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DITERPENOID TOTAL SYNTHESIS, AN A→B→C APPROACH—VI

10-CYANO-12-HYDROXY-7-OXO-17-NORPODOCARPA-5,8,11,13-TETRAENE, A MODEL FOR TRICYCLIC C-AROMATIC DITERPENOIDS*†‡

W. L. MEYER, R. W. HUFFMAN, and P. G. SCHROEDER

Departments of Chemistry, University of Arkansas, Fayetteville, Arkansas, 72701,§ and Indiana University, Bloomington, Indiana 47405

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Abstract—Reaction of 2,2-dimethyl-6-hydroxymethylenecyclohexanone (**10**) with hydroxylamine hydrochloride produces a mixture of the isomeric isoxazoles **11** and **13**. The less predominant of these (**13**) is the exclusive product from reaction of hydroxylamine hydrochloride with the isopropyl enol ether of **10**, and is converted by methoxide into 6-cyano-2,2-dimethylcyclohexanone (**14**). This cyano ketone (**14**) reacts with methyl vinyl ketone and base to form 10-cyano-4,4-dimethyl-Δ^5-7-octalone (**16**), which is hydrogenated exclusively to the corresponding *trans*-7-decalone.

The 8-hydroxymethylene derivative of octalone **16** is oxidized by 2,3-dichloro-5,6-dicyanoquinone to 10-cyano-4,4-dimethyl-8-formyl-$\Delta^{5,8}$-7-hexalone (**20**). The latter reacts with the sodium enolate of ethyl acetoacetate at both C-9 and C-5 to produce the tricyclic adduct **25**, but with t-butyl acetoacetate it undergoes Michael addition only at C-9. Treatment of the resulting adduct **21** with *p*-toluenesulfonic acid brings about cleavage of the t-butyl group, decarboxylation, and aldol cyclodehydration to produce the tricyclic dienedione **22**. Dehydrogenation of the latter with dichlorodicyanoquinone produces the title keto phenol **23**. This sequence is a model for synthesis of various C-aromatic tricyclic diterpenoids.

POLYCYCLIC diterpenoids of many degrees of structural and functional complexity occur in nature. In considering possible new synthetic approaches to the various members of this family of natural products, we were intrigued by the possibility of devising a sequence of reactions which would be applicable with a minimum of modification to preparation of a large number of naturally occurring diterpenoids. The present paper describes the general nature of the synthetic sequence which is being examined with this goal, and illustrates its application to synthesis of a model of the tricyclic diterpenoid nucleus.

Illustrative of the types of diterpenoids we wished to encompass in this program are such compounds as manoöl (**1**), isopimaric acid (**2**), dehydroabietic acid (**3**), nimbiol (**4**), totarol (**5**), carnosic acid (**6**), phyllocladene (**7**), and veatchine (**8**). The rationale for our choice of a synthetic sequence stemmed from consideration of several structural features which many such related terpenoids have in common: (a) an A/B

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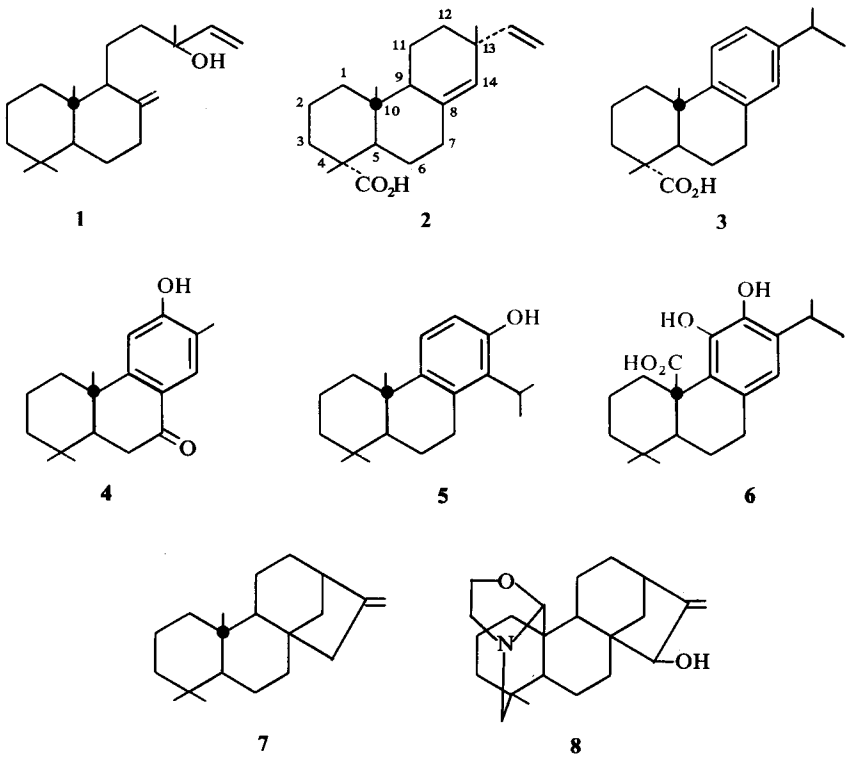
‡ Paper V, W. L. Meyer and D. C. Shew, *Tetrahedron Letters* 2963 (1968).

§ Correspondence regarding this work should be directed to W. L. M. at this address.



