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A STEREOSELECTIVE TOTAL SYNTHESIS OF PODOCARPIC ACID

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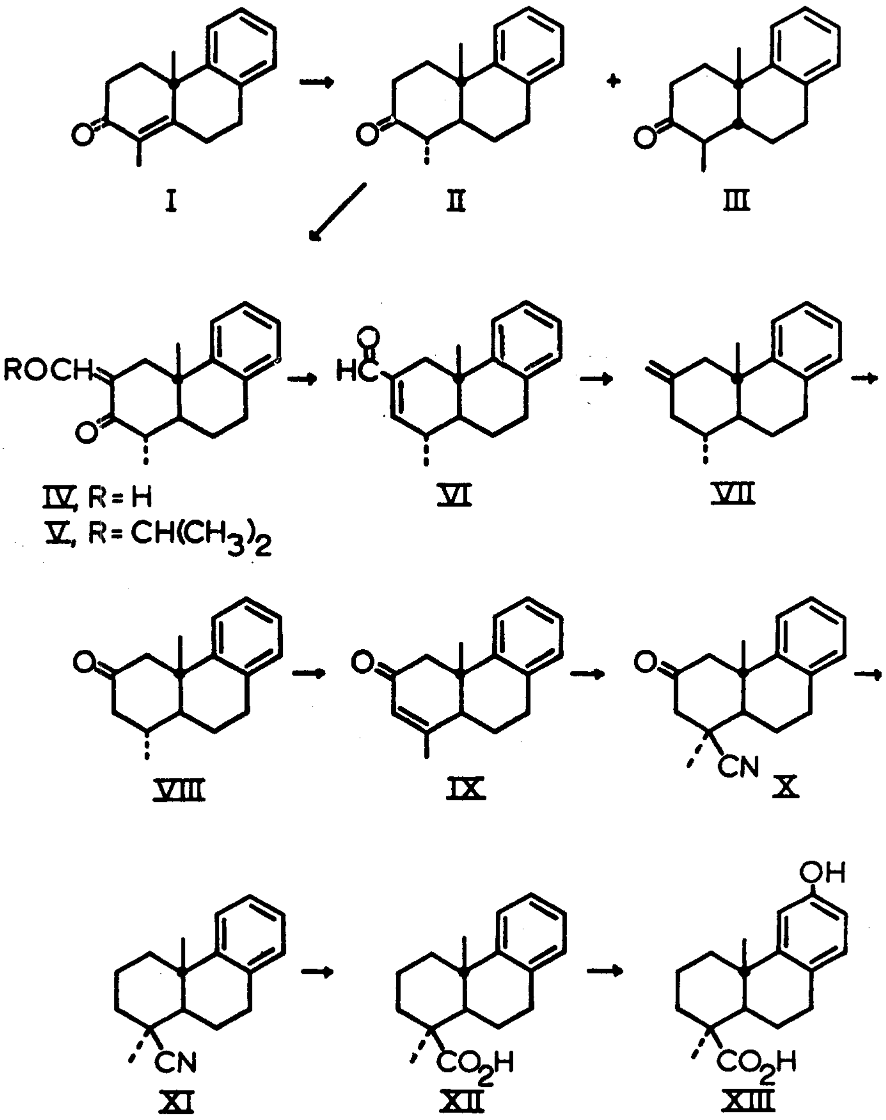
One of the foremost problems encountered in synthesis of diterpenoid resin acids is that of stereoselective introduction of methyl and carboxyl substituents at the quaternary 4-position in the correct configuration relative to the C-10 angular methyl. Most previous syntheses have attacked this stereochemical problem in one of two general ways: through stereoselective alkylation of a bi- or tricyclic 3-keto or Δ^4-3-keto derivative (1-3) or through generation of the angular C-10 asymmetric center by closure of the 9,10-bond in an aromatic alkylation process after the C-4 substitution pattern has been established (4-7). Such approaches have met with various degrees of stereochemical success. We now describe a new and highly stereoselective total synthesis of podocarpic acid (XIII) in which the crucial C-4 configuration is established in a quite different manner, namely during 1,4-addition of hydrogen cyanide to a 4-methyl-Δ^3-2-keto intermediate (IX). This type of reaction proves to be very efficient for the purpose.

dl-1,4a-Dimethyl-2,3,4,4a,9,10-hexahydro-2-phenanthrone (I) (7), prepared by condensation of 1-methyl-2-tetralone with 1-diethylamino-3-pentanone methiodide, was reduced by lithium in liquid ammonia-ether to an 82:18 mixture of the crystalline trans-fused saturated ketone II,


I
II
III
IV, R = H
V, R = CH(CH3)2
ROCH
HC
O
VI
VII
VIII
IX
X
CN
XI
CN
XII
CO2H
XIII
CO2H
OH

m.p. 99-100°,* and its cis-fused isomer III, an oil. Condensation of the trans-ketone with ethyl formate affords the hydroxymethylene derivative IV, m.p. 101-102°, the isopropyl ether of which (V, m.p. 107-108°) was reduced by lithium aluminum hydride to produce the unsaturated aldehyde VI, m.p. 113-114°. Wolff-Kishner reduction of the corresponding semicarbazone proceeded with double bond migration, and the resulting exocyclic methylene derivative VII was converted by ozonolysis to the 2-ketone VIII, m.p. 66-67.5°. Bromination and dehydrobromination completed synthesis of the required Δ^3-2-ketone IX, m.p. 84.5-85°.

Conjugate addition of hydrogen cyanide to bi- and polycyclic enones has recently been used in a variety of instances to introduce angular cyano groups (8). In most cases where attack occurs at the angular position of a β-decalone system, the resulting product contains substantially more trans-fused than cis-fused material. From these and other related results (9) it appeared to us that at least in large measure this selectivity is due to stereoelectronic effects which favor a transition state in which the cyanide is becoming axially attached to the ketonic ring, so that the developing cyanide-β-carbon bond and the enolate π-system retain most efficient orbital overlap during bond formation. Similar additions to a non-angular quaternary center have not been explored from this view, but it is clear that if such stereoelectronic control is important (rather than hindrance to approach of the nucleophile) the Δ^3-2-ketone IX should lead to a podocarpic configuration at C-4. In the event this proved to be the case; the addition is completely stereoselective, and the single cyanoketone produced (X, m.p. 153-154°) indeed has the podocarpic configuration because

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* Although only one enantiomer is depicted in structural formulas, the intermediates I-XI were handled only as racemates. All new compounds for which melting points are reported have been adequately characterized by spectral and microanalytical data.

Clemmensen reduction affords *dl*-desoxypodocarponitrile (XI, m.p. 65-66°) whose infrared and n.m.r. spectra are identical with those of the authentic *l*-isomer (10). The racemic nitrile was converted to *dl*-desoxypodocarpic acid (XII) by lithium aluminum hydride reduction and oxidation (11), and the product was identical in all respects with an authentic sample (12). Inasmuch as the racemic acid has been resolved (2a) and *d*-desoxypodocarpic acid has been converted to *d*-podocarpic acid (12), the present work constitutes a total synthesis of podocarpic acid with better than 80% stereoselectivity at every step. It also provides evidence which clearly implies that stereoelectronic effects are important in controlling the stereoselectivity of 1,4-addition of hydrogen cyanide to conjugated enones.

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