TOTAL SYNTHESIS OF A KEY INTERMEDIATE FOR THE TRITERPENE SHIONONE

Thesis by
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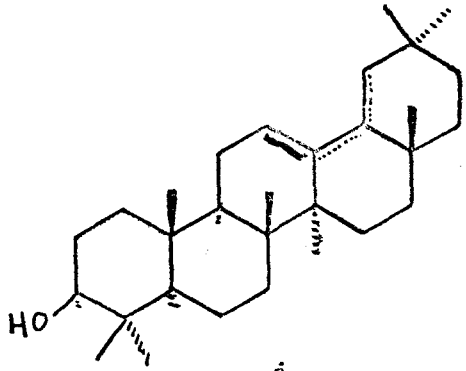
ABSTRACT

Total synthesis of a key intermediate, in a synthetic scheme aimed at the tetracyclic triterpene Shionone, has been accomplished by two closely related routes.

While the synthetic pathways towards the pentacyclic triterpene structure i, of the oleanenes, β-amyrin, and germanicol have been explored with some success (1a,2), few efforts have been directed towards the backbone rearranged triterpenes alnusenone ii, friedelin iii, and shionone iv (1b,3,4). As yet, no synthesis has been published for any of these molecules, due in part to the great difficulty of introducing the trans angular methyl groups at the C-D ring juncture. Recent



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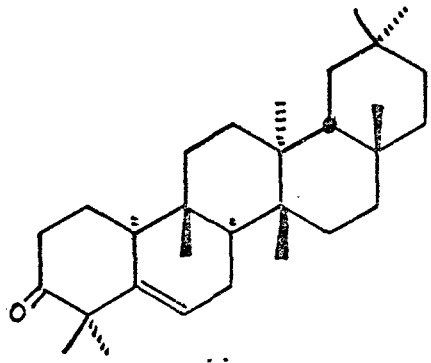

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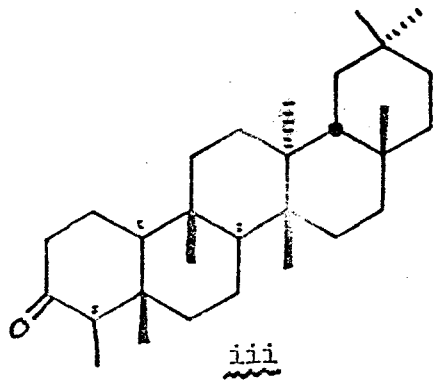

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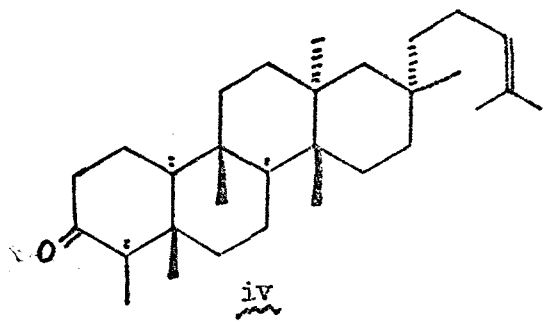
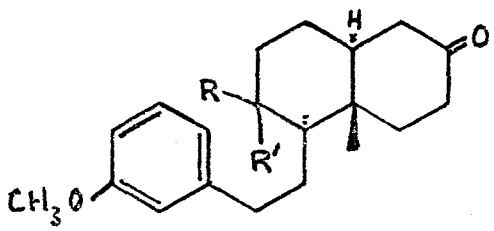


iv

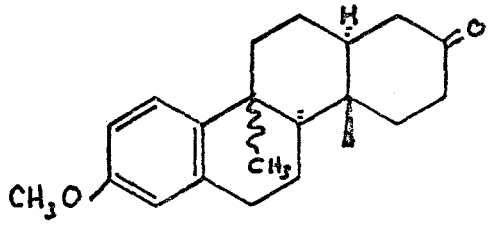
developments by W. Nagata (5), however, on the trans incorporporation of cyanide at ring junctures, have opened potential new pathways to these molecules; an important key intermediate along one of these paths, which contains the elusive trans angular methyl groups, and allows for the synthesis of ii, iii, and iv, is the molecule A-15. The total synthesis of this intermediate has been the object of this research.

The original synthetic plan is outlined in Chart A. When the plan

was proposed, compound A-8 had already been made by H. Smith and co-workers (6), using essentially the same annellation procedure. Nagata's hydrocyanation techniques (5) were to generate the trans-fused compound A-9 (possibly utilizing a protecting group for the alcohol function, to prevent base cleavage), and this was to be reduced to the trans-dimethyl compound A-12 via the imine (7). The only remanining crucial step, acid cyclization, had been worked out by S.C. Welch in our lab (8) on the model compounds v(a), (b) and (c). In all three cases, treatment with polyphosphoric acid (PPA) at 60° gave the same mixture of trans-anti-trans and cis-anti-trans cyclized material vi in the ratio of 70:30 respectivly. The intermediate A-15 thus seemed an attainable goal.



v (a) R=CH_3 , R'=OH
(b) R=OH , R'=CH_3
(c) R=R'= =CH_2



vi

In practice, the unsaturated ketone A-5 could be obtained in 67% overall yield. Michael addition to this compound appeared to work well, but subsequent ring closure lowered the two step yield to 54%; the reaction conditions have been variously modified, but with no improvment. Sodium borohydride reduction gave a high (80% crystalline) yield of A-8.

Treatment of A-8 with Et_2AlCN in benzene (5b) gave a mixture from which a single cyano ketone crystallized in 80% yield. While chromatography of the mother liquors could not be made to efficiently separate the remanining components, a small amount (4%), though not all, of an

CHART A

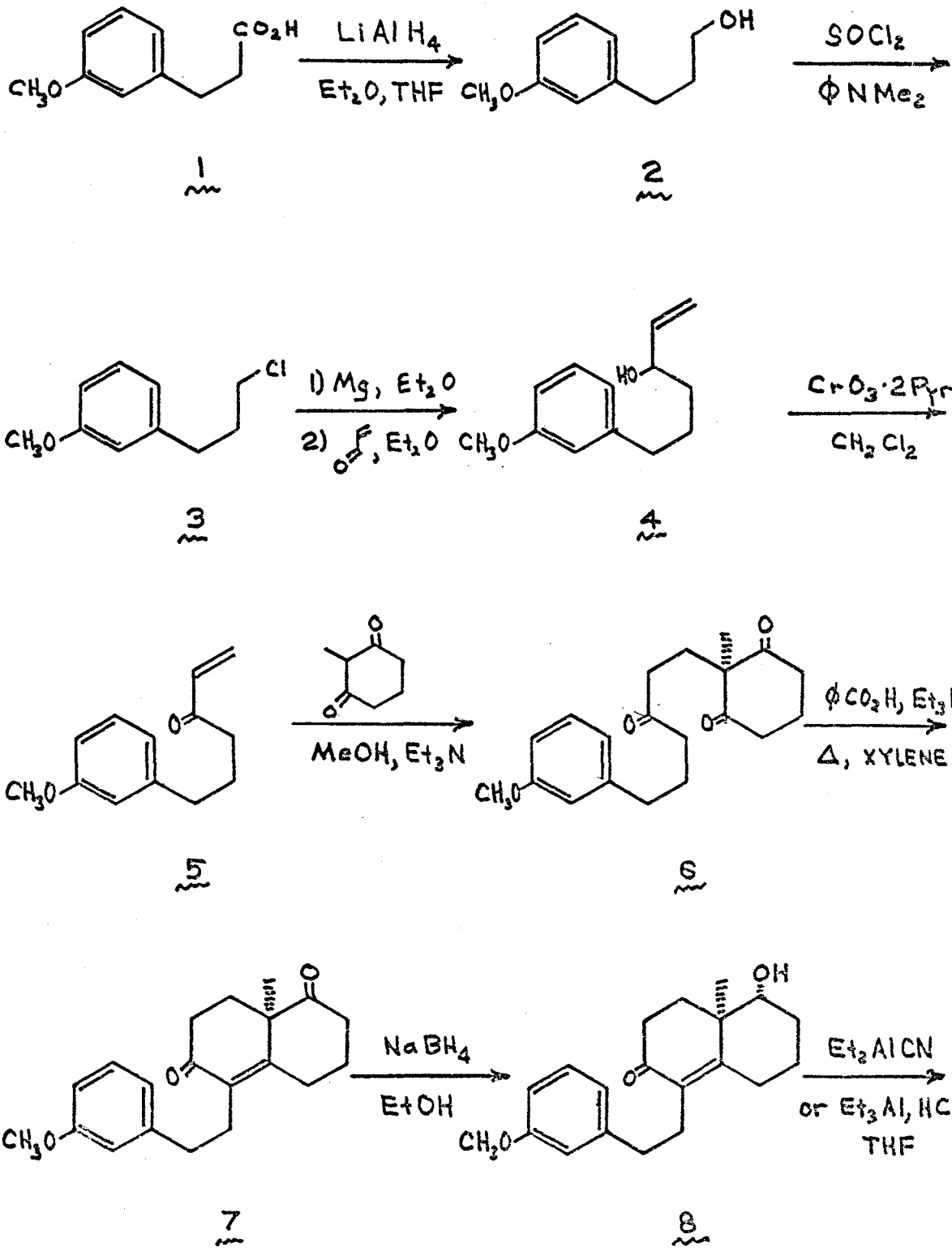
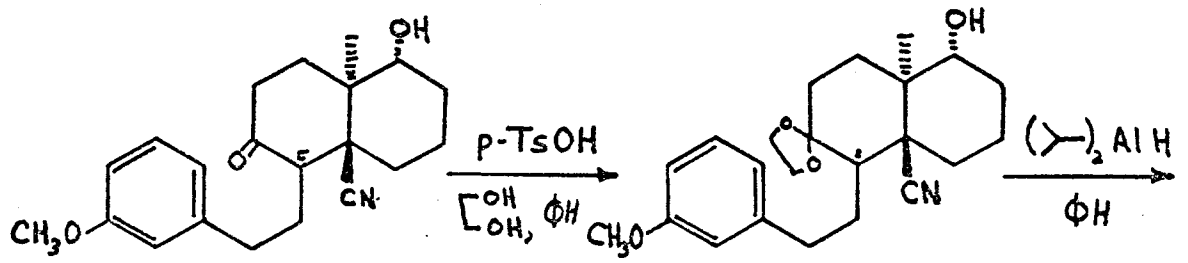