1 2 3 4 5 6 7 8

ring system which is a 4,4,10-trisubstituted-*trans*-decalin,* (b) 4,4,10-substituents which are methyl or carbon functions, and (c) additional substituents at positions 8 and 9, either as side-chains or further rings. On the basis of these considerations we settled on a so-called A→B→C approach to diterpenoid synthesis, schematically depicted in Fig. 1. Ring A was envisioned to originate as a trisubstituted cyclohexanone carrying

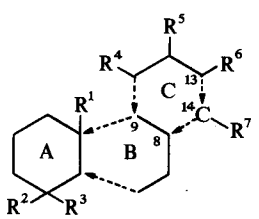


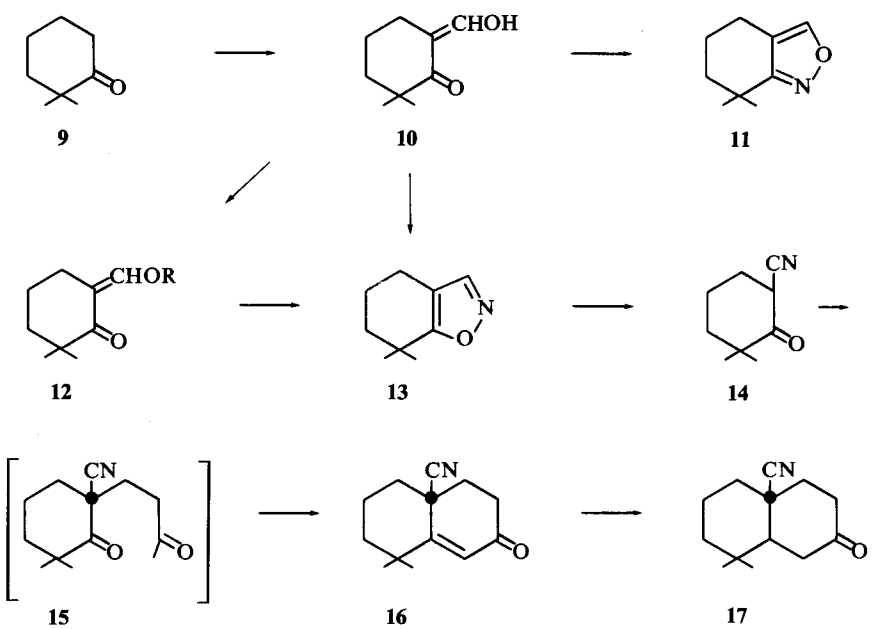
FIG. 1.

the three ultimate A/B substituents (R^1, R^2 and R^3). These three substituents would be chosen so that as many as possible of the diterpenoid A/B extranuclear oxidation patterns could be obtained by later synthetic transformation of the same set of

* Throughout the discussion we will use the steroid-terpenoid numbering system shown in structure **2** to name tricyclic compounds, and the corresponding A/B ring numbering system to apply to bicyclic intermediates. The configurational notations α and β indicate a *trans* or *cis* relationship to the C-10 angular group. Although all synthetic compounds were examined only in racemic form, the prefix DL is omitted and only one enantiomer is depicted in structural formulations.

R^1, R^2 and R^3. The B-ring would be added in a manner which would activate C-8 and C-9 for attachment of the C-ring or side-chains, and as will be seen, we chose 4,4,10-trisubstituted-7-decalones as the appropriate bicyclic intermediates. The C-8 and C-9 substituents were to be subsequently introduced as fragments which could be connected by 13,14-bond formation if a C-ring were desired or modified without 13,14-bond formation if bicyclic derivatives (e.g. **1**) were the goal. These fragments would also contain groups (R^6 and R^7) which could become C-ring substituents or additional rings (*cf.* **3**, **5** and **7**).

10-*Cyano*-4,4-*dimethyl*-*trans*-7-*decalone* (**16**). The first stage of such a general synthesis involves preparation of a suitable series of β-decalone derivatives containing the three extranuclear carbons in appropriate oxidation states. We have already recorded synthesis of one of these, 10-carbethoxy-4,4-dimethyl-*trans*-7-decalone, by condensation of 6-carbethoxy-2,2-dimethylcyclohexanone with methyl vinyl ketone followed by stereoselective hydrogenation of the resulting octalone.[1] Although this intermediate was suitable for transformation to carnosic acid (**6**),[2] for certain other objectives we considered that an angular cyano group, with its smaller steric requirement and greater synthetic versatility, might be superior to the angular carboxyl. Thus for the model study we set out to synthesize 10-cyano-4,4-dimethyl-*trans*-7-decalone (**17**) via 6-cyano-2,2-dimethylcyclohexanone (**14**).

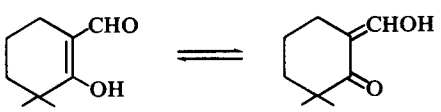


2,2-Dimethylcyclohexanone (**9**) was most conveniently prepared by methylation of 2-methylcyclohexanone using potassium t-butoxide and methyl iodide in t-butanol. A number of alternate base-solvent combinations have been reported for this reaction, but most of them produce more or less complex mixtures of methylated

cyclohexanones in which the 2,2-dimethyl ketone is predominant.[1,3] The t-butoxide-catalyzed process, however, affords a relatively simple mixture in which the 2,2-dimethyl ketone is accompanied by its 2,2,6-trimethyl homolog as the only major contaminant in a ratio of about 4:1.

