the acids was achieved by the procedure employed. The acids **9c** and **9d** were reduced ($LiAlH_4$) to the 26-alcohols **5d** and **5e**, respectively.

The authentic 25*R* acid **10b** was prepared from **1a** derived from kryptogenin. The diol **1a** was converted to the 26-trityl ether **1c** and acetylated to **1d**. Acid hydrolysis provided the 3-acetoxy-26-hydroxy **1f** which was oxidized to **10a** and saponified to **10b**. To test the optical purity of **10b** attempts were made to resolve it via the quinine salt as described above. However, both the acid **10c** recovered from the crystalline salt and the acid **10d** recovered from the mother liquor had the same $[\alpha]^{24}D$ −33.6°. No further attempts were made to determine the configurations of the acids **9c** and **9d** and the configurations of the derived alcohols **5d** and **5e**, respectively.

The identity of the $[\alpha]D$ of **10c** and **10d** tends to indicate their near 100% "optical purity" and consequently the near "optical purity" of **1a** and of the kryptogenin diacetate **2**.

Registry No.—**1a**, 20380-11-4; **1c**, 56792-57-5; **1f**, 56845-81-9; **2**, 56792-58-6; **3a**, 56792-59-7; **3c**, 56792-60-0; **4**, 24583-89-9; **5a**, 24583-90-2; **5b**, 13095-61-9; **6a**, 56845-82-0; **6b**, 56845-83-1; **6d**, 56906-69-5; **7a**, 19257-21-7; **7c**, 56845-84-2; **8a**, 41530-25-0; **8b**, 41530-31-8; **8c**, 56792-61-1; **9a**, 56792-62-2; **9b**, 56845-85-3; **9c**, 6561-58-6; **9e**, 56845-86-4; **10a**, 56792-63-3; **10b**, 56845-87-5; **11a**, 24583-91-3; **12**, 54575-47-8; triphenylchloromethane, 76-83-5; [25-^{3}H]cholest-5-ene-3β,26-diol 3-tetrahydropyranyl ether, 56792-64-4.

References and Notes

(1) (a) Worcester Foundation for Experimental Biology. (b) Postdoctoral Fellow, 1966–1969. (c) Postdoctoral Fellow, 1970–1972. (d) The work at the Worcester Foundation was supported by Grants AM 12156 and GM 19882 from the National Institutes of Health.

(2) (a) Columbia Univeristy. (b) The work at Columbia University was supported by Grant AI 10187 from the National Institutes of Health.

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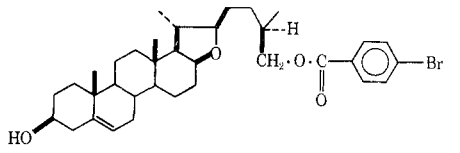
(20) A word of caution is in order. The presence of other chiral centers in the side chain will influence significantly the CD spectra of 26-*p*-bromobenzoates as exemplified by the CD of the dihydrodiosgenin derivative which showed $\Delta\epsilon_{245}$ −1.74 (MeOH).



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Diterpenoid Total Synthesis, an A → B → C Approach. VII. Total Synthesis of DL-Sugiol, DL-Ferruginol, and DL-Nimbiol[1]

Walter L. Meyer,* George B. Clemans, and Richard A. Manning

Department of Chemistry, University of Arkansas, Fayetteville, Arkansas 72701

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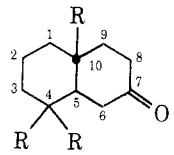
Cyanoethylation of 2,2,6-trimethylcyclohexanone followed by saponification affords 3-(1′,3′,3′-trimethyl-2′-ketocyclohexyl)propionic acid (**5**), the carboxyl of which is converted to acetyl (**9**) either by treatment of **5** with methyllithium or by sequential exposure to oxalyl chloride, diazomethane, hydrogen chloride, and zinc–acetic acid. Reaction of **5** with thionyl chloride affords chloro lactone **10** rather than the normal acid chloride. Pyrrolidine-catalyzed cyclodehydration of diketone **9** produces 4,4,10-trimethyl-Δ^5-7-octalone, which undergoes hydrogenation to a 4:1 mixture of the corresponding trans and cis decalones (**12** and **13**). Decalone **12** is also available from 10-cyano-4,4-dimethyl-*trans*-7-decalone by the sequence ketalization, lithium aluminum hydride reduction of cyano to imino, Huang-Minlon reduction of imino to methyl, and ketal hydrolysis, or from 10-carbethoxy-4,4-dimethyl-*trans*-7-decalone by the sequence ketalization, lithium aluminum hydride reduction, Sarett oxidation to the angular aldehyde, Huang-Minlon reduction, and ketal hydrolysis. 4,4,10-Trimethyl-*trans*-decalin was prepared by reduction of **12**. Condensation of **12** with ethyl formate affords exclusively the 8-hydroxymethylene derivative, which is dehydrogenated by 2,3-dichloro-5,6-dicyanoquinone to form the $\Delta^{8,9}$-unsaturated keto aldehyde **23**. Michael addition of the sodium enolate of *tert*-butyl isovalerylacetate or *tert*-butyl propionylacetate produces adducts **24**, which in the presence of *p*-toluenesulfonic acid in acetic acid undergo *tert*-butyl ester cleavage, decarboxylation, and cyclodehydration, thereby forming the tricyclic enediones **25a** and **25b**, respectively. On the basis of ^1H NMR data these are tentatively assigned the trans-syn-cis configuration, and the adducts **24** are formulated with a 9α side chain. Exposure of the enediones to pyridine hydrobromide perbromide in acetic acid brings about aromatization of ring C to form DL-sugiol and DL-nimbiol, respectively. Hydrogenolysis of the former affords DL-ferruginol.

Earlier we described a general scheme of synthesis which was planned to allow stereoselective construction of a variety of polycyclic members of the diterpenoid family of natural products.[1b] In essence this involves preparation of a 4,4,10-trisubstituted *trans*-7-decalone (**1**)[2] which is to become the A/B ring system of the terpenoid, followed by attachment of a C ring which carries the appropriate carbon substituents and functional groups. In this paper we de-

scribe details of adaptation of this sequence for synthesis of several typical tricyclic diterpenoids in which the three substituents at C-4 and C-10 are methyl and in which the C ring is a 12-phenol, DL-sugiol (**2a**),[3] DL-nimbiol (**2b**),[4] and DL-ferruginol (**2c**).[5]



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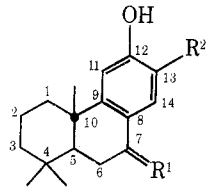
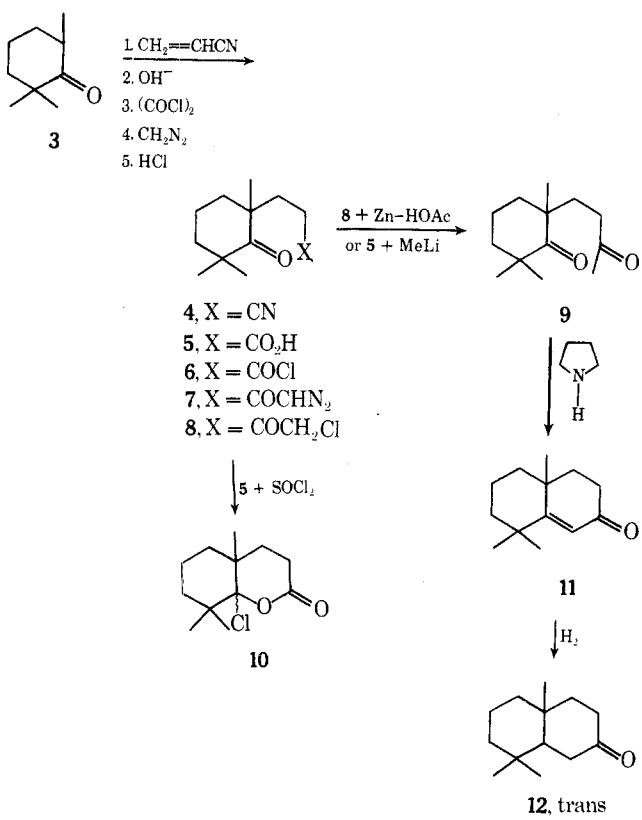


2a, $R^1 = O$; $R^2 = CH(CH_3)_2$
b, $R^1 = O$; $R^2 = CH_3$
c, $R^1 = H_2$; $R^2 = CH(CH_3)_2$

4,4,10-Trimethyl-*trans*-7-decalone (12). The appropriate *trans*-7-decalone (1) for use in preparation of these and many other terpenoids by this sequence is the 4,4,10-trimethyl derivative **12**.[6-8] One might visualize its preparation in a manner analogous to that used for synthesis of its angular cyano[1b] and angular carbethoxy[9] counterparts, viz., by condensation of 2,2,6-trimethylcyclohexanone (**3**) with methyl vinyl ketone to produce octalone **11**, followed by stereospecific hydrogenation. However, Michael–Robinson annulations of simple cyclohexanones such as **3** in which the appropriate α hydrogen is not activated by a second electron-withdrawing group often proceed poorly, particularly when the ketone is sterically hindered,[10] and such was the case with this system. Under none of the conditions we examined[10,11] were more than meager yields of the octalone or an intermediate ketol produced, and consequently more circuitous syntheses of octalone **11**[12,13] were explored (Scheme I).