CO2H
LiAlH4
Et2O, THF
OH
SOCl2
ΦNMe2
CH3O
1
2
Cl
1) Mg, Et2O
2)
HO
CrO3·2Pyr
CH2Cl2
3
4
MeOH, Et3N
ΦCO2H, Et3N
Δ, XYLENE
5
6
NaBH4
EtOH
Et2AlCN
or Et3Al, HCN,
THF
7
8

CHART A



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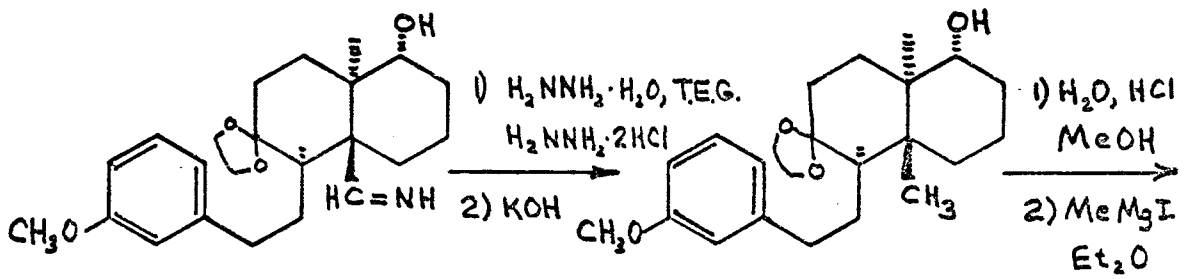

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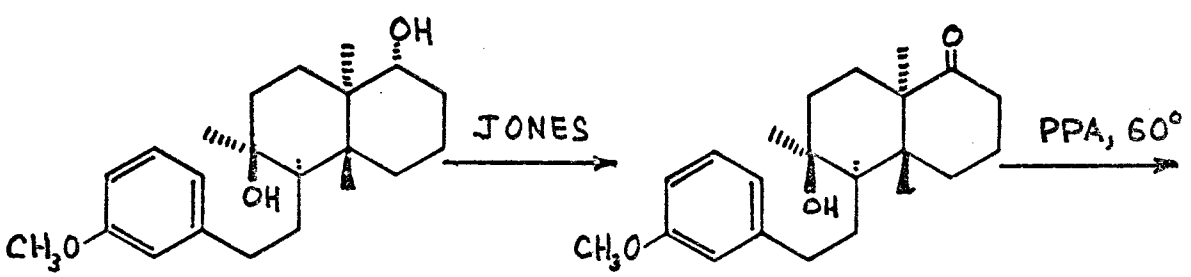
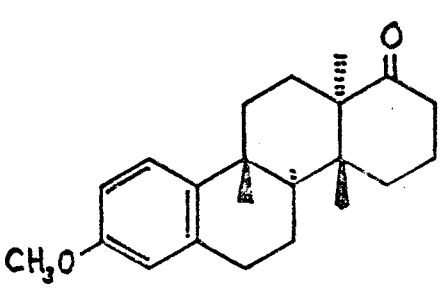


13 14



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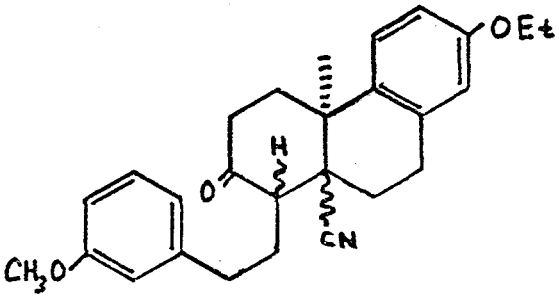
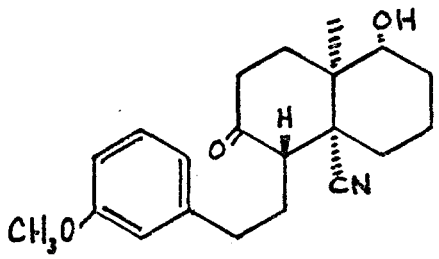
isomeric cyano ketone was obtained from the mixture. Comparison of the nitrile absorption in the infrared spectra of the two compounds, shows the minor product to have a much more intense absorption, indicative of a cis ring fusion (9); thus the major isomer appears to be the desired compound A-9. Further comparisons of the NMR spectra of these compounds, with the closely analogous series of S.C. Welch, vii(a), (b) and (c) (10), leads to assignment of viii as the structure of the minor isomer.



vii (a) α-H, β-CN
(b) β-H, α-CN
(c) α-H, β-CN



viii

Interestingly enough, treatment of A-8 with Et_3Al and HCN in THF (5c) gave the identical (by NMR) product mixture obtained with Et_2AlCN.

Ketalization of the product A-9 worked well (91%), but diisobutyl aluminum hydride (DIBAH) reduction of the nitrile to an imine, with subsequent Wolff-Kishner reduction to a methyl, could not be accomplished in appreciable yield. The DIBAH reduction proceeded with difficulty, resulting in what appeared to be a mixture of non-, mono-, and di-reduced material; even when the imine seemed maximized in the mixture, the Wolff-Kishner reduction resulted in very low return, concentrated in the unreduced cyano starting material. Other trans-cyano ketals have been successfully reduced using similar techniques (7), but none with a substituent α to the ring junction bearing the nitrile, nor with a nearby

hydroxyl. An attempted Wittig reaction of $\phi_3P{=}CH_2$ with the cyano ketone A-9 also failed, returning pure starting material.

Upon failure of the direct conversion of the nitrile to a methyl, a different approach (Chart B) was tried. Grignard addition of MeMgI to A-9 (excess did not affect the nitrile), gave the cyano di-ol B-1 in good (80% crystalline) yield. Treatment of this di-ol with acid or base gave the imino lactone B-2, which could not be hydrolyzed further even with HNO_2 (11). Jones oxidation of the alcohol function, however, allowed easy acid hydrolysis to the lactone B-3 (93%), presumably via assistance of the hydrated ketone.

While it was hoped to cyclize this lactone to B-4, using either PPA or P_2O_5 in benzene, such attempts always led to decarboxylation. Attempts to reduce the keto lactone with BH_3 in THF to obtain the lactol alcohol (hopefully susceptible to Wolff-Kishner reduction), gave only the lactone alcohol B-5, which equilibrated with B-6 in acid or base. Treatment of these lactone alcohols with hot PPA, gave B-7 (15%), B-8 (66%), and B-9 (9%), the structures of which were assigned on the basis of IR and NMR spectra (12).

Although all these hindered lactones resisted reduction with BH_3 in THF and with $LiAlH_4$ in refluxing THF/ether, treatment of B-8 with diisobutyl aluminum hydride (DIBAH) in benzene gave the di-ol B-10. DIBAH has been used to reduce lactones to lactols (13), and by using an equivalent amount of DIBAH at 0°, a 1:1 mixture of B-10 and the lactol B-11 was obtained. Wolff-Kishner reduction of the lactol gave mostly starting material, but also yielded 20% of an alcohol B-12, containing three angular methyl groups by NMR; Jones oxidation of this alcohol gave 7mg of a ketone, spectrally consistent with the structure A-15.

CHART B

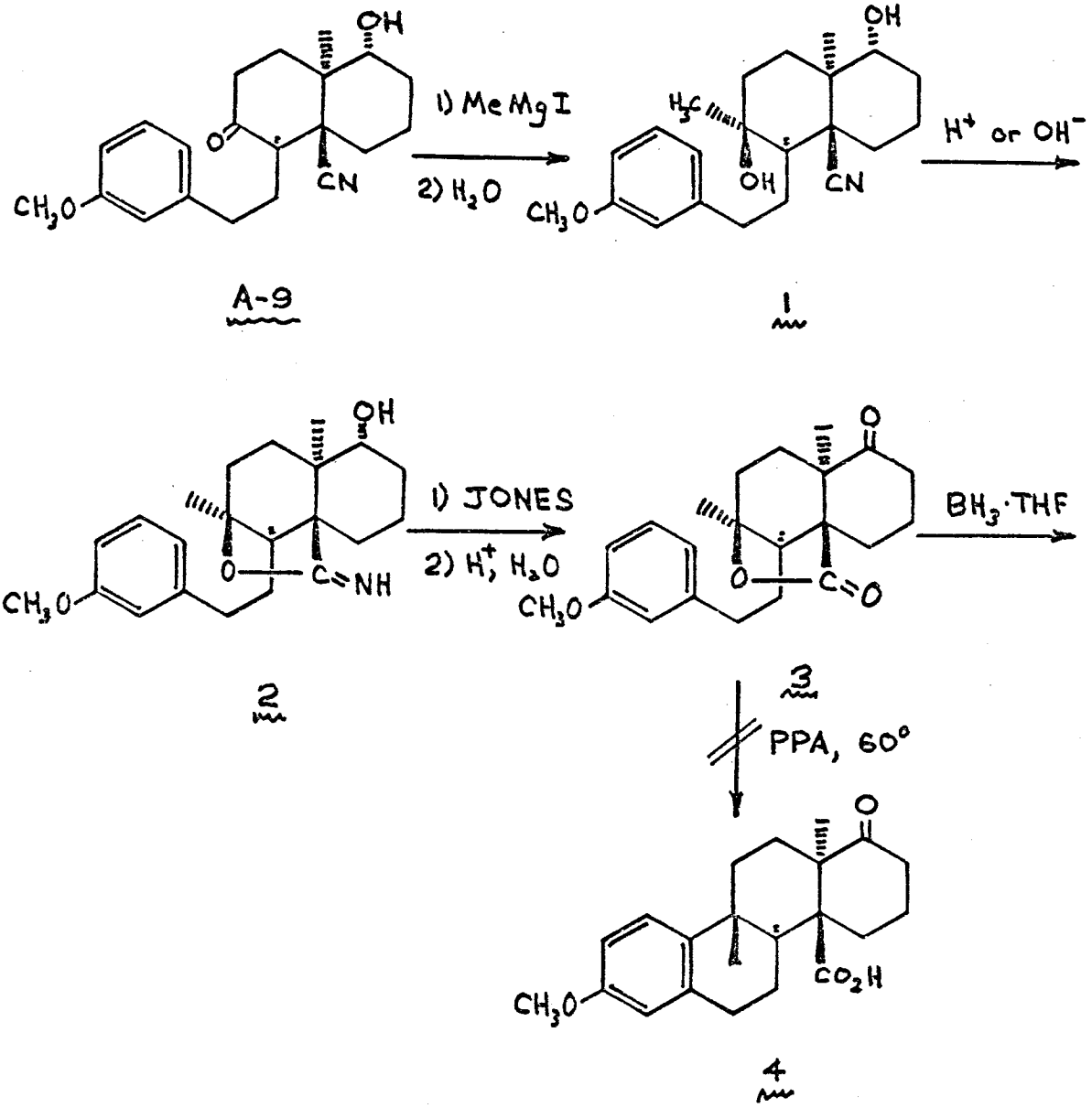
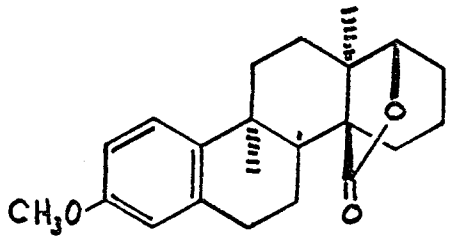