Conversion of the dimethyl ketone to its cyano derivative **14** proved to be less direct than was anticipated. The classic sequence for conversion of a cyclohexanone to an α-cyanocyclohexanone has involved conversion of the ketone to its α-hydroxymethylene derivative, reaction with hydroxylamine hydrochloride to produce an isoxazole, and base-catalyzed isomerization of this intermediate to the cyano ketone.[4,5] This sequence would be unusually advantageous in the present instance, for its first step, condensation with ethyl formate, can be carried out directly on the mixture of ketones formed in the methylation reaction; only the 2,2-dimethyl ketone in this mixture reacts, so the reaction represents a purification stage as well as a synthetic stage in the sequence. Unlike the reaction of hydroxymethylenecyclohexanone[4] or its 6-methyl derivative,[4] however, oximation of 6-hydroxymethylene-2,2-dimethylcyclohexanone (**10**) produced the desired isoxazole **13** in but 34% yield; an isomeric isoxazole was the major product. That this product has structure **11** is clear from its IR and UV absorption (6·21 μ and 222 mμ, $\varepsilon = 3840$) which are characteristic of the isoxazole chromophore, its base-stability (no proton α to nitrogen), and its NMR spectrum, which showed the presence of one aromatic proton (2·0 τ). It is probably also significant that the aromatic proton in this product is more strongly coupled to the β-methylene ($J = 1$ c/s) than is that of the isoxazole **13** (J unresolved, but less than 1 c/s); this relationship is expected for long-range coupling across a bond of order nearer two than one.[6]

Although analogous 3,4-disubstituted isoxazoles have been produced in reactions of hydroxylamine hydrochloride with other α-hydroxymethylenecyclohexanones,[4,5] they have invariably been minor products of the reaction. It is not clear why the *gem*-dimethyl group produces such a change in the product ratio. This is not a consequence of equilibration of the isomeric isoxazoles subsequent to their formation, for both are stable to the preparative conditions. In spite of the fact that it seemed unlikely that the position of the hydroxymethylene ketone: aldo enol equilibrium (**18** ⇆ **10**) would be responsible for this change, owing to the rapidity of this tautomerization compared with the probable rate of reaction of either tautomer with hydroxylamine,

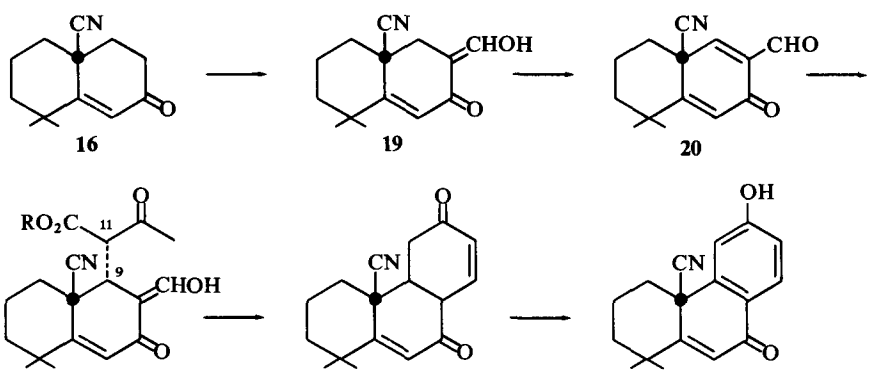


18 **10**

we did ascertain that the position of this equilibrium is not substantially different from that of the desmethyl analogs. The hydroxymethylene proton resonance of **10** falls at 1·37 τ which compares favorably with that of hydroxymethylenecyclohexanone (1·39 τ[7]). Treatment of this datum as described by Garbisch[7] leads to a value of 0·30 for the pertinent equilibrium constant, a figure which is quite similar to that found by Garbisch for the cyclohexanone derivative.[7]

In order to circumvent predominant formation of the "wrong" isoxazole, the hydroxymethylene ketone **10** was converted to its isopropyl enol ether **12** prior to oximation. Although reaction of many enolic β-diketones with hydroxylamine produces mixtures of isoxazoles corresponding to nitrogen attachment at each of the carbonyl carbon atoms, Weygand and Bauer[8] found that under certain conditions the corresponding enol ethers are transformed only to that isoxazole which corresponds to nitrogen attack at the enol ether carbon. Furthermore, von Auwers[4] reported that 6-ethoxymethylene-2-methylcyclohexanone reacts with hydroxylamine in methanol to produce an oxime at the enol ether carbon. Thus this modification clearly offered promise of producing the necessary structural selectivity for our purpose. As anticipated, a quantitative yield of the correct isoxazole (**13**) was produced by this sequence, and a 58% overall yield of cyano ketone **14** could thus be produced from 2,2-dimethylcyclohexanone. Methoxide-catalyzed condensation of the cyano ketone with methyl vinyl ketone produces the octalone **16** directly, rather than the intermediate diketone (**15**) as had been encountered in the angular carbethoxy series.[1] This enhanced reactivity toward cyclization of **15** is no doubt a consequence of the smaller steric requirement of the cyano group, which can more readily tolerate the developing diaxial methyl-angular group interaction in the transition state leading to **16** than can carbethoxy. Inasmuch as the isoxazole cleavage and the Michael addition are both base-catalyzed processes it seemed feasible to combine them into a single step, and indeed the bicyclic enone **16** is isolated in 68% yield from the isoxazole **13** by exposure to methoxide, neutralization of part of the methoxide,* and addition of methyl vinyl ketone. Hence four steps are required to convert 2,2-dimethylcyclohexanone to the octalone **16** in 52% yield.

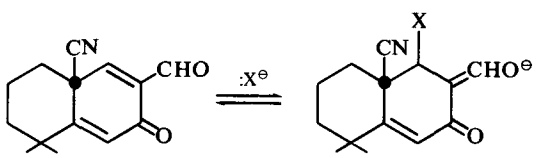
As in the angular ester series,[1] hydrogenation of the octalone **16** affords a single saturated ketonic product. This keto nitrile was initially assigned the *trans* configuration **17** because the α-face of the octalone should offer less hindrance to catalyst approach than does the β-face.[1] Substantiation of this relative configuration of keto nitrile **17** is ultimately found in its conversion to DL-sugiol[9] and a number of other terpenoids which are known to contain the A/B trans ring-fusion.