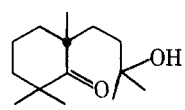
Scheme I



At least part of the difficulty in methyl vinyl ketone addition to trimethylcyclohexanone seemed to originate from competitive self-condensation of methyl vinyl ketone or further condensation of methyl vinyl ketone with the initial Michael adduct, and thus we initially turned to an alternate Michael acceptor which could still lead through diketone **9** to octalone **11**. Cyanoethylation of trimethylcyclohexanone proceeds excellently, and saponification of keto nitrile **4** affords the corresponding keto acid **5** in 76% overall yield. However, exposure of the keto acid to thionyl chloride does not produce the keto acid chloride **6**, but an isomeric substance with a single carbonyl absorption at 5.68 μ rather than two near 5.5 and 5.9 μ. Several features in its ^1H NMR spectrum differ sufficiently from those in spectra of keto nitrile **4**, keto acid **5**, diazo ketone **7**, chloro ketone **8**, and diketone **9** (see below) to suggest that this product is not a structural analog of those substances. For example, in spectra of all five of these monocyclic compounds the resonance patterns from the $CH_2C{=}O$ protons and the other methylene protons show considerable similarity to one another both in chemical shift and spin-splitting fine structure, while the corresponding resonances of the thionyl chloride product are quite different in both respects. Also, the three methyl resonances of the thionyl chloride product are clearly separated from one another, while in spectra of the five monocyclic derivatives the methyl resonances are either all superimposed or two are superimposed with the third no more than a few hertz removed at 60 MHz. From these data this substance is formulated as one of the diastereomeric chloro lactones **10**, presumably formed from the normal acid chloride under the influence of acid.[14] This derivative is stable toward dimethylcadmium. Although methyllithium and the Grignard reagent were considered as alternative reagents for converting it to the desired diketone, these reactions have not been explored.

Exposure of the sodium salt of keto acid **5** to oxalyl chloride, conditions which avoid the presence of a proton donor, forms the normal acid chloride **6**. This was treated sequentially with diazomethane, hydrogen chloride, and zinc–acetic acid[14] to produce diketone **9** in 79% yield.

A shorter preparation of the diketone was found in direct treatment of the keto acid with methyllithium.[15] While yields of diketone from this reaction were lower than from the foregoing sequence, and varied considerably from run to run (generally 30–50%), the majority of the remaining material was starting keto acid which could be reused. Usually only minor amounts of by-products were evident in gas chromatograms of the total neutral product, although occasionally substantial quantities of one or more other substances were found. These were not isolated nor definitely characterized, but spectroscopic properties of such mixtures suggested that at least the ketol **14** was among the capricious contaminants. Seldom when the methyllithium for this reaction was freshly prepared from methyl iodide[15] was evidence for significant formation of the isomeric ketol **15**, diol **16**, hydroxy acid **17**, or its lactone **18** encountered (but see Experimental Section for a comment on use of commercial methyllithium). It certainly appears, as was anticipated, that steric hindrance to ketone attack is substan-



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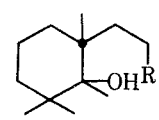
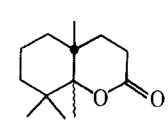


15, $R = COCH_3$
16, $R = C(CH_3)_2OH$
17, $R = CO_2H$



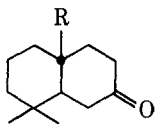
18

tial, and allows selective reactivity at the carboxyl group. Detailed development of this reaction for synthetic purposes was not pursued in light of developments discussed below, but it appears capable of improvement by careful study of reaction conditions.

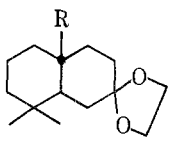
Pyrrolidine-catalyzed cyclodehydration[9] smoothly converts diketone **9** into the corresponding octalone **11**,[12,13] the overall yield from trimethylcyclohexanone being 60% through the diazo ketone or 52% by the methyllithium route (taking recovered keto acid into account).

The enone was subjected to palladium-catalyzed hydrogenation. Such reduction of the analogous 10-cyano-[1b] and 10-carbethoxy-4,4-dimethyloctalones[9] had been completely stereospecific, affording only the trans decalones, so it was with some surprise that we isolated a mixture of decalones in the present instance (Scheme I). From the relative intensities of the methyl resonances in ^{1}H NMR spectra and from GLC analysis it is apparent that the two isomers are formed in an approximately 4:1 ratio. The major product proved to be identical with the product subsequently derived from cyano decalone **19a** (below), and it has ir and ^{1}H NMR spectra which are superimposable on those of the levorotatory degradation product of dehydroabietane.[8] It is thus the trans-fused racemate. The minor hydrogenation product, by exclusion, is the cis decalone. The results of this hydrogenation[16] reaffirm that 4,4-dimethyl substitution may not play as important a steric role in directing catalyst approach as has been often assumed.[17] The angular functions obviously contribute a significant directive influence in reduction of the angular cyano and carbethoxy octalones,[1b,9] just as they are known to do in hydrogenation of 10-substituted octalones devoid of 4,4-dimethyl groups.[17f,18]

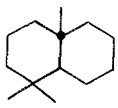
The lack of stereoselectivity in hydrogenation of trimethyloctalone **11**, combined with the difficulty in purifying the trans decalone from the isomer mixture, made this route to decalone **12** less than attractive for synthetic purposes. One of the reasons the cyano decalone **19a** had been chosen for initial investigation was the potential synthetic versatility of the cyano group.[1b] Inasmuch as the cyano decalone can be synthesized stereoselectively in good overall yield,[1b] it was of interest to examine its reduction to the trimethyldecalone. Ketalization, lithium aluminum hydride reduction of its cyano group to imino,[19] direct Huang-Minlon reduction of the imine without prior hydrolysis to the aldehyde,[20] and ketal hydrolysis (**19a** → **20a** → **20b** → **20c** → **12**) proceed in nearly quantitative yield to afford the crystalline trans trimethyldecalone, which is thus available in 52% overall yield from 2,2-dimethylcyclohexanone. This decalone is also obtained efficiently (68% overall) from its angular carbethoxy counterpart **19b**[9] by the sequence ketalization, lithium aluminum hydride reduction, Sarett oxidation, Huang-Minlon reduction, and ketal hydrolysis (**19b** → **20d** → **20e** → **20f** → **20c** → **12**). The alternate sequence $RCO_2Et \rightarrow RCH_2OH \rightarrow RCH_2OTs \rightarrow RCH_3$ to convert the angular ester of **20d** to a methyl was unsatisfactory, however, because lithium aluminum hydride reduction of the *p*-toluenesulfonate **20g** resulted only in S–O bond cleavage, regenerating alcohol **20e**. It may be noted that these interconversions, together with ultimate transformation of trimethyldecalone **12** to natural products of known trans A/B configuration, serve to substantiate the assignment of a trans configuration to all of these derivatives. Inasmuch as 4,4,10-trimethyl-*trans*-decalin (**21**) promised to be potentially useful as a reference substance for the determination of configuration of other trimethyldecalin derivatives in our own and other laboratories, a sample of this hydrocarbon[7,21] was prepared by Huang-Minlon reduction of the corresponding decalone **12**.