OH
O
CN
CH3O
1) MeMgI
2) H2O
H3C
OH
CN
CH3O
H+ or OH-
A-9
1
OH
O
C=NH
CH3O
1) JONES
2) H+, H2O
O
O
C=O
CH3O
BH3·THF
2
3
PPA, 60°
O
CO2H
CH3O
4
OH
O
C=O
CH3O
H+ or OH-
O
OH
C=O
CH3O
5
6
PPA, Δ

CHART B



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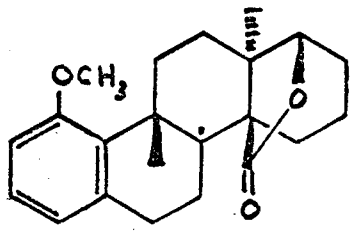

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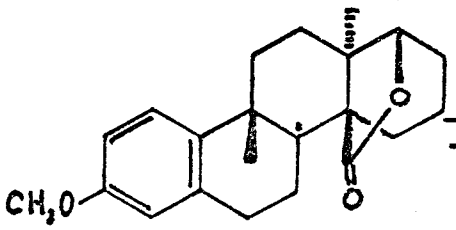
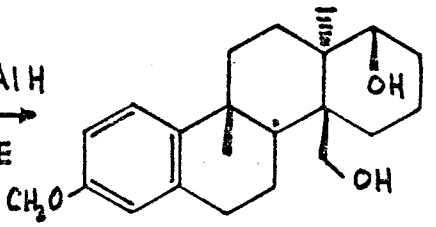


8

$(\text{iBu})_2\text{AlH}$

TOLUENE

0°



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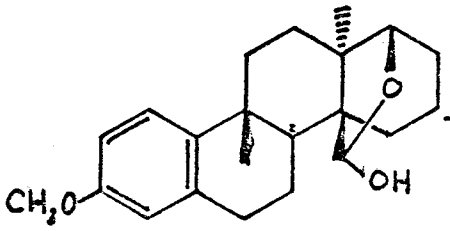
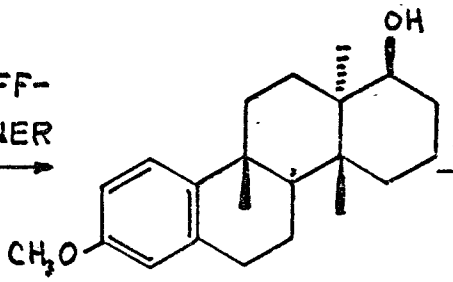
+



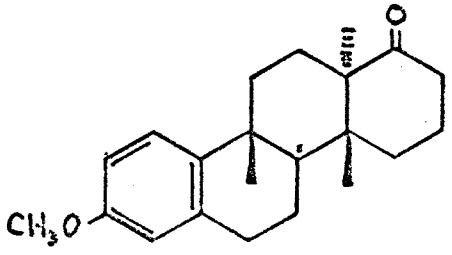
11

WOLFF-KISHNER



12

JONES



(A-15)

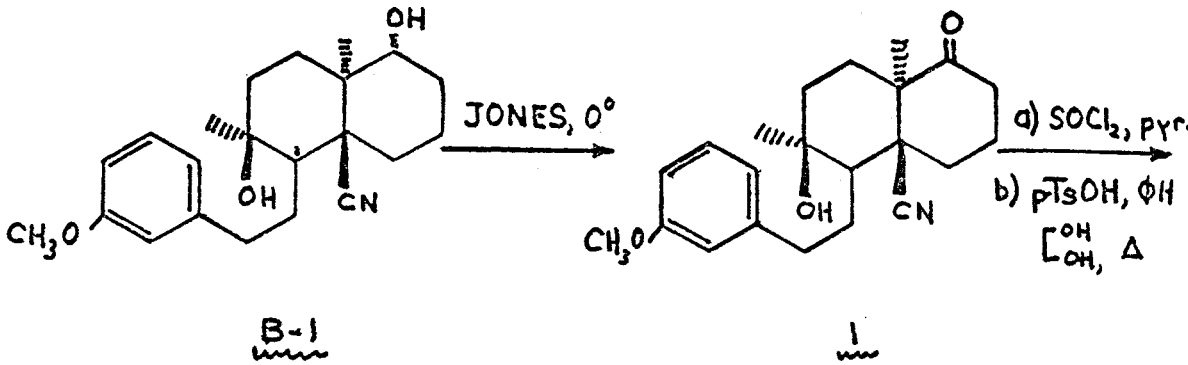
Although not enough of this material was available for analysis, it was later shown to be spectrally identical and have the same melting point as the product finally characterized as A-15.

The roundaboutness of the lactone route brought attention back to the problem of directly reducing the nitrile group. Outlined in Chart C, a reduction scheme was proposed via a derivative containing no free hydroxyl group. The mixture of olefinic ketones C-2a was formed by careful Jones oxidation of B-1, followed by dehydration of the tertiary alcohol. Ketalization of this mixture led to a new mixture C-2b, which proved inert to $LiAlH_4$ in refluxing THF. DIBAH in benzene gave much the same results as A-10, unsatisfactory reduction leading to a mixture which could not effectively undergo Wolff-Kishner reduction. An attempt to hydrolyze the supposed imine to an aldehyde (7), did not give any recognizable aldehyde product.

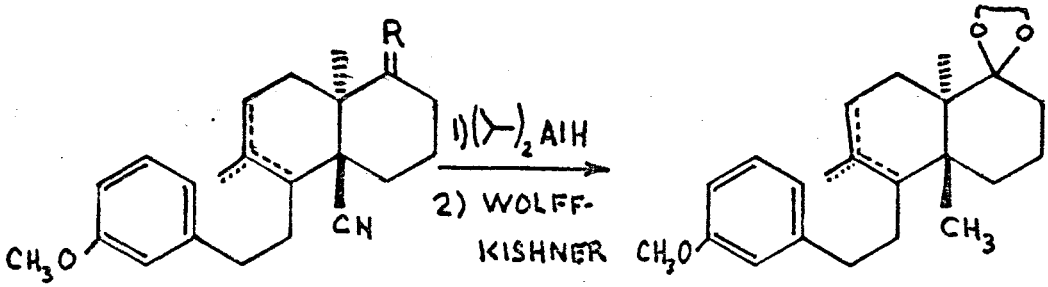
It would appear that the hydroxyl group in A-10 is thus not responsible for the difficulty in converting the nitrile to a methyl group. As angular nitriles bearing 1-3 diaxial relationships to ketals have been successfully reduced (7), it was thought that perhaps the bulky β-(m-methoxyphenyl)-ethyl side chain might be responsible for the problem. In this respect, it appeared worthwhile to investigate the reduction of C-6.

Addition of Et_2AlCN in benzene, or Et_3Al and HCN in THF, to the eneone alcohol C-4 (14), gave the same (by NMR) product in both cases. A pure cyano ketone crystalized from each of these products (50% yield from the first crop), which, except for some very minor impurities, was identical in the NMR with the crude product; no isomeric nitriles could be isolated from the mother liquors by chromatography (very much the

CHART C

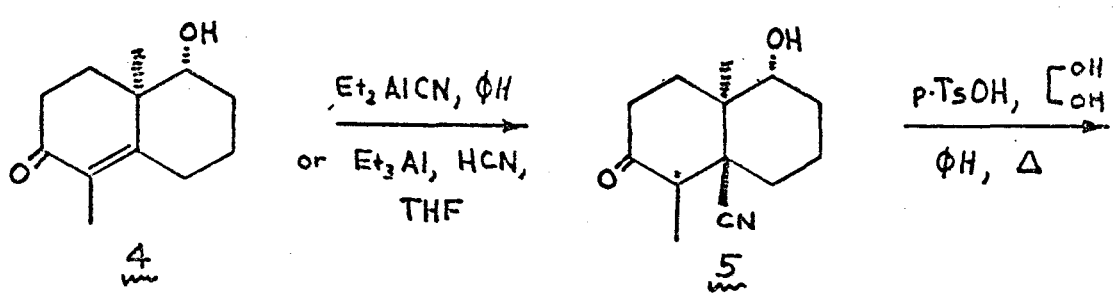


B-1 1

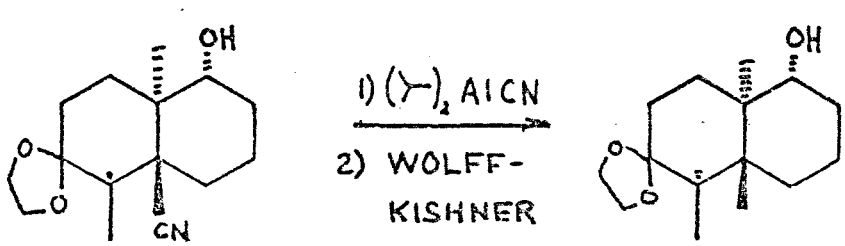


2 a) R = O
b) R = [O O]

