(62.5 ml, 100 mmol) was added with stirring (glass-covered magnetic bar). After 5 min the mixture was black, chloride **24** (1.91 g, 10.0 mmol) was added, and stirring was continued for 24 hr at room temperature. Water was added dropwise until gas evolution ceased and then 50 ml of water was introduced. The ether layer was separated, and the water layer was extracted with ether. The ether was distilled through a Vigreux column, and the residual oil was molecularly distilled to give 1.11 g of a mixture of **24**, **25**, and **14**. These were separated by chromatography on silica gel–silver nitrate (elution with ether) to furnish 660 mg of **25**: $\delta_{TMS}^{CDCl_3}$ 1.54 (br s, 3, methyl), 2.3–2.8 (m, 6, methines), 5.57 (m, 1, olefinic proton on substituted cyclobutene ring), 5.65–5.84 (m, 2, olefinic), and 5.87 (s, 2, cyclobutene). *Anal.* Calcd for $C_{13}H_{14}$: C, 91.71; H, 8.29. Found: C, 91.88; H, 8.29.

***exo*-3-Methyltricyclo[4.4.2.0^{2,5}]dodecatetraene (26).** A 200-mg sample of **25** was passed through a quartz tube packed with quartz chips at 10 mm and 550° with a slow stream of nitrogen. Gas chromatography of the pyrolysate (collected at −70°) showed low boilers, a small amount of starting material, one large product peak, and trace amounts of several other materials. The product was purified by preparative scale vpc (58 mg): $\delta_{TMS}^{CDCl_3}$ 1.54 (br s, 3, methyl), 2.5–2.9 (m, 2, methine), 3.10 (br s, 2, methine), and 5.5–6.2 (m, 7, olefinic). *Anal.* Calcd for $C_{13}H_{14}$: C, 91.71; H, 8.29. Found: C, 91.54; H, 8.30.

Pyrolysis of 24. A 380-mg sample of **24** was pyrolyzed as above at 575° and 2 mm. Vpc analysis (SF-96 column at 140°) of the condensate signaled the presence of **24** (10%), **27** (86%), and **28** (4%). Preparative scale vpc gave 120 mg of **27**: $\delta_{TMS}^{CDCl_3}$ 2.80 (m, 2, methine), 3.15 (m, 1, methine), 3.33 (m, 1, methine), and 5.5–6.3 (m, 7, olefinic). *Anal.* Calcd for $C_{12}H_{11}Cl$: C, 75.59; H, 5.82. Found: C, 75.81; H, 5.62.

Chloride **28** was similarly isolated (16 mg); $\delta_{TMS}^{CDCl_3}$ 2.7 (m, 2, methine), 3.35 (br s, 2, methine), 5.65 (m), 6.85 (br s), 5.96, 6.16, and 6.32 (total olefinic, 7 H).

Another thermal rearrangement at 500° and 15 mm gave low boilers and the same three substances in a ratio of 39:48:12.

Reduction of 27.[34] A mixture of 90.9 mg (0.476 mmol) of **27**, 1 ml of *tert*-butyl alcohol, and *ca.* 200 mg (~9 mg-atoms) of sodium was added to 2 ml of anhydrous tetrahydrofuran and refluxed under nitrogen for 4 hr. After cooling, the excess sodium was removed and 10 ml of water was added. After extraction with pentane and methylene chloride, the combined organic layers were dried and evaporated to yield a pale yellow oil which was purified by preparative vpc (SF-96, 6 ft, 140°). There was obtained 15.5 mg of **29**: $\delta_{TMS}^{CDCl_3}$ 2.47 (br s, 6, methylenes and methines), 2.90 (m, 2, methines), 5.22 (t, 2, cyclobutene), and 5.80 (m, 4, olefinic). *Anal.* Calcd for $C_{12}H_{14}$: C, 91.08; H, 8.92. Found: C, 91.12; H, 8.99.

Acknowledgment. We wish to thank Badische Anilin und Soda Fabrik for a generous gift of the cyclooctatetraene required for this research endeavor.

(34) The authors thank M. J. Kukla for his assistance in performing this experiment.

The Stereocontrolled Total Synthesis of *dl*-Gibberellin A_{15}

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Abstract: The first total synthesis of *dl*-gibberellin A_{15} (**1**) is described. The tetracyclic α,β-unsaturated ketone **6**, a key intermediate in our previous total synthesis of diterpene alkaloids, was transformed by B ring contraction to the B-nor tetracyclic intermediate **40a**, lacking only the D ring of the gibbane skeleton. This intermediate was converted into the α,β-unsaturated ketone **54**, to which hydrocyanation was successfully applied giving the *cis*-9aβ-cyano 7-ketone (**55**) stereoselectively. The stereochemistry of **55** was determined by dipole moment measurement. Two-carbon chain lengthening of the 9aβ-formyl derivative **60b** derived readily from **55** gave **61a**, which, after tosylation of the 7α-hydroxyl and diacetoxylation of the formyl group, was ozonized selectively giving the 10β-formyl derivative **66**. This intermediate was subjected to a new cyclization method devised for the present purpose giving the hexacyclic intermediate **69** as a mixture of four possible stereoisomers, which, by a three-step sequence, was transformed, with loss of unnecessary asymmetries at C_8, C_9, and C_{13}, into the pentacyclic carboxylic acid **73a** having the complete A–B–C–D structure of gibberellin A_{15}. The intermediate **73a** was finally transformed to *dl*-gibberellin A_{15} by seven-step conversion. The synthesis is perfectly stereocontrolled, and also regioselective except for the final δ-lactone formation step. As expected, the synthetic *dl*-gibberellin A_{15} shows half of the activity of the natural material on rice (Tanginbozu) seedling bioassay.

The discovery[1a] in 1938 of an important class of plant hormones, gibberellins, in the metabolites of *Gibberella fujikuroi*, led to a great deal of interest in the study of the isolation, separation, and structural elucidation of each component,[1b] culminating in the X-ray crystallographical determination[2] of the structure of gibberellic acid, a representative of this class. Since then, interest has been directed toward synthetic and biogenetic studies, and many ingenious approaches to construct gibberellin molecules have been reported in the past decade.[3] Very recently, Mori, *et al.*,[4] by connecting their totally synthetic intermediate with

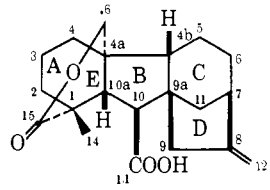
(1) (a) T. Yabuta and Y. Sumiki, *Nippon Nogei Kagaku Kaishi*, 14, 1526 (1938). (b) For a review, see J. R. Hanson, "The Tetracyclic Diterpenes," Pergamon Press, Oxford, 1968, p 41.

(2) F. McCapra, A. I. Scott, G. A. Sim, and D. W. Yong, *Proc. Chem. Soc.*, 185 (1962).

(3) (a) H. J. E. Loewenthal and S. K. Malhotra, *ibid.*, 230 (1962); *J. Chem. Soc.*, 990 (1965); (b) Y. Kos and H. J. E. Loewenthal, *ibid.*, 605 (1963); (c) G. Stork, S. Malhotra, H. Tompson, and M. Uchibayashi, *J. Amer. Chem. Soc.*, 87, 1148 (1965); (d) L. J. Dolby and R. J. Milligan, *ibid.*, 88, 4536 (1966); (e) A. Tahara and O. Hoshino, *Tetrahedron Lett.*, 5031 (1966); (f) R. A. Bell, R. E. Ireland, and L. N. Mander, *J. Org. Chem.*, 31, 2536 (1966); (g) H. J. E. Loewenthal and H. Rosenthal, *Tetrahedron Lett.*, 3693 (1968); (h) U. R. Ghatak, J. Chakravarty, and A. K. Banerjee, *Tetrahedron*, 24, 1577 (1968); (i) H. O. House, J. F. Sauter, W. G. Kenyon, and J. J. Riehl, *J. Org. Chem.*, 33, 957 (1968); (j) Y. Kitahara, T. Kato, M. Funamizu, N. Ototani, A. Inoue, and H. Izumi, *Chem. Commun.*, 1632 (1968); (k) D. J. Beames and L. N. Mander, *ibid.*, 498 (1969); (l) S. K. Dasgupta, S. R. Ghosh, and U. R. Ghatak, *ibid.*, 1253 (1969); (m) E. E. Ziegler and M. E. Condon, *Tetrahedron Lett.*, 2315 (1969); (n) T. Hori and K. Nakanishi, *Chem. Commun.*, 528 (1969); (o) A. A. Shchegolev and V. F. Kucherov, *Bull.*

four relay compounds, have succeeded in formal total syntheses of the C-19 gibberellins: GA_2, A_4, A_9, and A_{10}.

