Stereospecific Syntheses of Epimeric Diterpenoid Resin Acids through Enolate Anion Reactions

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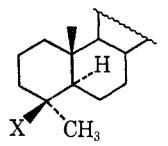
Epimeric α-cyano-α-methyl ketones were prepared by stereospecific reactions of enolates in bicyclic and tricyclic compounds. The latter were used in syntheses of podocarpic and abietic acids. Alkylations of β-keto nitriles were found to be stereochemically opposed to those of corresponding β-keto esters in two analogous series. Steric control in these and other enolate reactions is discussed. New reactions described are syntheses of α-cyano enones by opening of epoxy ketones with cyanide or reaction of enone enolates with cyanogen chloride and syntheses of α-cyano ketones by two reductions of α-cyano enones or by trapping of enolates, obtained in Birch reductions of enones, with cyanogen chloride.

Partial structures **1** and **2** are representative of a variety of natural products. Thus, the diterpenes podocarpic acid and sandarocopimaric acid and diterpene alkaloids such as atisine are characterized by the stereochemical arrangement of **1**, while the diterpenes of the abietic acid family are described by **2**. Stereospecific attainment of these relative arrangements presents a stimulating synthetic challenge. Next to acid-catalyzed cyclizations of polyunsaturated systems or their derivatives[2a-2i] and some other schemes,[2h,3] the most fruitful approach to this problem resulted from the synthesis and modification of enone precursors of type **3**.[4-8] While reduction of the enone **3** to a *trans*-decalone system **4** by alkali metals in liquid ammonia leads predictably[9] to the required *trans* ring fusion, the subsequent introduction of functional and tertiary methyl groups at the desired position (C-4, steroid numbering) adjacent to the carbonyl group in **4** is stereochemically more ambiguous and necessitates blocking of the alternative α-methylene group (C-2).[10]



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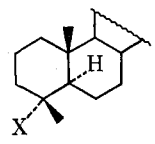

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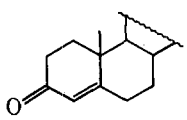
X = CO_2H, CH_2OH, $CH_2N(CH_3)_2$



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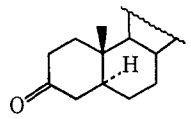

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In the present report we show some new reaction sequences and remarkably stereoselective alkylation reactions which are solutions to these problems and allow exclusive syntheses of **1** or **2** at will. In addition, an attempt has been made to clarify the results of enolate alkylations found in this work as well as in previous empirical approaches to some natural-product syntheses.

In contrast to the preferred reactions at C-2 in the *trans*-decalone system **4**, one could expect preferential substitution of the enone **3** at C-4.[10] However, earlier attempts at carboxylation of a tricyclic enone had given only a low yield[11] of the desired 4-carbomethoxy product as well as substitution at C-2. Therefore, we devised indirect sequences for functionalizing such enone systems. The reactions were carried out on model bicyclic compounds and on tricyclic intermediates for diterpene syntheses.

Results

Oxidation of the octalone **5** with hydrogen peroxide and base gave mixtures of the α- and β-epoxides **6** and **7** in a ratio of 1:3–4, the latter predominating in analogy to the products of epoxidation of Δ^4-3-keto steroids[12-15] and a related octalone.[16,17] Nuclear magnetic resonance spectra of the epoxides showed the angular methyl groups at δ 1.15 and 1.25, respectively. The dual shielding influences of carbonyl and epoxide functions on the angular methyl group let one hesitate to base a configurational assignment on the relative chemical shifts of the angular methyl group[18] in this epoxide pair. However, the relative chemical shifts of the C-4 protons in **6** at δ 3.10 and **7** at δ 3.02 were consistent with relative positions in equatorial and axial

(1) Alfred P. Sloan Fellow, 1965–1968.

(2) (a) R. D. Haworth and R. L. Barker, *J. Chem. Soc.*, 1299 (1939); (b) R. D. Haworth and B. P. Moore, *ibid.*, 633 (1946); (c) B. K. Bhattacharryya, *J. Indian Chem. Soc.*, **22**, 165 (1945); (d) W. E. Parham, E. L. Wheeler, and R. M. Dodson, *J. Amer. Chem. Soc.*, **77**, 1167 (1955); (e) J. A. Barltrop and A. C. Day, *J. Org. Chem.*, **24**, 671 (1959); (f) U. R. Ghatak, D. K. Datta, and S. C. Ray, *J. Amer. Chem. Soc.*, **82**, 1728 (1960); (g) S. N. Mahapatra and R. M. Dodson, *Chem. Ind.* (London), 253 (1963); (h) M. Sharma, U. R. Ghatak, and P. C. Dutta, *Tetrahedron*, **19**, 985 (1963); (i) D. A. H. Taylor, *J. Chem. Soc.*, 1553 (1963).

(3) (a) J. A. Barltrop and A. C. Day, *ibid.*, **14**, 310 (1961); (b) B. Shimizu, A. Ogiso, and I. Iwai, *Chem. Pharm. Bull.* (Tokyo), **11**, 766, 770, 774 (1963); (c) C. T. Mathew and P. C. Dutta, *Proc. Chem. Soc.*, 135 (1963); (d) W. L. Meyer and K. K. Maheshwari, *Tetrahedron Lett.*, 2175 (1964); (e) R. W. Guthrie, A. Philipp, Z. Valenta, and K. Wiesner, *ibid.*, 2945 (1965); (f) R. E. Ireland and R. C. Kierstead, *J. Org. Chem.*, **31**, 2543 (1966).

(4) G. Stork and J. W. Schulenberg, *J. Amer. Chem. Soc.*, **84**, 284 (1962).

(5) E. Wenkert, A. Afonso, J. B. Bredenberg, C. Kaneko, and A. Tahara, *ibid.*, **86**, 2038 (1964), and references cited therein.

(6) M. E. Kuehne, *ibid.*, **83**, 1492 (1961).

(7) T. A. Spencer, T. D. Weaver, R. M. Villarica, R. J. Friary, J. Posler, and M. A. Schwartz, *J. Org. Chem.*, **33**, 712 (1968).

(8) T. A. Spencer, R. J. Friary, W. W. Schmiegel, J. F. Simeone, and D. S. Watt, *ibid.*, **33**, 719 (1968).

(9) G. Stork and S. D. Darling, *J. Amer. Chem. Soc.*, **86**, 1761 (1964).

(10) R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives, and R. B. Kelly, *J. Chem. Soc.*, 1131 (1957).

(11) E. Wenkert and B. G. Jackson, *J. Amer. Chem. Soc.*, **81**, 5601 (1959).

(12) P. A. Plattner, H. Heusser, and A. B. Kulkarni, *Helv. Chim. Acta*, **31**, 1822 (1948).

(13) H. J. Ringold, E. Batres, O. Mancera, and G. Rosenkranz, *J. Org. Chem.*, **21**, 1432 (1956).

(14) D. J. Collins, *J. Chem. Soc.*, 3919 (1959).

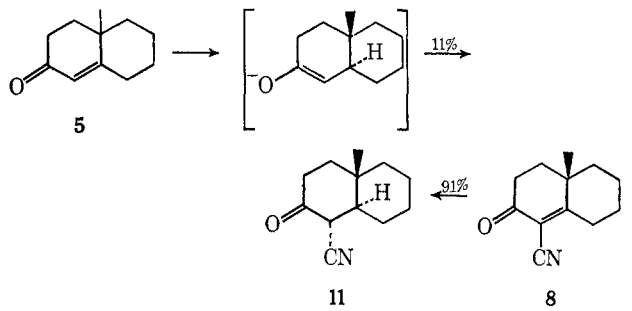
(15) H. H. Westen, *Helv. Chim. Acta*, **47**, 575 (1964).

(16) A corresponding epoxide of unspecified stereochemistry or physical properties has been used by J. Schreiber, D. Felix, A. Eschenmoser, M. Winter, F. Gautschi, K. H. Schulte-Elte, E. Sundt, G. Ohloff, J. Kalvoda, H. Kaufmann, P. Wieland, and G. Anner, *Helv. Chim. Acta*, **50**, 2101 (1967); *Tetrahedron Lett.*, 3943 (1967).

α-acetoxy ketones (opposite of usual relationship of axial and equatorial protons).[19]

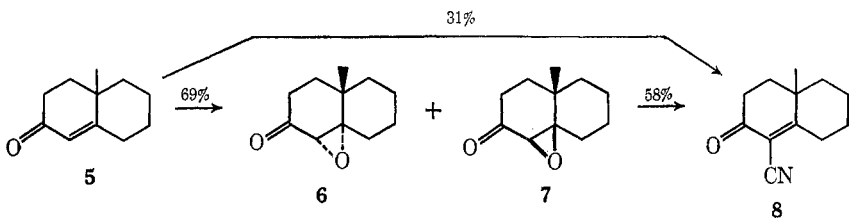
Treatment of the epoxide mixture with aqueous ethanolic sodium cyanide and pyrolytic dehydration on distillation gave the cyano enone **8**. An intermediate α-cyano-β-hydroxy ketone and/or α-cyano-β,γ-unsaturated ketone was separated from neutral components of the reaction mixture by base extraction, but not characterized further and converted to the α-cyano-α,β-unsaturated product **8**. The same compound could also be obtained in lower yield by direct cyanogenation of the enone **5** with sodium hydride and cyanogen chloride.

As an alternative sequence we considered the reaction of the dienamine **9** with cyanogen chloride. We had previously found the reaction of enamines with cyanogen chloride useful in the preparation of α-cyano ketones.[20] However, the dienamine nitrile obtained from **9** showed an nmr vinyl hydrogen singlet and was converted to a semicarbazone derivative which was not identical with the corresponding derivative prepared from the cyano enone **8**. Consequently, a δ-cyano dienamine structure **10** was assigned. This reaction

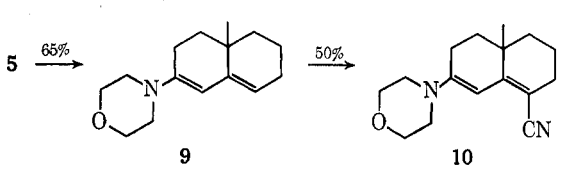


A third successful sequence for the introduction of a nitrile group was achieved by reduction of the enone **5** with lithium in liquid ammonia and trapping of the kinetically produced Δ^3-enolate anion[22] with cyanogen chloride. The keto nitrile **11** thus formed was identical with that obtained by reduction of the cyano enone **8** with lithium in liquid ammonia.