19a, R = CN
b, R = CO_2Et



20a, R = CN
b, R = CH=NH
c, R = CH_3
d, R = CO_2Et
e, R = CH_2OH
f, R = CHO
g, R = CH_2OTs



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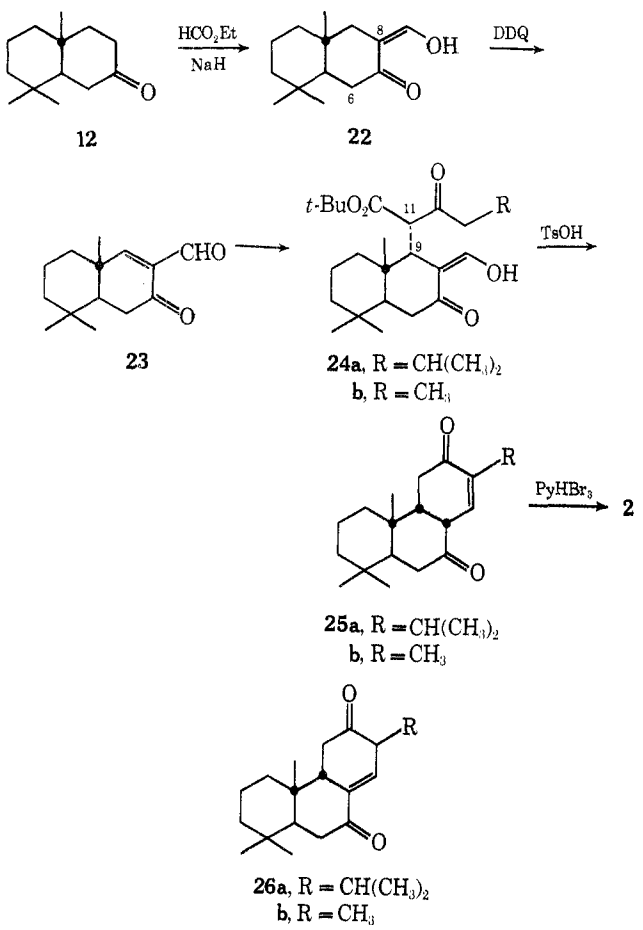
Addition of the C Ring. Condensation of trimethyldecalone **12** with ethyl formate produces exclusively one α-hydroxymethylene ketone in 92% yield. That this is the 8-hydroxymethylene derivative **22** (Scheme II), rather than the 6-substituted isomer, is clear from the appearance in its ^{1}H NMR spectrum of resonances from four rather than three protons of the type =C–CH and from the properties of subsequent reaction products. Such selectivity in this condensation is not unanticipated. Base-catalyzed acylations of this type are often reversible and thus thermodynamically controlled,[22] and the enolate of a hydroxymethylene substituent at C-6 would experience destabilizing nonbonded interactions with the 4α-methyl which are not present in the 8-hydroxymethylene isomer. However, it should be noted that the same result would be predicted if in this instance the controlling factor were condensation through the more stable enolate of decalone **12**, for the conformationally favored enolization of trans β-decalones in this direction is well known.[23] Indeed, inasmuch as it is presumably in large measure the nonbonded interaction between the syn-axial 4 and 10 substituents which preferentially destabilizes the Δ^6 enol compared to the Δ^7 enol,[23,24] selectivity should be enhanced in systems such as **12** with axial methyls at *both* C-4 and C-10. Even if the relative stabilities of the Δ^6 and Δ^7 enolates were also not important, in this system one would expect kinetic factors to favor Δ^7 enolate production and substitution. Approach of a base to the 6β-axial position is sterically hindered by two syn-axial methyls whereas only one methyl hinders axial approach to C-8. The same substituents would preferentially inhibit axial approach of ethyl formate to the 6β position of the enolate, and owing to the conformational restrictions placed on ring B by the trans fusion of the rings, transition states with proper stereoelectronic properties (orbital overlap)[25] for 6α-attack of the formic ester on the Δ^6 enolate or of a base on the ketone would need to approach true boat character whereas those for 8α-attack can be twist–boat in form. Thus both thermodynamic and kinetic factors should favor condensation at C-8 of decalone **12**, and the 5,6 double bond which was present in the model system[1b] is not necessary to control the regioselectivity of this process.

Dehydrogenation of hydroxymethylene ketone **22** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[1b,26] affords unsaturated keto aldehyde **23** in excellent yield. The appearance of resonance from one vinyl proton in its ^{1}H NMR spectrum confirms location of the formyl group at C-8 rather than C-6. By virtue of its double conjugation the olefinic bond of this aldehyde is unusually reactive toward nucleophilic addition, for the product is the resonance-stabilized enolate of a hydroxymethylene ketone.[1b] Thus Michael addition of the sodium enolates of *tert*-butyl isovalerylacetate and *tert*-butyl propionylacetate leads rapidly and in good yield to the adducts **24a** and **24b**, respectively. In each instance the ^{1}H NMR spectrum of the adduct contains two *tert*-butyl resonances, two C-11 H resonances,

Scheme II



and two CHOH resonances, indicating the product to be a mixture of two diastereomeric racemates. These were not separated, nor were the adduct mixtures purified, but direct exposure of the crude adducts to *p*-toluenesulfonic acid in glacial acetic acid induces cleavage of the *tert*-butyl group, decarboxylation, and cyclodehydration with efficient production of a single crystalline enedione (**25a** and **25b**) in each instance. Inasmuch as both diastereomers of each adduct **24** lead to the same enedione and it seems unlikely that the acidic cyclization conditions should produce a change in configuration at C-9 in either the adduct or the enedione, the diastereomers of adducts **24** are considered to differ from one another only in their relative configurations at C-11. Subsequent demonstration that the enediones **25** are of the trans-syn-cis configuration supports this deduction, for if any 9β-alkyl adduct had been formed, or if acid-catalyzed 9-epimerization had occurred, the cyclization product would have been expected to contain the thermodynamically preferred trans-anti-trans enedione.

The overall yield of this four-stage C-ring elaboration sequence, from decalone **12** to enedione **25**, was 60% in the sugiol series (**25a**) and 63% in the nimbiol series (**25b**). It would thus seem that the general sequence may offer an attractive addition to the variety of other methods for constructing functional six-membered rings in organic synthesis. The scope and limitations of this sequence are presently under study.

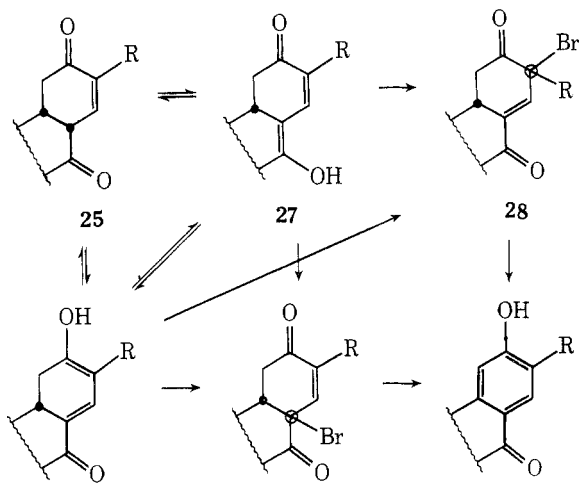
The double bond location and 9 configuration in enediones **25** were tentatively assigned on the basis of ^{1}H NMR data.[27] Both the τ 8.20 chemical shift of the 13-methyl and its long-range coupling with the vinyl proton (J = 1 Hz) indicate that the methyl is allylic and that the 13-methyl compound must have the $\Delta^{13,14}$ structure **25b** rather than the isomeric $\Delta^{8,14}$ structure **26b**. The decision is not as clear from spectra of the 13-isopropyl enedione. Both structures **25a** and **26a** are consistent with the observed long-range coupling (J = 0.9 Hz) between the 14-vinyl proton and *one* allylic proton (C-9 H in **26** or the isopropyl methine in **25**), and the resonances of both C-9 H and the isopropyl methine proton are obscured by other resonances in the 60-MHz spectrum so one cannot observe which of these shows an allylic chemical shift and the 0.9-Hz coupling. Thus the structure of this enedione was tentatively assigned by analogy with the methyl derivative; the general similarity of ^{1}H NMR and uv spectra of the two compounds lends credence to this formulation.[28]

Two new asymmetric centers have been produced in the enedione, those at C-8 and C-9, and thus the cyclization products **25a** and **25b** correspond to one of four possible diastereomeric racemates (trans-anti-trans, trans-anti-cis, trans-syn-trans, or trans-syn-cis). In many of these structures the dihedral angular relationships among the B- and C-ring protons are quite different, and should give rise to significantly different spin-coupling constants. Of these couplings $J_{8,14}$ is clearly discernible from the H-14 resonance even in 60-MHz spectra of the two enediones; it is approximately 6 Hz in each compound, which corresponds to a dihedral angle near either 25 or 125°.[29] Examination of Dreiding models of the reasonable conformations for each of the four enedione configurations, including those with nonchair forms of rings B and C (which might be significant in view of the location of trigonal carbon in those rings),[30] indicates that in no case can an appropriate 8,14 dihedral angle near 125° be attained, and only three possible structures incorporate an angle sufficiently near 25° to accommodate the observed 6-Hz coupling. One of these structures is a trans-anti-cis form and the other two are trans-syn-cis conformers. However, the configuration of the enedione at C-8 should certainly be the more stable of the two possibilities, for the acidic conditions under which it was formed would have led to equilibration at that site through enolization of the vinylogous β-diketone system. The trans-anti-cis form which satisfies the required dihedral angle relationship contains a B-ring boat conformation with a very severe eclipsed (or nearly eclipsed) interaction between the angular methyl and C-11 as well as a 5,8 prow–stern interaction. There is thus no reason to expect it to be lower in energy than its C-8 epimer (trans-anti-trans), and hence it should not be present after C-8 equilibration. Accordingly, the trans-syn-cis configuration is tentatively assigned to the enediones,[27] and their precursors, the adducts **24**, are considered to contain a 9α (axial) side chain. It may furthermore be recalled that in a related series, Michael addition of a β-keto ester to an unsaturated keto aldehyde similar to **23** but containing a 5,6 double bond led to a product from double Michael addition at both C-9 and C-5.[1b] This could only have occurred if the additions were α; the corresponding product from β-addition would contain an energetically prohibitive (and unknown) *trans*-bicyclo[4.2.0]octanone system as part of its skeleton.