As part of our series of studies on total syntheses in the diterpene and diterpene alkaloid field,[5] we planned to synthesize the gibberellins and selected gibberellin A_{15} (**1**) as the first target. This compound was chosen because gibberellin A_{15}, isolated from metabolites of *Gibberella fujikuroi*, is a member of the C-20 gibberellin family exhibiting potent biological activity as a plant growth stimulator, because it has been speculated that this gibberellin is an intermediate in a biogenetic pathway from (−)-kaurene to gibberellin A_3,[6,7] and also because the molecule offers several structural advantages. Thus, the structure, as elucidated by Hanson,[8] and depicted in formula **1**, shows an absence of the A-ring functionalities and the C_7-hydroxyl group usually contained by other members of the series; also the attachment of the C_{16} carbon, which could subsequently be removed to afford C-19 gibberellins, was expected to reduce the stereochemical problems in the synthesis. We have successfully synthesized this



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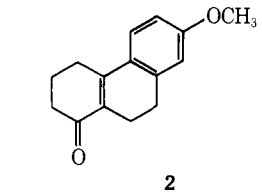
compound, albeit in a racemic form, thus representing the first total synthesis of a C-20 gibberellin in a rigorous sense. The present paper provides a full account of this work, an outline of which has previously been reported.[9]

I. The General Synthetic Plan

At the outset of the work, a general synthetic plan was made as follows. It appeared to us advantageous to initiate construction by build-up of the AEB ring system prior to the BCD ring system on the following grounds. (1) The AEB ring is regarded as a derivative of *trans*-hydrindane, whereas the BCD ring moiety is a *cis*-hydrindane derivative; since, generally speaking, synthesis of a *trans*-hydrindane derivative is more difficult than that of a cis counterpart, the precedence of the AEB ring construction may be preferable. (2) If the stereochemistry of the AEB part (three asymmetries at C_1, C_{4a}, and C_{10a}) is first secured, production of the remaining four asymmetries at C_{4b}, C_7, C_{9a}, and C_{10} should be easy, unless any strong acid is subsequently employed. As for the B ring precursor, a six-membered ring located intermediately in a perhydrophenanthrene system was considered to be most suitable, since from this the trans–anti relation at C_{10a}, C_{4a}, and C_{4b} of the B ring might be easily produced, functionalization and subsequent ring contraction then yielding the required cyclopentanecarboxylic acid moiety readily.

In our previous work on the total synthesis of diterpene alkaloids, we prepared the tetracyclic compounds **4** and **6** as key intermediates from the tricyclic conjugated ketone **2** *via* the cyano compound **3** by seven and nine



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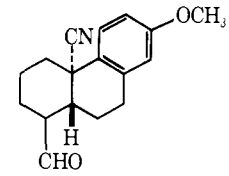
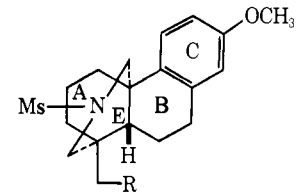
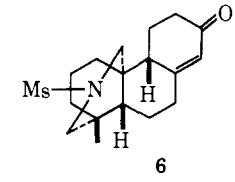


3



4, R = H
5, R = OH



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steps, respectively. Now, these intermediates and the related compound **5** are clearly promising candidates for starting synthesis on the above lines. They are already provided with the correct stereochemistry for the AEB ring system. The *N*-mesylpiperidine ring is expected to be stable to further elaboration and readily convertible to the E ring δ-lactone *via* the azomethine by applying the method of ApSimon, *et al.*,[10] developed in diterpene alkaloid chemistry. Moreover, suitable functionalization of the B ring for ring contraction should be possible in several ways.

For the ring D construction, we planned to apply a new hydrocyanation method[11] developed in our laboratory for a hydrindenone intermediate such as **7**, since the steric course of the hydrocyanation of such a compound has been known to lead exclusively to a *cis*-cyano ketone[12] such as **8**, which is undoubtedly an excellent base for the ring D construction. The cyano ketone **8** may be converted into the next intermediate **9** by two-carbon chain lengthening at the nitrile carbon and by conversion of the 7-keto group into an appropriate α-oriented leaving group Y. Double cyclization of **9** comprising intramolecular Michael-type addition and concomitant substitution would give the hexacyclic intermediate **10**, which subsequently would lead to the bridged α,β-unsaturated aldehyde **11** by β elimination. The Wolff–Kishner reduction of **11** yielding the desired D ring with the exo methylene was thought to be readily realizable by

Acad. Pol. Sci., Ser. Sci. Chim., 1456 (1969); (p) E. J. Corey, M. Narisada, T. Hiraoka, and R. A. Ellison, *J. Amer. Chem. Soc.*, **92**, 396 (1970); (q) K. Mori, M. Matsui, and Y. Sumiki, *Tetrahedron Lett.*, 429 (1970).

(4) (a) K. Mori, M. Shinozaki, N. Itaya, T. Ogawa, M. Matsui, and Y. Sumiki, *ibid.*, 2183 (1968); (b) K. Mori, M. Shinozaki, N. Itaya, M. Matsui, and Y. Sumiki, *Tetrahedron*, **25**, 1293 (1969).

(5) (a) W. Nagata, T. Sugasawa, M. Narisada, T. Wakabayashi, and Y. Hayase, *J. Amer. Chem. Soc.*, **85**, 2342 (1963); **89**, 1483 (1967); (b) W. Nagata, M. Narisada, T. Wakabayashi, and T. Sugasawa, *ibid.*, **86**, 929 (1964); **89**, 1499 (1967).

(6) 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.

(7) *Cf.* (a) B. E. Cross and K. Norton, *Chem. Commun.*, 535 (1965); (b) B. E. Cross, R. H. B. Galt, and K. Norton, *Tetrahedron*, **24**, 231 (1968).

