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# Synthesis of Bridged Steroids. VII.[1] B-Norsteroids having a Gibbane B-C-D Ring System. (2). Synthesis of the 7-Deoxygibberellin Type Ring System

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Synthesis of 3a-methylene-3β,5β-ethano-B-nor-5β-androstane 6β-carboxylic acid (**1**) having a gibbane B-C-D ring system is described. 5β-Cyano-6β-vinyl-B-nor-5β-androstan-3-one (**5**), the starting material, was transfomed stereoselectively to 3α-tosyloxy-5β-(*trans*-β-formyl)vinyl-6β-vinyl-5β-androstane (**22d**), the key intermediate, by the eight-step synthesis. The latter, after selective ozonization was subjected to a new cyclization method involving participation of 6β-hemiacetal function to afford 3β,5β-etheno derivative (**38**), which on subsequent oxidation and the Wolff–Kishner reduction, led to the desired compound (**1**). Some attempted experiments for homologation at the 5β-nitrile function are also described.

In the preceding paper,[1] we described syntheses of 5-cyano-B-norsteroids. In this paper our studies are extended to explore a new method for synthesis of the B-norsteroid (**1**), having the bicyclo[3,2,1]octane ring system and requisite functionalities for gibberellin $A_{15}$[3] (**2**), a compound with high potency[4] as a plant hormone. This work was carried out in the hope of finding some biologically interesting compounds and also provided model experiments for our total synthesis of *dl*-gibberellin $A_{15}$[5] (**2**).

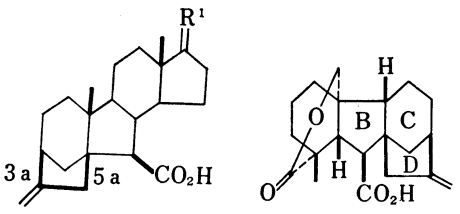



Chart 1

It seemed desirable to start with the *cis*-cyanoketones (**3**, **4**, and **5**) whose syntheses were described in the preceding paper,[1] since the B-C-D ring part in gibberellin $A_{15}$ (**2**) is regarded as a derivative of *cis*-hydrindane.

In our synthetic program, two routes were investigated. First, if it were possible to obtain an ethylation product (ii) by treatment of a cyanoketone ketal (i) with alkyl metals (*e.g.* EtLi, EtMgBr) followed by hydrolysis, cyclization of (ii) would then yield (iii) as depicted in the following; (i)→(ii)→(iii). The cyanoketone (**3**) was subjected to ketalization to afford the cyanodiketal (**6**), mp 133.5—134°, in a 79% yield. Ethylation of **6** with ethyllithium followed by hydrolysis gave a crude netural product (**7**) and a crude basic one (**8**) in a ratio of 1:5. The structure of **7** was assigned on the basis of bands

1) Part VI: W. Nagata, M. Narisada, T. Wakabayashi, Y. Hayase, and M. Murakami, *Chem. Pharm. Bull.* (Tokyo), **19**, 1567 (1971).
2) Location: *Fukushima-ku, Osaka*; *a*) Present address: *Faculty of Science, Osaka City University.*
3) J.R. Hanson, *Tetrahedron*, **23**, 733 (1967).
4) B.E. Cross, R.H. B. Galt, and J.R. Hanson, "Regulations Naturels de la Croissance Vegetale," Centre National de la Recherche Scientifique, Paris, 1964, p. 265.
5) W. Nagata, T. Wakabayashi, Y. Hayase, M. Narisada, and S. Kamata, *J. Am. Chem. Soc.*, **92**, 3202 (1970).

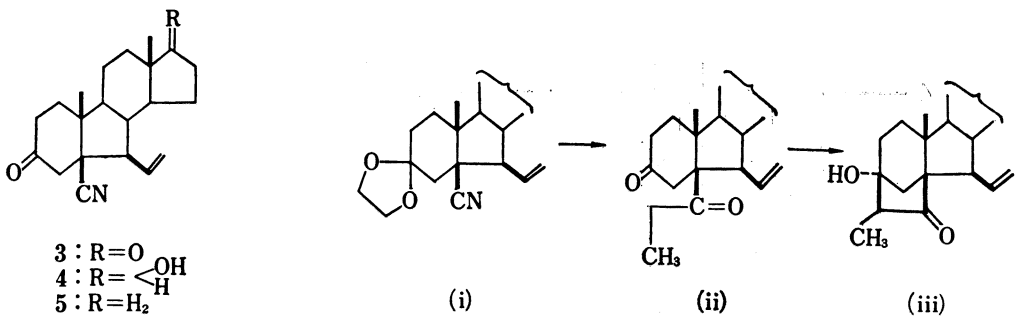



Chart 2

at 3032, 1840, 1632, and 924 $cm^{-1}$ ($CH=CH_2$), 1743 $cm^{-1}$ ($C_{17}CO$), 1722 ($C_3CO$), and 1706 $cm^{-1}$ ($COCH_2CH_3$) in its infrared (IR) spectrum. The structure of **8** was also supported by its IR (1635, C=N; 1744, $C_{17}CO$; 1722 $cm^{-1}$, $C_3CO$) and nuclear magnetic resonance (NMR) spectrum (8.80, doublet, $CH_3$-CH, $J$=7.3, 8.78, triplet, $CH_3$-$CH_2$, $J$=7.2, 6.17 $\tau$ quartet of doublets, =N-CH($CH_3$)CH, $J$=7.3, 3.0 Hz). The yield of **7** was not satisfactory for pursuing the synthesis further. This reaction was therefore abandaned. Next we used ethylmagnesium bromide.

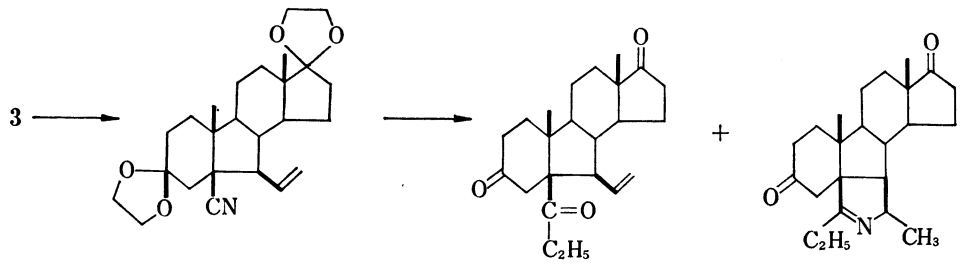



Chart 3

The cyanoketone (**4**) was converted to the cyanoketal derivative (**10**), mp 162—163°, by the sequence of reactions; ketalization of the 3-ketone, and tetrahydropyranylation of the 17-hydroxyl. The Grignard reaction of **10** with ethylmagnesium bromide in anisole–ether at 70° for 7 hr gave the imine (**11**), mp 178—182° in 11% yield and a 38% recovery of the starting material (**10**). The assigned structure of **11** was based on the IR and NMR spectra and analyses. This fact showed that under these conditions the $C_3$-ketal group as well as the $C_{17}$-tetrahydropyranyloxy group in **10b** was also attacked by the reagent. Considering the solubility factor and to avoid the complexity arising from reaction at the $C_{17}$ position, we next used as a substrate the 3-tetrahydropyranyloxy derivative (**12**), obtained by reduction of the cyanoketone (**5**) with aluminum isopropoxide in benzene followed by tetrahydropyranylation of the 3$\alpha$-hydroxyl. Treatment of **12** with ethylmagnesium bromide in anisole at 113° for 5 hr yielded not the desired imine (**14**) but the isopropyl imine (**13a**), whose structure was deduced from its NMR spectrum [8.94 (d, CH-$CH_3$, $J$=6.2), 8.74 (d, $CHCH_3$, $J$=6.2), 6.11 (multiplet (m), CH-N=C), 7.4 $\tau$ (m, $CH_3CHCH_3$)] and its NMDR spectrum (the doublets at 8.94 $\tau$ and 8.74 $\tau$ collapsed to singlets by irradiating at 7.4 $\tau$). The IR spectrum of its picrate (**13b**), mp 201—202°, showed vinyl (1631 $cm^{-1}$) and imine (1615 $cm^{-1}$) bands. Treatment of **13a** with *m*-chloroperbenzoic acid in chloroform yielded the nitrone (**15**) (oil).