3



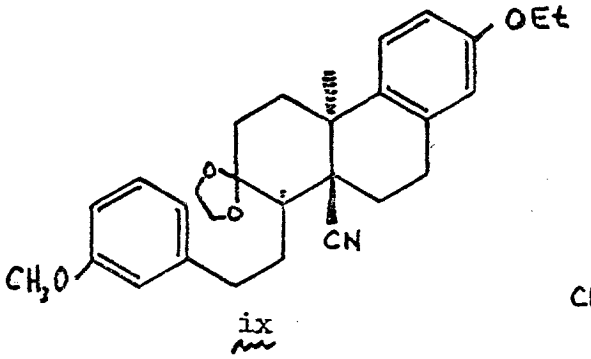
4 5



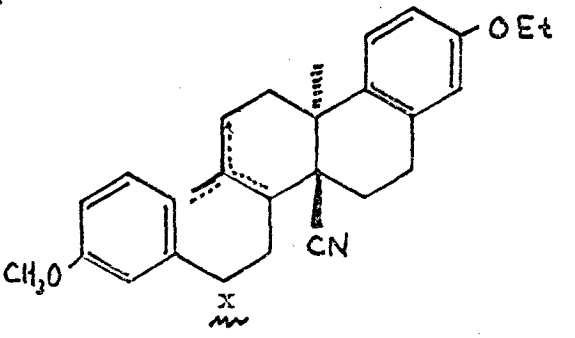
6 7

same situation as encountered with small scale hydrocyanation reactions of A-8). Due to the close analogy of the compounds A-8 and C-4, and their very similar reaction patterns on hydrocyanation by both methods, it seems likely that the reaction products A-9 and C-5 would be steriochemically similar; that is, it seems likely that C-5 would also have a trans ring fusion.

Attempts at reducing the cyanide in C-5 after ketalization to C-6, met with no success, yielding results similar to those obtained with A-10 and C-3. Even a single methyl group, then, α to both the ketal and ring juncture bearing the nitrile, is sufficient to block the reduction sequence. S.C. Welch has since realized this same difficulty in his unsuccessful attempts to convert the nitrile in compound ix. His subsequent success with the olefin mixture x however, showed that substituted cyano compounds of this type are susceptible to reduction if no serious 1,3 diaxial interactions exsist (15).



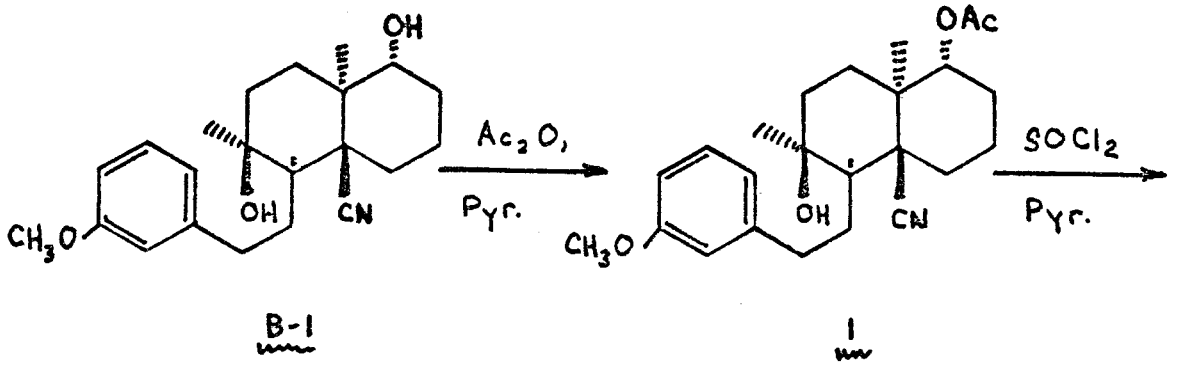
ix



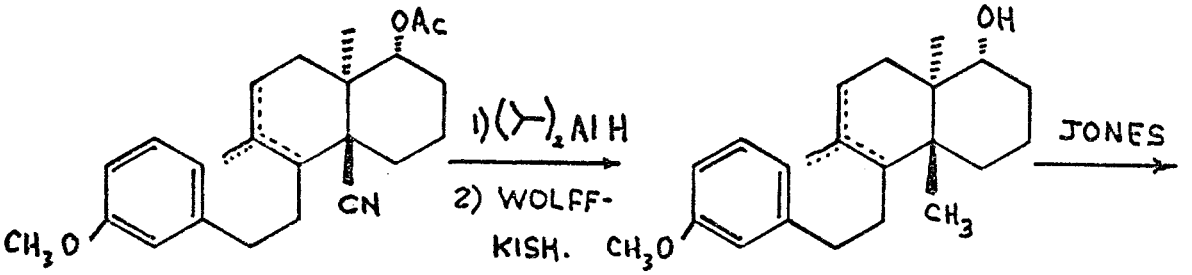
x

The next logical approach at reducing the nitrile of A-9, therefore, involves the route outlined in Chart D, through the intermediate D-2 which contains no serious 1,3 diaxial interactions with the nitrile. Selective acetylation of the cyano di-ol B-1 proceeded well to give crystalline mono-acetate D-1 in 75% yield. This was dehydrated to the olefinic isomer mixture D-2 in 91% yield (after chromatography), which

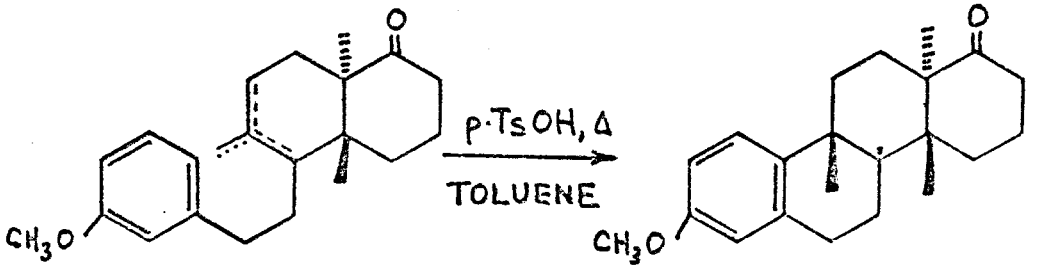
CHART D



B-1 1



2 3



4 A-15

was submitted to the same cyanide reduction procedures which had failed so frequently before. Happily, the di-methyl olefin mixture D-3 resulted, in 71% yield. The major obstacle to the synthesis of A-15 had been overcome.

Jones oxidation of the D-3 olefinic alcohols, yielded the corresponding ketones D-4 in 93%. Cyclization of these with strong acid in refluxing toluene, gave a mixture of two components in the ratio of 82:18 by GLC. A portion of the major component crystallized out to give 52% of a pure white solid; the mother liquors, still containing both comonents could not be separated by chromatography. NMR spectrum of the mother liquors reveals a very high field angular methyl signal (δ_{TMS}=.33) due to the minor component, indicative of a cis fused B-C ring in which the aromatic ring strongly shields the angular methyl derived from the nitrile (8). On the basis of the model compounds v(a),(b) and (c) mentioned earlier, one would also expect the cis closed compond to be the minor isomer. The major isomer, then , should be the desired end product of this research, the tetracyclic ketone A-15, and indeed it appears to be so. Spectrally identical with the material obtained via the lactone route (chart B), this compound analyzes correctly for, and is spectrally consistent with the structure A-15.

Two other routes aimed at the tetracyclic A-15 have since reached their ends; the final products obtained by C. Lipinski (16) and J.W.Tilley (17) in this lab, have proved to be identical with the product from Chart D. Except for the very last cyclization step, all three routes are very different; thus there is no doubt that the Cand D rings are correct. The spectral evidence and evidence from model compounds, coupled with the identical product from Chart B (with somewhat differnt last steps),

strongly indicates that the A,B and C rings are properly connected. The synthesis is done.

The total yield of A-15 from A-1 is 3%; the scheme represents a reasonable pathway to an important intermediate for the total synthesis of some polycyclic triterpenes, and better defines some of the important reactions along that route.

EXPERIMENTAL

ALL REACTIONS WERE RUN UNDER A NITROGEN ATMOSPHERE unless otherwise noted. "Dry" ether and THF were distilled from $LiAlH_4$ and subsequently protected from moisture; dry benzene was distilled from calcium hydride; dry pyridene and CH_2Cl_2 were distilled from P_2O_5.

All melting points labled "(vac)" were taken in evacuated capillaries on a Hoover Capillary Melting Point Apparatus; all others were taken on a Kofler Hot Stage. All melting and boiling points are uncorrected. Nuclear magnetic resonance spectra were run on a Varian T-60 Analytical N.M.R. Spectrometer. Infrared spectra were run on a Perkin-Elmer Model 237B Infrared Spectrometer. Analytical G.L.C. work was done on an F&M Model 810 Gas Chromatograph, using 4% SE-30 columns.

Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Michigan.