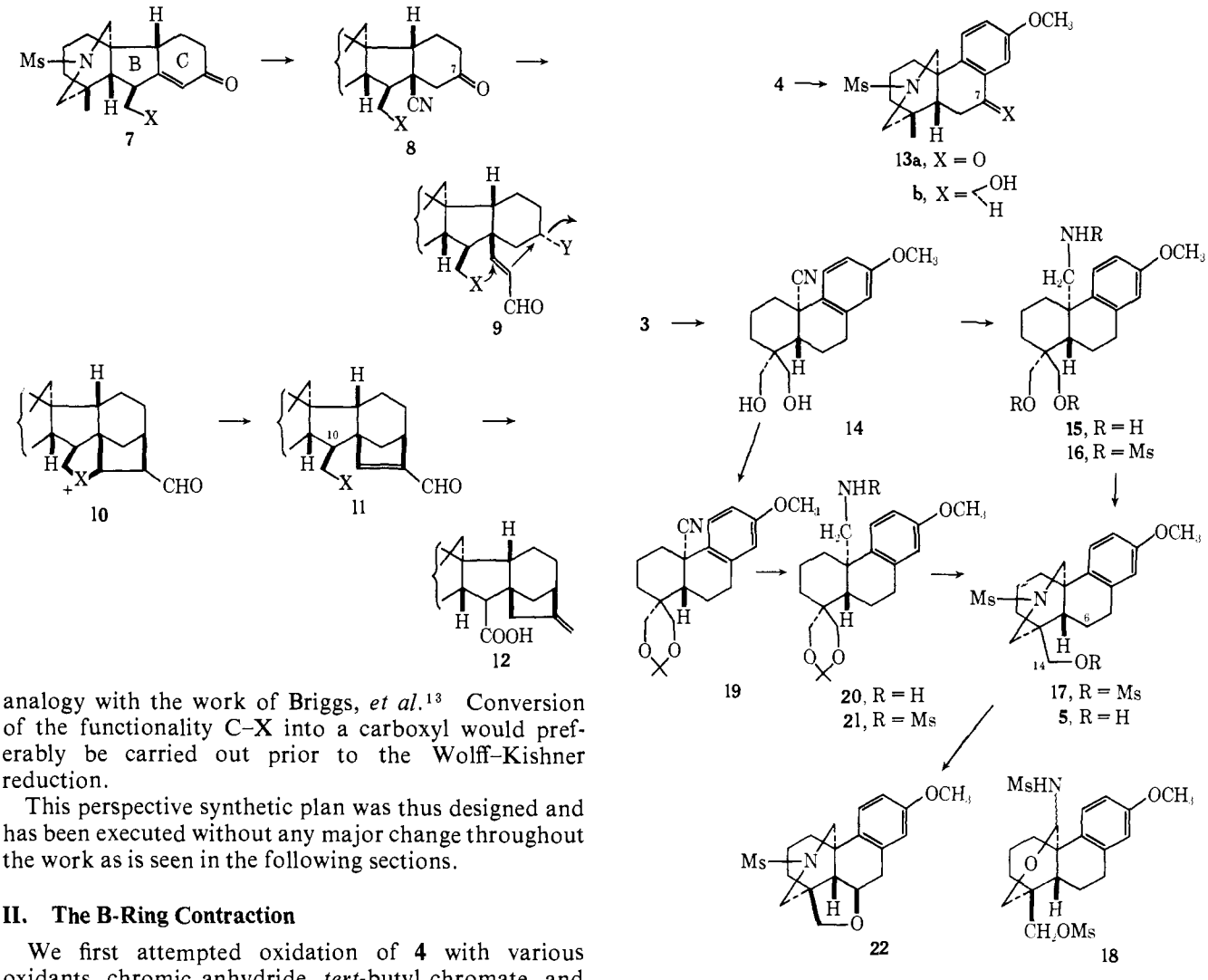
(8) J. R. Hanson, *ibid.*, **23**, 733 (1967).

(9) W. Nagata, T. Wakabayashi, Y. Hayase, M. Narisada, and S. Kamata, *J. Amer. Chem. Soc.*, **92**, 3202 (1970).

(10) J. W. ApSimon, O. E. Edwards, and R. Howe, *Can. J. Chem.*, **40**, 630 (1962).

(11) (a) W. Nagata, M. Yoshioka, and S. Hirai, *Tetrahedron Lett.*, 461 (1962); (b) W. Nagata and M. Yoshioka, *ibid.*, 1913 (1966); (c) for a full account, see W. Nagata, M. Yoshioka, and S. Hirai, submitted for publication.

(12) W. Nagata, M. Yoshioka, and T. Terasawa, submitted for publication.



analogy with the work of Briggs, *et al.*[13] Conversion of the functionality C–X into a carboxyl would preferably be carried out prior to the Wolff–Kishner reduction.

This perspective synthetic plan was thus designed and has been executed without any major change throughout the work as is seen in the following sections.

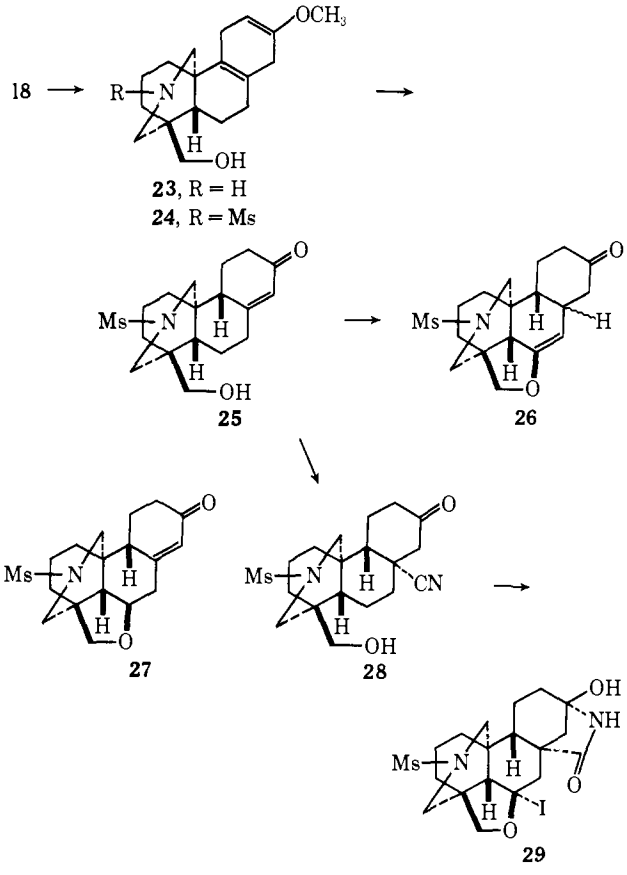
II. The B-Ring Contraction

We first attempted oxidation of **4** with various oxidants, chromic anhydride, *tert*-butyl chromate, and lead tetraacetate, in the hope of obtaining the 7-oxygenated product **13**. However, the results were by no means satisfactory for pursuing the synthesis further, the desired oxidation products **13a**, mp 174–175.5°, or **13b**, mp 175–176°, being formed only in low yield, with considerable recovery of starting material. This route was, therefore, abandoned without any detailed study.

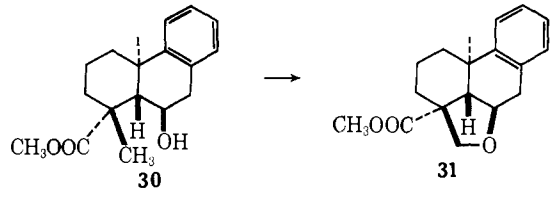
Next we intended to functionalize the B ring by intramolecular radical oxidation at C_6 by use of the hydroxyl at C_{14} in **5**. For this purpose, compound **5** was prepared by two routes starting from the cyano aldehyde **3**. Aldolization and concomitant reduction of **3** produced in good yield the diol **14**, mp 203–205°, which on lithium aluminum hydride reduction at 110° gave the hydroxylamine **15**, mp 217–218°. Crude **15**, after mesylation (**16**), was cyclized with sodium hydride in tetrahydrofuran giving **17**, mp 198–200°, accompanied by a small amount of **18**, mp 206–209°, which was obviously derived from an aldimine formed in the reduction step. Compound **17** was demesylated with lithium aluminum hydride to yield **5**, mp 170–170.5°. The overall yield of **5** was 37% based upon the cyano aldehyde **3**. In an alternative route, the cyano diol **14** was first converted into the acetonide **19**, mp 126–128°, which after reduction with lithium aluminum hydride (**20**) and subsequent mesylation (**21**, mp 156–157°), was cyclized directly to **5** by heating **21** with 5.5 equiv of *p*-toluenesulfonic acid hydrate in benzene. The second route gave 27% overall yield based upon the same starting compound **3**. The well-known oxidation method for bridging an ether linkage was applied to compound **5**. Refluxing a benzene solution of **5** with 1.5 equiv of lead tetraacetate gave, besides 35% recovery of the starting material, a less polar product of mp 216–217°, in 23% yield, whose analyses and spectral data were consistent with the formula **22**. Attempts, including use of iodine together with lead tetraacetate, to raise the yield were in vain. Considering that the presence of the anisole ring might disfavor the oxidation, we reduced the aromatic ring first. Compound **5** was, thus, reduced with lithium in liquid ammonia to yield **23**, mp 178–180°, which, after remesylation with mesyl chloride and aqueous alkali **24**, mp 165–168°, was treated with hydrochloric acid giving the enone **25**, mp 210–211°, in 73% overall yield. The trans-anti configuration of this enone was assigned by analogy with the result of analogous reduction of the 14-deoxy derivative **4** leading to the enone **6**.[5] The hydroxyenone **25** was subjected to lead tetraacetate–iodine oxidation under visible light according to the method of Meystre, *et al.*,[14] and the crude product was treated

(13) L. H. Briggs, B. F. Cain, R. C. Cambie, and B. R. Davies, *J. Chem. Soc.*, 1850 (1962).

