 8·0 g (93%) of **12** (R = CN) was obtained, m.p. 115–118°. The sample was crystallized from ether–MeOH, m.p. 118–118·5°; IR (KBr) 4·45 μ (CN) and 5·76 μ (CO_2Me). (Found: C, 63·92; H, 7·79; N, 8·54. $C_{17}H_{24}O_4N_4$ requires: C, 63·67; H, 7·55; N, 8·74%).

Conversion of dicyanide **12** (R = CN) *to the diacid-dinitrile* **4**. The dicyanide **12** (R = CN) (8·0 g, 25 mmoles) and KOH (4·2 g, 75 mmoles) in 25 ml water were stirred at room temp for 24 hr. Acidification with conc HCl yielded 7·0 g of **14**, m.p. 76° (softens), 140–143° (dec). On drying this material in a desiccator over P_2O_5, water of hydration appeared to be lost, wt 6·55 g (93%), m.p. 143–144° (dec). The analytical sample was recrystallized from water and predried under vacuum, m.p. 146–147° (dec); IR (KBr) 2·87 μ (acid OH stretch), 4·42 μ (CN) and 5·38 μ (CCOH) with a shoulder at 5·73 μ. (Found: C, 61·49; H, 6·69; N, 9·77. $C_{15}H_{20}N_2O_4$ requires: C, 61·63; H, 6·90; N, 9·58%).

Decarboxylation of **14** *to yield* **15**. A soln of **14** (3·7 g, 12 mmoles) in 50 ml pyridine was refluxed for 2 hr On removal of the pyridine, water and 5 drops conc HCl were added, and the collected solid was dried in a desiccator overnight, 2·8 g (91%), m.p. 120° (softens), 135–140°. The analytical sample was crystallized from water, m.p. 127–144°; IR (KBr) 5·85 μ (COOH) and 4·42 μ (CN). (Found: C, 67,90; H, 8·21; N, 11·60. $C_{14}H_{20}O_2N_2$ requires: C, 67·71; H, 8·12; N, 11·28%).

Preparation of **16**. The crude **15** (2·9 g, 11·7 mmoles) in 250 ml benzene was added over a 1-hr period to a refluxing soln of KOtBu (5·0 g. 45 mmoles) in 250 ml benzene. The mixture was refluxed for 100 hr, water was added and the benzene was removed by distillation. A soln of 10 ml of conc HCl in 20 ml water was added to the residue, the mass was gently heated, and a solid formed after ½ hr. After heating for 2 hr and cooling, the solid was filtered and dried in a desiccator, 2·1 g (72%), m.p. 205° (softens, 212–215°), IR (KBr) 4·50 μ (—C≡C—CN), 5·87 μ (COOH) and 6·12 μ (—C=C—OH).

Hydrolysis and decarboxylation of **16** *to* **17** (R = H). Crude **16** (0·52 g, 2·1 mmoles) and 4 ml 85% H_3PO_4 in 0·5 ml water were heated in an oil bath by gradually raising the temp to a maximum of 175° over a period of 50 min. On cooling, 50 ml ice water was added, and the solid collected. Crude **17** (R = H) (0·27 g) was readily purified by sublimation (0·24 g, 51%), m.p. 138–139°; IR (KBr) 5·85 μ (COOH shoulder) and 5·9 μ (—C=O). (Found: C, 69·45; H, 8·86. $C_{13}H_{20}O_3$ requires: C, 69·61; H, 8·99%).

Conversion of acid **17** (R = H) *to ester* **17** (R = Me). The acid **17** (R = H) (1·14 g, 5·1 mmoles) in 60 ml ether was treated with an ethereal soln of diazomethane and concentrated. The residual solid was crystallized from pentane, 1·0 g (83%), m.p. 65–66°; IR (KBr) 5·78 μ (CO_2Me) and 5·90 μ (—C=O); NMR ($CDCl_3$) δ 0·98 (d, 6H, J = 6Hz, CH_3), 1·5–3·0 (m, 13H) and 3·73 (s, 3H, CH_3O—C=O). (Found: C, 70·32; H, 9·27. $C_{14}H_{22}O_3$ requires: C, 70·55; H, 9·31%).

Conversion of ester **17** (R = Me) *to the ethylene ketal* **18**. A mixture of **17** (R = Me) (0·70 g, 3 mmoles) in 60 ml dry benzene, ethylene glycol (11 drops), and a few crystals *p*-toluenesulfonic acid monohydrate were refluxed for 40 hr (Dean–Stark water trap). Periodically portions of benzene were removed from the trap (six 5 ml portions). The soln was cooled, washed twice with $NaHCO_3$ aq and the benzene was dried over Na_2SO_4. On removal of the solvent a colorless solid, 0·78 g, remained. The solid was crystallized from 5 ml pentane to yield 0·72 g (85%) of **18** of m.p. 57–58°; IR (KBr) 5·76 μ (CO_2Me); NMR ($CDCl_3$, external TMS) δ 0·95 (d, 6H, J = 6·5 Hz, CH_3—CH—), 1·1 to 3·0 (m, 13H), 3·73 (s, 3H, CH_3O—C=O) and 3·97 (s, 4H, —CH_2—O—CH_2—). (Found: C, 68·19; H, 9·36. $C_{16}H_{26}O_4$ requires: C, 68·05; H, 9·28%).

Conversion of **18** *to* **19**. A soln of **18** (0·56 g, 2 mmoles) in 12 ml ether was added dropwise to excess MeMgI soln. The mixture was refluxed for 30 hr, cooled, water was added dropwise and the ethereal layer was decanted. The ether concentrate was dried over Na_2SO_4 and concentrated to a viscous yellow oil (0·63 g). No attempt was made at further purification as the crude oil was hydrolyzed to the keto alcohol in the next step. Crystals formed on long standing in pentane in the freezer; IR (neat) 2·92 μ (OH).