A-2 : 3-(m-methoxyphenyl)-n-propanol (18)

To a rapidly stirred suspension of 52g (1.38 moles) of $LiAlH_4$ in 640ml of dry ether, a solution of 100g (.56 moles) of m-methoxy cinamic acid in 400ml of dry THF was added over a period of 2 hrs so as to maintain gentle reflux. The mixture was then stirred at reflux for an additional 2 hrs, cooled in an ice bath, and the excess $LiAlH_4$ destroyed with 95% EtOH. The mixture was poured onto 1500g ice + 100ml conc. H_2SO_4, extracted with ether (6 x 500ml), and the combined organic phases washed with 5% NaOH soln. (2 x 150ml) and brine (150ml). The organic phases were dried over Na_2SO_4 and the solvent removed in vacuo to give 85g (91%) of a yellow oil, 97% pure by GLC. Short path distillation of the oil at 98-106°, 0.1mm, resulted in 56.8g (61%) of a nearly colorless liquid.

Infrared: ν_{max}^{film} 3330 cm^{-1}, broad (alcohol)
1601,1580,1490 cm^{-1} (aromatic)
1270cm^{-1} (Ar-OCH_3)

A-3 : 3-(m-methoxyphenyl)-n-propyl chloride (19)

To a stirred solution of 56.8g (0.342 moles) of the alcohol A-2 in 40ml of N,N-dimethyl aniline, chilled in an ice bath, 26.5ml (0.37 moles) of thionyl chloride (freshly distilled) was added dropwise over a period of 20 min.. Stirring was continued first for 30 min. more in the ice bath, then at 100° for 15 min., after which the mixture was cooled, treated with 200ml of 10% HCl + 100ml of brine. This mixture was extracted with ether (5 x 150ml), and the combined organic phases washed with 5% NaOH soln. (2 x 100ml), water (2 x 100ml), dried over $MgSO_4$ and stripped of solvent in vacuo to give a quantitative yield of brown liquid. Short path distillation of the product at 82-87°, .15mm, resulted in 58.6g (93%) of a yellow liquid.

Infrared;	ν film max	1601,1580,1495 cm^{-1}	(aromatic)
		1270	($Ar-OCH_3$)

A-4 : 6-(m-methoxyphenyl-)-hex-1-ene-3-ol

In a dried apparatus, 6.36g (0.262 moles) of Mg shavings were covered with 15ml dry ether, stirred, and about 6ml of a solution of 43.8g (0.237 moles) of the chloride A-3 in 35ml of dry ether was added. A drop of MeI initiated the reaction, and once reflux had begun 150ml of dry ether was added. The remainder of the chloride soln. was added over a period of 15min. so as to maintain reflux, after which reflux and stirring were continued for two hrs. more. To this solution, rapidly stirred and chilled in an ice bath, 17.4ml (0.262 moles) of freshly distilled acrolein in 30ml of dry ether, was added over 30 min., after which the temperature was raised to room temperature for 30 min. more. The mixture was then poured onto 500g ice+water, 200ml of sat'd NH_4Cl soln. added, and the organic phase separated. The aqueous layer was extracted with ether (4 x 300ml), and the combined organic phases washed with water (300ml), sat'd $NaHCO_3$ (2 x 300ml) and brine (300ml). After drying over $MgSO_4$, they were stripped of solvent in vacuo leaving a green liquid; the liquid was distilled from a trace of BaO*, giving 0.92g of forerun, bp 39-40°, .15mm, and 41.0g (84%) of greenish tinged product, bp 111-115°, .07mm.

Infrared:	film max	3360 cm^{-1}, broad	(-OH)
		1645	(vinyl)
		1601,1580,1495	(aromatic)
		1260	(Ar-OMe)

*note: the product must be protected from acid at all times.

A-5 : 6-(m-methoxyphenyl)-hex-1-en-3-one

To a vigorously stirred solution of 44.4g (170 mmoles) of $CrO_3 \cdot 2Pyr$ in 600ml of dry CH_2Cl_2 (freshly distilled from P_2O_5), 5.40g (26.2 mmoles) of the vinyl alcohol A-4 was added in 50ml dry CH_2Cl_2. After stirring for 15 min., the solution was filtered through 250g alumina, and the reaction flask and filter washed with an additional 300ml CH_2Cl_2. The solvent was stripped in vacuo, and the resultant oil pumped under high vacuum for 1 hr., leaving 4.98g (93%) of a clear oil (smelling faintly of pyridine). As the enone tends to polymerize, it was used directly.

Infrared: ν_{max}^{film} 1675 cm^{-1} (unsat'd carbonyl)
1601,1580,1485 (aromatic)
1260 cm^{-1} (Ar-OMe)

A-7 : 1-3'-methoxyphenethyl-10β-methyl-$\Delta^{1(9)}$ octal-2,5-dione (6)

Freshly prepared crude vinyl ketone A-5 (4.98g, 24.4 mmoles) was conbined with 125ml MeOH, 2.86g (22.7 mmoles) of 2-methyldihydroresorcinol and 1.4ml Et_3N, and stirred at room temperature for 23 hrs.. The reaction mixture was stripped of solvent in vacuo to give the yellow brown oil A-6. Infrared $_{max}^{film}$ 1695,1715,1725 cm^{-1} (carbonyls).

Ring closure was done following the method of H. Smith and co-workes (6). The above trione A-6 was combined with 51ml xylene, 3.3g of benzoic acid, and 2.75ml Et_3N, and refluxed through a Dean-Stark apparatus. Ten ml of xylene were collected in the side arm, and reflux continued for 24 hrs.. The solution was cooled, combined with 500ml ether, and washed with sat'd $NaHCO_3$ (5 x 100ml), 2% HCl (3 x 100ml), and brine (2 x 100ml). The solvent was removed in vacuo leaving 6.52g of a brownish oil. Fractional distillation of this oil gave one major fraction, bp 175-205°

at .01mm, which contained a small amount of sublimed 2-methyldihydr-resorcinol. The product was washed from the impurity with acetone to give 4.11g (54%) of the ene-dione A-7.

Infrared ν_{max}^{film} 1710, 1665 cm^{-1} (sat'd and unsat'd ketone)
1601, 1580, 1485 (aromatic)

A-8 : 5β-hydroxy-1-3'-methoxyphenethyl-10β-methyl-$\Delta^{1(9)}$octal-2-one (6)

The selective reduction of the ene-diketone was done using the method of H. Smith and co-workers (6). To a rapidly stirred solution of 11.0g (35.2 mmoles) of A-7 in 290ml absolute ethanol, chilled between 0-5°, a solution of 2.0g (53 mmoles) of $NaBH_4$ in 390ml of absolute ethanol was added dropwise over a 20 min. period, so that the internal temperature never rose above 5°. After the addition, stirring was continuedat the low temperature for 10 minutes, then 14ml of acetic acid was carefully added, followed by 50ml of water. Most of the ethanol was then removed in vacuo, 150 ml water added, and the mixture extracted with ether (5 x 150 ml). The combined organic phases were washed with 2% NaOH soln. (3 x 150ml), water (2 x 150ml), dried over $MgSO_4$, and stripped of solvent in vacuo to give a yellow oil. This oil was crystallized from ether/hexane to give 8.74g (79%) of white crystals in 2 crops.

Infrared: $\nu_{max}^{CHCl_3}$ 3615 cm^{-1}, sharp (-OH)
1665 (unsat'd ketone)

A-9 :

a) Hydrocyanation using Et_2AlCN in benzene (5b).

To a stirred solution, ice bath cooled, of 21.9g (69.8 mmoles) of A-8 in 230ml dry benzene, 140ml (210 mmoles) of 1.5M Et_2AlCN in benzene was added in a slow stream over several minutes. Stirring was then

continued at room temperature for 2.5hrs., after which the mixture was poured into a solution of 100g NaOH in 2000 ml of ice + water with vigorous stirring. The solution was extracted with CH_2Cl_2 (4 x 800ml), and the combined organic phases washed with 10% NaOH soln (500ml), water (2 x 500 ml), dried over Na_2SO_4 and stripped of solvent in vacuo to give a quantitative yield of a heavy gum. The gum was crystalized from ether/hexane to give 19.04g (80%) of white, crystalline trans-cyano ketone A-9 in two crops (mp 115-121°). Two more recrystallizations raised the melting point to a constant 122-125°.

Analysis calc. for $C_{21}H_{27}NO_3$: C, 73.87; H, 7.97; N, 4.10
found C, 73.96; H, 7.96; N, 4.06

Infrared: $\nu_{max}^{CHCl_3}$ 3615,3480 cm^{-1} (-OH)
2225 (-CN)
1720 (sat'd ketone)

NMR: $\delta_{TMS}^{CDCl_3}$

1.12ppm	(s)	C 10 methyl,	3
3.70ppm	(m)	C 5 proton,	4
3.80ppM	(s)	$-OCH_3$	
6.7-7.4 ppm	(m)	aromatic	4

NMR of the mother liquors showed two compounds other than A-9 to be present, with C 10 methyl signals at δ 1.03 and 1.18 ppm. Column chromatography over 1 kg of silica gel, eluted with pure ether, gave almost no separation of the three compounds, except for several of the very last fractions which contained 947 mg (4%) of pure viii (much of this compound was eluted impure in earlier fractions). The compound formed crystals in EtOH, but turned into a white glass on standing.

Analysis calc. for $C_{21}H_{27}NO_3$ C 73.87; H 7.97; N 4.10
found C 73.73; H 7.97; N 4.07

Infrared: $\nu_{max}^{CHCl_3}$ 3620,3500 cm^{-1} (-OH)
2250 (-CN)
1720 (sat'd ketone)

NMR: $\delta_{TMS}^{CDCl_3}$ 1.18 ppm (s) C 10 methyl
3.80 ppm (s) -OMe
4.0 ppm (m) C 5 proton
6.7-7.4 ppm (m) aromatic

b) Hydrocyanation using Et_3Al and HCN in THF (5c).

To 2.0ml (.34 mmoles) of a stirred solution of 0.696M Et_3Al in THF, chilled with an ice bath, 0.18 ml (1.05 mmoles) of a 5.81M solution of HCN in dry benzene was added dropwise. To this mixture, 108 mg (0.34 mmoles) of the ene-one A-8 was added dropwise in dry THF (3 x 1ml), and stirring continued for 2 hrs. with ice bath cooling, and for 18 hrs. at room temperature. The mixture was poured into 80 ml of 5% NaOH soln. + 40g ice, extracted with $CHCl_3$ (4 x 50ml), and the combined $CHCl_3$ extracts washed with water (2 x 50ml) brine (2 x 50ml), dried over Na_2SO_4 and stripped of solvent in vacuo. A quantitative yield of a yellowish oil was obtained, having an NMR spectrum essentially identical with the crude product spectrum from part (a) above. Pure A-9 (60mg, 51%) crystallized from the oil, but no other products could be isolated from the mother liquors.