Addition of a nitrile function to the enone **12**, which bears an α-methyl substituent, was studied next. A mixture of epoxide epimers **13** and **14** could again be obtained with hydrogen peroxide and base, but attempts at opening of the epoxide with cyanide did not give an identifiable β-keto nitrile product. However, reduction of the enone **12** with lithium in liquid ammonia and capture of the enolate anion with cyanogen chloride gave the equatorial α-cyano ketone **15**. The assignment of stereochemistry in **15** was based on a comparison with the epimeric keto nitrile described below. Reduction of the keto nitrile with zinc and hydrochloric acid in ethanol led to an olefin **16**, which was hydrogenated on a palladium catalyst to the bicyclic nitrile **17**.



may be contrasted with the course of other dienamine substitutions, which take place at the desired β position.[21]

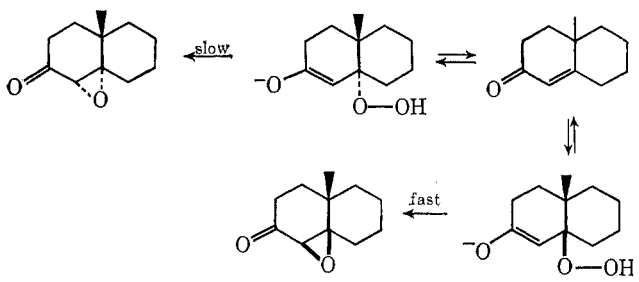


Alkylation of the cyano ketone **11** with lithium amide and methyl iodide in benzene gave a small amount of the enol ether **18** and the α-cyano ketone **19** as the major product. The epimeric keto nitrile **15** was not formed in larger than trace amounts, if at all. Methylation of the cyano ketone **11** with sodium hydride in dimethyl sulfoxide led only to the enol ether **18**.

The cyano enone **8**, on methylation with a variety of bases and solvents, gave only the dienol ether product **20**, which was characterized by catalytic reduction to the enol ether **18**.

Stereochemical assignments of the two methyl-substituted keto nitriles **15** and **19** were based on spectroscopic evidence and correspondence with analogous tricyclic compounds, which were correlated with natural products of known stereochemistry (see below). Thus, the relative positions of infrared carbonyl absorption found at 1720 cm^{-1} for the epimer **15** with an equatorial α-nitrile group and at 1710 cm^{-1} for the epimer **19** with an axial α-nitrile substituent correspond to the previously observed carbonyl absorptions of

(17) The predominant formation of a β-epoxide may be based on a kinetic control due to an intramolecular electrophilic reaction of a β-peroxide with the enolate anion. This would be stereoelectronically favored on the axial side of C-4. The result may also be ascribed to stereoselective addition to the enone, owing to factors analogous to those seen in catalytic hydrogenation of such enones, which lead to *cis*-decalones. Distant structural dependence was found by H. B. Henbest and W. J. Jackson, *J. Chem. Soc., C*, 2459 (1967).



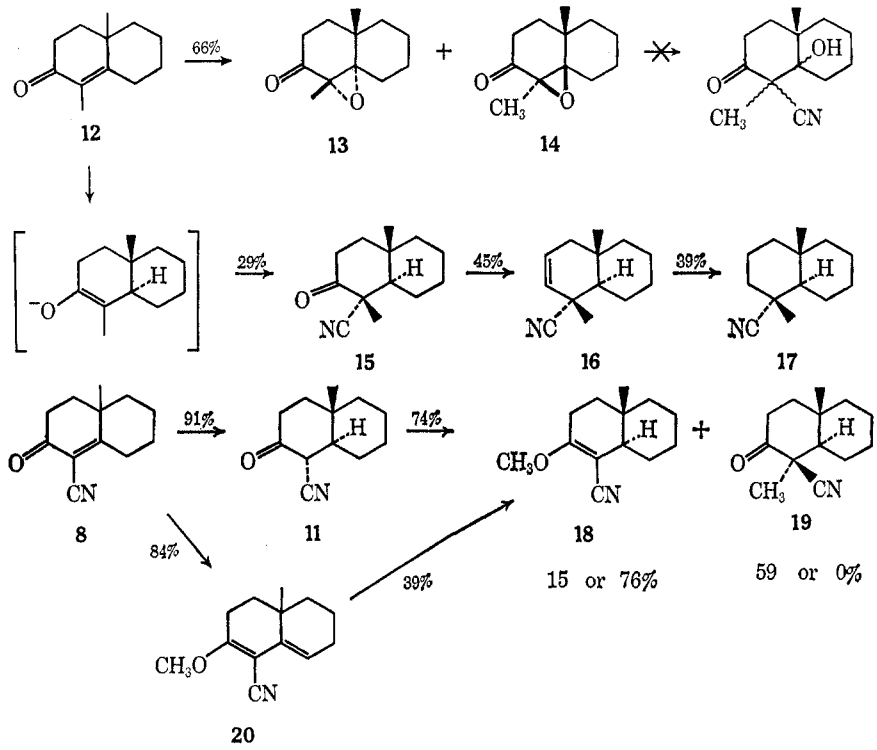
(18) K. Tori, T. Komeno, and T. Nakagawa, *J. Org. Chem.*, **29**, 1136 (1964).

(19) M. E. Kuehne and T. Giacobbe, *ibid.*, **33**, 3359 (1968).

(20) M. E. Kuehne, *J. Amer. Chem. Soc.*, **81**, 5400 (1959).

(21) G. Stork and G. Birnbaum, *Tetrahedron Lett.*, 313 (1961).

(22) G. Stork, P. Rosen, N. Goldman, R. V. Coombs, and J. Tsuji, *J. Amer. Chem. Soc.*, **87**, 275 (1965).



epimeric α-cyano ketones.[20] The two epimers were also characterized by the relative nmr chemical shifts of the angular methyl groups, where one finds a downfield displacement for the compound **19** (δ 1.42) with an axial nitrile substituent relative to its epimer **15** (δ 1.13).[23]

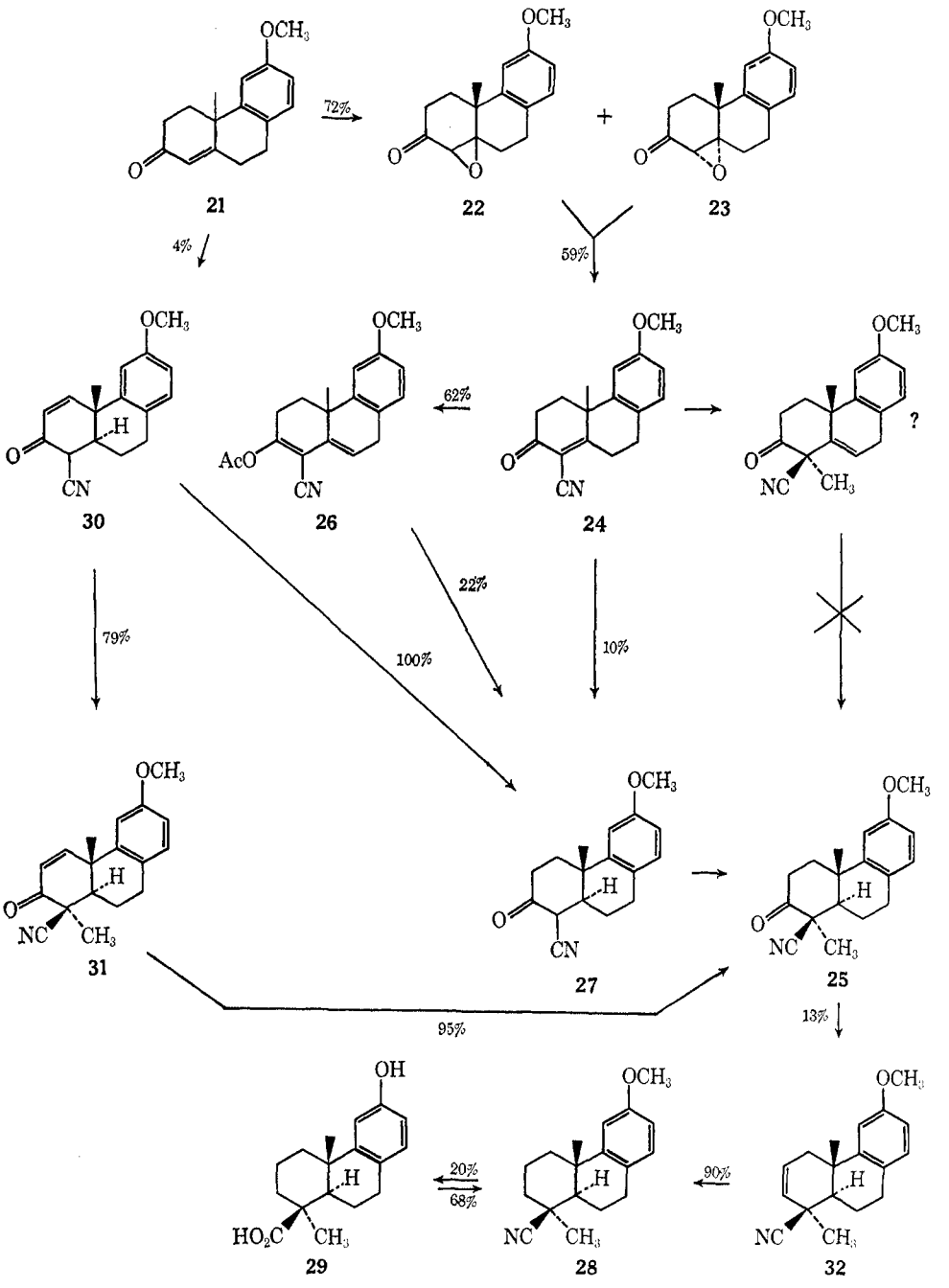
The new synthetic reaction sequences were next applied to stereoselective total syntheses of podocarpic acid and abietic acid. Epoxidation of the tricyclic enone **21**[6] with hydrogen peroxide and base gave a 2:1 mixture of epoxy ketones **22** and **23**. Treatment of this mixture with aqueous sodium cyanide and subsequent distillation furnished the enone nitrile **24**. While some C-methylation of this compound may have been achieved (in contrast to analogous reaction in the bicyclic series), it was not possible to obtain the corresponding dihydro compound **25** from catalytic reduction of the alkylation mixture. However, reduction of the enone nitrile **24** with lithium in ammonia or catalytic reduction of the enol acetate derivative **26**, and subsequent methylation of the keto nitrile **27** with methyl iodide and lithium amide in benzene, gave only the product **25** with the stereochemistry of podocarpic acid. Removal of the carbonyl group by Clemmensen and catalytic reduction led to the nitrile **28**, which had infrared, nuclear magnetic resonance, and mass spectra identical with the nitrile methyl ether of podocarpic acid. This nitrile has been converted to podocarpic acid (**29**).[6]

Previously,[6] we had studied the methylation of the related enone nitrile **30** and erroneously ascribed the abietic acid stereochemistry to its product **31**, on the basis of a failure to convert this product to a sample identical with the nitrile **28**. We have now found that both Clemmensen reduction and thioketal desulfurization of ketones such as **25** lead to products containing large amounts of olefin. The olefin **32** was readily recognized by nmr and mass spectra and could be hydrogenated to the saturated nitrile **28**. Thus, the saturated keto nitrile **27** and the unsaturated keto nitrile **30** gave only methylation products **25** and **31** with equatorial methyl substituents.