(14) (a) Ch. Meystre, J. Kalvoda, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, 46, 2844 (1963); (b) Ch. Meystre, K. Heusler, J.



with zinc and acetic acid. The result was quite disappointing, none of the expected product **27** being isolated. The major part (61%) of the starting enone **25** was recovered and the crystalline product isolated in only 2% yield was **26**, mp 185–186°, whose structure was tentatively assigned as depicted in the formula on the basis of spectral data. We attempted the same reaction with the cyano ketone **28**, mp 204–205° or mp 230–231° (dimorphism), which was prepared in 58% yield by hydrocyanation of the enone **25** using triethyl aluminum and hydrocyanic acid and was deduced to have the trans C–D configuration by analogy with the 14-deoxy series.[5] Oxidation, zinc–acetic acid reduction, and successive treatment with alkali gave the product **29**, mp 285–287° dec, in only 9% yield. The structure of **29** was consistent with the physical data. In view of the poor yields of the oxidation products **22**, **26**, and **29**, the route *via* oxidative cyclization was abandoned. It may be worth noticing that the poor result in the present oxidation is in marked contrast to that obtained by Tahara and Hirao.[15] They succeeded in preparing the cyclized product **31** in good yield by oxidation of methyl 6β-hydroxydeoxyenantiopodocarpate (**30**) by the same method.[14] The poor



Kalvoda, P. Wieland, G. Anner, and A. Wettstein, *Experientia*, 17, 475 (1961).

(15) A. Tahara and K. Hirao, *Chem. Pharm. Bull.*, **12**, 984 (1964).

results in the present cases may be accounted for in terms of unfavorable entropy factors in the transition state, since other factors are by no means considered to disfavor the present oxidation, *e.g.*, the distances between the hydroxyl oxygen and the hydrogen to be abstracted as a radical are almost the same in both cases, and, moreover, formation of a carbon radical should even be favored in the present case because of the secondary nature of the carbon atom attacked.

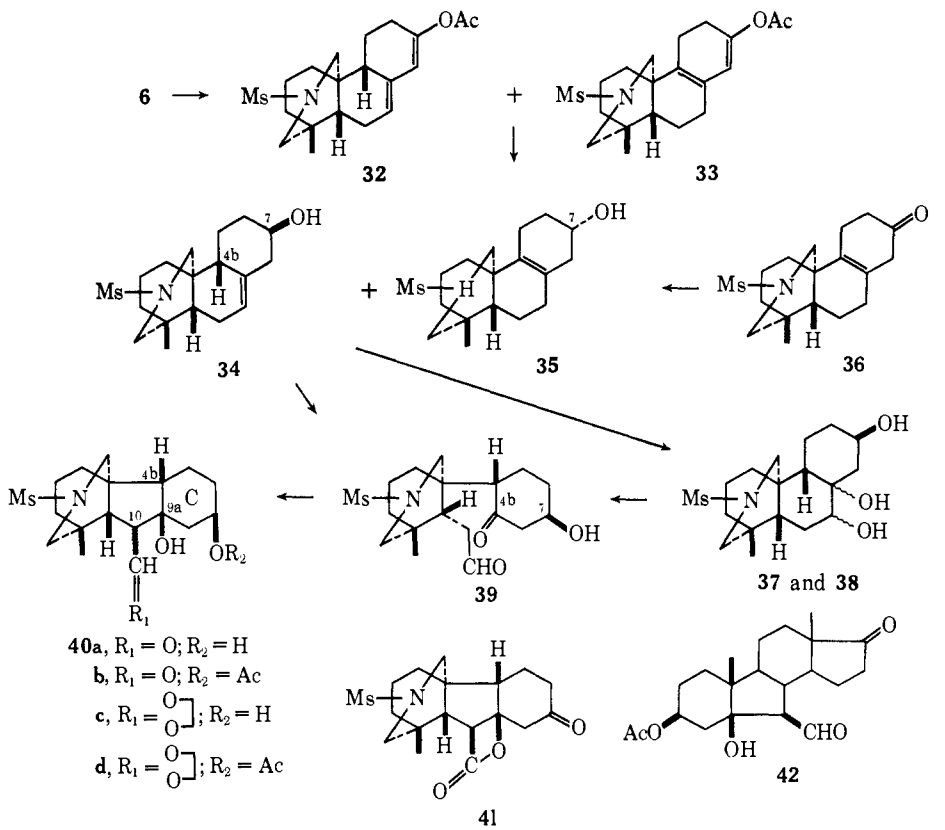
We finally adopted another route, which was initially thought to be most promising, and by which the successful B-ring contraction has been realized. The route consists of two well-known transformation methods used often in the steroid field, the first being used for conversion of a steroidal 4-en-3-one into a corresponding 5-en-3β-ol[16] and the second for conversion of the latter to a B norsteroid.[17] Thus, heating the enone **6** with isopropenyl acetate at reflux in the presence of *p*-toluenesulfonic acid yielded a mixture of isomeric dienol acetates, **32** and **33**, with **32** predominating. Partial formation of the homoannular dienol acetate **33** was evident from the uv spectrum of the crude product showing a maximum (ε 1800) at 281 mμ besides a strong absorption (ε *ca.* 10,000) at 235.5 mμ. The crude reaction mixture was, without purification, subjected to sodium borohydride reduction in alkaline medium. The resulting crystalline product, despite its sharp mp of 177–179°, was revealed to be a mixture of two isomeric hydroxyolefins, **34** and **35**, in a ratio of *ca.* 4:1 with **34** predominating. Separation of this mixture failed and, therefore, the ratio was estimated from the intensity of the olefinic proton signal of **34** in the nmr spectra of the mixture. The isomer **35**, mp 238–239°, was, however, obtained in pure state from this mixture by utilizing its lower reactivity in subsequent oxidations, or from the known enone **36**[5b] by sodium borohydride reduction, as described below, and its nmr spectrum was used as a criterion for its estimation. Clearly, the desired hydroxyolefin **34** originates from the corresponding dienol acetate **32** and the isomer **35** from **33**. Configurational assignment of the 4bβ-hydrogen and the 7β-hydroxyl (equatorial) in **34** was based upon stability considerations and the modes of the reactions. The structure assigned to **35** was confirmed by its identity with an authentic specimen derived from the enone **36**. Configuration of the 7-hydroxyl in **35** was tentatively assigned α (equatorial) by analogy with a result from reduction of a steroidal 5(10)-en-3-one.[18]

The hydroxy olefin mixture was first subjected to osmium tetroxide oxidation yielding two epimeric triols, **37** and **38**, separated chromatographically, and the unchanged hydroxyolefin **35** in 14% yield, the last compound of mp 236–238° thus being obtained in pure state. No effort was made to assign the stereochemistry of the two triols and these were separately subjected to periodic acid oxidation followed by cyclization (see below) giving the same tetracyclic aldehyde **40a** *via* the ketoaldehyde **39**. The spectral data of **39** were consistent with the assigned structure. The same com-

(16) B. Belleau and T. F. Gallagher, *J. Amer. Chem. Soc.*, 73, 4458 (1951).

(17) K. Tanabe and Y. Morisawa, *Chem. Pharm. Bull.*, 11, 536 (1963).