* Isoxazole cleavage is nearly instantaneous in the presence of an equimolar amount of methoxide, whereas the Michael reaction proceeds with formation of fewer by-products with only trace quantities of base.

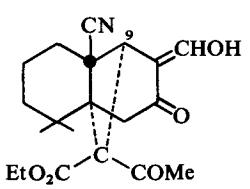
The C-ring sequence. If a tricyclic diterpenoid model with no carbon substituents on ring C is desired, the general plan at this stage involves attachment of a one-carbon fragment to C-8, activation of C-9, introduction of a three-carbon side-chain at C-9, and closure of ring C. In the model series we decided to employ the octalone **16** rather than decalone **17** for this series of reactions, in order to learn whether a 5,6 double bond could be retained through the sequence and thus be available if it were desired for introduction of B-ring functionality at a later stage.

Condensation of the enone **16** with ethyl formate produces the hydroxymethylene derivative **19** in 94% yield. Exposure to 2,3-dichloro-5,6-dicyanoquinone in dioxan solution[10] for 5 min converted this hydroxymethylene ketone to the 8,9-unsaturated aldehyde **20** in 60% yield, thereby introducing the functionality necessary for attachment of the remaining ring C carbons to C-9. Conjugation of the double bond of **20** with two carbonyl groups allows nucleophilic attack at C-9 to afford the highly stable enolate of a hydroxymethylene ketone (**24**), and hence the formyl dienone is extremely reactive toward such additions. Indeed, it is undoubtedly due to salt formation by such a nucleophilic addition[10] that the formyl dienone is soluble in aqueous base, for such basic solutions have ultraviolet absorption which is similar to that of the hydroxymethylene ketone **19** in base (348 mμ, ε 9000 vs. 360 mμ, ε 10,500 for **19**).



20 **24**

Another example of the high reactivity of the formyl dienone **20** to nucleophiles was provided by the next step in the synthetic sequence. Only five minutes at room temperature in benzene with the sodium enolate of ethyl acetoacetate was required for quantitative conversion to a one-to-one adduct. This adduct, however, clearly did not possess the desired structure **21a**, for although the NMR spectrum showed the presence of a hydroxymethylene group (singlet at 1·73 τ), a methyl ketone (singlet at 7·77 τ), and an ethoxyl group (5·80 τ triplet and 8·62 τ quartet), there was no resonance for vinyl protons either α or β to the ketone. An AB quartet resonance with chemical shifts at 6·78 τ and 7·45 τ and a coupling constant of 20 c/s was indicative of a methylene group at C-6, α to the ketone, and since its resonance showed no further splitting, there must be no proton on C-5. These data lead to structure **25** for the adduct, and its other spectral properties are in accord with this assignment

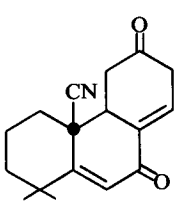


25

(Experimental). This product is formed, of course, by a double Michael addition of ethyl acetoacetate to the formyl dienone. This interesting result, although it is not synthetically useful, is not totally without value, for formation of **25** indicates that nucleophilic attack at C-9 of the dienone is from the α-face of the molecule (axial), a point which will be of considerable importance when one is dealing with synthesis of terpenoids which are asymmetric at that center.

Substitution of t-butyl acetoacetate for ethyl acetoacetate in the Michael addition produced the desired adduct **21b**. Apparently the steric requirement of the t-butyl group inhibits its incorporation into the more hindered tricyclic system of **25**. The adduct **21b** consisted of a mixture of isomers, for its NMR spectrum showed resonances from two acetyl groups, two hydroxymethylene protons, and two t-butyl groups. Whether this isomerism involves differences in configuration at C-9, C-11, or both was not unequivocally determined, for the isomers were not separated or subjected to further structural examination. However, the results of several analogous additions to be discussed in future publications lead us to believe that the difference is only at C-11, and that the Michael addition proceeds exclusively from the α-face of the formyl dienone to produce products with a 9β-hydrogen.

Treatment of the crude adduct with *p*-toluenesulfonic acid in acetic acid brought about cleavage of the t-butyl ester, decarboxylation of the resulting β-keto acid, and aldol cyclodehydration to form the tricyclic dienedione **22**. This product was not purified, but its infrared spectrum has no carbonyl absorption below 5·98 μ. Both this result and the appearance in the NMR spectrum of vinyl resonance characteristic of two protons α and one β to carbonyl groups indicated that stereoisomers of structure **26** were absent. Such preferential dehydration of the presumed 14-hydroxy-7,12-diketone intermediate **27** toward C-13 rather than C-8 has subsequently also been found in several analogous series. Examination of molecular models suggests that this location of the double bond is somewhat less strained than the 8,14 alternative when the C-10–C-9 configuration is *syn*,* due to the steric requirements of the C-ring. Inasmuch as the preparative conditions should produce an equilibrium mixture of the enones **22** and **26** it is probably this steric factor which causes **22** to be the isolable product.