These results indicate that Michael addition of the enolate to the unsaturated keto aldehyde **23** is kinetically controlled (the 9β equatorial configuration of the bulky side chain would certainly be the product of thermodynamic control), and that it occurs with complete stereoselectivity from the α face of the molecule. This stereoselectivity is in fact that expected on the basis of either stereoelectronic control (axial approach of the nucleophile) or steric approach control (approach of the nucleophile from the less hindered direction).

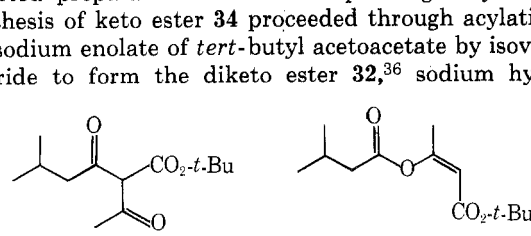
Ring C in the enediones is but one oxidation level below that of the phenolic natural products. In our earlier work,[1b] C-ring dehydrogenation to form a 7-keto-12-phenol was

brought about by DDQ, albeit in disappointing yield. Considerable examination of reaction conditions for this aromatization has been conducted in this series and several others. Catalytic dehydrogenation over palladium on carbon, either with or without maleic acid as an acceptor, is no more efficacious than the DDQ process. However, exposure to pyridine hydrobromide perbromide in acetic acid[31] converts the enediones **25a** and **25b** rapidly and almost quantitatively to the corresponding keto phenols DL-sugiol (**2a**) and DL-nimbiol (**2b**). Presumably this facile aromatization proceeds by initial bromination of one or both of the enolic forms of the enedione (**27** and **29**) to form bromo enediones **28** and/or **30.** In both of these substances further enolization of the enedione system is blocked, and either 1,2-dehydrobromination of **30** or 1,4-dehydrobromination of **28** to the keto phenol is the only available course of reaction. On the other hand, we have no evidence to rule out initial addition to form a dibromide followed by a double dehydrobromination.



Hydrogenolysis of DL-sugiol (**2a**) over 30% palladium on carbon[32] removes the benzylic ketone and produces DL-ferruginol (**2c**).[5] Infrared and/or ^{1}H NMR spectra of these substances are superimposable on those of authentic natural products or identical with those reported in the literature for the natural enantiomers or suitable derivatives.[33,34] Total synthesis of the racemates of sugiol,[3] ferruginol,[5] and nimbiol[4] is thus confirmed.

For elaboration of the C ring, the *tert*-butyl β-keto esters **34** and **35,** which contain the ultimate 13-alkyl group of the natural products, needed to be prepared. *tert*-Butyl propionylacetate (**35**) was synthesized by condensation of *tert*-butyl acetate with *p*-diphenyl propionate in analogy to the reported preparation of the corresponding ethyl ester.[35] Synthesis of keto ester **34** proceeded through acylation of the sodium enolate of *tert*-butyl acetoacetate by isovaleryl chloride to form the diketo ester **32,**[36] sodium hydride



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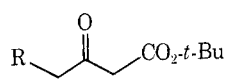

34, R = $CH(CH_3)_2$
35, R = CH_3

being used as the base. This compound is readily separated from the small amount of O-acylation product **33** by basic extraction. Ammonolysis has been reported[37] as a procedure for selectively cleaving the acetyl group in analogous diketo esters, but we have found that 1% aqueous sodium hydroxide is faster and at least equally selective,[37,38] affording the γ-substituted β-keto ester **34** in high yield.

Experimental Section

Spectra were obtained using Perkin-Elmer Models 137, 137G, and 337 (ir), Cary Model 14 (uv), and Varian A-60 (^{1}H NMR) spectrometers. The ^{1}H NMR reference was Me_4Si as an internal standard, with chemical shifts reported in τ units and coupling constants (J) in hertz. Mass spectra were obtained on a Perkin-Elmer Hitachi RMU-6E double-focusing spectrometer with direct sample introduction at an ionization potential of 80 eV; data is in the form *m/e* (percent base peak intensity). Glc was conducted on a 2-m 10% silicone gum SE-30 on Chromosorb W column at the indicated temperature, using an F & M Model 609 chromatograph with N_2 as carrier gas and with a hydrogen flame ionization detector. Melting points and boiling points are uncorrected. Microanalyses are by Alfred Bernhardt, Mulheim, Germany. Unless indicated otherwise the drying agent for organic solutions was $MgSO_4$. When no temperature is specified, the reaction was conducted at room temperature, ca. 23°.

3-(1′,3′,3′-Trimethyl-2′-ketocyclohexyl)propionitrile (4). In an adaptation of an analogous procedure[39] a solution of 74.2 g (1.40 mol) of freshly distilled acrylonitrile in 100 ml of MeOH was added over 1 hr to an ice-cold mixture of 300 ml of MeOH and 6.72 g of a 55% dispersion of NaH in mineral oil (0.15 mole of NaH) in a N_2 atmosphere. The mixture was stirred for 1 hr in the cold to form β-methyoxypropionitrile, and 28.0 g (0.20 mol) of 2,2,6-trimethylcyclohexanone,[40] bp 176–178°, was slowly added. The solution was stirred at ca. 23° for 4 hr and under reflux for 4.5 days, neutralized with glacial HOAc, and concentrated at reduced pressure, and the residue was poured onto ice and extracted with ether which was washed with brine, dried, and evaporated in vacuo. The residue was distilled to yield a forerun of 83 g of an approximately equimolar mixture (GLC, 150°) of reactants followed by 22.8 g (59%) of keto nitrile **4** as a colorless oil, bp 136–145° (1.5 mm). Redistillation yielded 20.6 g (54%) of pure **4:** bp 104–105° (0.3 mm); ir (film) 4.43, 5.90 μ; uv max (95% EtOH) 244 nm (ϵ 21), 295 (26); ^{1}H NMR (CCl_4) τ 8.86 (s, 6 H), 8.94 (s, 3 H).

Anal. Calcd for $C_{12}H_{19}NO$: C, 74.61; H, 9.84; N, 7.25. Found: C, 74.44; H, 9.57; N, 7.40.

The combined foreruns of two such reactions were subjected to reaction with fresh acrylonitrile to afford an additional 18.9 g of once-distilled **4,** bp 135–145° (1.5–2.0 mm) (total conversion 84%).

3-(1′,3′,3′-Trimethyl-2′-ketocyclohexyl)propionic Acid (5). A mixture of 150 g of 15% aqueous KOH and 10.0 g (0.052 mol) of keto nitrile **4,** bp 104–105° (0.3 mm), was refluxed under N_2 for 24 hr, cooled, washed with ether, and acidified with concentrated HCl. The precipitate was extracted into ether which was washed with water, dried, and removed in vacuo to afford 10.7 g (97%) of a viscous yellow oil. Crystallization from pentane yielded 9.0 g (82%) of keto acid **5** as white prisms: mp 48–49°; ir (CCl_4) 5.83 μ; uv max (95% EtOH) 305 nm (ϵ 26); ^{1}H NMR (CCl_4) τ −1.83 (s, 1 H), 8.94 (s, 9 H). Concentration and crystallization of the mother liquors yielded an additional 1.0 g of **5,** mp 47–48° (total yield 91%).

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.92; H, 9.43. Found: C, 67.99; H, 9.27.

3-(1′,3′,3′-Trimethyl-2′-chloro-2′-hydroxycyclohexyl)propionic Acid Lactone (10). Over a 1.0-hr period 5.36 g (0.045 mol) of purified[41a] $SOCl_2$ was added to 6.36 g (0.030 mol) of keto acid **5,** mp 46–47°, at 0° under N_2. The solution was stirred in the cold for 0.5 hr, heated at 60° for 2 hr, and excess $SOCl_2$ was removed by codistillation with C_6H_6 to leave a yellowish crystalline mass with ir (CCl_4) 5.68 (s), 5.90 μ (w). Recrystallization from pentane yielded chloro lactone **10** as white prisms: mp 59–60°; ir (CCl_4) 5.68 μ; ^{1}H NMR ($CDCl_3$) τ 8.68 (s, 3 H), 8.75 (s, 3 H), 8.78 (s, 3 H); positive Beilstein test for halogen.

Anal.[42] Calcd for $C_{12}H_{19}ClO_2$: C, 62.47; H, 8.30. Found: C, 62.61; H, 7.93.