In order to synthesize the C-4 epimer of the methylation product **25**, the tricyclic enone **33**, obtained from ethyl vinyl ketone and 7-methoxy-2-tetralone, was reduced with lithium in liquid ammonia and the resultant enolate was trapped with cyanogen chloride. A comparison of the keto nitrile product **34** with the previously obtained epimer **25** again showed the expected higher carbonyl stretching frequency and upfield chemical shift of the angular methyl group in the equatorial nitrile epimer **34**. This compound was also reduced with zinc and hydrochloric acid, or by Raney nickel desulfurization of the thioketal, to an olefin-containing product, **35**, which was reduced by catalytic hydrogenation to **36**, the epimer of the compound **28**. While infrared and nuclear magnetic resonance spectra of the final epimeric nitriles **28** and **36** were clearly different, one could not differentiate their mass spectra.

Finally, this reaction sequence was applied to the synthesis of the isomeric methoxy compound **40**. Repeated attempts at removal of the carbonyl group in **38** by desulfurization of a thioketal or by Clemmensen reductions and hydrogenation resulted in very low yields of **40**. However, reduction to the alcohol **41** with sodium borohydride, formation of the mesylate **42** with sulfene, and dehydromesylation at 210° in dimethylformamide with lithium carbonate and lithium chloride gave the olefin **39** in good yield. Tosylation of the alcohol **41** with tosyl chloride in pyridine or in benzene with lithium hydride was not achieved here, in contrast to the epimeric nitrile series, where it was quantitative with the alcohol derived from **25**. While

(23) Similar relationships have already been observed in epimeric nitriles derived from podocarpic and dehydroabietic acids and the expected opposite order in the corresponding esters: (a) A. Tahara and K. Hirao, *Chem. Pharm. Bull.* (Tokyo), **12**, 984, 1121 (1964); (b) E. Wenkert, A. Afonso, P. Beak, R. W. J. Carney, P. W. Jeffs, and J. D. McChesney, *J. Org. Chem.*, **30**, 713 (1965); (c) see ref 7.



dehydrotosylation of the C-4 epimeric tosylate gave **32** in refluxing dimethylformamide, the higher temperature was required for the mesylate **42**.

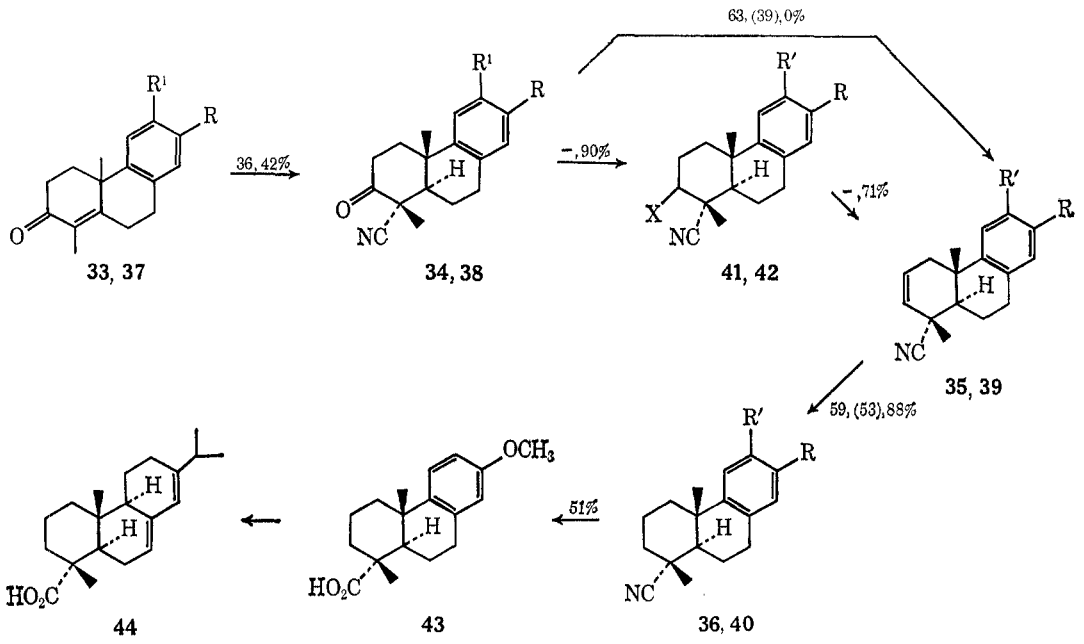
Hydrolysis of the nitrile **40** gave the corresponding acid **43**. Comparison of this product with a specimen of the compound, which was previously converted to abietic acid **44**,[24] showed complete identity of mass spectra and retention times on thin layer chromatography. Comparison with the racemic compound prepared by a different route[25] and used as an intermediate in the syntheses of resin acid degradation products and a route to polyalthic acid showed identical melting points, mixture melting points, and ir spectra.

(24) A. W. Burgstahler and L. R. Worden, *J. Amer. Chem. Soc.*, **86**, 96 (1964). We thank Professor Burgstahler for providing a sample of his compound obtained by degradation of abietic acid.

(25) A. Ogiso and S. W. Pelletier, *Chem. Commun.*, 94 (1967). We thank Professor Pelletier for a comparison sample of the *dl* compound.

Discussion

The methylations of the keto nitriles **11**, **27**, and **30**, which led to the equatorial alkylation products, are in striking contrast to methylations of the analogous β-keto esters,[5,7,8] where preponderant or exclusive axial alkylation was observed. Two principal factors may account for this difference. Association of the ester function with the metal cation of the enolate may favor a transition state in which coplanarity of the ester and carbonyl functions is locked. Thus, an axial alkylation process, which passes from the planar enolate to a cyclohexanone chair conformation with coplanar equatorial ester and carbonyl groups, may be favored over a transition state that approaches a twist conformation. Only in a true boat conformation, with higher conformational energy, could coplanarity of the functional groups also be maintained. This concept should be



33–36, R′ = OCH_3; R = H
37–42, R′ = H; R = OCH_3
41, X = OH
42, X = OMes

useful in the prediction of alkylation products of other β-keto esters.[26]

As a corollary, cyclohexanones with bulky α-alkyl groups, which can crowd a proximate metal–enolate complex, should show a preference for introduction of an equatorial substituent,[27,28] and unsubstituted cyclohexanones[29] should not display stereospecificity. These expectations will be modified by considerations of relative nucleophilicities of enolates and 1,3-diaxial shielding (see below).

A second directive influence must be the 1,3 shielding to β alkylation due to the angular methyl group. If the transition state of the reaction resembles the product (low enolate nucleophilicity), 1,3-diaxial interaction should prevent β alkylation. With a more nucleophilic enolate (new bonding at greater distance of reactants), this steric interaction should be diminished.

With the β-keto esters, but not the corresponding nitriles, interaction of the C-4 substituent with C-6 *peri* hydrogens must be considered. In the enolate, the bond of the C-4 substituent to the ring bisects the bond angle formed by the α and β protons at C-6 and, with coplanar carbonyl groups in the β-keto ester anion, the alkoxy substituent points to the C-6 α hydrogen. When C-4 becomes tetrahedral, a C-4 β substituent in a boat conformation still lies between the C-6 α and β bonds, with an ester alkoxyl group pointing below the C-6 α proton. In the chair conformation, C-4 α and C-6 α bonds are coplanar and an ester alkoxyl group points into the angle formed by C-6 α and β substituents. While a strong *peri* interaction in the enolate of the β-keto ester (but not the β-keto nitrile) is thus clear, a preference for going to chair or boat conformations is not obvious on this basis.

Contrasting the results obtained on alkylation of the bi- and tricyclic β-keto esters and β-keto nitriles, one also notes that these compounds differ markedly in their acidities. Thus, in 0.1 *N* sodium hydroxide in methanol, 85% of the keto nitrile **11** but only 0.9% of a corresponding keto ester[7] was converted to the sodium enolate. This difference may be ascribed to the *peri* interaction found in the ester but not in the nitrile enolate. Under the same conditions, 2-carbethoxycyclohexanone was completely converted to its enolate salt, but this compound was still found to be only one-tenth as acidic as 2-cyanocyclohexanone. In competitive methylations of the corresponding enolates in benzene, 2-carbethoxycyclohexanone was more reactive than 2-cyanocyclohexanone.[30] Thus, if the difference in acidities of the bicyclic and tricyclic β-keto nitriles and esters also reflects their relative nucleophilicities, one would expect more axial shielding for the β-keto nitriles than for the β-keto esters.

The foregoing interpretation may be employed for categorization of all previous experimental results obtained in reactions of alicyclic enolates[4,5,28,31–39] and

(26) F. Nerdel, D. Frank, and K. Rehse, *Chem. Ber.*, **100**, 2978 (1967). This, and the following references, provides examples which support the general concept of enolate alkylation described here. However, our interpretation does not necessarily correspond to that of the respective authors.