A-10 :

In a flask were combined 423mg (1.24 mmoles) of cyano ketone A-9, 1 ml of ethylene glycol, 6mg of p-toluene sulfonic acid, and 20 ml benzene. The mixture was stirred and refluxed with separation of water (Dean-Stark apparatus) for 160 minutes, after which it was cooled, washed

washed with sat'd $NaHCO_3$ (3 x 50 ml), water (5 x 50 ml), dried over $MgSO_4$ and stripped of solvent in vacuo to give a quantitative yield of white gum. Preparative TLC of the product on a 20 x 40 cm silica plate, eluted twice with 80% ether/petroleum ether, gave one major band, rf = .26. This band contained 436 mg (91%) of the ketal A-10 as a glass, .96% pure by GLC.

Infrared: $\nu_{max}^{CHCl_3}$ 3620, 3480 cm^{-1} (-OH)
2230 (nitrile)
1150, 1100, 1050 (ketal)

NMR: $\delta_{TMS}^{CDCl_3}$ .97 ppm (s) C 10 methyl, 3
3.75 ppm (m) C 5 proton
3.80 ppm (s) $-OCH_3$
4.05 ppm (m) ketal protons
6.7-7.4 ppm (m) aromatic

Attempted conversion of the A-10 nitrile to a methyl.

To a stirred solution of 180 mg (.468 mmoles) of the cyano ketal A-10 in 10ml dry benzene, 3.46 ml (1.17 mmoles) of the .338 M diisobutyl aluminum hydride (DIBAH) in benzene soln. was added dropwise. Attempts to follow the reaction by GLC and TLC were wholly unsuccessful. After 8 hrs. of stirring, the mixture was poured into 20ml of 5% NaOH soln, with 15g of ice, separated, and the aqueous phase extracted with ether (4 x 25ml). The combined organic phases were washed with water (3 x 30ml), brine (30ml), dried over $MgSO_4$ and stripped of solvent in vacuo to give 156 mg (86%) of a yellow oil, hoped to be the imine A-11.

Infrared shows considerably weaker nitrile (2230), with a slight new band at 1625 (imine).

The crude product from above was combined with 13.5ml of triethylene

glycol, 1.35 ml of 85% hydrazine hydrate, and 338 mg of hydrazine dihydrochoride, and stirred for 3 hrs. in a 140-145°bath. Pellets of 85% KOH (2.12g) were added portionwise as a stream of N_2 was passed through the vessel, and the bath temperature raised to 175-180°. The temperature was so maintained, as was the N_2 stream, for 4.5 hrs., after which the mixture was cooled, poured into 50ml of water, and extracted with ether (6 x 30 ml). The combined organic phases were washed with water (10 x 20ml) dried over $MgSO_4$, and stripped of solvent in vacuo to give 110 mg of a yellow oil. Preparative TLC of the product on a 20 x 20 cm silica gel plate, eluted once with 30% acetone/petroleum ether, gave two major components, rf= .21 and .39. The fraction having rf=.21, ammounted to 30mg and appeared to be mostly starting material by GLC. The fraction having rf=.39 ammounted to 24mg (11%) of an oil, 80% pure by GLC.

NMR: $\delta^{CDCl_3}_{TMS}$

.95 ppm (s)	trans angular methyls
1.00 ppm (s)	
3.80 ppm (s)	-OMe
3.9 ppm (m)	ketal protons

It would appear that this was the desired product A-12; however, not enough was available to characterize, and upon varying the reaction conditions, no better, or even comparable yield could be obtained to generate more.

B-1:

To a stirred solution of 4.30g (14.05 mmoles) of the cyano ketone A-9 in 30 ml dry benzene + 70 ml dry ether, 50 ml (70 mmoles) of 1.4 M MeMgI in ether (prepared by the traditional method) was added dropwise with ice bath cooling. The white suspension formed was stirred at R.T. for 1 hr., poured into 100 g ice + 150ml sat'd NH_4Cl, and extracted with

chloroform (6 x 100ml); the combined organic extracts were washed with water, brine, dried over $MgSO_4$ and stripped of solvent in vacuo to leave a quantitative yield of white solid. This solid was treated once again with MeMgI, exactly as before, to give 4.75g (95%) of a white solid. Upon recrystalization from ether/acetone, 4.02g (80%) of the desired diol B-1 was obtained, mp 170-173°. After two more recrystalizations, constant melting material mp 175-178°was obtained.

Analysis calc. for $C_{22}H_{31}NO_3$: C 73.92: H 8.74: N 3.92
found 73.82 8.69 3.81

Infrared: $CHCl_3$ 3610 CM^{-1} (-OH)
2220 (-CN)
1601, 1580, 1485 (aromatic)

NMR: $\delta^{CDCl_3}_{TMS}$

.93 ppm	s,	$-CH_3$,	3
1.13 ppm	s,	$-CH_3$,	3
3.80 ppm	s,	-OMe,	3.8
3.8 ppm	m,	C 5 proton	
6.7-7.4 ppm	m,	aromatic	4

B-2:

A solution of 375mg of the cyano diol B-1 in 20ml EtOH, 4 ml conc. HCl, and 2 ml water, was stirred with mild warming (50°) for five hours. It was poured into 25ml sat'd $NaHCO_3$, extracted with ether (5 x 30ml), and the combined extracts washed with water and brine, and dried over $MgSO_4$. The solvent was removed in vacuo leaving 335mg (89%) of a dirty solid. Upon recrystalization from MeOH/ether, 264mg (70%) of fine white crystals were obtained, mp 150-152°. After a second recrystalization, the melting point was constant at 153-153.5°.

Analysis for $C_{22}H_{31}NO_3$: C 73.92: H 8.74: N 3.92
found: 73.79 8.78 3.81

Infrared: $CHCl_3$ 3610 cm^{-1} (-OH)
1675 (imino lactone)

NMR: δ $CDCl_3$ / TMS
.97 ppm s, $-CH_3$
1.37 ppm s, $-CH_3$
3.80 ppm s, $-OCH_3$
3.85 ppm m, C 5 proton

B-3 :

To a stirred solutionof 195mg (.52mmoles) of imino lactone B-2, in 20ml acetone, chilled in an ice bath, 1 ml of 8 N Jones reagent was added and stirring continued for 15 min.. Isopropanol (3ml) was added, then 5ml water and 5ml conc. HCl. The mixture was stirred for three hours with mild heating (50°), poured into 20ml water, extracted with $CHCl_3$ (5 x 30ml), and the combined organic extracts washed with brine. After drying over $MgSO_4$, the solvent was stripped in vacuo to give a yellow oil, which crystallized from ether/chloroform to give 181mg (93%) of the desired lactone B-3. Upon three recrystalizations from ether, the melting point became constant at 162-164°.

Analysis calc. for $C_{22}H_{28}O_4$: C 74.13: H 7.92
Found: 73.91 7.88

Infrared: $CHCl_3$ 1770 cm^{-1} (γ-lactone)
1715 (ketone)

NMR: δ $CDCl_3$ / TMS
1.22 ppm s, -Me, 3
1.42 ppm s, -Me 3
3.80 ppm s, -OMe 3
6.7-7.4 ppm m, aromatic, 4

B-5 :

To a stirred solution of 106 mg (.30mmoles) of the γ-lactone B-3 in 2 ml dry THF, .9 ml (.9 mmoles) of BH_3·THF soln was added at R.T. and stirring continued for 2 hrs.. This mixture was then poured into 20 ml ice/ 2% NaOH soln, extracted with $CHCl_3$ (5 x 25ml), and the combined organic phases washed with water and brine. After drying over $MgSO_4$, the solvent was stripped in vacuo to give a quantitatine yield of a cloudy oil. Upon crystallization from ether/hexane, 85mg (79%) of isomeric lactone B-5, mp86.5-88.5°. One final crystalization raised the melting point to 87-89°.

Analysis for $C_{22}H_{30}O_4$:	calc.	C 73.71:	H 8.44
	found	73.63	8.41

Infrared:	$CHCl_3$	3550 cm^{-1}	(-OH)
		1740	(γ-lactone)
		1601, 1580, 1485	(aromatic)

NMR:	δ $CDCl_3$ TMS	.98 ppm	s, -Me
		1.45 ppm	s, -Me
		3.33 ppm	m, C 5 proton
		3.80 ppm	s, -OMe

B-7, B-8, B-9 :

To 1.215g (3.39 mmoles) of the -lactones B-5 and B-6 and 7 drops of benzene, about 75 ml of polyphosphoric acid (preheated to 78°) was added rapidly, and rapid stirring begun. The temperature was maintained at 78° for 45 min, after which the mixture was poured into 300 g ice + 100 ml water, extracted with ether (6 x 100 ml), and the combined etherial phases washed with $NaHCO_3$ soln and brine. After drying over $MgSO_4$ the

solvent was removed in vacuo to give 1.093 g (95%) of a white foam. This product was chromatographed over 200 g silica gel, eluted with 40% ether/petroleum ether to give three fractions B-9, B-8, and B-7 in order of elution. 105mg (9.1%) of B-9 was obtained reasonably pure from the column. Upon two recrystallizations from EtOH, it gave a constant melting point, 142-144°.

Analysis for $C_{22}H_{28}O_3$: calculated C 77.61: H 8.29
found 77.41: 8.38

Infrared: $CHCl_3$ 1770 cm^{-1} (γ-lactone)
1599,1575,1470 (cyclized aromatic)

NMR: $\delta^{CDCl_3}_{TMS}$

1.05 ppm	s,	-Me ,	3
1.32 ppm	s,	-Me,	3
3.75 ppm	s,	-OMe	3
4.2	m,	C 5 proton,	1
6.6-7.4	m,	aromatic	3

760 mg (65.8%) of B-8 was obtained from the column; upon two recrystalizations in EtOH, a constant melting point 142-143° was reached.