3-(1′,3′,3′-Trimethyl-2′-ketocyclohexyl)propionyl Chloride (6). The procedure was adapted from one by Stork and Clarke.[14] A solution of 2.14 g (0.025 mol) of $NaHCO_3$ and 5.28 g (0.025 mol) of keto acid **5,** mp 45–46°, in 15 ml of water was washed with ether and evaporated to dryness in vacuo. The salt was dried over $CaSO_4$

at 0.5 mm for 24 hr, suspended in 75 ml of ether, treated with 0.75 ml of pyridine, and cooled in ice, and 12 ml of oxalyl chloride was added during 45 min. The mixture was stirred for 1.0 hr in the cold, filtered, and solvent was removed in vacuo to afford acid chloride **6** as an oil, ir (CCl_4) 5.55, 5.90 μ, in quantitative yield. The near absence of chloro lactone **10** was indicated by very weak absorption at 5.68 μ.

4-(1′,3′,3′-Trimethyl-2′-ketocyclohexyl)-2-butanone (9). A. Diazo Ketone Route. Procedures were adapted from Stork and Clarke.[14] An ice-cold solution of crude acid chloride **6** [freshly prepared from 9.42 g (0.045 mol) of keto acid **5**, mp 46–47°] in 100 ml of ether was added over 20 min to a cold solution of CH_2N_2 [prepared from 60 g (0.58 mol) of *N*-methyl-*N*-nitrosourea[43a] and dried over KOH[43b]] in 400 ml of ether, and the solution was allowed to stand in the cold for 1.5 hr. Diazo ketone **7** could be obtained as a pale yellow oil, ir (CCl_4) 4.74, 5.90, 6.06 μ, ^{1}H NMR (CCl_4) τ 4.83 (s, 1 H), 8.93 (s, 6 H), 8.95 (s, 3 H), by evaporation of solvent; in general, however, the solution was directly treated with dry HCl at 0° until N_2 evolution ceased, approximately 15 min being required. Evaporation of solvent in vacuo afforded crude chloro ketone **8** as an orange oil: ir (CCl_4) 5.78, 5.90 μ; ^{1}H NMR (CCl_4) τ 4.72 (s, 2 H), 8.93 (s, 6 H), 8.96 (s, 3 H). Crude **8** and 135 g of Zn dust were added to a mixture of 27 g of KI in 350 ml of glacial HOAc in a N_2 atmosphere, stirred for 10 hr, treated with 70 ml of water, stirred for 11 hr, and filtered. The filtrate was concentrated in vacuo, diluted with water, and extracted with ether which was washed with water, dried, and removed in vacuo to afford 8.29 g (88%) of crude diketone **9** as a pale yellow oil which was 90% pure (GLC, 150°). A small sample was evaporatively distilled at 125–135° (bath temperature, 2 mm) to afford a spectrally pure sample of colorless **9**: ir (CCl_4) 5.80, 5.90 μ; ^{1}H NMR ($CDCl_3$) τ 7.90 (s, 3 H), 8.93 (s, 9 H).

B. Methyllithium Route. The procedure was adapted from one by Tegner.[15] During 2.5 hr 420 ml of a 0.48 *M* solution of MeLi in ether (0.20 mol of MeLi freshly prepared from MeI[15]) was added to a solution of 21.1 g (0.10 mol) of keto acid **5**, mp 46–47°, in 170 ml of ether. The solution was refluxed for 10 min, decomposed with 20 ml of water,[44] washed with water, dried, and evaporated in vacuo to afford 12.1 g (58%) of a pale yellow oil which consisted predominantly of diketone **9** (GLC assay). Distillation afforded 6.90 g (33%) of nearly pure **9** as a colorless oil, bp 90–95° (0.55 mm), with an ir spectrum nearly identical with that of the sample described above.

Acidification of the combined aqueous phases with dilute HCl precipitated 11.0 g (52%) of **5** identified by its ir spectrum.

When commercial MeLi in ether (Foote Mineral Co.) was used in the above procedure, a mixture of products was obtained. From 20.04 g (0.0945 mol) of keto acid **5**, mp 46–47°, there was obtained 8.1 g of a pale yellow neutral oil. Crystallization from pentane afforded 1.43 g (7%) of white needles, mp 84.0–84.5°, identified spectrally as ketol **15**: ir ($CHCl_3$) 2.76, 5.79 μ; ^{1}H NMR ($CDCl_3$) τ 7.88 (s, 3 H), 8.87 (s, 3 H), 8.92 (s, 3 H), 9.00 (s, 3 H), 9.08 (s, 3 H). The remainder of the neutral product mixture was not further investigated.

4,4,10-Trimethyl-Δ^5-octalone-7 (11). A solution of 2.32 g (0.011 mol) of crude (90%) diketone **9** and 1.56 g (0.022 mol) of freshly distilled pyrrolidine in 25 ml of C_6H_6 was refluxed for 20 hr under a Dean-Stark trap[9] and poured into brine. The C_6H_6 layer was washed with 4% HCl, aqueous phases were acidified with 3 ml of concentrated HCl and extracted with ether, and the aqueous phase was neutralized with solid NaOH[45] and extracted with ether. The combined organic phases were washed with 4% HCl and brine, dried, and evaporated in vacuo to afford 2.08 g (98%) of a pale yellow oil which was distilled in a microstill to afford 1.79 g (85%) of enone **11** as a colorless oil, bp 90–100° (0.6 mm), homogeneous by GLC (185°): ir (film) 6.00, 6.26 μ; ^{1}H NMR ($CDCl_3$) τ 4.10 (s, 1 H), 8.65 (s, 3 H), 8.82 (s, 3 H), 8.87 (s, 3 H); uv max (95% EtOH) 242 nm (ϵ 13400) [lit. bp 129–130° (10 mm);[13] uv max (95% EtOH) 240 nm (ϵ 13000);[12] uv max (95% EtOH) 242 nm (ϵ 13700)[13].

4,4,10-Trimethyl-5α-decalone-7 (12) and 4,4,10-Trimethyl-5β-decalone-7 (13). A mixture of 1.41 g (0.0073 mol) of enone **11**, bp 90–100° (0.6 mm), and 67 mg of 30% Pd/C in 30 ml of 95% EtOH was hydrogenated at 1 atm until absorption ceased (ca. 30 min). Filtration of catalyst and distillation of solvent in vacuo left 1.40 g (98%) of a partially crystalline oil: ir (film) 5.83 μ, no OH absorption; ^{1}H NMR ($CDCl_3$) τ 8.88 (s, 3 H), 9.15 (s, 6 H) (major component), and 8.80 (s, 3 H), 9.08 (s, 3 H), 9.17 (s, 3 H) (minor component). Low-temperature crystallization from pentane afforded 1.16 g (83%) of the decalone mixture as white needles which partially liquefied at room temperature. Repeated recrystallization from pentane afforded a small quantity of a pure sample of the preponderant isomer, mp 39–40°, which was identical with **12** described below. Chromatography over neutral alumina failed to give a satisfactory separation of the two isomers, although enriched samples could be obtained. From the relative intensities of methyl resonances in ^{1}H NMR spectra of the hydrogenation mixture the ratio of trans to cis decalones was approximately 4:1.[47]

10-Cyano-4,4-dimethyl-7,7-ethylenedioxy-5α-decalin (20a). A mixture of 4.0 g (0.02 mol) of cyano decalone **19a**,[1b] mp 58–60°, 3.0 ml of ethylene glycol, and 0.05 g of TsOH in 100 ml of C_6H_6 was refluxed with azeotropic separation of water for 9.5 hr. Pyridine (0.5 ml) was added and the solution was poured into 50 ml of 2 *N* KOH and extracted with ether which was washed with water and brine, dried, and removed in vacuo to afford 5.2 g (107%) of ketal **20a** as a white solid. Fractional sublimation at reduced pressure afforded 4.8 g (99%) of **20a** as white needles: mp 116–117°; ir ($CHCl_3$) 4.49 μ; ^{1}H NMR ($CDCl_3$) τ 6.07 (s, 4 H), 8.97 (s, 3 H), 9.10 (s, 3 H).

Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.29; H, 9.24; N, 5.62. Found: C, 72.14; H, 9.27; N, 5.85.