(27) J. M. Conia and P. Briet, *Bull. Soc. Chim. Fr.*, 3881 (1966).

(28) (a) E. J. Eisenbraun, F. Burian, J. Osiecki, and C. Djerassi, *J. Amer. Chem. Soc.*, **82**, 3476 (1960); (b) C. Djerassi, J. Osiecki, and E. J. Eisenbraun, *ibid.*, **83**, 4433 (1961); (c) M. R. Cox, H. P. Koch, W. B. Whalley, M. B. Hursthouse, and D. Rogers, *Chem. Commun.*, 212 (1967).

(29) H. O. House, B. A. Tefertiller, and H. D. Olmstead, *J. Org. Chem.*, **33**, 935 (1968).

(30) Experiments by Mr. David Donner in our laboratory.

(31) J. H. Fried, G. E. Arth, and L. H. Sarett, *J. Amer. Chem. Soc.*, **82**, 1684 (1960).

(32) J. H. Fried, A. N. Nutile, and G. E. Arth, *ibid.*, **82**, 5704 (1960).

(33) W. S. Johnson, D. S. Allen, R. R. Hindersinn, G. W. Sausen, and R. Pappo, *ibid.*, **84**, 2181 (1962).

(34) The preference for *cis*-9-methyl-3-octalin but *trans*-9-methyl-2-octalin structures can be extended to other bicyclic systems with trigonal positions 7 and 8.[6] Thus, the products in ref 30–32 are in accord with the generalized alkylation concept. See also L. Velluz, J. Valls, and G. Nominé, *Angew. Chem. Intern. Ed. Engl.*, **4**, 181 (1965).

(35) L. H. Sarett, W. F. Johns, R. E. Beyler, R. M. Lukes, G. I. Poos, and G. E. Arth. *J. Amer. Chem. Soc.*, **75**, 2112 (1953).

(36) J. Schmidlin, G. Anner, J.-R. Billeter, K. Heusler, H. Ueberwasser, P. Wieland, and A. Wettstein, *Helv. Chim. Acta*, **40**, 1034 (1957).

(37) L. Velluz, G. Nominé, and J. Mathieu, *Angew. Chem.*, **72**, 725 (1960).

(38) C. L. Graham, F. J. McQuillin, and P. L. Simpson, *Proc. Chem. Soc.*, 136 (1963).

(39) V. Permutti and Y. Mazur, *J. Org. Chem.*, **31**, 705 (1966).

be useful in predicting the outcome of future reactions. For this purpose one can summarize as follows. When the energy difference between epimeric products in their initial conformation is increased in enolate reactions, this may be reflected in corresponding transition states and result in increased stereospecificity,[31-36] with the degree of such stereospecificity inversely dependent on the relative nucleophilicity of the enolate. Decreasing nucleophilicity should favor axial alkylation except when axial substituents β to the site of alkylation shield the enolate from close approach of the electrophile. Interaction of an α substituent with the carbonyl function must also be considered.[40] Decreased nucleophilicity may explain the stereospecificity and products found in the alkylation of cyclohexenones,[4,5,28,37-39] as contrasted with related cyclohexanones.[31-36]

Experimental Section

1α-Cyano-1β,4aβ-dimethyl-1,2,3,4,4a,5,6,7,8,8aα-decahydro-2-naphthalone (15).—To a stirred solution of 0.35 g (0.050 g-atom) of lithium metal in 150 ml of anhydrous ammonia, 4.00 g (0.022 mol) of the enone **12**,[41,42] bp 80–85° (0.3 mm), ν_{max}^{neat} 1665 cm^{-1}, $\lambda_{max}^{ethanol}$ 247 mμ (ε 14,000), in 50 ml of dry tetrahydrofuran was added quickly. The mixture was stirred under reflux for 30 min, the ammonia was distilled at room temperature overnight under anhydrous conditions, and final traces of ammonia and tetrahydrofuran were removed under reduced pressure. The residue was suspended in 100 ml of dry benzene under nitrogen, the mixture was cooled to 10°, 15.0 g (0.24 mol) of freshly distilled cyanogen chloride in 50 ml of dry benzene was added dropwise, and the mixture was stirred at room temperature for 10 hr. The solution was concentrated under reduced pressure. Water was added to the resultant semisolid residue and the mixture was extracted with ether. The combined ethereal solutions were washed with dilute hydrochloric acid and water, dried over magnesium sulfate, and concentrated under reduced pressure. Vpc analysis (10% SE-30 on Floropac at 200°) of the oily residue indicated the presence of three components in the ratio of 3:30:68 with retention times of 4.9, 5.7, and 13.0 min, respectively.

The crude mixture was distilled from a jacketed flask in two fractions. The first, bp 100–140° (0.07 mm), afforded 1.23 g of a colorless oil. The infrared spectrum of this oil indicated the presence of two carbonyls (ν_{max}^{neat} 1710 and 1670 cm^{-1}) and the absence of a nitrile function. Vpc analysis showed two components with retention times of 4.9 and 5.7 min. Isolation of the two components by preparative vpc and spectral information identified the two components as the starting enone **12** (t_R 5.7 min, ν_{max}^{neat} 1670 cm^{-1}), and the reduced enone (t_R 4.9 min, ν_{max}^{neat} 1710 cm^{-1}).

The second fraction, bp 150–180° (0.05 mm), afforded 1.36 g of a viscous liquid. Vpc analysis indicated one component with a retention time of 13.1 min. This oil crystallized from petroleum ether (bp 30–60°): mp 82–83°; ν_{max}^{KBr} 2240 and 1720 cm^{-1}; nmr (CDCl$_3$) 1.13 (s, 3 H) and 1.40 ppm (s, 3 H).

Anal. Calcd for $C_{13}H_{19}NO$: C, 76.05; H, 9.33; N, 6.82. Found: C, 76.32; H, 9.29; N, 7.04.

1α-Cyano-1β,4aβ-dimethyl-1,2,3,4,4a,5,6,7,8,8aα-decahydronaphthalene (17).—A suspension of zinc amalgam was prepared by stirring 4.0 g of zinc moss in a solution of 0.35 g of mercuric chloride, 0.3 ml of concentrated hydrochloric acid, and 5.0 ml of water for 15 min. The undissolved zinc was then filtered and washed with water, and the suspension of zinc amalgam, 0.20 g (1.0 mmol) of the cyano ketone **15** in 4.0 ml of ethanol, and 8 ml of 15% hydrochloric acid was refluxed for 45 hr. Every 6 hr, 1.0 ml of concentrated hydrochloric acid was added to the refluxing mixture. The solution was cooled, filtered, diluted with water, and extracted several times with ether. The combined ethereal extracts were washed with dilute hydrochloric acid and saturated salt solution. The organic solution was dried over magnesium sulfate and concentrated under reduced pressure. The resulting oil was chromatographed over Florisil and eluted with benzene to afford 0.090 g of a volatile, colorless olefin: ν_{max}^{neat} 2225 cm^{-1}; nmr (CDCl$_3$) 0.95 (s, 3 H) 1.34 (s, 3 H), and 5.7 ppm (m, 2 H). No further identification of this olefin was made. Also, 0.02 g of the starting keto nitrile was recovered from the chromatography.

The olefin **16** was dissolved in 20 ml of ethanol and hydrogenated at atmospheric pressure over 0.05 g of 10% Pd-C until the hydrogen volume remained constant. The reaction mixture was filtered and the catalyst was washed with hot ethanol. The combined ethanolic solutions were evaporated under reduced pressure at room temperature. The resultant volatile oil was chromatographed by tlc on Silica Gel G and eluted with dichloromethane to afford 0.035 g of the colorless oily nitrile **17**: ν_{max}^{neat} 2225 cm^{-1}; nmr (CDCl$_3$) 0.95 (s, 3 H) and 1.35 ppm (s, 3 H). No further identification of the nitrile was made.

1,8a-Epoxy-4a-methyl-1,2,3,4,4a,5,6,7,8,8a-decahydro-2-naphthalone (6,7).—To a solution of 5.0 g (0.031 mol) of the enone **5**[41] in 150 ml of methanol, 4.6 ml of 4 *N* sodium hydroxide solution and 10 ml of 30% hydrogen peroxide were added simultaneously, dropwise at 0°, with rapid stirring. The mixture was stirred at 0° for 24 hr, the solution was concentrated to 50 ml under reduced pressure at room temperature, water was added, and the mixture was extracted several times with ether. The combined ethereal extracts were washed with water, dried over magnesium sulfate, and concentrated. The resultant colorless oil was distilled to afford 3.8 g of product: bp 72° (0.2 mm); ν_{max}^{neat} 1710 cm^{-1}; λ_{max}^{EtOH} 301 mμ (ε 400). The nmr showed two angular methyl groups at 1.25 and 1.15 ppm which indicated a mixture of epoxides **7** and **6**. The ratio of isomers based on the angular methyl group ranged from 3:1 to 4:1, respectively. The vpc analysis on UCON polar and SE-30 columns could not be used to establish the ratio of isomers, owing to decomposition of the reaction product on the columns.

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.31; H, 8.95. Found: C, 72.67; H, 8.91.

On cold storage the distilled epoxide mixture partially formed a crystalline, white solid. Filtration and recrystallizations from petroleum ether gave the major isomeric β-epoxide **7**: mp 58–60°; ν_{max}^{KBr} 1710 cm^{-1}; nmr (CDCl$_3$) 1.25 ppm (s, 3 H).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.31; H, 8.95. Found: C, 73.56; H, 9.09.

1-Cyano-4a-methyl-2,3,4,4a,5,6,7,8-octahydro-2-naphthalone (8). Procedure A.—A solution of 1.8 g (0.01 mol) of the epoxide mixture (**6** and **7**) in 100 ml of ethanol and 2.4 g of sodium cyanide dissolved in 10 ml of water was refluxed for 6 hr and stored at room temperature overnight. The solution was concentrated under vacuum to a dark brown, solid residue, which was dissolved in iced 4% sodium hydroxide solution and washed three times with ether. The aqueous layer was acidified with 5% iced hydrochloric acid and extracted with dichloromethane five times. The combined dichloromethane extracts were washed with water and concentrated under reduced pressure. The viscous residue was distilled, bp 110–140° (0.5 mm), to afford 1.10 g of a yellow, viscous oil which crystallized from ether: mp 88–90°; ν_{max}^{KBr} 2220 and 1690 cm^{-1}; λ_{max}^{EtOH} 246.5 mμ (ε 16,000); nmr (CDCl$_3$) 1.39 ppm (s, 3 H).