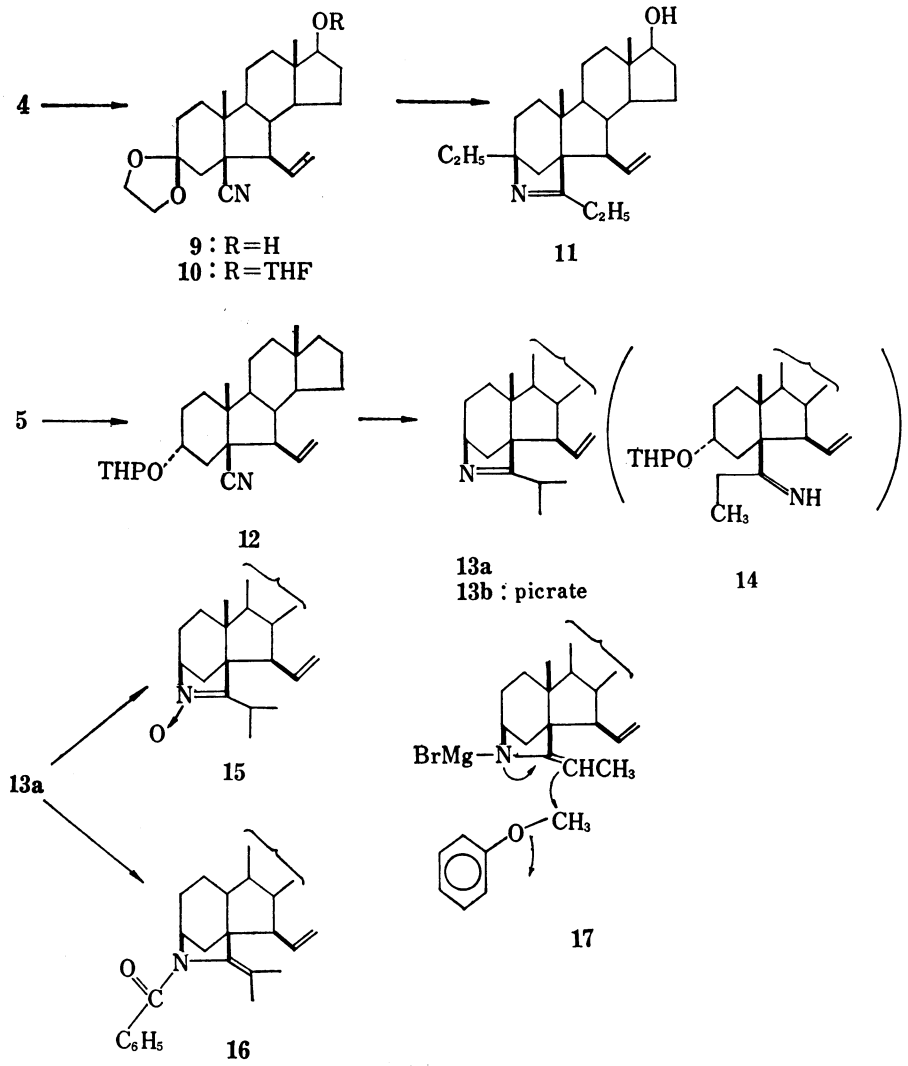



Chart 4

Schotten–Baumann reaction[6] of **13a** with benzoyl chloride afforded the benzoyl amide (**16**) (oil). The spectral data of **15** and **16** were in keeping with the assigned structures. The mechanism of the isopropyl group formation in **13a** can be understood as an $S_N2$-like displacement[7] of the phenoxy function by the nucleophilic enamide anion (**17**). We therefore abandaned this first route, and investigated a second one, which was to convert the *cis*-cyanoketone (i) into the 5$\beta$-formyl derivative (IV) and then to lengthen the formyl group to furnish the compound (V) having a three-carbon chain at the $C_5$ position. It was hoped that, on treatment of V with base, double cyclization, *i.e.* initial nucleophilic addition of Z to $C_a$=$C_b$ bond and concomitant displacement between $C_b$ and the leaving X group, would take place, giving VI, which then would be converted into the ring opened VII by $\beta$-elimination. This reaction scheme would provide a unique cyclization method in the sense, that the neighboring

6) V. Cerny and F. Sorm, *Collection Czech. Chem. Commun.*, **25**, 2841 (1960).
7) I.T. Harrison, *Chem. Commun.*, **1969**, 616.

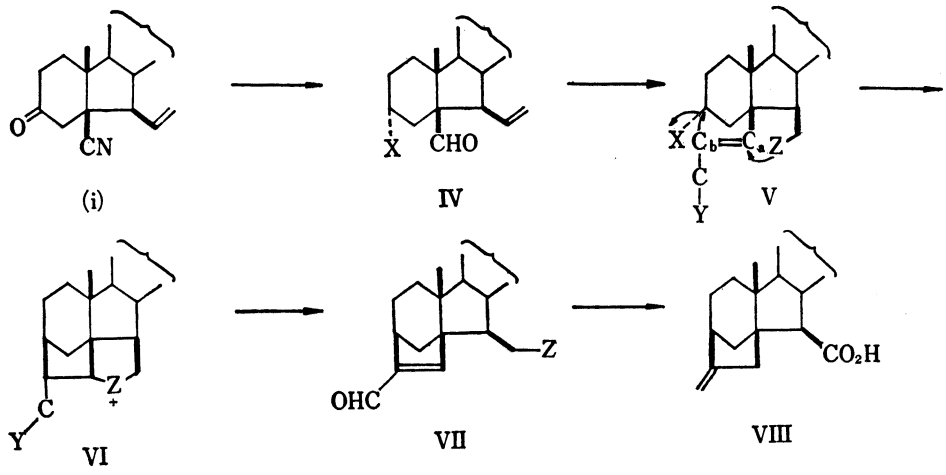
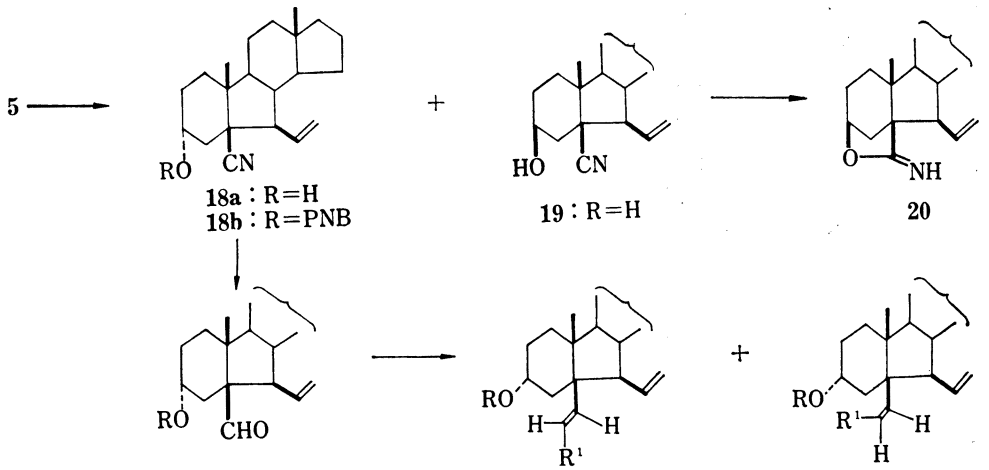



Chart 5

Z group plays an important role in the *cis* bicyclo[3,2,1]octane ring formation. Finally, Wolff–Kishner reduction of VII would afford the desired compound (VIII). The prospective synthetic plan was thus designed as shown in Chart 5.