(18) S. G. Levine, N. H. Eudy, and E. C. Farthing, *Tetrahedron Lett.*, 1517 (1963).



pound was obtained more conveniently from the hydroxyolefin mixture by a sequence of reactions: ozonization, zinc and acetic acid reduction of the ozonide, treatment of the resulting ketoaldehyde with aqueous sodium hydrosulfite, and decomposition of the adduct with a cold alkaline solution *in a two-phase system*. The ketoaldehyde **39** was readily cyclized to the tetracyclic aldehyde **40a** in contact with neutral alumina. For preparative use, isolation of the ketoaldehyde **39** was not necessary and the sodium hydrosulfite adduct was decomposed with sodium hydroxide in an aqueous solution giving **40a** directly. This key intermediate was thus prepared in 38% overall yield based upon the starting enone **6**. It is noteworthy that the isomeric hydroxyolefin **35** resisted the above ozonization and could therefore be recovered from the nonaldehydic fraction.

Configurations of the three asymmetries at C_{4b}, C_{9a}, and C_{10} relative to that of the 7β-hydroxyl in compound **40a** were assigned as depicted in the formula on the following grounds. It may be plausible to conclude that the stereochemistry of C_{4b} was retained throughout the transformation from **34**, since, firstly, no epimerization at C_{4b} is considered to have occurred along the path **34** → **37** (or **38**) → **39** → **40a**, in which no basic reagents were used (neutral alumina used in the last step should hardly epimerize the 4b carbon). Secondly, if epimerization had actually occurred in the last step, especially through the use of an aqueous alkaline solution for the cyclization, a configuration of the A–E ring residue trans to the 7β-hydroxyl in **39** (a diequatorial relation with regard to a chair cyclohexanone ring) is thought to be more stable than that of a cis relation, at least in a polar aqueous medium as employed; the hydrogen at C_{4b} should thus be oriented β. These arguments concerning the stereochemistry at C_{4b} were supported experimentally by the measurement of dipole moments of the 9a-carbonitriles **55** and **56** (see below). For determination of the configurations of the 9a-hydroxyl and the 10-formyl groups relative to the 7β-hydroxyl group, some derivatives, **40b**, **40c**, and **40d**, were prepared in the usual manner and their ir spectra were measured, the results being listed in Table I together with those for the other

Table I. Spectral Data of Several Perhydrofluorene Derivatives

	Ir, cm^{-1}, in CCl_4				Nmr (τ) in $CDCl_3$
	Hydroxyl		Ace-	Car-	OAc
Compd	C_7	C_{9a}	toxy	bonyl	C / H
40b		3588	1749	1717	4.77 br m
40c	3515	3555 (shoulder)			
40d		3560	1735		4.90 br m
46		3541		1725	
48b		3577	1749	1724	
53		3571		1726	
42					4.83 quin (J = 4 Hz)

related compounds. The band frequencies of the relevant functional groups indicate that the 9a-hydroxyl is hydrogen bonded[19] to the 7β-acetoxyl in **40b**, mp 209–212°, to the acetal oxygen in **40c**, mp 177–178°, **40d**, mp 203–205°, and **46**, mp 197.5–198°, to the 13-acetoxyl oxygen in **48b**, and to the vinyl group in **53**, and that the 7β-hydroxyl is hydrogen bonded to the 9a-hydroxyl in **40c**. It follows that all the substituents at C_7, C_{9a}, and C_{10} in these compounds are oriented cis and therefore β. At this stage, however, one cannot

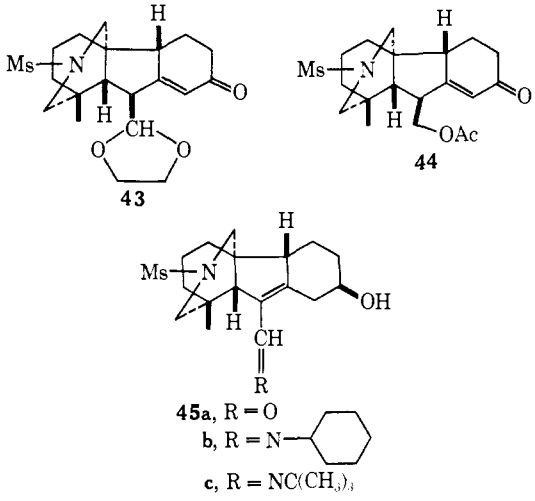
(19) *Cf.* Y. Matsui, M. Takasuka, and T. Kubota, *Shionogi Kenkyusho Nempo*, **15**, 125 (1965).

conclude a 10β configuration of the formyl group existing originally in **40a**, since one cannot rigorously exclude its possible epimerization at C_{10} during the transformations into the other functional groups. Decisive evidence for this point was provided by the fact that compound **40a** on mild oxidation with chromic anhydride–pyridine complex in methylene chloride[20] afforded the β-lactone **41**. Although its isolation failed owing to its instability, a strong band at 1830 cm^{-1} together with an additional band at 1724 cm^{-1} in the ir strongly indicated the formation of the keto β-lactone **41**. Thus, all the configurations in **40a** were established as depicted in the formula.

Finally, we briefly refer to the conformation of ring C in **40b** and **40d**. The nmr spectra of both compounds show a complex broad multiplet of C_7 hydrogen at τ 4.77 in **40b** and at 4.90 in **40d** as listed in Table I. These signal patterns are in contrast with those of the steroid analog **42**, which shows a typical quintet for an equatorial proton at τ 4.83, indicating that the conformation of ring C in **40b** and **40d** deviates from a normal chair.

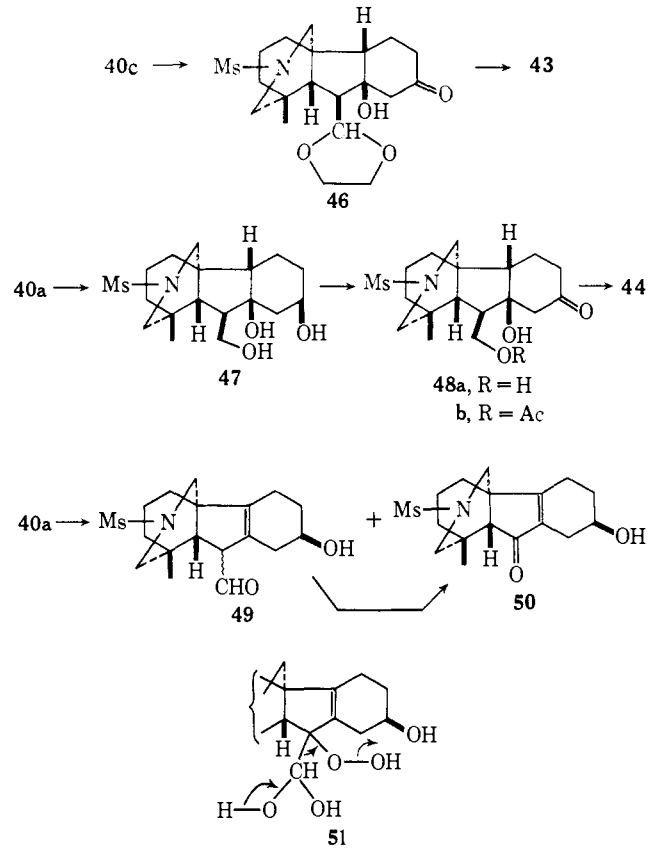
III. Build-up of the D Ring. Accomplishment of the Gibbane Skeleton Synthesis

We at first presumed that the enones **43** and **44** and the enal **45a** would be suitable precursors for construction of ring D, since these compounds were expected to undergo conjugate hydrocyanation smoothly to give 9a-cyano derivatives (although in order to effect 1,4 addition, the enal **45a** should be converted into the cyclohexylimino **45b** or the *tert*-butylimino derivative **45c** prior to hydrocyanation).[21] It was also anticipated that, whereas **45b** or **45c** having the imino function outside of the hydrindene ring would on hydrocyanation afford predominantly the C–D trans addition products,[12,21] compounds **43** and **44** having