Anal. Calcd for $C_{12}H_{15}NO$: C, 76.13; H, 7.99; N, 7.40. Found: C, 75.95; H, 7.96; N, 7.45.

The 2,4-dinitrophenylhydrazone (from ethanol) had mp 250–251°.

Anal. Calcd for $C_{18}H_{19}N_5O_4$: C, 58.53; H, 5.19; N, 18.96. Found: C, 58.72; H, 5.31; N, 18.57.

The semicarbazone (from methanol) had mp 230–231°.

Anal. Calcd for $C_{13}H_{18}N_4O$: C, 63.39; H, 7.37; N, 22.75. Found: C, 63.44; H, 7.56; N, 22.33.

The ether washings were combined, washed with dilute sodium hydroxide solution and water, dried over magnesium sulfate, and concentrated to afford 0.3 g of colorless oil. An ir spectrum indicated that the oil did not contain a nitrile function; however, it did contain a hydroxyl group (ν_{max}^{neat} 3300 cm^{-1}) and a carbonyl function (1695 cm^{-1}; $\lambda_{max}^{ethanol}$ 255 mμ).

Without water, under the initial reaction conditions, a neutral, yellow, amorphous solid was obtained as 50–60% of the reaction products. The ir spectrum showed that this material did not contain a nitrile group and that the carbonyl region was very broad.

(40) In this connection the preferred conformations of isomenthone as a chair with an axial α-isopropyl group or as a twist form are of interest: (a) G. Ohloff, J. Osiecki, and C. Djerassi, *Chem. Ber.*, **95**, 1400 (1962); (b) C. Djerassi and W. Klyne, *Proc. Nat. Acad. Sci. U. S.*, **48**, 1093 (1962); (c) C. Djerassi, P. A. Hart, and C. Beard, *J. Amer. Chem. Soc.*, **86**, 85 (1964).

(41) N. C. Ross and R. Levine, *J. Org. Chem.*, **29**, 2341 (1964).

(42) M. Yanagita and R. Futakz, *ibid.*, **21**, 949 (1956).

Procedure B.—A mixture of 10.0 g (0.061 mol) of the enone **5**, 3.5 g (0.073 mol) of 50% sodium hydride in an oil suspension, and 100 ml of dioxane was refluxed for 24 hr under nitrogen with rapid stirring and cooled to 0°, and 20.0 g (0.32 mol) of freshly distilled cyanogen chloride in 50 ml of dioxane was added slowly. The solution was stirred for 20 hr at 0° and concentrated under reduced pressure, and water was added to the resultant dark brown residue. The mixture was extracted with dichloromethane, and the combined organic layers were washed with water, dried over magnesium sulfate, and concentrated under reduced pressure to an oil which was fractionally distilled. The first fraction, bp 60–100° (0.05 mm), afforded 3.9 g of the starting enone **5**. The last fraction, bp 160–190° (0.05 mm), afforded 2.8 g of a yellow, semisolid material, which was chromatographed over 30 g of Florisil. Elution with benzene afforded 2.2 g of an oil, which was crystallized from petroleum ether: mp 88–89°; ν_{max}^{KBr} 2220 and 1690 cm^{-1}; λ_{max}^{EtOH} 246.5 mμ. The ir and uv spectra were identical with those of the cyano enone **8** obtained in procedure A and a mixture melting point was not depressed.

1-Cyano-4aβ-methyl-1,2,3,4,4a,5,6,7,8,8aα-decahydro-2-naphthalone (11). Procedure A.—To a solution of 0.34 g (0.050 g-atom) of lithium in 200 ml of anhydrous liquid ammonia, 0.90 g (0.0048 mol) of the cyano enone **8** in 50 ml of anhydrous ether was added quickly with rapid stirring. After the mixture was stirred for 7 hr under reflux, solid ammonium chloride was added until the deep blue color disappeared. The solvents were distilled at room temperature overnight, water was added to the solid residue, and the mixture was extracted with ether. The combined ethereal solutions were washed with water and saturated salt solution, dried over magnesium sulfate, and concentrated under reduced pressure. The resultant white solid product, 0.82 g, was recrystallized from ether: mp 102.5–103.5°; ν_{max}^{KBr} 2245 and 1710 cm^{-1}; nmr ($CDCl_3$) 1.10 ppm (s, 3 H).

Anal. Calcd for $C_{12}H_{17}NO$: C, 75.34; H, 8.96; N, 7.32. Found: C, 75.09; H, 9.12; N, 7.46.

The 2,4-dinitrophenylhydrazone (from ethanol) had mp 198–199°.

Anal. Calcd for $C_{18}H_{21}N_5O_4$: C, 58.21; H, 5.70; N, 18.86. Found: C, 57.99; H, 5.80; N, 18.85.

Procedure B.—To a solution of 0.28 g (0.04 g-atom) of lithium in 100 ml of anhydrous liquid ammonia, 3.0 g (0.018 mol) of the enone **5** in 20 ml of anhydrous ether was added slowly, with rapid stirring. The mixture was refluxed for 1 hr and the solvents were distilled at room temperature overnight under anhydrous conditions. Traces of solvent were removed under reduced pressure, 50 ml of dry benzene was added to the solid residue, and the suspension was cooled to 10°. With rapid stirring, 4.0 g (0.065 mol) of freshly distilled cyanogen chloride in 50 ml of dry benzene was added slowly to the suspension and the mixture was stirred for 12 hr at room temperature. The solution was concentrated under reduced pressure and iced 4% sodium hydroxide solution was added to the black residue. The basic aqueous layer was washed with ether and acidified with iced 5% hydrochloric acid. The resultant aqueous solution was extracted with dichloromethane, and the organic layers were washed with water, dried over magnesium sulfate, and concentrated under reduced pressure to 0.6 g of a brown, viscous oil. The acidic material was chromatographed over Florisil and eluted with dichloromethane to afford 0.40 g of a white crystalline material, which was recrystallized from ether; mp 102°. The ir spectrum was identical with that of the keto nitrile **11** obtained in procedure A and a mixture melting point was not depressed.

The combined ethereal solutions were washed with dilute sodium hydroxide, water, and saturated salt solution, and dried over magnesium sulfate. Upon concentration, 2.2 g of a slightly yellow, neutral oil was obtained (ν_{max}^{neat} 1710 and 1675 cm^{-1}) and analyzed by vpc (10% SE-30 column at 175°). This oil contained two components with a ratio of 2:1 and retention times of 3.5 and 6.3 min, respectively. The retention times were identical with those of the starting material **5** (6.3 min) and with the reduced enone, 10β-methyl-1,2,3,4,5α,6,7,8,9,10-decahydro-3-naphthalone (3.5 min).

1β-Cyano-1α,4aβ-dimethyl-1,2,3,4,4a,5,6,7,8,8aα-decahydro-2-naphthalone (19).—A suspension of 0.10 g of the keto nitrile **11** and 0.058 g (0.83 mmol) of lithium amide in 15 ml of dry benzene was refluxed for 14 hr under nitrogen and with rapid stirring. The solution was cooled to room temperature and a mixture of 3.0 ml of methyl iodide, 2.0 ml of dimethylformamide, and 5 ml of benzene was added dropwise. The mixture was allowed to stir for 20 hr, 100 ml of ether was added, and the organic solution was washed with 2% sodium hydroxide and saturated salt solution. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The resultant oil, 0.08 g, was chromatographed by tlc on Silica Gel G, and, when eluted with dichloromethane, gave 0.063 g of a colorless oil, which was distilled at 60° (0.05 mm): ν_{max}^{neat} 2239 and 1710 cm^{-1}; nmr ($CDCl_3$) 1.42 (s, 3 H) and 1.50 ppm (s, 3 H). The 2,4-dinitrophenylhydrazone (in EtOH) had mp 178–180°.

Anal. Calcd for $C_{19}H_{23}N_5O_4$: C, 59.21; H, 6.02; N, 18.17. Found: C, 58.91; H, 6.06; N, 17.96.

Tlc and nmr study of the crude reaction mixture indicated the presence of a small amount of the enol ether **18**. A trace of the other diastereoisomer **15** may have been present, as indicated by a small singlet in the nmr spectrum at 1.10 ppm. However, none of this isomer could be isolated by preparative tlc.

The combined aqueous sodium hydroxide washings were acidified with 5% hydrochloric acid and extracted with ether. The ether was washed with water, dried over magnesium sulfate, and concentrated under reduced pressure. An ir spectrum of the resultant acidic, semisolid material, 0.011 g, was identical with that of the starting keto nitrile **11**.

1-Cyano-2-methoxy-4aβ-methyl-3,4,4a,5,6,7,8,8aα-octahydronaphthalene (18).—A solution of 0.32 g (1.7 mmol) of the keto nitrile **11**, 15 ml of dry dimethyl sulfoxide, and 0.165 g of a 50% sodium hydride in oil mixture was stirred at 45–50° under nitrogen for 2 hr. The mixture was cooled to room temperature and 5.0 ml of methyl iodide was added dropwise. The mixture was stirred at 40° for 15 hr. The solution was diluted with 100 ml of 5% potassium hydroxide solution and extracted with ether, and the extract was washed with saturated salt solution, dried over magnesium sulfate, and concentrated under reduced pressure. The sodium hydride oil was separated from the product by tlc on Silica Gel G and elution with petroleum ether. The product was eluted with dichloromethane and crystallized from petroleum ether. After several recrystallizations, 0.14 g was obtained: mp 107–108°; ν_{max}^{KBr} 2208 and 1626 cm^{-1}; nmr ($CDCl_3$) 0.84 (s, 3 H) and 3.83 ppm (s, 3 H). The ir and nmr spectra indicated that the carbon-alkylated product **19** was not formed, but that oxygen alkylation had taken place, resulting in the formation of the methyl enol ether **18**.