Initial reduction of the 3-keto group of the 5$\beta$-cyanoketone (**5**) to a 3$\alpha$-hydroxy group was required: so, following the literature,[8] in which 5$\beta$-cyano-17$\beta$-hydroxy-19-norandrostan-3-one was reported to be reduced exclusively to the 3$\alpha$-hydroxy (equatorial) derivative with LiAl $(Bu^tO)_3H$ reduction of **5** with LiAl $(Bu^tO)_3H$ was first carried out. This, however, led to a 1:2 mixture of the alcohols (**18a** and **19**) containing mainly the unfavorable 3$\beta$-alcohol (**19**). This unexpected result led us to reexamine the reduction of 5-cyano-3-ketosteroids with metal hydrides, and to find that the assignments were erroneously reversed in the liter-




**21a**: R=H
**21b**: R=$COC_6H_5$

**22a**: R=$COC_6H_5$, $R^1$=$CO_2Et$
**22b**: R=$COC_6H_5$, $R^1$=CN
**22c**: R=H, $R^1$=CHO
**22d**: R=Ts, $R^1$=CHO
**22e**: R=$COC_6H_5$, $R^1$=CHO

**23a**: R=$COC_6H_5$, $R^1$=$CO_2Et$
**23b**: R=$COC_6H_5$, $R^1$=CN
**23c**: R=H, $R^1$=CHO

Chart 6

8) J. Fishman and M. Torigoe, *Steroids*, **5**, 599 (1965).

atures.[8-10] Full details of this study will be published elsewhere.[11] The desired alcohol (**18a**) was prepared, therefore, by the Meerwein–Pondorf reduction under equilibrium condition. Refluxing of a benzene solution of **5** in the presence of aluminum isopropoxide yielded a mixture of epimeric alcohols (**18a** and **19**).

Treatment of the mixture with *p*-toluenesulfonic acid gave the 3α-alcohol (**18a**) [*p*-nitrobenzoate (**18b**), mp 136—137°, 72%] and the basic iminolactone (**20**), mp 100—101°, in a 9% yield. For two-carbon homologation by the Horner reaction, the angular cyano group in **18b** was first to be converted into the 5β-formyl group. Thus, reduction of **18b** with diisobutyl aluminum hydride followed by hydrolysis yielded the crude hydroxy aldehyde (**21a**). The hydroxy group of **21a** was then protected with benzoyl chloride in the usual way giving the benzoyloxy aldehyde (**21b**), mp 102—103° in 75% overall yield based upon **18b**. Condensation[12] of triethyl phosphonoacetate with **21b** gave a mixture of α,β-unsaturated esters (**22a** and **23a**), which was separated by a combination of column chromatography and preparative thin-layer chromatography (TLC) to give the crude *trans*-ester (**22a**) [71%; NMR: 3.84 (d, C=CHCO$_2$Et, $J$=16.4), 2.92 (d, CH-C-CO$_2$Et, $J$=16.4 Hz)] and the crude *cis*-ester (**23a**) (5%, IR: 1724, 1634, 909 cm$^{-1}$). The Horner reaction of (**21b**) using sodium diethyl cyanomethylphosphonate[13] yielded the *cis*-cyanide (**23b**), mp 160—161°, and the crude *trans*-isomer (**22b**) in a ratio of 5:3. Reduction of **23b** with diisobutylaluminum hydride followed by hydrolysis with 4N $H_2SO_4$ in benzene afforded the *cis*-aldehyde (**23c**), mp 158—159° (40% from **21b**). From the crude *trans*-cyanide (**22b**) the *trans*-aldehyde (**22c**), mp 65—66° (21% from **21b**), was obtained analogously. These steps could be simplified and improved by applying a novel formylolefination method[14] developed in our laboratory. Treatment of **21b** with sodium diethyl β-(cyclohexylamino)vinylphosphonate[14] in tetrahydrofuran followed by hydrolysis with aqueous oxalic acid in a two layer system and then by heating with 2N $K_2CO_3$ in aqueous methanol yielded exclusively the *trans* α,β-unsaturated aldehyde (**22c**) in 90% over-all yield based on **21b**. Conversion of the cyanoketone (**5**) into the formylolefin 3-ethyleneketal (**26a**) was successfully carried out by applying a similar reaction sequence (ketalization, reduction with diisobutyl aluminum hydride, hydrolysis with a buffer solution, formylolefination, and hydrolysis with a buffer solution) in 59% over-all yield based on the cyanoketal (**24**).

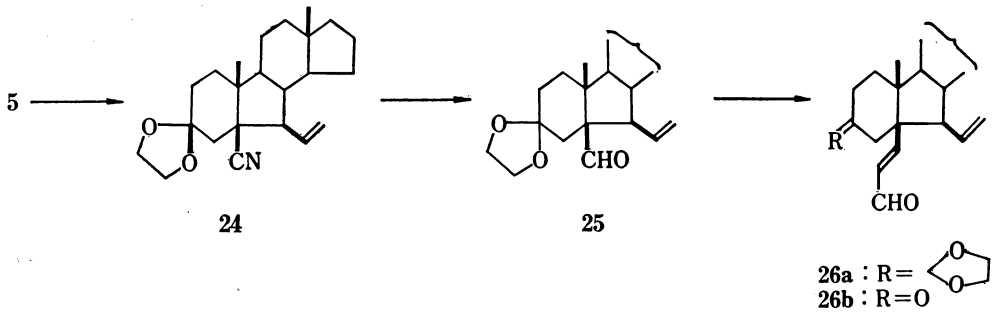



Chart 7

At this stage, we faced the major problem in the prsent synthesis, *i.e.*, double cyclization of V and subsequent ring opening leading to VII discussed earlier (Chart 5). Prior to investigation of this transformation, we attempted reductive cyclization of the tosylate (**22d**)

9) A. Bowers, *J. Org. Chem.*, **26**, 2043 (1961).
10) A.D. Cross and I.T. Harrison, *J. Am. Chem. Soc.*, **85**, 3223 (1963).
11) W. Nagata, T. Wakabayashi, M. Narisada, and Y. Hayase, *J. Chem. Soc.*, in prss.
12) W.S. Wadsworth and W.D. Emmons, *J. Am. Chem. Soc.*, **83**, 1733 (1961).
13) A.K. Bose and R.T. Dahill, Jr., *J. Org. Chem.*, **30**, 505 (1965).
14) W. Nagata and Y. Hayase, *Tetrahedron Letters*, **1968**, 4359; *J. Chem. Soc.*, **1969**, 460.

with lithium in liquid ammonia in the hope to obtain the cyclized product (**27**). However, the product isolated turned out **22c**, indicating reductive detosylation preceded double bond reduction. Next, Birch reduction of **26b**, prepared from **26a** by hydrolysis with 10% perchloric acid in tetrahydrofuran, did not yield the desired hydroxy aldehyde (**28**), but a mixture of the alcohol (**29**) and the hemiacetal (**30**) both in a crude state. The latter was oxdized with chromium trioxide in pyridine to afford a crude $\gamma$-lactone (**31**), whose structure was tentatively assigned on the basis of its IR spectrum (1789 $cm^{-1}$).