4,4-Dimethyl-7,7-ethylenedioxy-10-formimidoyl-5α-decalin (20b). A suspension of 1.71 g (0.045 mol) of $LiAlH_4$ in 225 ml of tetrahydrofuran (THF) was added over 45 min to an ice-cold solution of 4.0 g (0.016 mol) of cyano ketal **20a** in 50 ml of redistilled THF in a N_2 atmosphere.[19,20] The mixture was stirred in the cold for 1.5 hr and at ca. 23° for 5.0 hr, decomposed with aqueous saturated potassium sodium tartrate, and extracted with $CHCl_3$ which was washed with brine, dried, and removed in vacuo to afford 4.3 g (106%) of imino ketal **20b** as a colorless oil: ir (CCl_4) 2.93–3.10, 6.15 μ; ^{1}H NMR ($CDCl_3$) τ 1.52 (s, 1 H), 6.07 (s, 4 H), 9.10 (s, 3 H), 9.27 (s, 3 H).[48]

4,4-Dimethyl-7,7-ethylenedioxy-10-formyl-5α-decalin (20f). A solution of 343 mg (0.00135 mol) of distilled alcohol **20e**[30] in 6 ml of pyridine (dried over KOH) was added to a slurry of CrO_3–pyridine complex, prepared from 343 mg (0.00515 molar equiv) of CrO_3 and 3.4 ml of pyridine.[49] After being stirred for 20 min and refluxed for 4.5 hr (reaction time is critical), the mixture was diluted with 25 ml of water, shaken with 10 ml of ether, and filtered through Celite to remove inorganic salts. The aqueous phase was extracted with ether which was washed with water, dried, and evaporated under a N_2 stream on a steam bath, with the final traces of solvent being removed in vacuo at ca. 23° to afford 296 mg (86%) of aldehyde **20f** as a moist, pale yellow solid: ir ($CHCl_3$) 5.83, 9.05 μ; ^{1}H NMR ($CDCl_3$) τ −0.05 (s, 1 H), 6.05 (s, 4 H), 9.08 (s, 3 H), 9.25 (s, 3 H).

The instability of aldehyde **20f** precluded further purification and necessitated its use within 1 day.

7,7-Ethylenedioxy-4,4,10-trimethyl-5α-decalin (20c). A. From Imino Ketal 20b. The general procedure of Nagata[19] was adapted. A solution of 7.0 g (0.028 mol) of crude imino ketal **20b**, 9 g (0.16 mol) of KOH, and 60 ml (1.5 mol) of 80% aqueous N_2H_4 [from addition of 10 ml of water to 50 ml of 95(+)% N_2H_4] in 300 ml of triethylene glycol in a N_2 atmosphere was heated at 70° for 1 hr. The internal temperature was raised over 5 hr to 145°, distillation began, and 60 ml of distillate was collected in an attached Dean-Stark trap as the temperature was slowly raised to 210° where it was held for 10 hr. The colorless solution was cooled, poured into 400 ml of brine, and extracted with ether which was washed with brine and water and dried. The distillate was extracted with ether which was combined with the main organic fraction. Solvent was removed in vacuo to leave 6.6 g (100%) of ketal **20c** as a pale yellow oil with spectral properties identical with those of an analytical sample prepared as a colorless oil by evaporative distillation in a microstill, ^{1}H NMR (CCl_4) τ 6.08 (s, 4 H), 9.05 (s, 3 H), 9.15 (s, 3 H), 9.20 (s, 3 H).

Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.61; H, 10.92. Found: C, 75.37; H, 11.00.

B. From Formyl Ketal 20f. Reduction of 4.2 g (0.017 mol) of crude aldehyde **20f**, using 5.0 g (0.089 mol) of KOH and 40 ml (1.2 mol) of N_2H_4 [Eastman 95(+)%] in 350 ml of triethylene glycol was conducted as described for **20b** but with reaction conditions as follows: 130° for 1.5 hr, raise to 230° over 7 hr (distillation), 230° for 2 hr. Isolation as described afforded 4.0 g (100%) of ketal **20c** as a pale yellow oil which was spectrally indistinguishable from the sample described above.

4,4,10-Trimethyl-5α-decalone-7 (12). A solution of 158 mg (0.67 mmol) of crude ketal **20c**, 5 drops of water, and 2 drops of concentrated H_2SO_4 in 5 ml of acetone was refluxed for 4 hr, solvent was removed in vacuo, 20 ml of brine was added, and the product was extracted with $CHCl_3$ which was washed with 5%

$NaHCO_3$ and water, dried, and evaporated to leave 123 mg (95%) of ketone **12** as a yellowish oil spectrally indistinguishable from the analytical sample. Distillation (80°, 0.2 mm) followed by fractional sublimation at reduced pressure afforded pure **12** as colorless needles: mp 39–40°; ir (CCl_4) 5.88 μ; ^1H NMR ($CDCl_3$) τ 8.88 (s, 3 H), 9.15 (s, 6 H) [reported[7] bp 125–128° (5 mm)]. Ir and ^1H NMR spectra of this sample were superimposable on those of the authentic (−) enantiomer which were kindly provided by Professor Wenkert.[8]

Anal. Calcd for $C_{13}H_{22}O$: C, 80.41; H, 11.34. Found: C, 80.20; H, 11.30.

4,4,10-Trimethyl-5α-decalin (21). Reduction of 1.0 g (0.0052 mol) of distilled decalone **12** using 1.5 g (0.27 mol) of KOH and 10 ml of 90% N_2H_4 in 75 ml of triethylene glycol was conducted as described for **20b** but with reaction conditions as follows: 60° for 1 hr, raise to 210° over 9 hr (10 ml of distillate collected), 210° for 12 hr. Isolation as described for **20c** afforded 95 mg (10%) of decalin **21** as a yellow oil which was distilled from Na to afford a colorless oil, 70 mg, bp 45° (0.2 mm) [lit. bp 105–110° (17 mm),[21] 60–65° (0.2 mm)[7]]. A second vacuum distillation in a micro-Hickman flask afforded the analytical sample: ir (film) 3.42, 6.78, 6.85, 7.15, 7.25 μ; ^1H NMR ($CDCl_3$) τ 9.00 (s, 3 H), 9.18 (s, 3 H), 9.22 (s, 3 H); mass spectrum *m/e* 180 (4), 165 (100).

Anal. Calcd for $C_{13}H_{24}$: C, 86.74; H, 13.41. Found: C, 86.56; H, 13.41.

8-Hydroxymethylene-4,4,10-trimethyl-5α-decalone-7 (22). A mixture of 1.23 g (0.0064 mol) of trans decalone **12**, mp 39°, 0.94 g (0.0127 mol) of ethyl formate, bp 52°, and 0.79 g of a 58% dispersion of NaH in mineral oil (0.019 mol of NaH) in 50 ml of C_6H_6 was stirred for 24 hr under N_2,[1b] treated with 100 ml of water, and extracted with 1% NaOH. The aqueous extracts were washed with ether, acidified with concentrated HCl, and extracted with ether which was washed with water, dried, and evaporated in vacuo to afford 1.30 g (92%) of hydroxymethylene ketone **22** as pale yellow crystals: mp 29–31°; ir (CCl_4) 6.12, 6.34 μ; ^1H NMR ($CDCl_3$) τ −4.20 (s, 1 H), 1.63 (s, 1 H), 9.13 (s, 9 H).

8-Formyl-4,4,10-trimethyl-Δ⁸-5α-octalone-7 (23). The procedure is a modification of one developed by Shew in these laboratories. A solution of 2.7 g (0.012 mol) of DDQ and 25 drops of glacial HOAc in 25 ml of dioxane was added dropwise over 15 min to a stirred solution of 2.6 g (0.012 mol) of crude hydroxymethylene ketone **22** in 25 ml of dioxane. After 15 min the mixture was filtered into 300 ml of $CHCl_3$ which was washed with 10% $NaHCO_3$ until the wash was colorless and then with water. Drying and evaporation of solvent afforded 2.5 g (97%) of formyl enone **23** as an orange oil: ir (CCl_4) 5.87, 5.92, 6.21 μ; ^1H NMR ($CDCl_3$) τ −0.03 (s, 1 H), 2.58 (s, 1 H), 8.85 (s, 3 H), 9.05 (s, 3 H), 9.08 (s, 3 H). The ^1H NMR spectrum showed no significant resonance from contaminants. Attempts to further purify this substance were unsuccessful.

7,12-Diketo-Δ¹³-5α,8β,9β-abietene (25a). A mixture of 351 mg (1.75 mmol) of *tert*-butyl isovalerylacetate, bp 97–98° (2.6 mm), and 91 mg of a 58% dispersion of NaH in mineral oil (2.2 mmol of NaH) in 10 ml of C_6H_6 was stirred under N_2 for 15 min and a solution of 366 mg of crude keto aldehyde **23** (ca. 85% purity, 1.41 mmol; estimated to contain ca. 15% of **22** from its ^1H NMR spectrum) in 20 ml of C_6H_6 was added. The mixture was stirred for 2 hr, neutralized to pH 6 with glacial HOAc, poured into water, and extracted with $CHCl_3$ which was washed with brine, dried, and removed in vacuo to afford 694 mg of adduct **24a** as a pale yellow oil: ir (CCl_4) 5.72, 5.85, 6.07, 6.27 μ; ^1H NMR (CCl_4) τ 1.63 (s) and 1.70 (s) (total 1 H), 6.47 (d, J = 8 Hz) and 7.05 (d, J = 8 Hz) and 6.80 (s) (total 2 H), 8.57 (s) and 8.58 (s) (total 9 H).