Anal. Calcd for $C_{13}H_{19}NO$: C, 76.05; H, 9.33; N, 6.82. Found: C, 75.97; H, 9.41; N, 7.11.

The enol ether **18** had a uv spectrum (λ_{max}^{EtOH} 243 mμ) and was stable to dilute hydrochloric acid. There was no change in the uv spectrum when a sample was treated with dilute hydrochloric acid at room temperature for 24 hr.

The basic aqueous layer was acidified with 5% hydrochloric acid and extracted with ether. The extract was washed with saturated salt solution, dried over magnesium sulfate, and concentrated under reduced pressure. The resultant dark brown residue was crystallized from ether and afforded 0.15 g of the acidic starting material **11**.

Methylation of the Cyanoenone 8 Followed by Catalytic Reduction.—A solution containing 10.0 ml of dry *t*-butyl alcohol, 0.051 g (1.3 mg-atoms) of potassium, and 0.20 g (1.1 mmol) of the cyanoenone **8** was stirred at room temperature for 1 hr under nitrogen. The mixture was diluted with 20 ml of dry benzene and heated until a slow distillation took place. Fresh benzene was added periodically, keeping the reaction volume constant. In this manner, the excess *t*-C_4H_9OH was removed by azeotropic distillation from the reaction mixture, leaving the potassium salt of the cyano enone **8**. The distillation was stopped when the index of refraction of the distillate was identical with that of the benzene which was added to the reaction mixture. The solution was cooled to room temperature and a mixture of 4.0 ml of methyl iodide, 3.0 ml of dimethylformamide, and 7.0 ml of benzene was added dropwise. The reaction was stirred overnight, water and ether were added, and the organic layer was separated. The aqueous layer was washed with ether and the combined ethereal solutions were washed with saturated salt solution, dried over magnesium sulfate, and concentrated under reduced pressure. The resultant black residue, 0.18 g, could not be crystallized. Nmr analysis [3.85 ppm (s)] indicated formation of the methyl enol ether **20**.

The crude product was subjected to hydrogenation over 10% Pd–C in ethanol at atmospheric pressure and room temperature. After the hydrogen uptake ceased, the mixture was filtered and concentrated under vacuum. The dark residue was dissolved in

ether and washed with 3% sodium hydroxide solution and saturated salt solution. The ether solution was dried over magnesium sulfate and concentrated under reduced pressure. Tlc analysis of the resultant dark residue, 0.11 g, indicated one major component. Preparative tlc on Silica Gel G and elution with dichloromethane afforded 0.07 g of a white crystalline material, mp 107–109°, whose ir and nmr spectra were identical with those of the methyl enol ether **18**.

The carbon alkylation products **15** and/or **19** could not be isolated from the reaction mixture.

Other attempts were also made with the same general procedure as above, except that the bases and solvents were lithium amide in benzene, lithium *t*-butoxide in benzene, and potassium *t*-butoxide in *t*-butyl alcohol. Again in these experiments, **15** and **10** could not be isolated.

Attempted Cyanogenation of the Methylenone 12.—A solution containing 25 ml of dry benzene, 0.310 g (8.0 mmol) of sodium amide, and 1.00 g (5.6 mmol) of the enone **12** was refluxed for 1 hr under nitrogen and stirred at room temperature for 3 hr. The mixture was cooled to 15° and 0.62 g (10 mmol) of freshly distilled cyanogen chloride in benzene was added dropwise. The mixture was warmed to room temperature, stirred overnight, and concentrated under reduced pressure. The resulting oily residue was dissolved in ether and washed with water, and the organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The ir spectrum of the resulting oil was identical with that of the starting enone **12**.

1,4a-Dimethyl-1,8a-epoxy-1,2,3,4,4a,5,6,7,8,8a-decahydro-3-naphthalone (13 and 14).—To a solution containing 10.0 g (0.056 mol) of the enone **12** in 200 ml of methanol at 0°, 10.0 ml of 4 *N* sodium hydroxide solution and 20 ml of 30% hydrogen peroxide were added simultaneously with rapid stirring over a 45-min period. The reaction mixture was stored at 15° for 30 days and concentrated to one-half of its volume under reduced pressure at room temperature. Then 300 ml of water was added to the mixture and the aqueous layer was extracted with dichloromethane. The extract was washed with water, dried over magnesium sulfate, and concentrated under reduced pressure to yield 7.6 g of a light yellow oil. The oil was vacuum-distilled, bp 64–66° (0.1 mm), to afford 7.30 g of colorless, oily keto epoxides **13** and **14**: ν_{max}^{neat} 1700 cm^{-1}; nmr ($CDCl_3$) 1.03 (s) and 1.25 ppm (s).

Attempts to open the epoxide in **13** and **14** with cyanide according to the procedure used for **6** and **7** led to recovery of the epoxides. In refluxing ethylene glycol and sodium or potassium cyanide, the compounds decomposed.

Morpholine Enamine of 4a-Methyl-2,3,4,4a,5,6,7,8-octahydro-2-naphthalone (9).—A solution containing 1.29 g (7.9 mmol) of the enone **5**, 2.1 g (24 mmol) of morpholine, a few crystals of *p*-toluenesulfonic acid, and 60 ml of dry toluene was refluxed under nitrogen for 40 hr with a Soxhlet extractor containing calcium hydride. The solvent and excess morpholine were removed under reduced pressure and the dark brown, oily residue was distilled, bp 126–130° (0.05 mm), to afford 1.18 g of a yellow, oily enamine **9**: ν_{max}^{neat} 1625 cm^{-1}; λ_{max}^{EtOH} 265 mμ (ε17,800).

Anal. Calcd for $C_{15}H_{23}NO$: C, 77.23; H, 9.94; N, 6.01. Found: C, 76.91; H, 9.87; N, 5.85.

Morpholine Enamine of 8-Cyano-4a-methyl-2,3,4,4a,5,6,7,8-octahydro-2-naphthalone (10).—To a solution which contained 8.0 g (0.034 mol) of the morpholine enamine **9** and 40 ml of dry dioxane, 2.3 g (0.038 mol) of cyanogen chloride in 10 ml of dioxane was added dropwise, under nitrogen, with rapid stirring. The mixture was stirred at room temperature for 72 hr. The dioxane and excess cyanogen chloride were removed under reduced pressure and the resultant dark brown, solid residue was dissolved in 200 ml of ether. The ethereal solution was washed with water, dried over magnesium sulfate, and concentrated under reduced pressure and the semisolid residue was crystallized from ether. After three recrystallizations, 4.45 g (50%) of enamine **10** was obtained: mp 117–120°; ν_{max}^{KBr} 1590 and 2195 cm^{-1}; $\lambda_{max}^{Et_2O}$ 315 mμ (log ε 4.46); nmr ($CDCl_3$) 1.10 (s, 3 H) and 5.60 ppm (s, 1 H).

Anal. Calcd for $C_{16}H_{22}N_2O$: C, 74.36; H, 8.58; N, 10.84. Found: C, 74.02; H, 8.80; N, 10.53.

The semicarbazone (from methanol) had mp 210–211°.

Anal. Calcd for $C_{13}H_{18}N_4O$: C, 63.39; H, 7.37; N, 22.75. Found: C, 63.35; H, 7.51; N, 23.03.

After 24 hr the aqueous washings were extracted with ether and the extracts were dried and concentrated to afford 1.30 g of a clear yellow oil. The ir and uv spectra of this oil were identical with the spectra of the enone **5** (23.5% recovery of starting enone). The cyanodienamine **10** was resistant to hydrolysis in 2% hydrochloric acid at reflux for 30 min and to acetic acid and sodium acetate at reflux for 3 hr.

1,10a-Epoxy-4a-methyl-6-methoxy-1,2,3,4,4a,9,10,10a-octahydro-3-phenanthrones (22 and 23).—To a solution of 3.0 g (0.0124 mol) of the enone **21**[6] and 75 ml of methanol, 6 ml of 35% hydrogen peroxide and 2.4 ml of 10% sodium hydroxide solution were added simultaneously, dropwise, at 0°, with rapid stirring. The mixture was stirred for 24 hr at 0°, poured into 300 ml of water, and extracted five times with 200-ml portions of ethyl acetate. The combined organic extracts were washed with a saturated salt solution, dried over magnesium sulfate, and concentrated under reduced pressure. The resultant yellow semisolid crystallized from ethanol to afford 2.3 g of white crystalline solid epoxides **22** and **23**: mp 156–159°; ν_{max}^{KBr} 1710 cm^{-1}. The nmr analysis indicated a mixture of the α- and β-keto epoxides by the presence of two different angular methyl groups as singlets at 1.55 and 1.40 ppm. The ratio of the isomeric keto epoxides was *ca.* 2:1.

Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02. Found: C, 74.67; H, 7.05.

1-Cyano-4a-methyl-6-methoxy-2,3,4,4a,9,10-hexahydro-2-phenanthrone (24).—A solution which contained 3.0 g (0.0115 mol) of the keto epoxides **22** and **23**, 2.3 g of sodium cyanide dissolved in 10 ml of water, and 100 ml of ethanol was refluxed for 6 hr and stored for 12 hr at room temperature. The mixture was concentrated under reduced pressure, and the black residue was dissolved in iced 4% sodium hydroxide and washed with ether. The basic aqueous layer was acidified with 5% hydrochloric acid and extracted with ether. The extracts were washed with saturated salt solution, dried over magnesium sulfate, and concentrated. The resultant black residue was distilled at 170–210° (0.001 mm) to afford 1.95 g of a yellow oil, which crystallized from ethanol to yield yellow, needle-like crystals: mp 177–178°; ν_{max}^{KBr} 2220 and 1685 cm^{-1}; nmr ($CDCl_3$) 3.84 (s, 3 H) and 1.66 ppm (s, 3 H).

Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.67; H, 6.34; N, 5.35.