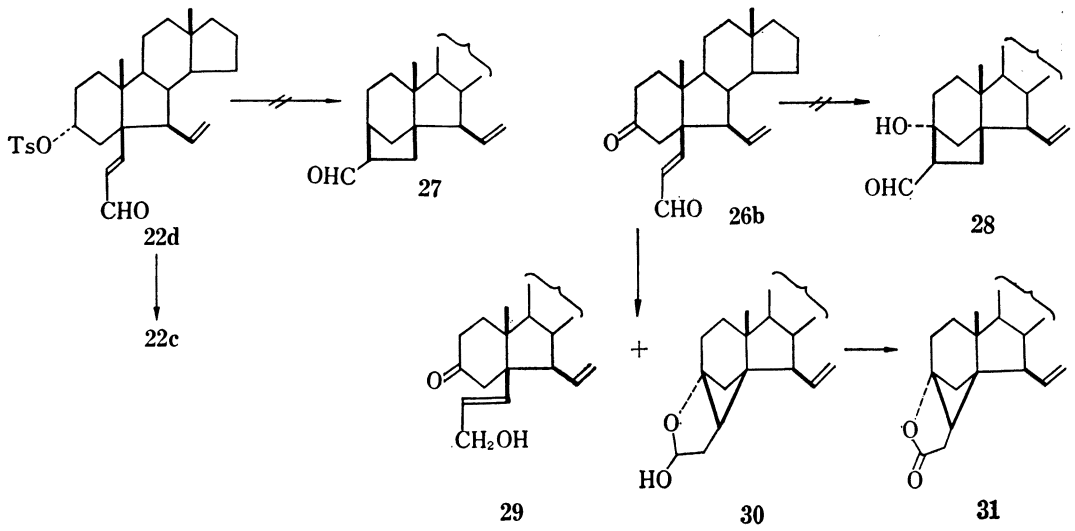



Chart 8

We now turned to investigation of the critical cyclization step following the planned reaction scheme. First, selective oxidation of the 6$\beta$-vinyl group of the tosylate (**22d**) into the formyl group was tested by several methods (*e.g.* $OsO_4$, Lemieux–Rudolff oxidation,[15])

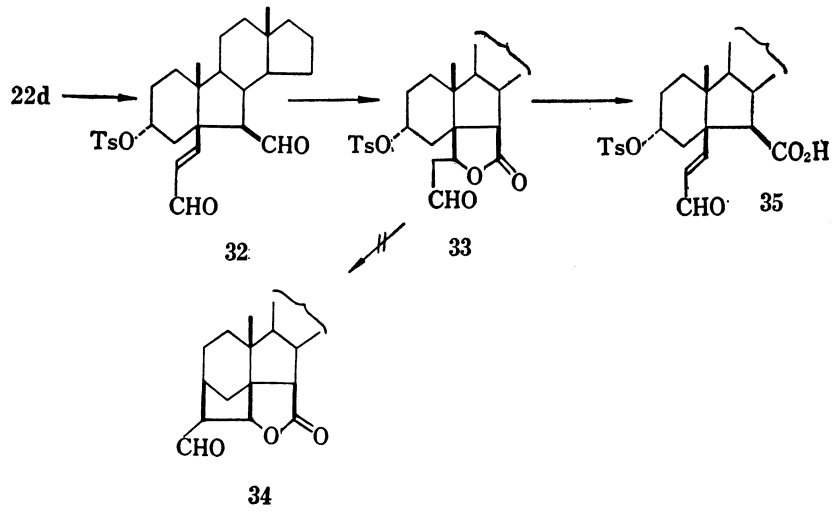



Chart 9

15) R.U. Lemieux and E. von Rudolff, *Can. J. Chem.*, 33, 1701 (1955).

epoxidation, and ozonization). Among these, ozonization and subsequent reduction of the ozonide was most promising. Treatment of the tosylate (**22d**) with ozone at −73° in methylene chloride followed by reduction with dimethylsulfide[16] afforded the crude dialdehyde (**32**), which was oxidized with chromium trioxide in aqueous pyridine to yield a crude lactone (**33**), whose structure was assigned by its IR spectrum [2730, 1728 $cm^{-1}$ (CHO), 1779 $cm^{-1}$ ($\gamma$-lactone)]. Cyclization of **33** with base (*e.g.* NaH, Bu$^t$OK) to **34** was attempted in vain, yielding only the crude ring opened product (**35**) [IR: 1716 $cm^{-1}$ (COOH), 1680 $cm^{-1}$ [CH=CH–CHO)]. The ease of ring opening of **33** may be due to the electron-withdrawing lactone group. Therefore, replacement of the lactone group by an acetal group was considered to be promising. The crude dialdehyde (**32**) was thus, treated with 3 equiv pyrrolidine in methanol at room temperature for 1 hr giving the salt (**37**) [IR: 1667 $cm^{-1}$ (C=N$^+$)] *via* the intermediate acetal (**36**) as expected. Hydrolysis of **37** with a pH 4.6 buffer solution yielded the

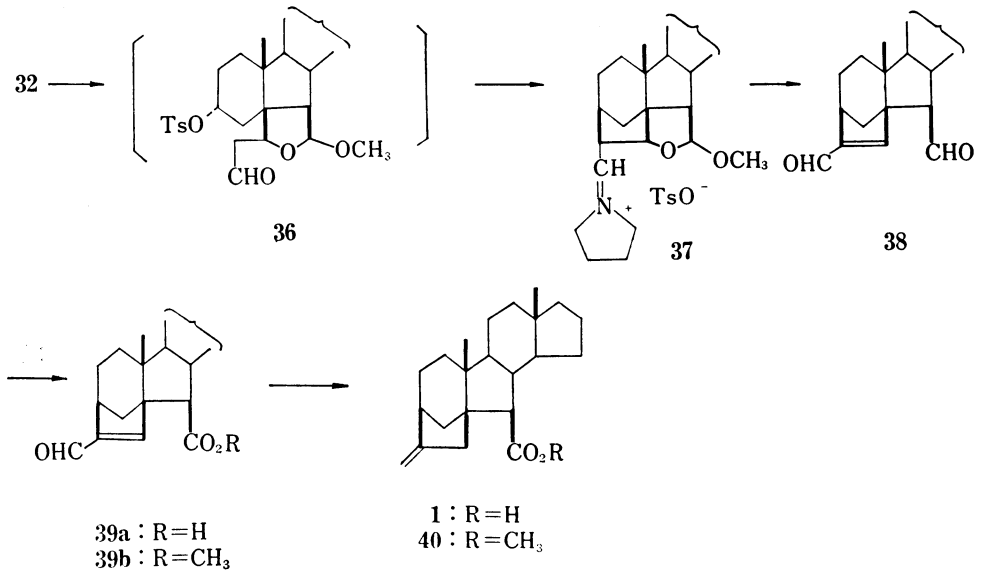



Chart 10

desired dialdehyde (**38**) (oil) in 36% yield from **22d**. The IR spectrum of **38** revealed the presence of an aldehyde group (2705, 1728 $cm^{-1}$) and an $\alpha,\beta$-unsaturated aldehyde carbonyl (1683 $cm^{-1}$). Selective oxidation of **38** with chromium trioxide in pyridine followed by esterification of the acid (**39a**) with diazomethane afforded the 6$\beta$-carbomethoxy aldehyde (**39b**) (oil) (2,4-dinitrophenylhydrazone, mp 275—258°). The red shift[17] of the ultraviolet (UV) absorption of **38** at 256 m$\mu$ ($\varepsilon$ 7500) from that of the usual $\alpha,\beta$-unsaturated aldehyde chromophor was in keeping with the assigned structure. The Wolff–Kishner reduction of the acid (**39a**) furnished the desired *exo*-methylene carboxylic acid (**1**) which is purified by esterification with diazomethane to give 3a-methylene-6$\beta$-carbomethoxy-3$\beta$,5$\beta$-ethano-B-nor-androstane (**40**) (oil) in 16% over-all yield based upon **38**. The assigned structure was consistent with its IR and NMR spectra. Assignment of the 6$\beta$-configuration to the carbomethoxy group in **40** is based on its negative Cotton effect curve.[18] The work aimed at a synthesis of B-norsteroid having a bicyclo[3,2,1]octane bridged ring system with the requisite function-

16) J.J. Pappas, W.P. Keaneney, E. Gancher, and M. Berger, *Tetrahedron Letters*, **1966**, 4273.
17) L.H. Briggs, B.F. Cain, R.C. Cambie, and B.R. Davies, *J. Chem. Soc.*, **1962**, 1850.
18) G. Gottarelli, W. Klyne, and P.M. Scoppes, *J. Chem. Soc.*, **1967**, 1366.

alities in the B-C-D ring of 7-deoxygibberellin was thus achieved, and the reaction sequence described in the present paper was successfully applied, with some minor variations, to the stereocontrolled total synthesis of *dl*-gibberellin $A_{15}$[5] (**2**).