43 44

the enone function inside of the ring would give exclusively the C–D *cis*-cyano ketones,[12] the stereochemistry being clearly favorable for D-ring synthesis. With these considerations in mind, preparation and hydrocyanation of **43** and **44** were attempted. Compound **40c** on oxidation with chromic anhydride in pyridine (**46**), followed by dehydration with thionyl chloride in pyridine, gave **43**, mp 200–201.5°. Compound **40a** was transformed into **44**, mp 135–136°, as outlined in the scheme by a sequence of reactions: sodium borohydride reduction giving **47** in a syrup, selective oxidation of **47** with *N*-bromosuccinimide to give **48a**, mp 208–209°, and dehydration of its acetate **48b**, mp 189–190°, with thionyl chloride in pyridine. Unfortunately, attempted hydrocyanation of both **43** and **44** failed even by our new methods,[11] resulting in recovery of the majority of the starting material. The failure of the hydrocyanation with these compounds seemed to be attributable to a retarding effect[11c] of the neighboring group oxygen by its participation with the C_{9a} reacting center. We therefore attempted preparation of **45a**, but in vain. Dehydration of **40a** with diluted aqueous base resulted in formation of the nonconjugated enal **49**, mp 175–177°, and the enone **50**, mp 180–182°, with **49** predominating, none of the desired conjugated enal **45a** being formed. The formation of **50** can be understood as a result of cooperation of molecular oxygen in the reaction giving primarily a hydroperoxide such as **51**, which then decomposes to **50**, as indicated. The view was supported by an independent experiment, in which compound **49**

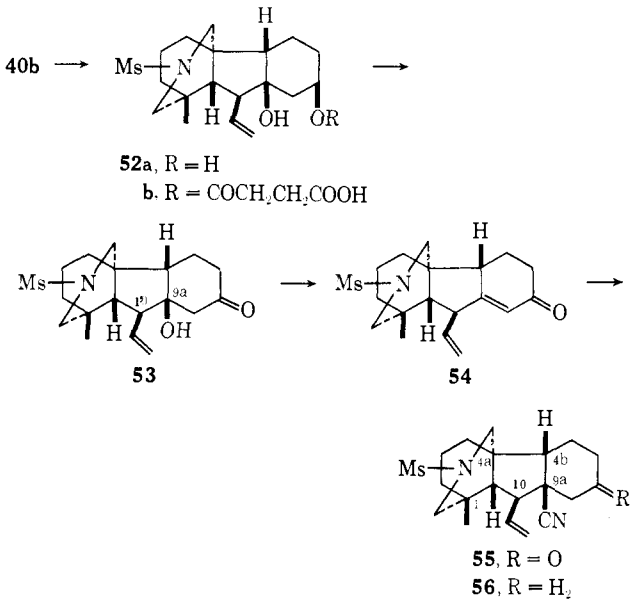


was converted into **50** by air oxidation in alkaline medium. Because of the probable instability, further study to prepare the conjugated enal **45a** was not carried out.

We next turned to the vinylic enone **54** as a more promising candidate for hydrocyanation, since the vinyl group acting as a precursor of the carboxyl was not thought to participate significantly with the C_{9a} reacting center. Thus, the Wittig vinylation of **40b** followed by alkaline hydrolysis gave **52a**, mp 196–198°, effectively

(20) J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968).
(21) W. Nagata, M. Yoshioka, T. Okumura, and M. Murakami, *J. Chem. Soc. C*, 2355 (1970).

isolated *via* the hemisuccinate **52b**, mp 96–102°. The overall yield was 60% based on the dihydroxyaldehyde **40a**. Compound **52a** was oxidized by Jones oxidation to **53**, mp 208–210° (92%), which on brief (2 min) treatment with 1.3 equiv of thionyl chloride in methylene chloride–pyridine at −73° afforded the desired dienone **54**, mp 216.5–218.5°, in 90% yield. The ir and uv data of **54** supported the assigned structure and not a doubly conjugated dienone structure. Hydrocyanation of the enone **54** with an excess of diethyl aluminum cyanide in methylene chloride at room temperature was now found to be successful as expected and gave the desired C–D *cis*-cyano ketone **55**, mp 214–215°, in 87% yield. The β configuration of the



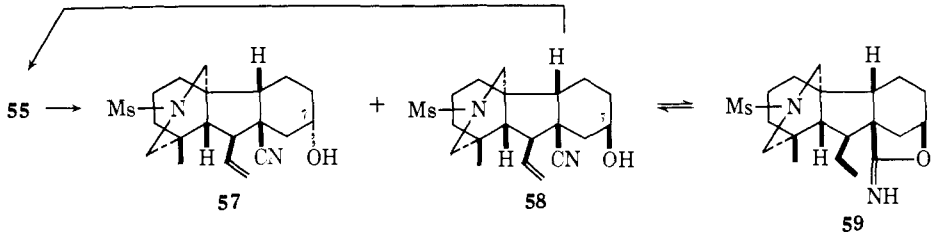
10-vinyl group in this series of compounds can be safely assigned, since the observed hydrogen bond between the 10-vinyl and the 9a-hydroxyl in **53** clearly shows the cis relation as discussed above and no epimerization was considered to occur at C_{10} during the transformation **52a** → **55**. A proof of the β configuration of the **4b** hydrogen has already been given and the assigned cis relation of the newly introduced cyano group to the 4bβ hydrogen was based on our empirical rule,[12] in which hydrocyanation of a hydrindenone gives a *cis*-cyano ketone predominantly or exclusively. Exclusive formation of *cis*-cyano ketones in hydrocyanation of 6β-vinylandrost-4-en-3-one derivatives performed as a model experiment[22a] supported this assignment. Confirmative evidence for the correctness of the assigned stereochemistry in **55** was provided by measurement of dipole moments of compound **55** and its deoxo derivative **56** as a reference compound, the latter being prepared by Wolff–Kishner reduction of the former. Using the values for the group moments of the keto, the cyano, and the methanesulfonyl amino group reported in the previous paper,[5a,23] calculations were carried out for the four possible stereoisomers of compounds **55** and **56**, on the assumption that the C ring may take a chair conformation and that the group moment of the 10β-vinyl does not affect the whole moment to a considerable degree. The values are summarized in Table II together with the observed values.

Table II. Dipole Moments Calculated and Observed for the 9a-Cyano Derivatives, **55** and **56**

	Configurations (C_{4b})	(C_{9a})	**55**, D	**56**, D
Calcd	β	β	4.24	3.85
	β	α	6.39	6.06
	α	β	6.87	6.57
	α	α	3.19	5.79
Obsd			3.8	3.45

As evident from Table II, only the values calculated for the isomers with a 4bβ and 9aβ configuration were found to be in good accordance with the observed values of 3.8 D for **55** and 3.45 D for **56**, supporting the presumed assignment. Thus, six of the seven asymmetries, at C_1, C_{4a}, C_{4b}, C_{9a}, and C_{10}, were correctly introduced in the key intermediate **55**.

We next turned to construction of the two-carbon bridge to form the D-ring portion with the exo methylene at C_8. For conversion of the 7-keto group into an α-oriented leaving group Y in **9**, the *cis*-cyano ketone **55** was subjected to lithium tri-*tert*-butoxyaluminum hydride reduction according to the literature,[24] in which 5β-cyano-17β-hydroxy-19-norandrostan-3-one was reported to be reduced with this reagent exclusively to the 3α-hydroxy (equatorial) derivative. Contrary to this result, the reduction product formed, also exclusively, was unequivocally proved to be the 7β-hydroxy (axial) carbonitrile **58**, mp 201–202°, by its quantitative conversion into the basic imino lactone **59**, mp 188–190°, on heating with *p*-toluenesulfonic acid in benzene. This contradictory result led us to reexamine the reduction of the steroid analog, and the product formed in *ca.* 90% yield was found to be the 3β-hydroxy-5β-cyano steroid in parallel with the result in the present case, indicating that the assignment was erroneously reversed in the literature.[25] The exclusive



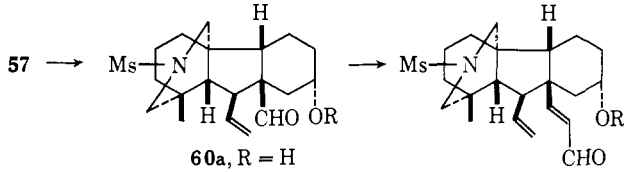
(22) (a) W. Nagata, M. Narisada, T. Wakabayashi, Y. Hayase, and M. Murakami, *Chem. Pharm. Bull.*, **19**, 1567 (1971); (b) W. Nagata, T. Wakabayashi, M. Narisada, M. Yamaguchi, and Y. Hayase, *ibid.*, **19**, 1582 (1971).