1-Cyano-4aβ-methyl-6-methoxy-1,2,3,4,4a,9,10aα-octahydro-2-phenanthrone (27). Procedure A.—To a solution containing 50 ml of liquid ammonia which contained 0.010 g (1.4 mg-atoms) of lithium metal, 0.040 g of the cyano enone **24** in 4 ml of dry tetrahydrofuran was added rapidly with stirring. The mixture was stirred for 6 hr under reflux by employing a Dry Ice condenser. At the end of this reaction time, solid ammonium chloride was added slowly until the blue color disappeared; the solvents were then allowed to evaporate at room temperature overnight. Water was added to the residue, and the mixture was acidified with dilute hydrochloric acid and extracted with ether. The ethereal solution was washed with water until neutral and concentrated under reduced pressure to afford a brown, semisolid residue. The ir analysis indicated two carbonyl absorptions of equal intensity at 1720 and 1685 cm^{-1}, which were characteristic of the carbonyl functions of the desired β-keto nitrile **27** and the starting enone **24**, respectively. Separation of this mixture by preparative tlc on Silica Gel G with dichloromethane gave 0.004 g of the β-keto nitrile **27** as a crystalline solid, mp 162–163°. The ir (KBr) comparison of this product with that of an authentic sample[6] of the β-keto nitrile **27** proved identity. The remaining material recovered by tlc contained mixtures of the keto nitrile **27** and the cyano enone **24**.

Further attempts to improve reaction conditions by increasing reduction time and by addition of a larger excess of lithium metal were unsuccessful.

Procedure B (Preparation of the Enol Acetate 26, Followed by Catalytic Hydrogenation and Acid Hydrolysis to Afford the β-Keto Nitrile 27).—A solution containing 0.225 g (0.84 mmol) of the cyano enone **24**, 7 ml of acetic anhydride, and 8 ml of acetyl chloride was refluxed for 7 days under nitrogen, and the excess acetyl chloride and acetic anhydride were removed under reduced pressure to afford a yellow, viscous oil. This oil was dissolved in 30 ml of ether and washed with dilute aqueous sodium hydroxide (in order to remove any unreacted cyano enone **24**) and with water until the ethereal solution was neutral. This solution was concentrated under reduced pressure to afford 0.160 g of the crude, yellow, viscous enol acetate **26**, ν_{max}^{neat} 2200 and 1770 cm^{-1}. No further purification of the enol acetate **26** was made. The aqueous, basic wash was acidified with dilute hydrochloric acid and extracted with ether. The ethereal solution

was washed with water until neutral and evaporated to dryness, affording 0.067 g of the crude recovered cyano enone **24**.

The crude enol acetate **26** was dissolved in 30 ml of ethanol, 0.050 g of 10% Pd–C was added, and the mixture was stirred under a hydrogen atmosphere until no further hydrogen uptake was observed. The Pd–C was removed by filtration and washed with ethanol. The combined ethanol solution was concentrated under reduced pressure to *ca.* 5 ml, 5 ml of 10% hydrochloric acid solution was added, and the mixture was stirred for 30 min to hydrolyze the enol ester. Following the acid hydrolysis, a 10% sodium hydroxide solution was added slowly until the reaction mixture was basic (pH *ca.* 12). The aqueous basic solution was washed with ether, acidified with dilute hydrochloric acid, and extracted with dichloromethane. The dichloromethane solution was washed with water until neutral and concentrated under reduced pressure to afford 0.075 g of an acidic material. From this acidic material, 0.030 g of the β-keto nitrile **27** was obtained as a crystalline substance from ether; mp 160–162°. The ir (KBr) comparisons with the product obtained from procedure A and with an authentic sample of the β-keto nitrile **27**,[6] and undepressed mixture melting points, showed identity.

A neutral material, contained in the ethereal wash, was also isolated from the hydrogenation and hydrolysis reactions. On work-up of the combined ethereal washes, 0.050 g of a yellow, viscous oil was obtained, bp 140–160° (0.001 mm). The ir indicated that this product contained an alcohol function (3300 cm^{-1}) and a conjugated nitrile function (2200 cm^{-1}). However, no carbonyl bands were present. No further structure determination was made on this neutral material.

1β-Cyano-1α,4aβ-dimethyl-6-methoxy-1,2,3,4,4a,9,10,10aα-octahydro-2-phenanthrone (25).—A mixture of 18 mg (0.067 mmol) of the cyano ketone **27**,[6] 9.0 mg (0.39 mmol) of lithium amide, and 5 ml of dry benzene was stirred for 15 hr. A solution of 2 ml (32 mmol) of methyl iodide in 2 ml of dry dimethylformamide was added; the mixture was stirred for 24 hr, poured into water, and extracted with ether. The ether extracts were washed with 1% sodium hydroxide solution and water, dried over magnesium sulfate, and concentrated under vacuum. An nmr spectrum of the residue showed the characteristic superposition of the two C-methyl groups at 1.58 ppm (s, 6 H) for **25**,[6] seen in the catalytic reduction product of the olefin **31** and none of the epimeric alkylation product **34** with the corresponding methyl groups at 1.40 (s, 3 H) and 1.60 ppm (s, 3 H).

1β-Cyano-1α,4aβ-dimethyl-6-methoxy-1,2,3,4,4a,9,10aα-octahydrophenanthrone (*dl*-Podocarponitrile Methyl Ether, 28).—Hydrogenation of 15 mg (0.060 mmol) of the nitrile **32**[6] (which showed vinyl protons at 5.85 ppm in the nmr spectrum and *m/e* 267) in 10 ml of absolute ethanol, with 5 mg of 10% Pd–C, at room temperature, was stopped after 45 min when the theoretical amount of hydrogen had been absorbed. The reaction mixture was filtered and the ethanol was removed under vacuum. The resultant colorless oil was distilled at 125–145° (0.03 mm); $\nu_{max}^{CS_2}$ 2220 cm^{-1}; nmr ($CDCl_3$) 1.40 (s, 3 H), 1.44 (s, 3 H), and 3.80 ppm (s, 3 H); mass spectrum *m/e* 269.

The ir, nmr, and mass spectra were identical with those of an authentic sample of *d*-podocarponitrile methyl ether.[6]

1,4a-Dimethyl-6-methoxy-2,3,4,4a,9,10-hexahydro-2-phenanthrone (33).—Nitrogen was bubbled through 100 ml of methanol which contained 1.10 g (0.02 mol) of potassium hydroxide. The solution was cooled to 0°, 3.10 g (0.016 mol) of 7-methoxy-1-methyl-2-tetralone[6] in 25 ml of methanol was added quickly, and the reaction mixture was cooled to −20°. At this temperature, 1.50 g (0.018 mol) of freshly distilled ethyl vinyl ketone was added dropwise, under nitrogen, with rapid stirring. After 1 hr, the solution was allowed to warm to room temperature and stirred overnight. The mixture was refluxed for 1 hr, cooled, poured into ice–water, acidified with 5 ml of concentrated hydrochloric acid, and extracted five times with 100-ml portions of dichloromethane. The combined extracts were washed with water, dried over magnesium sulfate, and concentrated under reduced pressure. The remaining orange, viscous oil was distilled from a jacketed flask at 160–190° (0.001 mm). A quantitative yield of a pale yellow oil was obtained. The product crystallized from aqueous methanol, and after two recrystallizations, 2.53 g (62%) of the enone **33** was obtained: mp 57–58°; ν_{max}^{KBr} 1670 cm^{-1}; λ_{max}^{EtOH} 247.5 and 230 mμ (shoulder); nmr ($CDCl_3$) 1.50 (s, 3 H), 1.77 (s, 3 H), and 3.75 ppm (s, 3 H).

Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.37; H, 7.86.

1α-Cyano-1β,4aβ-dimethyl-6-methoxy-1,2,3,4,4a,9,10,10aα-octahydro-2-phenanthrone (34).—To a solution of 250 ml of anhydrous liquid ammonia containing 0.25 g (0.035 g-atom) of lithium, 0.90 g (0.0035 mol) of the enone **33** in 50 ml of anhydrous ether was rapidly added with stirring. The mixture was refluxed for 3 hr, the ammonia was distilled at room temperature overnight under anhydrous conditions, and the remaining traces of ammonia and ether were removed under reduced pressure. The resultant gray solid residue was suspended in 100 ml of dry benzene under nitrogen. This suspension was cooled to 10° and 5.0 g of freshly distilled cyanogen chloride (0.75 mol) in 50 ml of dry benzene was added dropwise with rapid stirring. The mixture was stirred at room temperature for 10 hr and concentrated under reduced pressure. The resultant black residue was dissolved in 200 ml of dichloromethane and washed several times with water. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure, and the resultant dark brown residue was chromatographed by tlc over Silica Gel G and eluted with 1% methanol in dichloromethane. Three products were isolated. The first product, 0.20 g of a yellow solid, was identical (by ir spectra) with the starting enone **33**. The second product, 0.34 g of a white solid, was recrystallized from ethanol three times to afford the desired cyano ketone **34**: mp 163–164°; ν_{max}^{KBr} 2248, 1723, and 1615 cm^{-1}; nmr ($CDCl_3$) 1.40 (s, 3 H), 1.60 (s, 3 H), and 3.80 ppm (s, 3 H).

Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47. Found: C, 75.56; H, 7.62.

The third isolated product was 0.06 g of a white solid. The spectral analysis of this solid indicated the presence of a saturated ketone, ν 1710 cm^{-1}; however, it did not indicate the presence of a nitrile group. This ketone resulted from the reduction of the enone **33** without cyanogenation taking place.

1α-Cyano-1β,4aβ-dimethyl-6-methoxy-1,2,3,4,4a,9,10,10aα-octahydrophenanthrone (36). Procedure A.—A suspension of zinc amalgam, prepared by stirring 3.0 g of zinc moss in a solution of 0.3 g of mercuric chloride, 0.2 ml of concentrated hydrochloric acid, and 4.0 ml of water for 15 min, filtering, and washing with water, and 0.16 g (0.56 mmol) of the keto nitrile **34** in 3 ml of absolute ethanol and 6 ml of 15% hydrochloric acid was refluxed for 45 hr. Every 6 hr, 1.0 ml of concentrated hydrochloric acid was added to the refluxing mixture. The solution was cooled, filtered, diluted with water, and extracted with ether. The extract was washed with dilute hydrochloric acid, dilute sodium bicarbonate, and water, dried over magnesium sulfate, and concentrated under reduced pressure. A quantitative yield of a yellow, viscous oil was obtained. The oil was chromatographed by tlc on Silica Gel G and eluted with dichloromethane to afford 0.095 g of the oily olefinic intermediate **35**: $\nu_{max}^{CS_2}$ 2240 cm^{-1}; nmr ($CDCl_3$) 1.48 (s, 3 H), 1.25 (s, 3 H), and 5.85 ppm (m, 2 H). The olefin **35** (0.095 g, 0.33 mmol) was dissolved in 20 ml of absolute ethanol and hydrogenated at atmospheric pressure over 0.04 g of 10% Pd–C for 1 hr; during this time the theoretical 1 equiv of hydrogen was consumed. The mixture was filtered and the ethanol was removed under vacuum. The resultant oil, 0.093 g, was chromatographed by tlc on Silica Gel G and eluted with dichloromethane to afford 0.053 g of an oily product which was crystallized from petroleum ether: mp 88–89°; $\nu_{max}^{CS_2}$ 2215 cm^{-1}; nmr ($CDCl_3$) 1.24 (s, 3 H) and 1.45 ppm (s, 3 H); mass spectrum *m/e* 269.