## Experimental

**General**——Melting points were measured Yazawa hot stage and uncorrected. Unless otherwise stated, UV spectra were taken in 95% ethanol with a Hitachi EPS-2 spectrometer, IR spectra in chloroform by use of a Koken DS-210B spectrometer, NMR spectra on deuteriochloroform solutions with a Varian A-60 spectrometer using tetramethylsilane as internal standard, optical rotatory dispersion (ORD) and circular dichroism (CD) spectra with a Jasco Model ORD, UV, CD 5. Unless otherwise specified, the extracts were dried over anhydrous sodium sulphate, and column chromatography was carried out according to the method reported by Reichstein an Shoppee[19] using Woelm neutral alumina (activity II).

**3,3-Ethylenedioxy-5β-cyano-6β-vinyl-17,17-ethylenedioxy-B-norandrostane** (**6**)——A solution of the cyanoketone (**3**) (1.000 g), ethylene glycol (762 mg), *p*-toluenesulfonic acid monohydrate (30 mg) in dry benzene (70 ml) was refluxed in the presence of a water separator for 4.5 hr. The reaction mixture was cooled, poured into cold 2N sodium carbonate, and extracted with benzene. The benzene extract was washed with sodium chloride solution, dried, and evaporated to leave a residue, which was crystallized from ether–methanol to yield 1.001 g of the diketal (**6**), mp 133—134°. An analytical sample melts at 133.5—134°. IR $\nu_{max}$ $cm^{-1}$: 3080, 2240, 1857, 1644, 944, 922. $[\alpha]_D^{25}+3.8\pm2°$ ($c$=1.035, $CHCl_3$). *Anal.* Calcd. for $C_{25}H_{35}O_4N$: C, 72.60; H, 8.53; N, 3.39. Found: C, 72.84; H, 8.62; N, 3.49.

**3α-Ethyl-3β,5β-nitrilometheno-5a-ethyl-6β-vinyl-B-norandrostan-17β-ol** (**11**)——A mixture of the crude cyanoketone (**4**) (1.111 g), *p*-toluenesulfonic acid monohydrate (90 mg), diethyleneglycol (9 ml), and dry benzene (90 ml) was refluxed for 3 hr. The mixture was cooled and then poured into ice–2N sodium carbonate, and extracted with methylene chloride. The methylene chloride extract was washed with water, dried and evaporated to leave 1.20 g of the crude ketalalcohol (**9**), 425 mg of which was dissolved in 10 ml of tetrahydrofuran. The solution was mixed with 0.5 ml of dihydropyrane and 20 mg of anhydrous (anhy.) *p*-toluenesulfonic acid, and allowed to stand at room temperature overnight. The reaction mixture was poured into ice–2N sodium carbonate (8 ml), and extracted with methylene chloride. The methylene chloride extract was washed with water, dried, and evaporated to leave 721 mg of a residue, which was chromatographed on alumina (15 g). Fractions eluted with petroleum ether–benzene (9:1) and benzene were collected to give 373 mg of a crude tetrahydropyranyloxy ketal (**10**). A solution of 259 mg of the above ketal (**10**) in 3 ml of dry anisole was mixed with solution of ethylmagnesium, prepared from ethyl bromide (0.44 ml), magnesium (140 mg), and dry ether (2 ml)–dry anisole (3 ml). The reaction mixture was heated at 73° for 7 hr, cooled, poured into cold 2N hydrochloric acid, and extracted with ether–methylene chloride (5:1). The organic extract was worked up as usual to leave 99 mg of starting material (**10**). The qaueous acidic layer was made alkaline with potassium carbonate, and extracted with methylene chloride. The methylene chloride extract was washed with water, dried and evaporated to leave 100 mg of a basic residue, which was purified by preparative TLC (silica gel AcOEt: benzene=4:1) to afford 22.3 mg of the imine (**11**), mp 178—182° on crystallization from chloroform–ether. IR $\nu_{max}$ $cm^{-1}$: 3602, 1636, 1614, 915. NMR $\tau$: 8.89 (6H, triplet (t), 5a-$CH_2$-$CH_3$, 3α-$CH_2CH_3$, $J$=7.5 Hz). $[\alpha]_D^{25}+54.0\pm2°$ ($c$=0.982, $CHCl_3$). *Anal.* Calcd. for $C_{25}H_{39}ON$: C, 81.24; H, 10.64; N, 3.79. Found: C,81.11; H, 10.64; N, 3.64.

**3β,5β-Nitrilometheno-5a-isopropyl-6β-vinyl-B-norandrostane** (**13a**)——The crude cyanoalcohol (**18a**) whose preparation is described later was used as a starting material. To a solution of 105 mg of **18a** in 8 ml of tetrahydrofuran was added 0.5 ml of dihydropyrane and 1 drop of concentrated hydrochloric acid. The mixture was refluxed for 4.5 hr under nitrogen, cooled, poured into ice–2N sodium carbonate, and extracted with methylene chloride. The methylene chloride extract was washed with water, and evaporated to leave 575 mg of a residue, which was chromatographed on alumina (15 g). Fractions eluted with petroleum ether–benzene (9:1 to 1:1) were collected to give 94 mg of the crude tetrahydropyranyl ethr (**12**) (TLC: one spot). To a ethereal ethylmagnesium bromide solution, prepared from ethyl bromide (1.6 ml), magnesium (294 mg), and dry ether 3 ml, was added 2 ml of dry anisole. Ether of the resulting solution was distilled off. To the solution of ethylmagnesium bromide in anisole thus obtained was added a solution of crude tetrahydropyranyl ether (**12**) (320 mg) in 2 ml of dry anisole. The mixture was heated at 113° for 5 hr, cooled, poured into cold 2N hydrochloric acid, and extracted with ether. The etheral extract was washed with water, and worked up as usual to leave 15.5 mg of a neutral residue, which was purified by preparative TLC to recover 41 mg of **12**. The aqueous (aq.) acidic layer was made alkaline with sodium carbonate, and extracted with methylene chloride. The methylene chloride extract was washed with water, dried, and evaporated to leave 138 mg of a basic residue, which was purified by preparative TLC (silica gel, benzene: AcOEt=1:2) to afford 74 mg of the isopropylimine (**13a**). The corresponding picrate (**13b**), mp 201—202°. IR $\nu_{max}$ $cm^{-1}$: 1631, 1615, 1570, 1552, 1365, 923. $[\alpha]^{24}+26.6+1.6°$ ($c$=0.304, $CHCl_3$).

19) T. Reichstein and C.W. Schoppee, *Discussions Faraday Soc.*, **1949**, 305.

*Anal.* Calcd. for $C_{29}H_{38}O_7N_4$: C, 62.80; H, 6.91; N, 10.10. Found: C, 63.18; H, 7.28; N, 9.99.

**Oxidation of the Isopropyl Imine (13a)**——To a cold (3°) solution the isopropyl imine (**13a**) (57 mg) in chloroform (2 ml) was added *m*-chloroperbenzoic acid. The mixture was stirred for 45 min, poured into cold 2N sodium carbonate, and extracted with methylene chloride. The methylene chloride extract was washed with water, dried, and evaporated to leave 54 mg of a res idue, which was purified bypreparative TLC (silica gel, AcOEt: EtOH=9:1) to afford 41 mg of the nitrone (**15**). Short-path distillation furnished an analytical sample; bp (bath) 200° ($10^{-3}$ mm). IR $\nu_{max}^{CCl_4}$ $cm^{-1}$: 3033, 1637, 1557, 915. UV $\lambda_{max}$ $m\mu$ ($\varepsilon$): 247 (7600). NMR $\tau$: 9.28 (3H, singlet(s), 18-$CH_3$), 9.09 (3H, s, 19-$CH_3$), 8.71 (3H, doublet(d), CH-$CH_3$, $J$=7.0 Hz), 8.53 (3H, d CH-$CH_3$, $J$=6.8 Hz), 5.0 (1H, doublet of doublets (d of ds), $-CH=C\langle^{H}_{H}$, $J$=2.8, 10.8 Hz), 4.89 (1H, d of ds, $CH=C\langle^{H}_{H}$, $J$=2.8, 16.0 Hz), 4.0 (1H, multiplet (m), $CH=CH_2$). $[\alpha]_D^{25}+46.5\pm2.4°$ ($c$=0.374, $CHCl_3$). *Anal.* Calcd. for $C_{24}H_{37}ON$: C, 81.07; H, 10.49; N, 3.94. Found: C, 80.85; H, 10.36; N, 4.16.