Conversion of crude **19** *to* **20** (R = H). Partially crystalline **19** (0·60 g, 2·1 mmoles) was added to 2 ml water and 6 drops conc HCl. The mixture was stirred overnight, extracted with pentane, the extracts were dried over Na_2SO_4, and the pentane was concentrated. On cooling (− 20°), the solid was filtered, wt 0·30 g. A second crop of crystals, wt 0·06 g, was obtained from the filtrate on further cooling, total wt 0·36 g (72%). The analytical sample was recrystallized from pentane, m.p. 63–64°; IR (KBr) 2·87 μ (OH), 5·92 μ (—C=O); NMR ($CDCl_3$, external TMS) δ 0·99 (d, 6H, J = 6 Hz, CH_3—CH—), 1·30 (s, 6H, CH_3—C(OH)—CH_3), 1·5–2·7 (m, 14H, an apparent doublet appears in this pattern at 2·4 for the protons adjacent to the CO group). (Found: C, 75,48; H, 11·19. $C_{15}H_{26}O_2$ requires: C, 75·58; H, 11·00%).

Conversion of **20** (R = H) *to acetate* **20** (R = Ac). The alcohol **20** (R = H) (0·053 g, 0·22 mmoles) and 1·5 ml Ac_2O were refluxed for 4 hr and allowed to stand for 12 hr. On removal of the Ac_2O and addition of water, the mixture was extracted with pentane and the pentane extracts were dried over Na_2SO_4. On removal of the pentane, a light yellow oil was obtained, wt 0·060 g (97%); IR (neat) 5·78 μ (OCOMe) and 5·90 μ (—C=O); NMR ($CDCl_3$, external TMS) δ 1·00 (d, 6H, J = 6 Hz, CH_3—CH—), 1,54 (s, 6H, CH_3—C(O—Ac)—CH_3), and 2·02 (s, 3H, CH_3—C=O). This product was utilized without any further purification.

Conversion of **20** (R = Ac) to **3**. To alcohol **20** (R = H) (0·108 g, 0·38 mmole) in 2 ml ether was treated with 12 drops BF_3–etherate.[3c] The mixture was allowed to stir at room temp for 1 hr and 5% K_2CO_3 aq was added dropwise. The aq layer was separated using an eye dropper and the aq layer was extracted with

ether. The ethereal extracts were dried over K_2CO_3 and filtered. The ether was removed and a yellow oil remained, wt 0·087 g, which was distilled to the cold finger of a sublimation apparatus under vacuum. The IR spectrum of this oil showed a small acetate peak at 5·77 μ. This material was recyclized in the BF_3–etherate reaction. The crude oil (0·060 g, 70%) was distilled to the cold finger of the sublimation apparatus and showed only a trace of acetate in the IR; IR (neat) 5·88 μ (–C(=O)–); NMR ($CDCl_3$) δ 0·98 (d), 1·68 (broad s, =C(CH$_3$)–CH$_3$), and 2·3 (complex pattern for –CH$_2$–C(=O)–CH$_2$– and allylic ring protons). A small peak appeared at δ 4·8 (–C(=CH$_2$)–CH$_3$) with a corresponding peak at 1·8 (–C(=CH$_2$)–CH$_3$); estimated methylene isomer, 10–20%. No attempt was made to purify this sample further although satisfactory analytical data were obtained on the crude isomer mixture.

Hydrolysis of the allophanate derivative of "dihydro-6,7-β-vetivol" (previously formulated as **21**). The allophanate derivative of optically inactive dihydro-6,7-β-vetivol (0·512 g, 1·66 mmoles) in 25 ml MeOH was treated with a soln of NaOH (1·0 g, 25 mmoles) in 10 ml MeOH and 5 ml water. The soln was refluxed overnight, cooled, filtered and concentrated. Water was added to the residue and the white crystalline material was filtered and dried, wt 0·34 g (92%), m.p. 108–109° (lit. m.p. 108·5–109°). The solid was crystallized from pentane with no change in the m.p; IR (KBr) 3·08 μ (OH). NMR ($CDCl_3$, external TMS) δ 0·88 (d, 6H, J = 6Hz, with peak at 0·94 about twice the intensity of the 0·84 peak, CH$_3$–CH), 1·0–2·6 (m, 19H, with a broad singlet at 1·67, C=C(CH$_3$)), and 3·65 (broad pattern, 1H, for –CH–OH).

Oxidation of "6,7-dihydro-β-vetivol" to 6,7-dihydro-β-vetivone". Chromium trioxide (0·135 g, 1·35 mmoles) was added to 1 ml pyridine which was cooled in an ice bath. The 6,7-dihydro-β-vetivol (0·10 g, 4·5 mmoles) in 2 ml pyridine was added dropwise to the cold oxidizing agent and the mixture was allowed to stir overnight (13 hr). Ether was added and the mixture was filtered. The filtrate was dried over Na_2SO_4 and concentrated to a yellow oil. No further purification was effected; IR (neat) 5·80 μ (–C(=O)–); NMR ($CDCl_3$) δ 0·95 (d, 6H, CH$_3$–CH), 1·2–2·6 (complex m, 18H, with peaks appearing at 1·68, CH$_3$–C(=O)–CH$_3$, and 2·3, –CH$_2$–C(=O)–CH$_2$–).

Acknowledgement—This research was generously supported by U.S. Public Health Service grant GM-08241.

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