A solution of the crude adduct in 30 ml of glacial HOAc containing ca. 20 mg of TsOH was refluxed under N_2 for 3.5 hr, treated with NaOAc, and evaporated at reduced pressure. The residue was partitioned between water and $CHCl_3$ which was washed with 1% NaOH and brine, dried, and removed in vacuo to afford 287 mg (67% based on aldehyde **23**) of enedione **25a** as pale yellow crystals. Recrystallization from EtOAc yielded pure **25a** as fine white needles: mp 147–148°; ir ($CHCl_3$) 5.87, 5.99 μ; uv max (95% EtOH) 232 nm (ϵ 8000); ^1H NMR ($CDCl_3$) τ 3.22 (dd, 1 H, J = 6 and 0.9 Hz), 6.40 (dd, 1 H, J = 5 and 6 Hz), 8.70 (s, 3 H), 8.94 (d, 3 H, J = 7 Hz), 8.97 (d, 3 H, J = 7 Hz), 9.10 (s, 3 H), 9.13 (s, 3 H).

Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.47; H, 9.93. Found: C, 79.35; H, 10.03.

DL-Sugiol (2a). A solution of 102 mg (0.339 mmol) of enedione **25a**, mp 145°, and 111 mg (0.346 mmol) of pyridine hydrobromide perbromide[41b] in 7 ml of glacial HOAc was allowed to stand for 0.5 hr.[31] Addition of 7 ml of water, filtration, and recrystallization from MeOH afforded 95 mg (93%) of DL-sugiol as white needles: mp 269–270° [reported for (+)-sugiol[3a] 295–297°]; ir (KBr) 3.25 (broad), 6.12, 6.41 μ; ^1H NMR (CD_3COCD_3) τ 2.18 (s, 1 H), 3.13 (s, 1 H), 8.77 (d, 3 H, J = 6.5 Hz), 8.79 (d, 3 H, J = 6.5 Hz), 8.79 (s, 3 H), 8.98 (s, 3 H), 9.05 (s, 3 H).

Acetylation according to the procedure of Brandt and Thomas[3a] afforded a colorless oil which did not crystallize; its ^1H NMR spectrum was identical with that reported[33] for the acetate of (+)-sugiol.

DL-Ferruginol (2c). A mixture of 48 mg (0.16 mmol) of DL-sugiol, mp 269–270°, 34 mg of 30% Pd/C, and 1 drop of concentrated H_2SO_4 in 8 ml of EtOAc was hydrogenated at 1 atm for 3.0 hr.[32] Catalyst was removed by filtration through Celite, and the filtrate was washed with water, dried, and evaporated in vacuo to yield DL-ferruginol[5] as a pale yellow resin: ir ($CHCl_3$) 2.78 μ; ^1H NMR ($CDCl_3$) τ 3.22 (s, 1 H), 3.42 (s, 1 H), 8.80 (d, 6 H, J = 7 Hz), 8.87 (s, 3 H), 9.08 (s, 6 H). The ^1H NMR spectrum was identical with that of a redistilled authentic sample of (+)-ferruginol.[34]

7,12-Diketo-13-methyl-Δ¹³-5α,8β,9β-podocarpene (25b). A mixture of 247 mg (1.28 mmol) of redistilled *tert*-butyl propionylacetate and 54 mg of a 58% dispersion of NaH in mineral oil (1.28 mmol of NaH) in 15 ml of C_6H_6 was stirred until the evolution of H_2 ceased (0.5 hr).[1b] A solution of 222 mg (1.01 mmol) of crude keto aldehyde **23** in 5 ml of C_6H_6 was added, and after 4.0 hr the mixture was neutralized with glacial HOAc and processed as described for adduct **24a** to afford 467 mg (118%) of a pale yellow oil consisting of adduct **24b** contaminated with some *tert*-butyl propionylacetate: ir (CCl_4) 5.85, 6.10, 6.29 μ; ^1H NMR (CCl_4) τ 1.65 (s) and 1.75 (s) (total 1 H), 6.42 (d, J = 8 Hz) and 7.05 (d, J = 8 Hz) and 6.78 (s) (total 2 H), 8.58 (s) and 8.60 (s) (total 9 H).

The crude adduct was cyclized in 20 ml of glacial HOAc containing ca. 5 mg of TsOH as described for preparation of enedione **25a** to afford 196 mg (71%) of crystalline, yellow enedione **25b**. Recrystallization from EtOAc afforded pure **25b** as fine, white needles: mp 209–210°; ir ($CHCl_3$) 5.85, 5.97 μ; uv max (95% EtOH) 231 nm (ϵ 9070); ^1H NMR ($CDCl_3$) τ 3.22 (dq, J = 5.5 and 1 Hz, 1 H), 8.20 (t, 3 H, J = ca. 1 Hz), 8.69 (s, 3 H), 9.10 (s, 3 H), 9.12 (s, 3 H).

Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.83; H, 9.49. Found: C, 78.76; H, 9.53.

DL-Nimbiol (2b). A solution of 95 mg (0.347 mmol) of enedione **24b**, mp 209°, and 114 mg (0.356 mmol) of pyridine hydrobromide perbromide,[41b] mp 132°, in 7 ml of glacial HOAc was treated as described for synthesis of DL-sugiol. Recrystallization of the crude product from MeOH afforded 42 mg (45%) of pure DL-nimbiol as white needles: mp 237.0–237.5°; ir ($CHCl_3$) 2.79, 6.02, 6.23, 6.35 μ; ^1H NMR ($CDCl_3$) τ 2.20 (s, 1 H), 3.26 (s, 1 H), 7.80 (s, 3 H), 8.81 (s, 3 H), 9.03 (s, 3 H), 9.11 (s, 3 H). The ir spectrum of this sample was identical with that of the (+) enantiomer.[34]

Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.41; H, 8.82. Found: C, 79.20; H, 9.08.

***tert*-Butyl α-Isovalerylacetoacetate (32).**[50] In an adaptation of an analogous procedure[36] 13.2 g (0.084 mol) of redistilled *tert*-butyl acetoacetate[51] in 100 ml of C_6H_6 was added over 0.5 hr to 5.5 g of a 58% dispersion of NaH in mineral oil (0.13 mol of NaH) in 200 ml of C_6H_6 and the mixture was stirred until evolution of H_2 ceased (2.0 hr). A solution of 10.0 g (0.084 mol) of isovaleryl chloride,[52] bp 113–114°, in 100 ml of C_6H_6 was added over 0.5 hr, and the mixture was stirred under N_2 for 18 hr, treated with 1 equiv of glacial HOAc, washed with brine, and dried. Distillation of solvent left 27.6 g (113%) of crude diketo ester **32** as a pale yellow oil. Distillation of a small portion through a spinning band column afforded a sample of bp 110–120° (4–5 mm) the ^1H NMR spectrum of which indicated the presence of 95% of the C-acylation product **32** [^1H NMR ($CDCl_3$) τ 7.72 (s, 3 H), 8.45 (s, 9 H), 9.02 (d, 6 H, J = 7 Hz); ir (film) 5.78, 6.23 μ], containing about 5% of the O-acylation product **33** [^1H NMR ($CDCl_3$) τ 4.23 (q, 1 H, J = 1 Hz), 8.07 (d, 3 H, J = 1 Hz), 8.59 (s, 9 H)]. Complete separation could not be achieved by distillation.

Five grams of the crude acylation product in 25 ml of ether was extracted with five portions of 1% NaOH, each extract being immediately neutralized with 10% HCl and extracted with ether which was washed with saturated aqueous $NaHCO_3$ and water and dried. Evaporation in vacuo afforded 3.13 g (63%) of a pale yellow oil devoid of the O-acylation product (^1H NMR assay). Distillation through a spinning band column afforded pure **32** as a colorless liquid, bp 114–118° (1–2 mm) [lit.[36] bp 126° (12.5 mm)].

***tert*-Butyl Isovalerylacetate (34).**[53] A solution of 13.5 g (0.0560 mol) of diketo ester **32**, bp 106–113° (0.5–0.8 mm), and 22.3 g of 1% aqueous NaOH (0.00560 mol of NaOH) in 150 ml of MeOH was held at ca. 23° under N_2 for 2.5 hr, acidified with 5 ml of 5% HCl, MeOH was distilled in vacuo, 100 ml of ether was added, and

the mixture was washed with brine and dried. Evaporation afforded 9.6 g (86%) of crude product which was distilled to give 83% of pure **34** as a colorless oil, bp 94–99° (1 mm). The analytical sample from microredistillation had ir (film) 5.75, 5.81, 6.06 μ; ^{1}H NMR (CCl_4) τ 6.80 (s, 2 H), 8.57 (s, 9 H), 9.09 (d, 6 H, J = 7 Hz).

Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.98; H, 10.07. Found: C, 65.97; H, 9.94.