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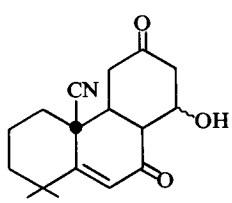

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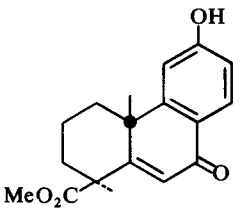
The crude dienedione underwent aromatization by dichlorodicyanoquinone to afford the keto phenol **23**, albeit in but 35% yield. The structure of this product, the desired terpenoid model, was clearly evident from its UV, IR, and NMR spectral properties. With the exception of the differences expected on the basis of the A-ring

* In addition to the formation of compound **25**, other evidence in related series of compounds suggests that the 9-β (*syn*) configuration is present in **22**, cf. footnote on page 4257 of Ref 9.
This point will be discussed in detail as it applies to many of our intermediates in a future publication.

functionality, these were quite similar to those of the known keto phenol **28**, a transformation product of podocarpic acid.[11]



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Adaptation of this type of sequence to total synthesis of various naturally occurring diterpenoids will be considered in future publications.

EXPERIMENTAL

IR spectra were obtained on Perkin–Elmer models 137, 137G, and 337 spectrophotometers, UV spectra on a Cary model 14 spectrophotometer, and NMR spectra on a Varian A-60 spectrometer. First-order multiplets in NMR spectra are described by the abbreviations (s) for singlet, (d) for doublet, (t) for triplet, and (q) for quartet, with (m) indicating a more complex multiplet. Chemical shifts, determined relative to internal TMS, are expressed in τ units and coupling constants (J) in c/s. GLC was run on an F and M model 609 chromatograph with a 2-m 10% silicone SE30 on Chromosorb W column using N_2 as the carrier gas and a hydrogen flame ionization detector. Compositions of mixtures were estimated as the ratios of peak areas. M.ps (corrected) were taken on a microscope hot stage. Microanalyses were by Alfred Bernhardt, Mulheim, Germany.

2,2-Dimethylcyclohexanone (**9**). This procedure was developed by N. G. Schnautz in these laboratories and is similar to one subsequently reported.[3b] A soln of 62·5 g (1·6 g atom) K in 1·8 l. refluxing t-butanol under a N_2 atm was placed in a cold water bath and 60 g (0·54 mole) 2-methylcyclohexanone was added over 15 min.* 15 min later 142 g (1·0 mole) MeI was added over a 1-hr period at a rate such that the temp remained below 30°. Stirring at room temp under N_2 was continued for 3 hr. The mixture was poured into 1 l. water and extracted with ether which was washed with brine. Ether and t-butanol were removed by distillation at atm press and the residue was taken up in ether and dried over Na_2SO_4. Distillation afforded 53 g (78%) of a colorless oil, b.p. 170–172°; λ_{max}^{film} 2·9 (weak), 5·9, and 6·9 μ. GLC (150°) indicated the product to be approximately 5% 2-methylcyclohexanone, 25% 2,2,6-trimethylcyclohexanone, and 70% 2,2-dimethylcyclohexanone. †

6-Hydroxymethylene-2,2-dimethylcyclohexanone (**10**) was prepared from the above mixture (70% **9** by GLC, b.p. 170–172°) by the procedure of Johnson and Posvic.[12] The distilled hydroxymethylene ketone **10** was obtained in 93% yield (based on available dimethylcyclohexanone) as a colorless oil, b.p. 108–110° (34 mm) (reported[12] b.p. 79–80° (11 mm)); $\lambda_{max}^{CHCl_3}$ 5·88, 6·78, and 6·87 μ; $\lambda_{max}^{95\%EtOH}$ 288 mμ (ε = 5470), in base 316 mμ (ε = 15,400); NMR ($CDCl_3$) 1·35 (s), 7·67 (m), and 8·83 τ (s).

6-Cyano-2,2-dimethylcyclohexanone (**14**) *from 6-hydroxymethylene-2,2-dimethylcyclohexanone* (**10**). This general procedure was adapted from one by Johnson and Shelberg.[5] A soln of 18·5 g (0·12 mole) of crude **10** and 16·1 g (0·23 mole) hydroxylamine hydrochloride in 120 ml glacial AcOH was stirred for 19 hr at room temp under N_2. The solvent was removed by distillation *in vacuo*, the residue was distributed between water and ether, and the aqueous phase was extracted with ether; the organic solns were washed with sat $NaHCO_3$ aq and water and dried over Na_2SO_4. Removal of ether by distillation *in vacuo* left 14·3 g (80%) of a mixture of **11** and **13** as a red oil, λ_{max}^{film} 6·1, 6·2, 6·75, and 6·85 μ.

* The t-butanol was previously refluxed over CaH_2 for 1 hr and then distilled; the 2-methylcyclohexanone and MeI were used as obtained from the Aldrich Chemical Company.

† The product ratio from this process varies somewhat from run to run. There is obtained from 60–80% of distilled product which consists of 0–5% 2-methylcyclohexanone, 65–80% 2,2-dimethylcyclohexanone, and 20–30% 2,2,6-trimethylcyclohexanone. Less than 2% of 2,6-dimethylcyclohexanone is present.

The oil (0·095 mole) was allowed to stand 1 hr at room temp in about 60 ml ether and 60 ml cold MeOH containing 5 g (0·22 g-atom) dissolved Na. The resulting mixture was extracted with 500 ml water and 200 ml 10% NaOH aq, and the aqueous solns were washed with ether, acidified with conc HCl, and extracted with ether. The extracts were washed with water, dried over Na_2SO_4, and evaporated to leave 4·8 g (34%) of a brown solid which was recrystallized from cyclohexane to give 3·2 g of **14** as brown prisms, m.p. 113–115° (see spectral and analytical data below).