(23) The values of either −4.771, 0.925, and 0.0361 D or 3.187 −3.670, and 0.0361 D for the *x*, *y*, and *z* components [μ_{MsN} (*x*, *y*, *z*)] reported in ref 4a of the previous paper[5a] should be corrected to the values of either −0.925, −4.771, and 0.0361 D or 3.670, 3.187, and 0.0361 D. This error arose from the calculations being based upon mistaken axes; it does not, however, alter the given values of the whole dipole moments as calculated for the relevant cyano ketones.

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

formation of the *cis*-hydroxycarbonitrile (**58**) clearly shows that the angular cyano group strongly hinders approach of the bulky metal hydride reagent from the same side. However, the more stable *trans*-hydroxycarbonitrile (**57**) desired was readily prepared by Meerwein–Pondorf reduction of **55** under equilibrium conditions. Thus, refluxing a toluene solution of **55** in the presence of aluminum isopropoxide for 1.5 hr gave a 5:1 mixture of the epimeric alcohols **57** and **58**, with **57** predominating. Removal of the undesired cis isomer **58** from the mixture could be carried out conveniently by its conversion into the aforementioned imino lactone **59**, which was readily separated. The major trans isomer **57**, mp 161–162°, was unchanged on this treatment and obtained in 71% yield. The imino lactone **59** could be reconverted by base into the cis isomer **58**, which in turn was oxidized to the original cyano ketone **55** in 70% overall yield, the material thus being recycled.

For the next task, to elaborate the formylolefin side chain in **9**, the angular cyano group in **57** was converted into a formyl group by reduction with diisobutylaluminum hydride followed by hydrolysis with aqueous acetic acid and sodium acetate in tetrahydrofuran. The hydroxy group of the resulting hydroxyaldehyde **60a** was then protected with dihydropyran in the usual way giving the tetrahydropyranyloxyaldehyde **60b** in 81% overall yield based upon **57**. The aldehyde **60b**, mp 150–154°, was now subjected to the new method for formylolefination, which was recently[28] devised particularly for the present purpose in our laboratory. Thus, exposure of compound **60b** to

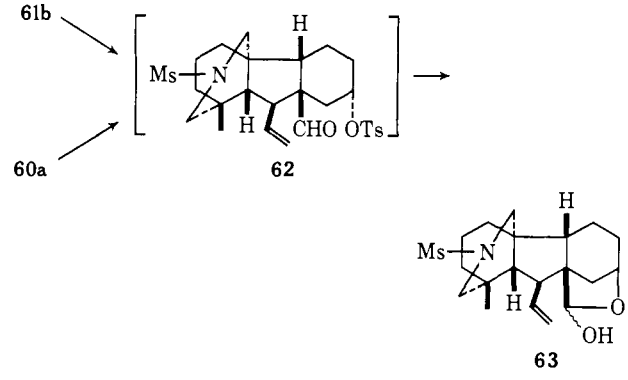


60a, R = H
b, R = THP

61a, R = H
b, R = Ts

sodium diethyl β-(cyclohexylamino)vinylphosphonate in dry tetrahydrofuran at room temperature followed by hydrolysis with aqueous oxalic acid in a two-layer system and subsequently with 10% perchloric acid in tetrahydrofuran gave the desired formylolefin **61a**, mp 194–197°, in excellent yield (87%) as expected. The assigned structure was supported by its spectral data and, in particular, the trans configuration of the newly formed double bond was verified by the large coupling constant of 16.2 Hz[29] between the two olefinic protons. It is conspicuous that only the trans formylolefin was formed in this reaction, as was the case in other examples reported in the previous paper.[28] The hydroxyformylolefin **61a** was then converted in quantitative yield into its amorphous tosylate **61b** provided now with an effective leaving group at the 7α position.

The next step required to reach the intermediate **9** in the general plan was the selective cleavage of the 10-vinyl to the formyl group. Model experiments[25b] using the steroidal analog suggested that, among the various ways, ozonization and subsequent reduction of the ozonide might be most promising in this case. Contrary to our expectation, however, difficulties arose in this selective ozonization. Thus, the tosyloxyformylolefin **61b** on exposure to ozone and successive treatment with zinc and acetic acid, or with dimethyl sulfide, in the standard manner, afforded a mixture in which the vinyl hemiacetal **63**, mp 181–183°, was detected as one of the major products. The same product



was obtained unequivocally on treatment of the hydroxyaldehyde **60a** with *p*-toluenesulfonyl chloride in pyridine, apparently *via* the same intermediate **62**, confirming the assigned structure of **63**. Formation of this compound clearly indicated a preferential attack of ozone at the conjugated double bond, which may be more exposed to the reagent than the 10β-vinyl group. Several unsuccessful attempts, *e.g.*, changing the polarity of the solvents, careful removal of moisture from the solvents, lowering the temperature to about −100°, careful control of the amount and flow speed of ozone, adding various Lewis acids or organic bases, etc., were made to improve the result. In view of the apparent difficulty in selective ozonization of **61b** itself, we considered making a structural change in the formylolefin side chain so as to deactivate the double bond both electronically and sterically. For this purpose diacetoxylation of the formyl group appeared to be suitable, since the two acetoxyl groups could participate with the double bond, as shown in **64a** or **64b**, protecting it from the outside reagent sterically as well as electronically, and, moreover, the acetoxyl groups could be removed easily to regenerate the formylolefin function. The tosylate **61b** was thus converted in 79% yield to the diacetoxy derivative **65**, mp 118–126°, with acetic anhydride in methylene chloride in the presence of zinc chloride. The assigned structure of **65** was consistent with the ir data. As expected, ozonization of **65** proceeded selectively in methylene chloride at −73° and, after reduction of the resulting ozonide with zinc and acetic acid, the desired 10β-formyl derivative **66** was obtained successfully as a foam, plus a small amount of the aforementioned hemiacetal, **63**. Although the product **66** could not be

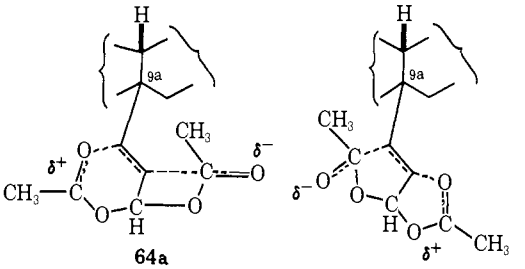
(25) According to a private communication from Dr. Fishman, the incorrect assignment was made by analogy with the results in analogous reductions of 5α-[26] and 5β-cyanoandrostan-17β-ol-3-one[27] reported by Bowers, and Cross and Harrison, respectively. We reinvestigated these reactions also and found that the configurational assignments of the products made by the Syntex chemists were likewise incorrect: W. Nagata, T. Wakabayashi, M. Narisada, and Y. Hayase, *J. Chem. Soc. C*, 2415 (1971).

(26) A. Bowers, *J. Org. Chem.*, **26**, 2043 (1961).

(27) A. D. Cross and I. T. Harrison, *J. Amer. Chem. Soc.*, **85**, 3223 (1963).

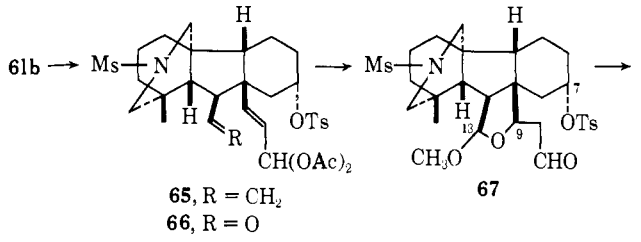
(28) W. Nagata and Y. Hayase, *Tetrahedron Lett.*, 4359 (1968); *J. Chem. Soc. C*, 460 (1969).

(29) N. S. Bhacca and D. H. Williams, "Application of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, p 86.



