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DITERPENOID TOTAL SYNTHESIS, AN A→B→C APPROACH.

II. TOTAL SYNTHESIS OF <u>dl</u>-SUGIOL AND <u>dl</u>-FERRUGINOL*

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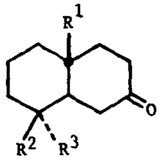
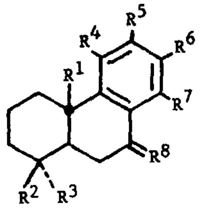
We wish to report a new approach to total synthesis of diterpenoids by an A→B→C sequence which appears to have considerable generality for synthesis of a variety of hydrophenanthrene diterpenoid types. The key intermediate in this synthesis is an 8,8,10-trisubstituted-*trans*-2-decalone (I) in which the 8- and 10-substituents are those of the particular terpenoid under investigation, and the sequence allows attachment of a C-ring with any of a variety of functional and substituent groups (II). The approach is illustrated here by synthesis of *dl*-sugiol (II, $R^1 = R^2 = R^3 = CH_3$, $R^4 = R^7 = H$, $R^5 = OH$, $R^6 = CH(CH_3)_2$, $R^8 = O$) and *dl*-ferruginol (same with $R^8 = H_2$).



I



II

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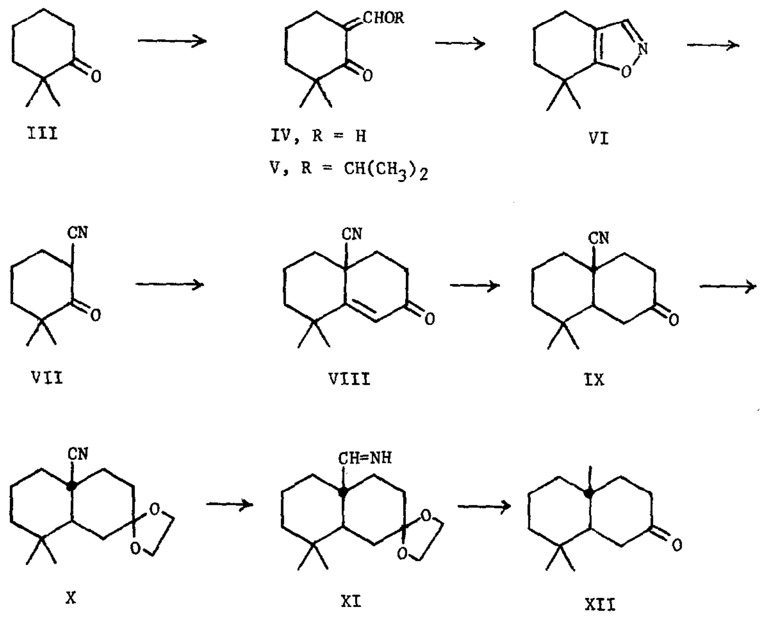
[*] Reference 4 may be considered Part I.

[**] Present address.

2,2-Dimethyl-6-cyanocyclohexanone (VII), m.p. 115°,[*] was prepared in 76% yield by condensation of 2,2-dimethylcyclohexanone with ethyl formate (1), conversion of the hydroxymethylene ketone IV to its isopropyl enol ether V (1), reaction with hydroxylamine hydrochloride (2), and treatment of the isoxazole VI with sodium methoxide (3).[**] Condensation of the



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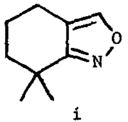
[*] Satisfactory elemental analyses were obtained for all new compounds for which m.p. or b.p. data are reported.

[**] If oximation is carried out directly on the hydroxymethylene ketone IV by the general procedure described in reference 3, isoxazole i is the major product, accompanied by isoxazole VI in but 34% yield.



i

cyanoketone with methyl vinyl ketone (4) affords 88% of the bicyclic enone VIII, m.p. 72-74°, which is hydrogenated over palladium on carbon exclusively to 10-cyano-8,8-dimethyl-*trans*-2-decalone (IX), m.p. 59-60°. Ketalization, lithium aluminum hydride reduction of the cyano group to imino (5), Huang-Minlon reduction of the imine, and ketal hydrolysis afford the trimethyl-*trans*-decalone XII, m.p. 39-40° (reported as the oily *d*- and *l*-enantiomers (6)), in 70% yield from its angular cyano counterpart.