**Schotten-Baumann Reaction of the Isopropyl Imine (13a)**——To a solution of the isopropyl imine (**13a**) (63 mg) in methylene chloride (0.7 ml) and benzene (0.7 ml) was added dropwise benzoyl chloride (1 ml) and 5% aq. sodium hydroxide (14 ml) under stirring over a period of 20 min at room temperature. The mixture was stirred for 1 hr, poured into ice–2N hydrochloric acid, and extracted with ether. The ethereal extract was washed with water, dried, and evaporated to leave 60 mg of a neutral residue, which was purified by preparative TLC (silica gel benzene: AcOEt=9:1) to afford 38 mg of the benzoyl amide (**16**). Short-path distillation furnished an analytical sample, bp (bath) 192° ($2\times10^{-3}$ mm). IR $\nu_{max}^{CCl_4}$ $cm^{-1}$: 3038, 3022, 1667, 1580, 913. NMR $\tau$: 9.15 (3H, s, 18-$CH_3$), 9.10 (3H, s, 19-$CH_3$), 8.97 (3H, s, C=C-$CH_3$), 8.23 (3H, s, C=C-$CH_3$). $[\alpha]_D^{24}+58.2+2.7°$ ($c$=0.364, $CHCl_3$). *Anal.* Calcd. for $C_{31}H_{41}ON$: C, 83.92; H, 9.32; N, 3.16. Found: C, 83.68; H, 9.17; N, 3.00.

**Reduction of 5β-Cyano-6β-vinyl-B-norandrostan-3-one (5) with $LiAl(Bu^tO)_3H$**——To a solution of **5** (265 mg) in tetrahydrofuran (4 ml) was added $LiAl(Bu^tO)_3H$ (280 mg) at room temperature. The mixture was stirred for 2 hr, poured into cold 5% aq. acetic acid, and extracted with methylene chloride. The methylene chloride extract was washed successively with water, 2N sodium carbonate, and water, dried, and evaporated to leave 287 mg of a residue, which was dissolved in dry benzene (15 ml). The solution was mixed with anhy. *p*-toluenesulfonic acid (230 mg), refluxed for 1 hr under removal of azeotropic distillate (7 ml), cooled, poured into ice–4N hydrochloric acid, and partitioned between 4N hydrochloric acid and ether. The ethereal layer was washed with water, and worked up as above to leave 105 mg of a neutral residue containing mainly the 3α-alcohol (**18a**). A solution of the above neutral residue (93 mg) in pyridine (5 ml) was treated with *p*-nitrobenzoyl chloride (200 mg) to give 110 mg of the *p*-nitrobenzoate (**18b**), mp 131—134° on crystallization from ether–pentane. An analytical sample melts at 136—173°. IR $\nu_{max}$ $cm^{-1}$: 2226, 1724, 1640, 1607, 1528, 1351, 921. $[\alpha]_D^{24}-36.6\pm1.1°$ ($c$=0.595, $CHCl_3$). *Anal.* Calcd. for $C_{28}H_{34}O_4N_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.76; H, 7.20; N, 5.70. The aq. acidic layer was made alkaline with 2N sodium carbonate, and extracted with methylene chloride. The methylene chloride extract was washed with water, dried, and evaporated to leave 160 mg of a basic residue, which was crystallized from ether–pentane to give 139 mg of tc iminolactone (**20**), mp 99—101°. An analytical sample melts at 100—101°. IR $\nu_{max}$ $cm^{-1}$: 3272, 1680, 1636, 908. $[\alpha]_D^{24}+14.3\pm2°$ ($c$=0.314, $CHCl_3$). *Anal.* Calcd. for $C_{21}H_{31}ON$: C, 80.46; H, 9.97; N, 4.47. Found: C, 80.23; H, 10.05; N, 4.60.

**Reduction of 5β-Cyano-6β-vinyl-B-norandrostan-3-one (5) with Aluminum Isopropoxide**——To a solution of the cyano ketone (**5**) (284 mg) in dry toluene (9 ml) was added aluminum isopropoxide (305 mg). The mixture was refluxed for 1 hr under removal of toluene (3 ml) as an azeotropic distillate, cooled, poured into cold 2N hydrochloric acid, and extracted with ether–methylene chloride (2:1). The organic extract was worked up to leave 301 mg of a residue, which was dissolved in dry benzene (14 ml). To the solution was added dry *p*-toluenesulfonic acid (107 mg). The mixture was refluxed for 1 hr in an atomosphere of nitrogen under removal of benzene (2.8 ml) as an azeotropic distillate, cooled, poured into cold 4N sulfuric acid, and partitioned between ether and 4N sulfuric acid. The ethereal layer was washed with water, dried, and evaporated to leave 264 mg of a neutral residue, which was treated with *p*-nitrobenzoyl chloride (197 mg) and pyridine (2.5 mg) to afford 356 mg of a residue. Crystallization of the residue from ether–pentane gave 258 mg of the *p*-nitrobenzoate (**18a**), mp 136—137°, and 35 mg of the second crop, mp 123—126°, in a 75% yield. The aqueous acidic layer was basified with sodium carbonate, and extracted with methylene chloride. The methylene chloride extract was worked up to leave 35 mg of a basic residue, which was crystallized from ether–pentane to yield 32 mg of the iminolactone (**20**), mp 99—101°.

**3α-Benzoloyx-6β-vinyl-B-norandrostane-5β-carboxaldehyde (21b)**——To a solution of the *p*-nitrobenzoate (**18b**) (7.737 g) in dry benzene (100 ml) was added a solution of diisobutylaluminum hydride in dry tetrahydrofuran (2.1 mmole/ml) over 5 min with stirring and ice-bath cooling under nitrogen. The solution was stirred for 1 hr at 3°, poured into a mixture of cold 4 N sulfuric acid (350 ml) and tetrahydrofuran (70 ml) with stirring over a period of 4 min. The mixture was diluted with ice–water, and extracted with ether. The ethereal extract was washed with water, dried, and evaporated to leave 5.65 g of a residue. The resulting residue was treated with benzoyl chloride (2.53 ml) and pyridine (32 ml) at room temperature overnight followed by usual work-up to leave 6.84 g of a residue, which was chromatographed on alumina (30 g). Fractions eluted with petroleum ether and petroleum ether–benzene (9:1 to 2:1) were crystallized from ether–

pentane to give 5.220 g of the benzoyloxy aldehyde (**21b**), mp 100—102°, in 74.5% yeild. An analytical sample melts at 102—103°. IR $\nu_{max}^{CCl_4}$ $cm^{-1}$: 2728, 1724, 1640, 1606, 919. $[\alpha]_D^{23}-46.9\pm0.9°$ ($c=1.034$, $CHCl_3$). *Anal.* Calcd. for $C_{28}H_{36}O_3$: C, 79.96; H, 8.63. Found: C, 79.98; H. 8.49.