Anal. Calcd for $C_{18}H_{23}NO$: C, 80.25; H, 8.61; N, 5.20. Found: C, 79.99; H, 8.54; N, 4.90.

The ir and nmr spectra showed marked differences between this compound and *d*-podocarponitrile methyl ether.

Procedure B.—Dry hydrogen chloride gas was bubbled into a solution of 0.093 g (0.33 mmol) of the keto nitrile **34** in 10 ml of ethanedithiol at 0° for 15 hr. The excess ethanedithiol was removed under reduced pressure. An ir spectrum of the residue showed no carbonyl band at ν_{max}^{neat} 1710 cm^{-1}, and retention of the nitrile band at ν 2210 cm^{-1}. The crude thioketal was refluxed for 12 hr with 2 g of deactivated Raney nickel (the Raney nickel was deactivated by first refluxing for 4 hr with ethyl acetate and then by refluxing for 4 hr with acetone) in 100 ml of ethanol. The mixture was cooled and filtered, the Raney nickel was washed with benzene, and the combined organic solutions were concentrated. The residue was distilled, at 115–175° (0.03 mm), and afforded 0.034 g of a colorless oil. The ir and nmr spectra were identical with those of the olefin intermediate **35** isolated in procedure A.

Hydrogenation of this olefin in the same manner as in procedure A afforded 0.018 g of a crystalline nitrile **36**, mp 87–88°.

The ir and nmr spectra were identical with those of the nitrile **36** obtained in procedure A.

1,4a-Dimethyl-7-methoxy-2,3,4,4a,9,10-hexahydro-2-phenanthrone (37).—This compound was prepared according to the procedure used for the 6-methoxy isomer **33**, except that the amount of methanol used in the reaction was reduced to one-third.[6] A 68% yield of product, mp 93–95° (lit.,[24] without experimental, mp 95°) was obtained.

1α-Cyano-1β,4aβ-dimethyl-7-methoxy-1,2,3,4,4a,9,10,10aα-octahydro-2-phenanthrone (38).—This compound was prepared according to the procedure used for the 6-methoxy isomer **34**, except for the following required changes. The enone **37**, 0.9 g (3.5 mmol), was reduced with 0.075 g (10.5 mg-atoms) of lithium in 200 ml of liquid ammonia, with 30 ml of tetrahydrofuran as cosolvent, in 3 hr. The solvents were removed rapidly, and the lithium enolate was dried at 0.1 mm for 1 hr and suspended in 50 ml of anhydrous benzene. A cold solution of 1.5 g of cyanogen chloride in 20 ml of dry benzene was added rapidly with cooling and stirring. The crude reaction mixture was separated into neutral and 0.19 g of acidic products by partitioning between dichloromethane and iced 1% sodium hydroxide. The neutral fraction gave 0.40 g of crystalline cyano ketone **38** from methanol: mp 156–157°; ν_{max}^{KBr} 2250 and 1730 cm^{-1}; nmr ($CDCl_3$) 1.37 (s, 3 H), 1.60 (s, 3 H), and 3.78 ppm (s, 3 H).

Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94. Found: C, 75.92; H, 7.58; N, 4.99.

Additions of cyanogen chloride to the enolate anion in tetrahydrofuran led mostly to an amorphous product with ν_{max}^{KBr} 2190 cm^{-1}, presumably the oxygen-cyanogenated enol.

1-α-Cyano-1β,4aβ-dimethyl-7-methoxy-1,4,4a,9,10,10aα-hexahydrophenanthrene (39).—A solution of 0.10 g (2.6 mmol) of sodium borohydride and 0.10 g (0.35 mmol) of the keto nitrile **38** was stored at 23° for 18 hr, poured into water, made strongly basic with sodium hydroxide, and, after 5 min, acidified with hydrochloric acid. Extraction with dichloromethane and concentration gave 0.090 g (0.32 mmol) of the alcohol **41**: mp 168–172°; nmr ($CDCl_3$) 1.18 (s, 3 H), 1.38 (s, 3 H), and 3.78 ppm (s, 3 H). Addition of a solution of 8 drops of methanesulfonyl chloride in 10 ml of dry benzene to a stirred solution of 0.11 g of the alcohol **41** in 20 ml of dry benzene, under nitrogen, during 20 min, resulted in crystallization of triethylamine hydrochloride. After 3 hr at 24°, water was added, the mixture was extracted with dichloromethane, and the extracts were washed with dilute hydrochloric acid and sodium bicarbonate solutions. Concentration gave an oily mesylate **42**: ν_{max}^{film} 1360 and 1175 cm^{-1} (mesylate); nmr ($CDCl_3$) 1.20 (s, 3 H, 4a-methyl), 1.47 (s, 3 H, 1-methyl), 3.18 (s, 3 H, 2-mesyl), and 3.78 ppm (s, 3 H, 7-methoxy). A mixture of this mesylate, 50 mg of lithium carbonate, 50 mg of lithium chloride, and 5 ml of dimethylformamide was heated in a sealed glass tube at 210° for 3.5 hr, poured into water, and extracted with dichloromethane. Concentration, crystallization from petroleum ether and aqueous methanol, and sublimation at 120° (0.001 mm) gave 60 mg of the olefin **39**: mp 131–132°; nmr ($CDCl_3$) 1.18 (s, 3 H), 1.48 (s, 3 H), and 3.78 ppm (s, 3 H).

Anal. Calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24. Found: C, 80.57; H, 7.72; N, 5.35.

Attempted tosylations of the alcohol **41** with excess *p*-toluenesulfonyl chloride in pyridine at 23° for 48 hr or in benzene with excess lithium hydride at 23° for 6 hr gave products with strong ir hydroxyl absorption (ν_{max}^{KBr} 3450 cm^{-1}) and little tosylate absorption (ν_{max}^{KBr} 1185 and 1175 cm^{-1}). An attempted dehydromesylation of **42** with lithium carbonate and lithium chloride in dimethylformamide at reflux for 8 hr gave primarily recovered mesylate.

1α-Carboxy-1β,4aβ-dimethyl-7-methoxy-1,2,3,4,4a,9,10,10aα-octahydrophenanthrene (43).—Reduction of 43 mg of the olefin **39** in 10 ml of ethanol, with 20 mg of 10% Pd–C and hydrogen at atmospheric pressure, showed a quantitative uptake of 4 ml of gas in 4 hr. Filtration, concentration, and distillation at 120° (0.001 mm) gave 38 mg of an oily nitrile, **40**: ν_{max}^{film} 2225 cm^{-1} (CN); nmr ($CDCl_3$) 1.17 (s, 3 H), 1.42 (s, 3 H), and 3.78 ppm (s, 3 H). This nitrile was heated at 170° for 24 hr with 7 ml of methanol and 1 g of potassium hydroxide in a steel bomb. Addition of water, extraction with ether, acidification, extraction with dichloromethane, concentration, crystallization from methanol, and sublimation at 130–140° (0.001 mm) gave 21 mg of **43**, mp 157–158°. This sample showed the same ir spectrum and mixture melting point when compared with a sample obtained by a different route by Professor S. W. Pelletier[25] and gave a mass spectrum which compared with that of the corresponding abietic acid degradation product, which was provided by Professor A. W. Burgstahler.[24] The acid **43** was obtained in much lower yield from **38** in repeated attempts at Clemmensen reduction and hydrogenation or through a thioketal, mp 204–207°, and desulfurization with several activity grades of Raney nickel, according to the procedures given for the reductions of **15**, **25**, and **34** and subsequent hydrolyses of the crude products according to the above procedure.

Enolization of β-Keto Esters and β-Keto Nitriles.—The uv absorption spectra of the following compounds were measured in 0.1 *N* potassium hydroxide solution with a Perkin-Elmer 202 instrument: 2-carbethoxycyclohexanone, λ_{max} 285 mμ (log ε 3.95); 1-carbethoxy-4aβ-methyl-5β-hydroxy-1,2,3,4,4a,5,6,7,8,-8aα-decahydro-2-naphthalenone, λ_{max} 285 mμ (log ε 1.90); 2-cyano-4-benzoyloxycyclohexanone, λ_{max} 266 mμ (log ε 4.07); 1-cyano-4aβ-methyl-1,2,3,4,4a,5,6,7,8,8aα-decahydro-2-naphthalone (**11**), λ_{max} 268 mμ (log ε 4.01).

Registry No.—**6**, 22241-35-6; **7**, 22241-36-7; **8**, 22241-37-8; **8** 2,4-dinitrophenylhydrazone, 22297-80-9; **8** semicarbazone, 22249-35-0; **9**, 22249-36-1; **10**, 22249-37-2; **11**, 22249-38-3; **11** 2,4-dinitrophenylhydrazone, 22297-81-0; **13**, 22249-39-4; **14**, 22249-40-7; **15**, 22249-41-8; **18**, 22249-42-9; **19**, 22249-43-0; **19** 2,4-dinitrophenylhydrazone, 22249-44-1; **22**, 22249-45-2; **23**, 22249-46-3; **24**, 22253-07-2; **27**, 22249-47-4; **28**, 22249-48-5; **33**, 1220-42-4; **34**, 22297-82-1; **36**, 22249-49-6; **38**, 22249-50-9; **39**, 22249-51-0.