The organic solns were combined, washed with water, dried over Na_2SO_4, and evaporated to leave 6·5 g (46%) of a red-brown oil which was distilled to afford **11** as a colorless oil, b.p. 116° (38 mm); $\lambda_{max}^{CHCl_3}$ 6·21, 6·75, and 6·90 μ; $\lambda_{max}^{95\%\,EtOH}$ 222 mμ (ε = 3,840); NMR ($CDCl_3$) 2·00 (t, J = 1) and 8·67 τ (s). (Found: C, 71·44; H, 8·56; N, 9·39. $C_9H_{13}NO$ requires: C, 71·49; H, 8·67; N, 9·26%).

6-*Hydroxymethylene*-2,2-*dimethylcyclohexanone isopropyl enol ether* (**12**). This procedure follows an analogous one of Johnson and Posvic.[12] A mixture of 26 g (0·17 mole) of **10** (b.p. 110–116° (36 mm)), 36 g (0·26 mole) anhyd powdered K_2CO_3, and 205 ml dry acetone was refluxed under N_2 while 19 g (0·155 mole) 2-bromopropane was added dropwise during 1·5 hr. Reflux was continued for 4 hr, 18 g (0·13 mole) K_2CO_3 was added, and 21 g (0·171 mole) 2-bromopropane was added dropwise over a 1 hr period. Reflux was continued overnight, 21 g 2-bromopropane was added dropwise during 1 hr, and reflux was continued for 7 hr. The mixture was cooled, diluted with 1 l. ether, filtered, washed with brine, and solvent was evaporated. The residue was taken up in ether and dried over Na_2SO_4 and solvent was distilled *in vacuo* to afford 30 g (90%) of a red oil. Distillation produced **12** as a colorless oil, b.p. 122° (10 mm); λ_{max}^{film} 5·98, 6·29, and 6·88 μ; NMR ($CDCl_3$) 2·62 (t, J = 2), 5·78 (m, J = 6), 8·72 (d, J = 7), and 8·88 τ (s).

6-*Cyano*-2,2-*dimethylcyclohexanone* (**14**) *from* 6-*hydroxymethylene*-2,2-*dimethylcyclohexanone isopropyl enol ether* (**12**). This procedure is a modification of those reported by Weygand and Bauer[8] and by Johnson and Shelberg.[5] The crude **12** (30 g, 0·153 mole) was treated for 21·5 hr at room temp with 21·3 g (0·306 mole) hydroxylamine hydrochloride in 200 ml MeOH. The reaction was exothermic and the soln slowly became bright red. MeOH was removed by distillation, the residue was distributed between water and ether, and the aqueous phase was extracted with $CHCl_3$. The organic solns were washed with $NaHCO_3$ aq and water and dried over Na_2SO_4, and solvent was distilled *in vacuo* to leave 36 g of a dark red oil. Distillation afforded 21 g (91%) of **13** as a colorless oil, b.p. 111° (28 mm); $\lambda_{max}^{CHCl_3}$ 6·13, 6·73, 6·85, and 7·31 μ; $\lambda_{max}^{95\%\,EtOH}$ 227 mμ (ε = 5400); NMR ($CDCl_3$) 2·03 (s), 7·58 (m), and 8·72 τ (s). None of the absorptions characteristic of **11** were present in spectra of this sample.

The crude **13** in 200 ml ether was treated with 100 ml cold MeOH containing 19 g (0·35 mole) MeONa. After 1 hr at room temp the soln was extracted with 500 ml water and two 100-ml portions 1% KOH aq, the aqueous solns were acidified and washed with ether and $CHCl_3$, and the extracts were combined, washed with water, treated with Norit, and dried over Na_2SO_4. Removal of solvent by distillation *in vacuo* produced 21 g (91% based on crude enol ether) of **14** as purple prisms, m.p. 111–116°. Recrystallization from cyclohexane produced 16 g (76%) of a purple solid, m.p. 130–134°, which was chromatographed over silicic acid to afford colorless prisms, m.p. 115–120°. Repeated recrystallization from cyclohexane produced an analytical sample as white prisms, m.p. 115°; $\lambda_{max}^{CHCl_3}$ 4·43 (sharp, weak), 5·81 (strong), and 6·88 μ; $\lambda_{max}^{95\%EtOH}$ 236 mμ (ε = 2900), 280 mμ (ε = 50), in base 268 mμ (ε = 1300); NMR ($CDCl_3$) 6·13 (m), 8·80 (s), and 8·90 τ (s). (Found: C, 71·46; H, 8·56; N, 9·17. $C_9H_{13}NO$ requires: C, 71·49; H, 8·67; N, 9·26%).

10-*Cyano*-4,4-*dimethyl*-Δ^5-7-*octalone* (**16**) *from* 6-*cyano*-2,2-*dimethylcyclohexanone* (**14**). This procedure was adapted from one developed by Wilds and Werth.[1,13] A soln of 15·5 g (0·102 mole) of **14**, m.p. 130–134°, in 163 ml dry benzene was added to 102 ml dry EtOH containing 103 mg (4·5 mg-atom) dissolved Na, and the soln was stirred at room temp under N_2 while a soln of 11·4 g (0·164 mole) methyl vinyl ketone in 29 ml dry EtOH and 82 ml dry benzene was added over 0·5 hr. The mixture was stirred overnight, poured into 500 ml brine, acidified with conc HCl, and extracted with $CHCl_3$ and ether. The extracts were washed with 1% NaOH aq, dried over Na_2SO_4, and distilled *in vacuo** to afford a forerun of 4-ethoxy-2-butanone followed by 18·3 g (88%) of **16** as a colorless oil, b.p. 111° (0·4 mm), which solidified to white prisms, m.p. 72–74°. Fractional sublimation produced white prisms, m.p. 70°; $\lambda_{max}^{CHCl_3}$ 4·47, 5·96, and 6·20 μ; $\lambda_{max}^{95\%EtOH}$ 232 mμ (ε = 18,900); NMR ($CDCl_3$) 3·87 (s), 8·60 (s), and 8·80 τ (s). (Found: C, 76·92; H, 8·37; N, 6·89. $C_{13}H_{17}NO$ requires: C, 76·81; H, 8·43; N, 6·89%).