**The Horner Reaction of 21b with Diethylphosphonoacetonitrile**——To a slurry of sodium hydride (86 mg, 54.5% mineral oil dispersion) in dry tetrahydrofuran (1.5 ml) was added a solution of diethylphosphonoacetonitrile (365 mg) in dry tetrahydrofuran (1.5 ml) with stirring and ice-bath cooling under argon. After 30 min of stirring at room temperature, a solution of the benzoyloxy aldehyde (**21b**) (281 mg) in tetrahydrofuran (1.3 ml) was added over 5 min. The reaction mixture was stirred at 41° for further 6 hr. To destroy the excess reagent paraform (170 mg) was added at 0°. The mixture was stirred for 1 hr at room temperature, diluted with ice-water, and extracted with ether–methylene chloride (3:1). The organic extract was washed with water, dried, and evaporated to leave a 369 mg of a residue, which was chromatographed on alumina (15 g). Fractions eluted with petroleum ether–benzene (9:1 to 1:1) were collected to give 240 mg of an oil, which was separated by preparative TLC (silica gel, pentane: MeOH=9:1). From the less polar fraction was obtained 84 mg of the *trans*-cyanide (**22b**). IR: nitrile band intensity, 2223 $cm^{-1}$ ($\varepsilon$ 154). NMR $\tau$: 4.49 (1H, d, CH=CHCN, $J=12.3$ Hz), 3.38 (1H, d, CH=CH-CN, $J=12.3$ Hz). The more polar compnent was the *cis*-cyanide (**23b**) (146 mg). IR: nitrile band intensity, 2221 $cm^{-1}$ ($\varepsilon$ 60). Crystallization of **23b** from ether–pentane furnished an analytical sample which melts at 160—161°. IR $\nu_{max}^{CCl_4}$ $cm^{-1}$: 3080, 2236, 1720, 1640, 1626, 1606, 920. NMR $\tau$: 4.18 (1H, d, CH=CH-CN, $J=16.9$ Hz), 3.21 (1H, d, CH=CH-CN, $J=16.9$ Hz). $[\alpha]_D^{24}+74.7\pm2.9°$ ($c=0.399$, $CHCl_3$). *Anal.* Calcd. for $C_{30}H_{27}O_2N$: C, 81.22; H, 8.41; N, 3.16. Found: C, 81.60; H, 8.77; N, 3.17.

**3α-Hydroxy-6β-vinyl-B-norandrostan-5β-trans-acrylaldehyde** (**22c**)——To a solution of the *trans*-cyanide (**22b**) (38 mg) in dry benzene (0.7 ml) was added a solution of diisobutylaluminum hydride in benzene (1.15 mmole/ml) (0.37 ml) with stirring and ice-bath cooling. After 1 hr of stirring at 5°, 4N sulfuric acid (2.5 ml) was added. Stirring was continued for 1 hr at 12° before the reaction mixture was diluted with ice-water and extracted with ether–methylene chloride (4:1). The organic layer was washed with water, dried, and evaporated to leave 28 mg of a residue, which was crystallized from ether–pentane to give 20 mg of the *trans*-aldehyde (**22c**), mp 62—63°. An analytical sample melts at 65—66°. IR $\nu_{max}^{CCl_4}$ $cm^{-1}$: 3616, 2750, 1693, 1639, 1628, 915. UV $\lambda_{max}$ m$\mu$ ($\varepsilon$): 231 (16600). NMR $\tau$: 3.87 (1H, q, CH=CH-CHO, $J=16.1$, 7.2 Hz), 3.09 (1H, d of d, CH=CH-CHO, 16.1, 1.5 Hz), 0.50 (1H, d, CHO, $J=7.2$ Hz). $[\alpha]^{23}-41.1+2.2°$ ($c=0.372$, $CHCl_3$). *Anal.* Calcd. for $C_{23}H_{34}O_2$: C, 80.65; H, 10.01. Found: C, 80.75; H, 10.23.

**3α-Hydroxy-6β-vinyl-B-norandrostan-5β-*cis*-acrylaldehyde** (**23c**)——To a solution of the *cis*-cyankde (**23b**) in dry benzene (1.2 ml) was added a solution of diisobutylaluminum hydride in benzene (1.15 mmole/ml) (0.88 ml) under nitrogen at room temperature. The mixture was stirred for 1 hr, treated with 4N sulfuric acid (3 ml), and worked up as above to leave 68 mg of a residue, which was crystallized from carbon tetrachloride to give 52 mg of the *cis*-aldehyde (**23c**), mp 157—159° in 79% yield. An analyticzl sample melts at 158—159°. IR $\nu_{max}$ $cm^{-1}$: 3587, 1677, 919. UV $\lambda_{max}$ m$\mu$ ($\varepsilon$): 239 (7,300). $[\alpha]_D^{24}-62.3\pm4.3°$ ($c=0.244$, $CHCl_3$).

**Formyloleffination of 21b with Sodium Diethyl β-(Cyclohexylamino)vinylphosphonate**——To a slurry of sodium hydride (346 mg), 52.9% oil dispersion, washed with dry tetrahydrofuran to remove oil, was added a solution of diethyl β-(cyclohexylamino)vinylphosphonate (2.05 g) in dry tetrahydrofuran with stirring and ice-bath cooling under argon. After 20 min of stirring at 3°, a solution of **21b** (1.003 g) in dry tetrahydrofuran (12 ml) was added. The reaction mixture was stirred at room temperature for 3 hr. To destroy the excess of the reagent paraform (300 mg) was added with ice-bath cooling. The mixture was stirred for 15 min at room temperature, poured into ice-water, and extracted with ether–methylene chloride (4:1). The organic extract was washed with water, dried, and evaporated to leave 2.44 g of a residue, which was dissolved in benzene (50 ml). The solution was mixed with a solution of oxalic acid (1.99 g) in water (150 ml). The mixture was allowed to stand at room temperature overnight, and extracted with ether–methylene chloride (6:1). The organic layer was worked up to leave 1.35 g of a residue, which was mixed with 2N potassium carbonate (50 ml) and methanol. The mixture was refluxed for 20 min under nitrogen, concentrated *in vacuo*, diluted with ice-water, and extracted with ether–methylene chloride (6:1). The organic extract was worked up as usual to leave 1.018 g of a residue, which was crystallized from ether–pentane to give 627.2 mg of *trans*-aldehyde (**22c**), mp 62—63°. The mother liquor was evaporated to leave 454 mg of a residue, which was chromatographed on alumina (13 g). Fraction eluted with benzene–$CHCl_3$ (9:1 to 2:1) were crystallized from ether–pentane to yield 110 mg of (**22c**), mp 60—62°. The total yield was 91.6%.

**3,3-Ethylenedioxy-5β-cyano-6β-vinyl-B-norandrostane** (**24**)——A mixture of the cyanoketone (**5**) (534 mg), *p*-toluenesulfonic acid monohydrate (32 mg), ethylene glycol (2 ml), and dry benzene (30 ml) was refluxed under removal of water with silica gel for 2 hr. The mixture was cooled, poured into cold 2N sodium carbonate, and extracted with methylene chloride. The methylene chloride extract was worked up to leave 604 mg of a residue, which was crystallized from ether–pentane to give 443 mg of the cyanoketal (**24**), mp 87—88°. IR $\nu_{max}^{CCl_4}$ $cm^{-1}$: 3082, 2220, 1642, 921. $[\alpha]_D^{23}+8.5\pm0.5°$ ($c=1.032$, $CHCl_3$). *Anal.* Calcd. for $C_{23}H_{33}O_2N$: C, 77.70; H. 9.36; N, 3.94. Found: C, 77.68; H, 9.57; N, 3.77.