Analysis for $C_{22}H_{28}O_3$: calculated C 77.61: H 8.29
found 77.58 8.27

Infrared: $CHCl_3$ 1770 cm^{-1} (γ-lactone)
1605, 1500 (aromatic)

NMR: $\delta^{CDCl_3}_{TMS}$

1.08 ppm	s,	-Me	3
1.17	s,	-Me	3
3.75	s,	-OMe	3
4.21	m,	C 5 proton	1
6.6-7.4	m	aromatic	3

167 mg (14.5%) of B-7 was obtained from this column.

Infrared: $CHCl_3$ 1775 cm^{-1} (γ-lactone)
1605,1575,1500 (aromatic)

NMR: $\delta^{CDCl_3}_{TMS}$

1.13 ppm	s,	-Me	6
1.17 ppm	s,	-Me	
3.75 ppm	s,	-OMe	3
4.0 ppm	m,	C 5 proton	1
6.5-7.3 ppm	m,	aromatic	3

B-10, B-11 :

To a stirred solution of 237 mg (.70mmoles) of the tetracyclic lactone B-8 in 25 ml toluene, chilled in an ice bath, 1.7 ml (.835 mmoles) of .492 M DIBAH in benzene was added, After 1 hour, the bath was removed and stirring was continued at R.T. for 3 hours; the mixture was then poured onto 70ml of 10% HCl + 40 g ice, extracted with ether (4 x 75 ml), and the combined organic phases washed with water and brine, dried over Na_2SO_4 and stripped of solvent in vacuo to give a white foam in quantitative yield. Preparative TLC on a silica gel plate gave 3 bands, rf's = .54,.44.and.19.

The first band, rf=.54, contained mostly starting lactone.

The second bane, rf=.44 contained 55mg (23%) of the lactol B-11. Two recrystalizations from EtOH/acetone gave white needles, mp 176-177°(vac).

Analysis for $C_{22}H_{33}O_3$: calculated C 77.16: H 8.83
found 77.06 8.96

Infrared; $CHCl_3$ 3600, 3350 cm^{-1} (-OH)
1605, 1575, 1500 (aromatic)

NMR:	$\delta^{CDCl_3}_{TMS}$				
		.98 ppm	s,	-Me	3
		1.25	s,	-Me	3
		3.70	m,	C 5 proton	4
		3.76	s,	-OMe	
		6.05	m,	hemiacetal	1
		6.6-7.4	m,	aromaic	

The final band, rf=.19, gave 60mg (25%) od the diol B-10, recrystalized from acetone to constant melting point, 185-187°(vac).

Analysis for $C_{22}H_{32}O_3$: calculated C 76.70: H 9.36
found 76.58 9.43

Infrared: $CHCl_3$ 3620, 3400 cm^{-1} (-OH)
1605,1575, 1500 (aromatic)

NMR:	$\delta^{CDCl_3}_{TMS}$				
		1.00 ppm	s,	-Me	3.1
		1.27	s,	-Me	3.0
		3.76	s,	-OMe	5.0
		3.55- 3.94	m,	$R-CH_2-O$	
		4.36- 4.60	m,	C 5 proton	1.0
		6.5 - 7.2	m,	aromatic	3.0

B-12, (A-15) :

In a flask, 55mg (.16mmoles) of the tetracylic lactol B-11 was combined with 2.7 ml of trietylene glycol,.27 ml of hydrazine hydrate (99%), and 81 mg of hydrazine dihydrochloride, and stirred at 140° (bath temp.) for 4 hours. The mixture ws cooled to 95°, a stream of nitrogen blown through the vessel, .52 g of 85% KOH added portionwise over ten minutes, and the temp. raised to 150°. The nitrogen stream was stopped after one hour, but the 150 temp. was maintained for a total of five hours. The mixture was then cooled, dissolved in 50 ml water + 50 ml brine, extracted with ether (5 x 25 ml), and the combined extracts washed with water

(5 x 25 ml), brine (2 x 25 ml), dried over Na_2SO_4 and stripped of solvent in vacuo to give a yellow foam. Preparative TLC of the foam, on a 20 x 20 cm silica gel plate, eluted twice with 40% ether/ petroleum ether, gave two bands. The major band, rf=.25 contained 39mg (71%) of slightly impure starting lactol B-11. The minor band, rf=.43, contained 11 mg of a compound that appeared to be B-12 (by NMR).

Crude NMR: $\delta^{CDCl_3}_{TMS}$				
	.95ppm	s,	angular methyl	3
	1.23	s,	2 angular methyls	6
	3.76	s,	-OMe	3
	6.5-7.4	m,	aromatic	3

As insufficient material was available for an analysis, the above product was oxidized to the ketone A-15, to see whether it would remain spectrally consistent with the assigned structure. Thus 9mg of the alcohol B-12 was combined with .5ml of 8 N Jones reagent in 3ml of acetone with ice cooling. After ten min., one ml isopropanol was added, then 10 ml water; the acetone was removed in vacuo, the product extracted with ether (4 x 20ml), and the extracts washed with water and brine. After drying over Na_2SO_4, the solvent was stripped in vacuo to give 7 mg of a yellowish oil which crystallized on standing. Upon recrystalization from Ether, the product melted at 149-152°(vac).

Infrared: $CHCl_3$ 1700 CM^{-1} (carbonyl)
1605,1575,1500 (aromatic)

NMR: $\delta^{CDCl_3}_{TMS}$				
	.90 ppm	s,		3
	1.18	s,	angular methyls	6
	1.22	s,		
	3.76	s,	-OMe	3
6.5-	7.4	m,	aromatic	3

C-1

To a stirred solution of 702 mg (1.96 mmoles) of the cyano diol B-1 in 10 ml acetone, chilled in an ice bath, 2 ml of 8 N Jones reagent was added dropwise. After stirring for 5 min., 5 ml of isopropanol, followed by 30 ml sat'd $NaHCO_3$ soln. was added. The mixture was extracted with ether (5 x 40ml), and the combined organinic phases washed with water and brine, dried over $MgSO_4$ and stripped of solvent in vacuo to give 672 mg (96%) of a white solid. The product was crystalized twice from EtOH to give crystals mp124-126°.

Analysis for $C_{22}H_{29}O_3N$:	calculated	C 74.33:	H 8.22:	N 3.94	
	found	74.26	8.15	3.87	

Infrared:	$CHCl_3$	3600 cm^{-1}	(-OH)
		2230	(-CN)
		1720	(Ketone)
		1601, 1580, 1485	(aromatic)

NMR:	δ $CDCl_3$ TMS	1.17 ppm	s,	$-CH_3$
		1.20	s,	$-CH_3$
		3.80	s,	-OMe
		6.7-7.4	m,	aromatic

C-2a :

To a stirred solution of 524 mg (1.47 mmoles) of the keto alcohol C-1 in ten ml dry pyridine, chilled in an ice-salt bath at -10°, .52 ml (7.2 mmoles) of thionyl chloride was added dropwise and the stirring continued at the low temperature for one hour, and then for 15 min. while warming to room temperature. The mixture was diluted with Ether (250ml), washed with 10% HCl, sat'D $NaHCO_3$, and brine, stripped of solvent in vacuo to give 491 mg (98%) of a yellowish solid.

Infrared: $CHCl_3$ 2220 cm^{-1} (nitrile)
1715 (ketone)

NMR: $\delta^{CDCl_3}_{TMS}$
1.15 ppm s, angular methyl
1.65 ppm s, olefinic methyl
3.80 s, Ar-OMe
4.98, 5.10 } olefinic protons (very weak)

C-2b :

In 25ml of benzene, 397 mg of the olefin mixture C-2a was combined with 4 ml of ethylene glycol and 6 mg p-toluenesulfonic acid, and refluxed with stirring through a Dean-Stark apparatuus. After 80 min. 20mg more p-TsOH was added to hurry the reaction, which appeared completed by GLC after five hours. The mixture was cooled, diluted with ether (200 ml), washed with sat'd $NaHCO_3$, water, and brine, dried over $MgSO_4$ and stripped of solvent in vacuo to give (quantitatively) a yellow oil. The oil was crystalized from ether/petroleum ether to give 417 mg (93%) of a white solid (95% pure by GLC).

Infrared: $CHCl_3$ 2220 cm^{-1} (nitrile)
1150, 1090, 1075, 1060 (ketal)

NMR: $\delta^{CDCl_3}_{TMS}$
1.02 ppm s, angular methyl
1.62 s, olefinic methyl
3.80 s, ArO-Me
4.00 m, ketal protons
4.99, 5.10 m, olefinic protons (very weak)

Attempted reduction of C-2b nitrile to a methyl group.

The reaction conditions employed for the attempted conversion of

85 mg of C-2b were essentially identical to those described for the parallel reduction of A-10; 1.2 equivalents of DIBAH were employyed, and the reduction carried out for 22hours. The Wolff-Kishner reaction was done in exactly the same way (slight scale difference) to give 59% of a yellow oil. IR showed a great deal of nitrile still remaining, while the NMR was that mainly of starting material. Varying conditions did not improve the result, and none of the desired C-3 was ever isolated.

C-5 :

a) Hydrocyanation using Et_2AlCN in benzene.

The ene-one alcohol C-4 (500 mg, 2.58 mmoles) was treated with 4.7 ml (6.45 mmoles) of 1.37 M Et_2AlCN in benzene exactly as described in the procedure used to make cyano ketone A-9. Upon workup, a quantitative yield of a white solid was obtained, which gave a first crop of 308 mg of white crystals. A portion of these was purified by sublimation at 130°, .25mm, to give crystals mp 173-174° (vac).