***tert*-Butyl Propionylacetate (35).** An analogous procedure of Abramovitch and Hauser[35] was modified. A solution of 0.05 mol of Ph_3CNa in 700 ml of ether under N_2 was cooled in a salt–ice bath, and 6.0 g (0.052 mol) of *t*-BuOAc, bp 96–97°, was added. The deep red color faded after 15 sec and a solution of 11.5 g (0.051 mol) of *p*-diphenyl propionate,[35] mp 96–97°, in 250 ml of ether was added. The mixture was stirred in the cold for 1.75 hr and at ca. 23° for 0.5 hr, treated with 5 ml of glacial HOAc, washed with water and 10% aqueous Na_2CO_3, and dried, and solvent was distilled at atmospheric pressure. The residue was twice evaporatively distilled to afford 1.05 g (12%) of pure **35** as a colorless liquid: ^{1}H NMR ($CDCl_3$) τ 6.66 (s, 2 H), 7.45 (q, 2 H, J = 7 Hz), 8.52 (s, 9 H), 8.90 (t, 3 H, J = 7 Hz).

Registry No.—**2a,** 10219-81-5; **2b,** 56760-98-6; **2c,** 10219-82-6; **3,** 2408-37-9; **4,** 56666-13-8; **5,** 56666-14-9; **6,** 56666-15-0; **7,** 56666-16-1; **8,** 56666-17-2; **9,** 56666-18-3; **10,** 56666-19-4; **11,** 56666-20-7; **12,** 16892-22-1; **13,** 56712-05-1; **15,** 56666-21-8; **19a,** 56666-22-9; **20a,** 56666-23-0; **20b,** 56666-24-1; **20c,** 56666-25-2; **20f,** 56712-04-0; **21,** 16886-12-7; **22,** 56666-26-3; **23,** 56666-27-4; (*R**)-**24a,** 56666-28-5; (*S**)-**24a,** 56666-29-6; (*R**)-**24b,** 56666-30-9; (*S**)-**24b,** 56666-31-0; **25a,** 56781-34-1; **25b,** 56666-32-1; **32,** 56666-33-2; **34,** 39140-54-0; **35,** 33400-61-2; acrylonitrile, 107-13-1; oxalyl chloride, 79-37-8; diazomethane, 334-88-3; methyllithium, 917-54-4; ethyl formate, 109-94-4; *tert*-butyl acetoacetate, 141-97-9; isovaleryl chloride, 108-12-3.

References and Notes

(1) (a) Supported by Grants AM-4215 and AM-10123 from the National Institute of Arthritis and Metabolic Diseases; the uv, ^{1}H NMR, and mass spectrometers were obtained with partial support of National Science Foundation Grants GP-8286, GP-3655, and GP-6978 respectively. (b) Part VI: W. L. Meyer, R. W. Huffman, and P. G. Schroeder, *Tetrahedron*, **24,** 5959 (1968). (c) Preliminary communication: W. L. Meyer, G. B. Clemans, and R. W. Huffman, *Tetrahedron Lett.*, 4255 (1966). (d) Abstracted in part from the Ph.D. Dissertation of R.A.M., University of Arkansas, 1971.

(2) All bicyclic and tricyclic compounds in this paper will be numbered by the steroid–terpenoid convention as in **1** and **2**, with the gem-dimethylated ring of decalins being ring A. The configurational notations α and β denote a trans or cis relation to the C-10 angular group, respectively. All synthetic substances were prepared only in racemic form, although the prefix DL is omitted and only one enantiomer is depicted.

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(16) Subsequent to our work Mukhopadhyay and Dutta[7] reported this hydrogenation to afford only the trans decalone **12,** which in their hands was noncrystalline. It may be that the difference in catalysts (10% vs. 30% palladium on carbon) leads to a difference in stereoselectivity, but no evidence was cited to demonstrate the purity of their sample, and it would appear that their procedures could well have failed to detect as much as 20% of the cis isomer.

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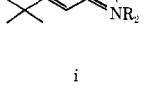
(45) Prior to basification a considerable proportion of the potential enone remains unextractable from the acidic aqueous phase, presumably as the unhydrolyzed eniminium salt i or perhaps as a β-ammonium ketone ii.[46] The free enone is instantaneously liberated in base. Analogous results have also occasionally been obtained with the cyclization described in ref 9.



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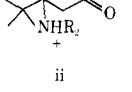

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Structures of Some *Knightia deplanchei* Alkaloids[1]

Mauri Lounasmaa

Chemical Laboratory, Technical Research Center of Finland, SF-02150 Otaniemi, Finland

Peter M. Wovkulich and Ernest Wenkert*

Department of Chemistry, Rice University, Houston, Texas 77001

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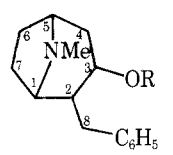
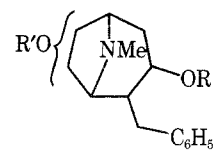
^{13}C NMR spectroscopy is utilized for the determination of the stereostructures of five alkaloids of the 2-benzyltropine type. Intramolecular hydrogen bonding by 6β- or 7β-hydroxy groups is shown to alter the normal conformation of the tropane *N*-methyl group. This phenomenon is modified greatly in a protic medium.

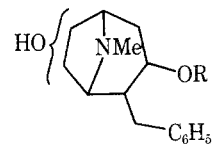
Several tropane alkaloids have been isolated recently from the New Caledonian plant *Knightia deplanchei* Vieill. ex Brongn. et Gris. Two compounds were shown to be 2-benzyltropanol derivatives **1a** and **1b** by spectral analyses[2,3] and synthesis,[4] while three others, **2a, 3a,** and **4**, were described as oxygenated variants of their congeners.[2,3] A ^{13}C NMR spectral study now has been undertaken in order to determine the complete structures of the last three substances and the stereochemistry of all five tropane bases.



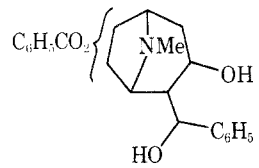
1a, R = COC_6H_5
b, R = Ac
c, R = H



2a, R = H; R′ = COC_6H_5
b, R = R′ = COC_6H_5
c, R = R′ = H

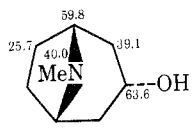


3a, R = *trans*-$COCH{=}CHC_6H_5$
b, R = H

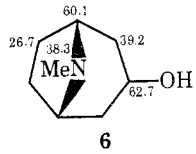


4

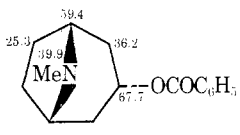
A previous investigation has revealed the carbon shifts of structurally simple tropanes, tropine (**5**), pseudotropine (**6**), and their benzoates (**7** and **8**, respectively) (δ values depicted on the formulas), and related alkaloids.[5] While the shift data could serve the present study well, their value was obscured in part by a recent report by Simeral and Maciel in which the assignment of the C(2), C(4) shifts of tropine (**5**) had been allotted to C(6), C(7).[7] Since, further, the tropine (**5**) spectrum had been taken in water solution, while the earlier δ values were obtained on deuteriochloroform solutions, a shift reevaluation had to precede the alkaloid structure study.



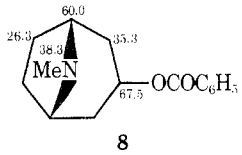
5



6



7



8

The coupling characteristics of the two carbon pairs were utilized to determine unambiguously the proper shift assignment. A series of off-resonance decoupling experiments designed to optimize possible carbon–hydrogen virtual coupling of C(6) were performed on deuteriochloroform solutions of tropine (**5**) and pseudotropine (**6**). The combination of strong residual coupling between C(6) and H(6α), but weak C(6)–H(7α) interaction and strong H(6α)–H(7α) coupling due to the identity of the two hydrogen shifts was expected to lead to virtual coupling of this ABX system.[8,9] The strong dissimilarity of the H(2) shifts from the resonances of the vicinal hydrogens precludes any C(2) virtual coupling. The observation of second-order coupling in the C(6) signal showed the earlier shift assignment[5] for compounds **5**–**8** to be correct. Furthermore, a similar observation in off-resonance decoupled spectra of an aqueous tropine (**5**) solution indicated the need for the reversal of the recent shift designation of C(2), C(4) and C(6), C(7).[7,10]

Close inspection of the fully proton-decoupled ^{13}C NMR spectrum of an aqueous solution of tropine (**5**) showed all lines except the oxymethine signal to be broad, the *N*-methyl and C(2), C(4) centers revealing the largest linewidths. While the broad 60.1-ppm signal was less intense than the 64.3-ppm resonance, the former covered an area nearly twice as large, showing it to constitute a two-carbon signal.[11] As a consequence the Simeral and Maciel assignment of the former resonance to C(3) and the latter to C(1), C(5)[7] needs reversal. The new assignment was confirmed by the residual coupling characteristics of the two resonances. A single-frequency, off-resonance decoupled (sford) spectrum in which the decoupling frequency was localized at the upfield end of the ^1H NMR spectrum exhibited expectedly lower residual coupling of the aminometh-