10-*Cyano*-4,4-*dimethyl*-Δ^5-7-*octalone* (**16**) *from the isoxazole* **13**. A freshly-prepared soln of 0·78 g (0·034 g-atom) of Na in 9 ml MeOH was added to a soln of 5·00 g (0·033 mole) of **13**, b.p. 55–58° (1·5–1·0 mm), in 50 ml dry benzene (distilled from CaH_2) under N_2 atm. After this mixture had been stirred at room temp for 20 min, a soln of 2·07 g (0·017 mole) benzoic acid in 10 ml MeOH was added slowly with rapid stirring, followed over the next 0·5 hr by a soln of 3·73 g (0·0532 mole) freshly distilled methyl vinyl ketone in 9 ml MeOH and 25 ml benzene. The mixture was stirred overnight, poured into 100 ml brine, and acidified with conc HCl. The layers were separated and the aqueous phase was extracted once with ether, twice with $CHCl_3$, and again with ether; the combined organic extracts were washed with 1% NaOH aq, dried over $MgSO_4$, and distilled *in vacuo* to yield a yellow oil. The oil was taken up in cyclohexane and filtered through a short column of Florisil. Evaporation of solvent gave 5·79 g (86%) of **16** as yellow crystals which were sublimed at 70° (0·5 mm) to produce 4·55 g (68%) of white prisms, m.p. 65–71°; this sample had spectra which were identical with those described above.

10-*Cyano*-4,4-*dimethyl*-trans-7-*decalone* (**17**). A soln of 2·0 g (8·0 mmoles) of **16**, m.p. 72–74°, in 100 ml 95% EtOH was stirred with 0·5 g 30% Pd–C under H_2 at atm press. After 30 min 1·15 equivs H_2 had been absorbed and absorption had ceased. The catalyst was removed by filtration and the solvent was distilled *in vacuo* to leave 2·0 g (100%) of **17** as a colorless oil which solidified to yellowish prisms, m.p. 59–60°. Fractional sublimation or recrystallization from pentane afforded the pure ketone as colorless prisms, m.p. 59–60°; λ_{max}^{film} 4·47 and 5·83 μ; NMR ($CDCl_3$) 8·90 (s) and 9·10 τ (s). (Found: C, 76·02; H, 9·24; N, 6·92. $C_{13}H_{19}NO$ requires: C, 76·05; H, 9·33; N, 6·82%).

10-*Cyano*-8-*hydroxymethylene*-4,4-*dimethyl*-Δ^5-7-*octalone* (**19**). This procedure is a modification of one by Ringold, *et al.*[14] A soln of 7·0 g (34·5 mmoles) of **16** (m.p. 72–74°), 5·1 g (69·1 mmoles) HCOOEt, and 300 ml benzene was stirred at room temp, 4·65 g (0·104 mole) NaH was added as a 54% dispersion in mineral oil, and the resulting suspension was stirred overnight under N_2. The mixture was extracted with 500 ml water and 500 ml 1% NaOH aq, and the aqueous solns were washed with ether, acidified with conc HCl, and extracted with ether which was washed with water, dried over Na_2SO_4, and evaporated to dryness to afford 7·5 g (94%) of **19** as a yellow solid, m.p. 106–111°. Sublimation yielded yellow prisms, m.p. 109°; $\lambda_{max}^{CHCl_3}$ 4·47, 6·07, 6·36, 6·90 and 7·05 μ; $\lambda_{max}^{95\%\,EtOH}$ 243 mμ (ε = 11,400), 308 mμ (ε = 6900), in base 238 mμ (ε = 16,500); NMR ($CDCl_3$) 2·28 (s), 3·73 (s), 8·63 (s) and 8·75 τ (s). (Found: C, 72·68; H, 7·39; N, 6·21. $C_{14}H_{17}NO_2$ requires: C, 72·70; H, 7·41; N, 6·06%).

10-*Cyano*-8-*formyl*-4,4-*dimethyl*-$\Delta^{5,8}$-7-*hexalone* (**20**). This procedure is a modification of that of Edwards *et al.*[10] Compound **19** (13 mmoles; 3 g; m.p. 106–111°), 2,3-dichloro-5,6-dicyanoquinone (3 g; 13·2 mmoles) and 100 ml dioxan were swirled until homogeneous, the dioxan was removed by distillation *in vacuo*, and the residue was chromatographed over 50 g silicic acid and 5 g filter cel. Rapid elution with benzene afforded 1·7 g (57%) of **20** as yellow prisms, m.p. 115–117°, which upon sublimation produced yellow prisms, m.p. 119°; $\lambda_{max}^{CHCl_3}$ 4·45, 5·68, 5·84, 5·99, 6·13 and 6·85 μ; $\lambda_{max}^{95\%\,EtOH}$ 237 mμ (ε = 11,900), 307 mμ (ε = 990), in base 233 mμ (ε = 14,500), 348 mμ (ε = 9030); NMR ($CDCl_3$) 0·23 (s), 2·58 (s), 3·55 (s), 8·47 (s) and 8·70 τ (s). (Found: C, 73·18; H, 6·62; N, 6·32. $C_{14}H_{15}NO_2$ requires: C, 73·34; H, 6·59; N, 6·11%).