Analysis for $C_{13}H_{19}NO_2$:	Calculated:	C 70.56;	H 8.65;	N 6.33
	Found	70.53	8.61	6.27

Infrared:	$CHCl_3$	3610, 3470 cm^{-1}	(-OH)
		2225	(nitrile)
		1715	(ketone)

NMR:	δ $CDCl_3$ TMS	1.17 ppm	d, J=8cps	C-1 methyl
		1.23	s,	C-10 methyl
		3.8	m,	C-5 proton

The crude product had essentially identcal spectra as the purified sample; no other conpounds could be isolated from the mother liquors by preparative TLC.

b) Hydrocyanation using Et_3Al and HCN in THF.

The ene-one alcohol C-4 (500mg, .58 mmoles) in 15 ml of dry THF, was treated with 19.6 ml (10.3 mmoles) of .525 M Et_3Al in THF, and 1.33ml (7.73 mmoles) of 5.81 M HCN in benzene, exactly as described for the making of A-9 (part b). The 560 mg (99%) of crude product obtained, was identical (IR and NMR) with that obtained in part a above.

C-6 :

In 35 ml of benzene, 511 mg (2.31 mmoles) of the cyano ketone C-5 was combined with 2 ml of ethylene glycol and 18 mg p-TsOH, and refluxed through a Dean-Stark apparatus for 1 hr. The reaction was then cooled, diluted with 400ml of ether, washed with sat'd $NaHCO_3$, water, and brine, and stripped of solvent in vacuo to give 424 mg (69%) of a white solid. This solid was sublimed at 130°, .05mm, and recrystallized twice from EtOH to give pure product, mp 165-166° (vac).

Analysis for $C_{15}H_{23}NO_3$: calculated C 67.90: H 8.74: N 5.28
found 67.77 8.68 5.31

Infrared: $CHCl_3$ 3610, 3460 cm^{-1} (-OH)
2240 (nitrile)
1105, 1070, 1030 (ketal)

NMR: δ $CDCl_3$ / TMS

1.02 ppm	s,		C-10 methyl	6
1.03 ppm	d,	J=7cps	C-1 methyl	
3.8 ppm	m		C-5 proton	5
4.0 ppm	m		ketal protons	

Attempted reduction of the nitrile in C-6

To a stirred solution of 51mg (.192 mmoles) of the cyano ketal C-6,

in 5ml of dry benzene, .86 ml (2.3 equivalents) of freshly prepared .518 M DIBAH in benzene was added. Stirring was continued at R.T. for 19 hrs, after which the mixture was poured into 10% NaOH + ice, extracted with $CHCl_3$ and washed with water and brine to give 28mg (55%) of a semi-crystalline oil. IR of the oil showed large amounts of nitrile still present ; other attemts did no better, for apparently the nitrile is not susceptible to mild reduction by DIBAH.

D-1 :

To a stirred solution of 200 mg (.56 mmoles) of the cyano diol B-1 in 4 ml of pyridine, .8ml of acetic anhydride was added at R.T. and stirring continued for 22 hours. The solution was diluted with 250 ml ether + 100 ml ethyl acetate, washed with water, sat'd $NaHCO_3$, water, and brine, dried over Na_2SO_4 and stripped of solvent in vacuo to give a quantitative return of a sticky solid. The solid was crystallized from ethyl acetate/chloroform to give 167mg (75%) of fine white crystals. Two more recrystalizations gave pure material, mp 163-165°.

Analysis for $C_{24}H_{33}NO_4$:	calculated	C 72.15:	H 8.33:	N .3.51
	found	72.22	8.22	3.48

Infrared: $CHCl_3$	3600 cm^{-1}	(-OH)	
	2220	(-CN)	
	1730	(acetate carbonyl)	

NMR: $\delta^{CDCl_3}_{TMS}$	1.02 ppm	s,	-Me	3
	1.12	s,	-Me	3
	2.03 ~~1.87~~	s,	acetate	3
	3.80	s,	ArO-Me	3
	5.1	m,	C 5 hyd.	1
	6.7-7.4	m,	aromatic	4

D-2 :

To a stirred solution of 167 mg (.418 mmoles) of the cyano alcohol D-1 in 3.5 ml of dry pyridine, chilled in an ice-salt bath to -10°, .15ml (2.1 mmoles) of thionyl chloride was added slowly; stirring was continued for 1.25 hrs with the temp. between -10 and 0°, then for .5 hrs as the mixture warmed to R.T. The mixture was diluted woth 100ml ether + 100ml ethyl acetate, washed with water and brine, dried over Na_2SO_4 and stripped of solvent in vacuo to give 157 mg (99%) of an oil. Preparative TLC of the product on a 20 x 20 cm silica gel plate, eluted once with 50% ether/ petroleum ether, gave one major band, rf=.34, containing 145mg (91%) of a semicrystaline white gun. A portion of this gum was crystallized from EtOH, resulting in crystals mp 89-108°.

Analysis for $C_{24}H_{31}NO_3$: calculated C 75.56: H 8.19: N 3.67
found 75.64 8.21 3.66

Infrared: $CHCl_3$ 2220 cm^{-1} (nitrile)
1730 (acetate carbonyl)
1650 olefin

NMR: δ $CDCl_3$ TMS

.95 ppm	s,	C 10 methyl
1.08	s,	"
1.62	s,	C 2 methyl
2.04	s,	acetate
3.80	s,	ArO-Me
5.0	m,	C 5 proton

D-3 :

To a stirred solution of 57 mg(.15 mmoles) of the cyano acetate olefin mixture D-2 in 2.3 ml dry benzene, .79ml (.575 mmoles) of .73 M DIBAH in benzene was added at R.T., and stirring continued for 3.5 hrs. After this time, the reaction mixture was poured into 20ml 7.5%NaOH, ex-

tracted with ether (4 x 20 ml), and the combined organic phases washed with water, brine, dried over Na_2SO_4 and stripped of solvent to give white foam quantitavely. IR of the product showed no nitrile (2220), but a broadened band in the region of 1620 (imine).

The crude product from above was mixed with 2.3 ml of triethylene glycol, .25ml hydrazine hydrate (99%), and 75mg of hydrazine dihydrochloride, and stirred for four hours in a 140° oil bath. The temperature was then cooled below 100°, and 85% KOH (.48g) added portionwise as a steam of nitrogen was passed over the mixture. The temp. was then raised to 150° for five hours, while the N_2 stream continued, after which the mixture was cooled, dissolved in 25ml water, and extracted with ether (4 x 25 ml). The combined extracts were washed with water (8 X 20ml), brine, dried over Na_2SO_4 and stripped of solvent in vacuo to give 43mg(88%) of an oil. Preparative TLC of the oil on a 10 x 20 cm silica gel plate, eluted once with 35% ether/ petroleum ether, gave one major band, rf=.20. This band contained 34mg (69%) of a white crystalline solid. The product was recrystallized twice from ether/hexane to give the olefin mixture D-3, mp 98-105°.

Analysis for $C_{22}H_{32}O_2$: calculated C 80.44: H 9.82
found 80.23 9.82

Infrared: $CHCl_3$ 3610 cm^{-1} (alcohol)
1601, 1580, 1485 (aromatic)

NMR: $\delta^{CDCl_3}_{TMS}$

.90 ppm	s,	
1.02	s,	angular methyls
1.63	s,	olefinic methyl
3.72	m,	C 5 hydrogen
3.80	s,	ArO-Me

D-4 :

To a stirred solution of 269 mg of the alcohol D-3 in 30ml of acetone, chilled in an ice bath, 2.5 ml of 8N Jones reagent was added dropwise. Stirring at the low temperature was continued for 10 minutes, then 10 ml of isopropanol was added, followed by 100 ml of water; most of the acetone was removed in vacuo, the mixture extracted with ether (4 x 80 ml), and the combined etherial extracts washed with water and brine, dried over Na_2SO_4, and stripped of solvent in vacuo to give a yellow oil quantitavely. A portion (254mg) of this oil was chromatographed on a 20 x 20 cm plate, eluted once with 30% Ether/petroleum ether. The only significant band, rf=.40, contained 237mg (93%) of a semi-crystalline oil; some of this was crystallized from ether to give a solid isomer mixture D-4, mp 68-93°.

Analysis for $C_{22}H_{30}O_2$: calculated C 80.94: H 9.26
found 81.02 9.38

Infrared: $CHCl_3$ 1700 cm^{-1} (ketone)
1601, 1580, 1485 (aromatic)

NMR: $\delta^{CDCl_3}_{TMS}$

.98 ppm	s,	angular methyls (major isomer)
1.18	s,	
1.65	s,	olefinic methyl
3.80	s,	ArO-Me
5.0,5.4	m,	olefinic protons (very faint)
6.7-7.4	m,	aromatic

A-15 :

In 13 ml toluene, 100 mg (.306 mmoles) of the keto olefin mixture D-4 was combined with 100 mg of p-TsOH and refluxed through a Dean-Stark apparatus (10 ml of toluene were distilled into the sidearm); after one hour, another 100 mg p-TsOH was added, and reflux with stirring continued

for 2.25 hours longer, after which the mixture was diluted with 100ml ether, washed with 2.5% NaOH, water, and brine, and dried over Na_2SO_4. The solvent was removed in vacuo to give a quantitative yield of brown oil, two peaks on the GLC. The components could not be separated by chromatographic means, but the major isomer partially crystallized out in ether to give 52 mg (52%) of a white solid. Upon three recrystallizations from ether, very pure A-15 was obtained, mp 150-152° (vac).

Analysis for $C_{22}H_{30}O_2$: calculated C 80.94: H 9.26
found 80.89 9.34

Infrared: $CHCl_3$ max
1700 cm^{-1} (ketone)
1605, 1575, 1500 (aromatic)
1385 (methyls)

NMR: $\delta^{CDCl_3}_{TMS}$

.90 ppm	s,	3	angular methyls
1.18	s,	6	
1.22	s,		
3.76	s,	3	Ar-O-CH_3
6.5-7.4	m,	3	aromatic

NMR of the mother liquors showed , that in addition to more A-15, there was perhaps 35% of an isomer present having a very high field resonance at =.33.

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