Condensation of the decalone XII with ethyl formate affords the hydroxymethylene derivative XIII, which is dehydrogenated by 2,3-dichloro-5,6-dicyanoquinone (7) to the unsaturated ketoaldehyde. Michael addition of the sodium enolate of t-butyl 5-methyl-3-ketohexanoate produces an adduct (XV) which upon exposure to p-toluenesulfonic acid in acetic acid undergoes cleavage of the t-butyl ester, decarboxylation, and cyclodehydration to the tricyclic enedione XVI, m.p. 146-147°.* Treatment with pyridinium bromide perbromide affords *dl*-sugiol (XVII) presumably by bis-dehydrohalogenation of the unisolated dibromide. The n.m.r spectrum of the acetate prepared from this sugiol sample is identical with that

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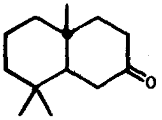
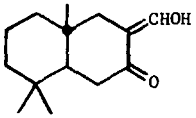
*The enedione XVI should posess the more stable relative configuration at C-8 (steroid-terpenoid numbering) and thus it is either *trans*-*anti*-*trans* or *trans*-*syn*-*cis*. Investigation of its configuration is not yet complete, but a *syn*-*cis* relationship has been tentatively assigned on the basis of the spin-couplings among protons at positions 8, 9, 13, and 14. In the *anti*-*trans* system the pertinent dihedral angles ϕ (measured from models) and the coupling constants which are expected to correspond to them (J, in c.p.s.) are approximately: $\phi_{8,14} = 90°$ ($J_{8,14} = 2.6$), $\phi_{8,13} = 90°$ ($J_{8,13} = -2.6$), and $\phi_{8,9} = 180°$ ($J_{8,9} = 8\text{-}14$) [E. W. Garbisch, Jr., *J. Amer. Chem. Soc.*, *86*, 5561 (1964); N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry", Holden-Day, Inc., San Francisco, 1964, p. 51]. The corresponding angles and coupling constants for the *syn*-*cis* system are: $\phi_{8,14} = 25°$ ($J_{8,14} = 5.9$), $\phi_{8,13} = 25°$ ($J_{8,13} = 0.6$), and $\phi_{8,9} = 60°$ ($J_{8,9} = 1\text{-}7$). Couplings of 6 c.p.s. (8-14), <1 c.p.s. (8-13), and 4-5 c.p.s. (8-9) are observed, the 8-13 coupling being taken from the spectrum of the desisopropyl analog of compound V of the accompanying paper. Thus it appears that attack of the enolate on unsaturated aldehyde XIV is stereoselective in the axial sense, a common stereochemical course for a kinetically-controlled nucleophilic conjugate addition, *cf*. W. L. Meyer and K. K. Maheshwari, Tetrahedron Letters, 2175 (1964) and references therein.

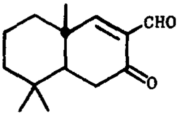
recorded in the literature for d-sugiol acetate (8). Hydrogenolysis affords dl-ferruginol (XVIII), n.m.r. and i.r. spectra of which are identical with those of an authentic sample of the corresponding d-form.



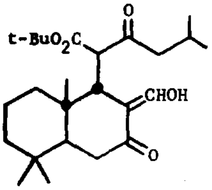
XII



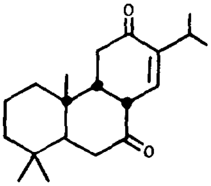
XIII



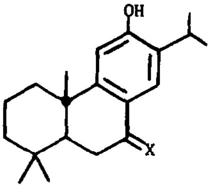
XIV



XV



XVI



XVII, X = O

XVIII, X = H_2

It appears that this sequence for attachment of the C-ring can be employed with a variety of substituents R^1, R^2, and R^3 in the decalone moiety, and experiments leading to resin acids of the podocarpic and dehydroabietic types are in progress with the appropriate bicyclic ketones (I: $R^1 = R^3 = CH_3$, $R^2 = CO_2CH_3$ and $R^1 = R^2 = CH_3$, $R^3 = CO_2CH_3$) (see also the accompanying communication). Likewise, by choice of the appropriate active methylene compound for Michael addition to the unsaturated ketoaldehyde, substituents R^4, R^5, and R^6 are capable of variation, as is R^7 by selection of the ester to be consensed with the β-decalone. Examination of these points of versatility and extension of the sequence to synthesis of more complex polycyclic diterpenoids will be reported in due course.

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