11-*Acetyl*-11-*carbethoxy*-10-*hydroxymethylene*-9-*oxo*-6,6-*dimethyl*-2-*cyanotricyclo*(5.3.1.$0^{2,7}$)*undecane* (**25**). To a soln of 57 mg (0·437 mmole) ethyl acetoacetate in 8 ml benzene was added 20 mg (0·437 mmole) NaH as a 53% dispersion in mineral oil. After bubbling had ceased (about 5 min) 100 mg (0·437 mmole) of **20**, m.p. 115–117°, was added and the resulting yellow–green soln was swirled and allowed to stand 10 min. Three drops of glacial AcOH were added and the resulting soln was poured into 50 ml water and extracted with $CHCl_3$; this was washed with water, dried over Na_2SO_4, and taken to dryness *in vacuo* to afford 170 mg (106%) of a yellow oil. Chromatography over 3 g silicic acid resulted in elution by benzene of the adduct **25** as white prisms, m.p. 114–121°. Repeated recrystallization from cyclohexane afforded white prisms, m.p. 129–130°; $\lambda_{max}^{CHCl_3}$ 4·45, 5·85, 5·97, 6·11, 6·30 and 6·85 μ; $\lambda_{max}^{95\%\,EtOH}$ 245 mμ (ε = 13,500), 293 mμ (ε = 5640), in base 240 mμ (ε = 10,000), 314 mμ (ε = 12,300); NMR ($CDCl_3$) 1·73 (s), 5·80 (q, J = 7), 6·47 (s), AB system (τ_A = 6·78, τ_B = 7·45, J = 20), 7·77 (s), 8·62 (s), 8·70 (t, J = 7), 8·88 τ (s). (Found: C, 66·98; H, 7·11; N, 3·94. $C_{20}H_{25}NO_5$ requires: C, 66·83; H, 7·01; N, 3·90%).

10-*Cyano*-12-*hydroxy*-7-*oxo*-17-*norpodocarpa*-5,8,11,13-*tetraene* (**23**). Compound **20** (100 mg; 0·437 mmole, m.p. 115–117°), and t-butyl acetoacetate[15] (70 mg; 0·443 mmole) were treated in a manner analogous to the preparation of **25**. The crude adduct amounted to 180 mg (100%) of brown gum; λ_{max}^{film} 2·95 (broad and weak), 4·45, 5·75, 5·80, 6·15, 6·30 and 6·75 mμ; NMR ($CDCl_3$) 2·03 (s), 2·18 (s), 3·72 (s), 6·33 (m), 7·80 (s), 7·97 (s), 8·57 (s), 8·63 (s), 8·67 (s) and 8·72 τ (s).

The crude gum was refluxed under N_2 for 3 hr in 12 ml glacial AcOH containing 7 mg *p*-toluenesulfonic acid and the AcOH was removed by distillation *in vacuo*. The residue was taken up in $CHCl_3$ which was

washed with sat $NaHCO_3$ aq and water, dried over Na_2SO_4, and taken to dryness *in vacuo* to afford 154 mg (100%) of crude **22** as a brown gum, $\lambda_{max}^{CHCl_3}$ 4·45, 5·70 (shoulder), 5·98 (very strong), 6·20 and 6·85 μ; $\lambda_{max}^{95\%\ EtOH}$ 235 mμ (ε = 9000), 307 mμ (ε = 14,500); NMR ($CDCl_3$) 2·63 (m) and 3·72 (m).

This reaction is a modification of that of Ringold and Turner.[16] A soln of 508 mg (1·9 mmoles) of the above crude gum, 417 mg (1·85 mmoles) of 2,3-dichloro-5,6-dicyanoquinone, 30 ml dioxan, and a few mg *p*-toluenesulfonic acid was refluxed for 12 hr under N_2. The mixture was cooled, 345 mg (83%) of 2,3-dichloro-5,6-dicyanohydroquinone crystallized as brown needles and was collected by centrifugation, the soln was refluxed 8 hr more, and upon cooling 70 mg (17%) more of the hydroquinone was collected. The dioxan was removed from the dark soln by distillation *in vacuo* and the residue was taken up in 50:50 ether–$CHCl_3$ which was extracted with $NaHCO_3$ aq, 1% NaOH aq, and water.

The NaOH extracts were acidified with conc HCl and extracted with ether which was washed with water, dried over Na_2SO_4 and distilled *in vacuo* to leave 143 mg (29%) of **23** as a brown solid which was fractionally sublimed to white needles, m.p. 261–262°; λ_{max}^{KBr} 3·01, 4·45, 6·03, 6·32, and 6·85 μ; $\lambda_{max}^{95\%\ EtOH}$ 238 mμ (ε = 17,800), 307 mμ (ε = 10,800), in base 240 mμ (ε = 18,200), 373 mμ (ε = 14,100); NMR (CD_3COCD_3) ABC system (τ_A = 2·02, τ_B = 2·77, τ_C = 2·95, J_{AB} = 0, J_{AC} = 9, J_{BC} = 3), 3·57 (s), 8·47 (s), and 8·70 τ (s). (Found: C, 76·41; H, 6·49; N, 5·37. $C_{17}H_{17}NO_2$ requires: C, 76·38; H, 6·41; N, 5·24%).

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