**3,3-Ethylenedioxy-6β-vinyl-B-norandrostane-5β-*trans*-acrylaldehyde** (**26a**)——To the cyanoketal (**24**)

(809 mg) was added a solution of diiosbutyl aluminum hydride in tetrahydrofuran at 3° under nitrogen. The mixture was allowed to stand at 3° for 5.5 hr, poured into cold 2N sodium hydroxide, and extracted with methylene chloride. The methylene chloride extract was washed with water, dried, and evaporated to leave 804 mg of a residue, which was dissolved in tetrahydrofuran (45 ml) and methanol (15 ml). The solution was mixed with a buffer solution (sodium acetate 1.5 g, 1.5 ml, and water 15 ml), refluxed for 10 min under nitrogen, cooled, poured into 2N sodium hydroxide, and extracted with ether–methylene chloride (3:1). The organic extract was worked up to leave 820 mg of the crude aldehyde (25 ). A solution of the above aldehyde (**25**) (820 mg) was added to a cold (3°) solution of sodium diethyl β-(cyclohexylamino)vinylphosphonate prepared from sodium hydride (348 mg), 52.9% oil dispersion diethyl β-(cyclohexylamino)vinylphosphonate (2.0 g), and dry tetrahydrofuran (20 ml) as previously described. The mixture was stirred at room temperature overnight under nitrogen, poured into water, and extracted with ether. The ethereal extradt was worked up to leave 2.203 g of a residue, which was dissolved in benzene (40 ml). The solution was mixed with sodium acetate (12.3 g), acetic acid (9.0 g), and water (40 ml). The mixture was shaken at room temperature overnight, poured into 2N sodium hydroxide, and extracted with ether. The ethereal extract was worked up to leave 1.803 g of a residue, which was chromatographed on alumina (30 g). Fractions eluted with petroleium ether–benzene (4:1 to 1:1) were crystallized from ether–pentane to yield 511 mg of the formylolefin (**26a**), mp 98—101°. An analytical sample melts at 104.5—105.5°. IR $\nu_{max}^{CCl_4}$ cm$^{-1}$: 3058, 2707, 1697, 1627, 917. *Anal.* Calcd. for $C_{25}H_{36}O_3$: C, 78.08; H, 9.44. Found: C, 77.83; H, 9.46. $C_{25}H_{36}O_3$: C, 78.08; H, 9.44. Found: C, 77.83; H, 9.46.

**3α-Tosyloxy-6β-vinyl-B-norandrostane-5β-*trans*-acylaldehyde (22d)**——A solution of the *trans*-aldehyde (**22c**) (500 mg) and *p*-toluenesulfonyl chloride (518 mg) in dry pyridine (6 ml) was allowed to stand at room temperature overnight. To the solution was added water (0.3 ml) with ice–bath cooling. The mixture was allowed to stand for 1 hr, poured into ice–water, and extracted with ether–methylenechloride (3:1). The organic extract was washed successively with 2N hydrochloric acid (50 ml), water, 2N sidoum hydroxice (10 ml), and water, dried, and evaporated to leave 702 mg of a residue, which was crystallized from ether–pentane to give 634.5 mg of the tosylate (**22d**), mp 156—157°. An analytical sample melts at 159—160°. IR $\nu_{max}$ cm$^{-1}$: 2730, 1686, 1626, 1600, 1361, 1172. UV $\lambda_{max}$ mμ (ε): 226.5 (26320). $[\alpha]_D^{25}$ −11.1±1.6° (*c*= 0.324, $CHCl_3$). *Anal.* Calcd. for $C_{30}H_{40}O_4S$: C, 72.54; H, 8.11. Found: C, 72.70; H, 8.14.

**Methyl 3β,5β-Etheno-3α-formyl-B-norandrostane-6β-carboxylate (39b)**——Through a cold (−73°) solution of the tosylate (**22d**) in dry methylene chloride (7 ml) and dry pyridine (0.1 ml) was introduced oxygen containing ozone until the solution acquired bluish violet color. The excess of ozone was expelled by passing dry argon. To the solution was added dimethyl sulfide (0.4 ml). The mixture was stirred at O° for 1hr, poured into ice–water, and extracted with ether–methylene chloride (9:1). The organic extract was worked up to leave 464 mg of a crude dialdehyde (**32**), to which was added a solution of pyrrolidine (0.1 ml) in dry methanol (10 ml) with stirring and ice–bath cooling under argon. The resulting mixture was stirred at room temperature for 1 hr, and evaporated *in vacuo* to dryness to leave 620 mg of crude salt (37), which was mixed with benzene (10 ml) and a pH 4.6 buffer solution prepared from acetic acid (1 ml), sodium acetate (1 g), and water (10 ml). The solution was stirred at room temperature for 2 hr, and then sodium bicarbonate (2 g) was added. Extraction of the mixture with ether–methylene chloride (5:1), followed by normal work-up of the extract, gave 269 mg of a residue, which was purified by preparative TLC (silica gel benzene: ether=4:1) to furnish 93 mg of the dialdehyde (**38**) in 36% over-all yield based on (**22d**). IR $\nu_{max}^{CCl_4}$ cm$^{-1}$: 2705, 1728, 1683, 1608. A mixture of the above dialdehyde (**38**) (39 mg) and chromium trioxide (40 mg)–pyridine (0.4 ml) complex was allowed to stand at 10° overnight. The mixture was diluted with ice–water containing sodium busilfite (400 mg), and partitioned between ether and 2N potassium carbonate. The ethereal layer was washed with water dried, and evaporated to leave 9.1 mg of a neutral residue containing mainly the unchanged dialdenyde (**38**). The aq. alkaline layer was acidified with 2N hydrochloric acid, and extracted with methylene chloride. The methylene chloride extract was worked up to leave 30.5 mg of a crude acid (**39a**). IR $\nu_{max}^{CCl_4}$ cm$^{-1}$: 2699, 2706, 1683. The above acid (**39a**) was esterified with diazomethane to afford 18 mg of the ester (**39b**). Short-path distillation gave an analytical sample, bp (bath) 200° (3×10$^{-3}$ mm). IR $\nu_{max}^{CCl_4}$ cm$^{-1}$: 2709, 1734, 1680, 1610. UV $\lambda_{max}$ mμ (ε): 256 (7500). $[\alpha]_D^{25}$ +53.0±1.2° (*c*= 0.758, $CH_3CH$). *Anal.* Calcd. for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.65; H, 9.09. The ester (**39b**) was converted to the corresponding 2,4-dinitrophenylhydrazone (**39c**), mp 257—258°. IR $\nu_{max}$ cm$^{-1}$: 3300, 1728, 1620, 1594. $[\alpha]_D^{25}$ +41.1±2.1° (*c*=0.382, $CHCl_3$). *Anal.* Calcd. for $C_{39}H_{36}O_6N_4$: C, 64.91; H, 6.76; N, 10.44. Found: C, 64.85; H, 6.74; N, 10.57.

**Methyl 3α-Methylene-3β,5β,-ethano-B-norandrostane-6β-carboxylate (40)**——A mixture of a crude acid (**39a**) (103 mg), 80% hydrazine hydrate (0.1 ml), and triethylene glycol (21 ml) was heated at 125° for 1 hr, and then potassium hydroxide (118 mg) was added. The temperature of the mixture was, raised to 210° over 30 min. The reaction solution was heated at this temperature for 1 hr, cooled, and partitioned between methylene chloride and 10% potassium hydroxide. The methylene chloride extract was washed with water, dried, and evaporated to leave 26 mg of a neutral residue. The aq. alkaline layer was acidified with 2N hydrochloric acid, and extracted with methylene chloride. The methylene chloride extract was worked up to leave 59 mg of an acidic residue containing the desired acid (**1**). Esterification of the residue with diazomethane afforded 65 mg of a residue, which was purified by preparative TLC to furnish 22 mg

of the ester (**40**). Short-path distillation afforded an analytical sample, bp (bath) 130° ($5\times10^{-3}$ mm). IR $\nu_{max}^{CCl_4}$ $cm^{-1}$: 3069, 1735, 1659, 876. NMR $\tau$: 9.25 (3H, s, 18-$CH_3$), 9.16 (3H, s, 19-$CH_3$), 6.38 (3H, s, $CO_2$-$CH_3$), 5.33 (1H, d, $J$=2.8 Hz), 5.20 (1H, d, $J$=2.8 Hz). $[\alpha]_D^{28}+34.4\pm1.4°$ ($c$=0.302, $CH_3OH$). CD (methanol) $[\theta]$ (m$\mu$): −4117 (220) (maximum). *Anal.* Calcd. for $C_{23}H_{34}O_2$: C, 80.65; H, 10.01. Found: C, 80.72; H, 10.07.