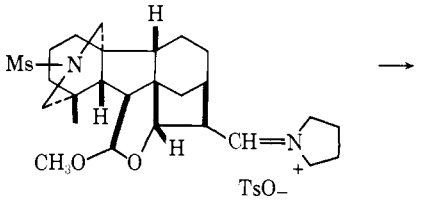
64a

64b

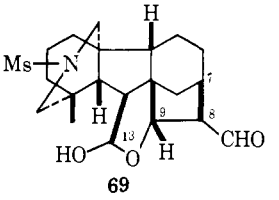


65, R = CH_2
66, R = O

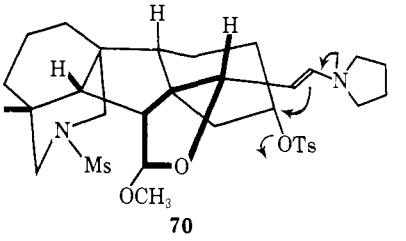
67



68



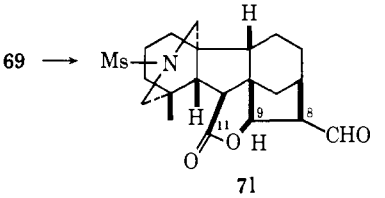
69



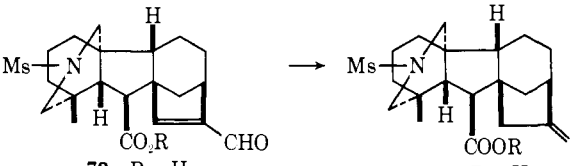
70

crystallized, the structure was supported by the appearance in the ir spectrum of a new band for a formyl group at 2722 and 1724 cm^{-1} in place of the vinyl group.

Compound **66** was now subjected to a unique cyclization method devised particularly for the present purpose to build up the BCD skeleton provided with the requisite functional groups. At first we attempted one-step cyclization of **66** leading to the hexacyclic intermediate **68** or **69** corresponding to **10** as mentioned in the foregoing section. The reaction comprises hydrolysis of the diacetoxyl group, Michael addition of a hemiacetal to the formylolefin double bond, and the subsequent substitution reaction between the resulting enolate and the 7α-tosyloxy leaving group. However, the results were rather complicated and a stepwise cyclization seemed to be advantageous. Thus, the compound **66**, without purification, was treated with 3 equiv of potassium hydroxide in dry methanol and tetrahydrofuran at $-8°$ for 5 min giving the intermediate **67** as a mixture of stereoisomers both at C_9 and C_{13}. This was immediately treated with 2 equiv of pyrrolidine in dry methanol and *N*-methylpyrrolidone at room temperature overnight and then at 70° for 1.5 hr. The ir spectrum of the crude product showed a medium strength band at 1661 cm^{-1} for an immonium chromophore, suggesting the formation of the intermediate **68**. This compound, without purification, was hydrolyzed by heating with 50% acetic acid at 100° for 1 hr giving the expected hexacyclic formylhemiacetal **69** (ir bands at 3390 (br) cm^{-1} for a hydroxyl and at 2722 and 1723 cm^{-1} for a formyl group). The tlc analysis showed that the product consisted of four stereoisomers epimeric both at C_8 and C_{13} as expected. The bridge hydrogen at C_9 was assigned as β on the basis of the favorable cis fusion of the relevant two five-membered rings. Separation of the isomers was not carried out, since the two asymmetries should be eliminated at the later stages of the synthesis. The two-carbon bridge from C_{9a} to C_7 across the C ring was thus achieved, producing the final asymmetry at the latter carbon. The cyclization may be interpreted as an intramolecular SN2-type displacement reaction of the intermediately formed enamine **70**.[30] Selective oxidation of the hemiacetal **69** was effected by employment of the Collins reagent[20] giving a mixture of the formyl lactone **71** epimeric at C_8. The assigned structure was supported by a γ-lactone band at 1766 cm^{-1} and a formyl band at 2724 and 1725 cm^{-1} in the ir spectrum. Treatment of this lactone with aqueous potassium carbonate effected ring opening to give the crystalline carboxylic acid **72a** with concomitant loss of two unnecessary asymmetries at C_8 and C_9. The bridged α,β-unsaturated aldehyde structure in **72a** was evident



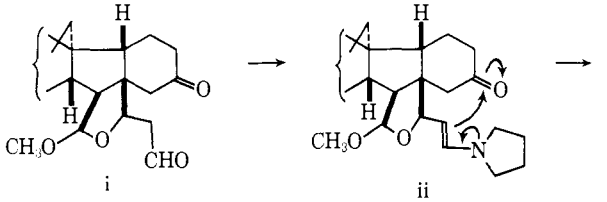
71



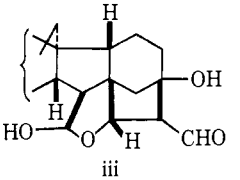
72a, R = H
b, R = CH_3

73a, R = H
b, R = CH_3

(30) We presume that, although not yet attempted, the sequence of the reactions for cyclization could be extended to the following 7-keto derivative i giving, *via* the intermediate enamine ii, the 7-hydroxy analog of **69**, iii, which might eventually lead to the 7-hydroxy-type gibberellins.



i ii



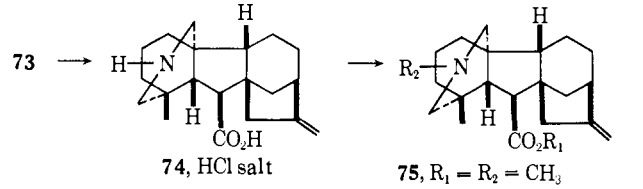
iii

from a characteristic uv band at 253.5 nm (ε 13,050)[13] and from the ir and nmr data of its methyl ester **72b**, mp 184–186°. Wolff–Kishner reduction of the acid **72a** was accompanied by double bond migration as expected giving finally the desired *exo*-methylenecarboxylic acid **73a**, mp 192–194°. The assigned structure was consistent with its ir data. In the sequence of reactions for ring D formation described so far, except for **72a**, it was found better not to purify each intermediate, owing to their instability. Thus, *ca.* 40% overall yield of crude but crystalline **72a** was obtained by eight steps and 30% overall yield of **73a** by nine steps based on the hydroxydiolefin **61a**. The method, although involving many steps, appears to be generally applicable for synthesis of the BCD ring moiety of 7-deoxygibberellins, which very often show higher biological potency than do the 7-hydroxy counterparts,[31] in view of the following advantages: (1) each step proceeds without any significant side reactions; (2) the simultaneous production of the required functional groups of C_8 and C_{10} can be realized with ultimate stereo- and regioselectivity.

IV. Elaboration of the E Ring

Having the intermediate **73a** with the complete structure of the ABCD ring system of gibberellin A_{15}, we executed the final elaboration of the E ring on the plan described in section I.

The first step for this elaboration was removal of the protecting *N*-mesyl group to recover the piperidine ring, which was ultimately to be converted into the δ-lactone ring. Reductive elimination was effected by treatment of **73a** with 12 equiv of lithium in liquid ammonia in the presence of *tert*-butyl alcohol as a proton source and the resulting amino acid was isolated conveniently as its poorly soluble hydrochloric acid salt **74**, mp >300°, in 56% yield. The assigned structure of **74** was supported by its ir spectrum and, as expected, a possible simultaneous reduction of the carboxyl group appeared to occur to a negligible extent. Exposure of the hydrochloride to an ethereal solution of diazomethane gave the *N*,*O*-dimethyl derivative **75**, its structure being evident from the ir spectrum. Unfortunately, attempts to effect selective O-methylation did not give a satisfactory result and an indirect route had to be taken. Thus, the secondary amino group was first reprotected as the trifluoroacetylamide **76a** by treatment of **74** with trifluoroacetic anhydride and pyridine in methylene chloride; this was then esterified with diazomethane to yield **76b**. This compound was selectively hydrolyzed by refluxing the methanol solution with 3 *N* potassium carbonate, now giving the

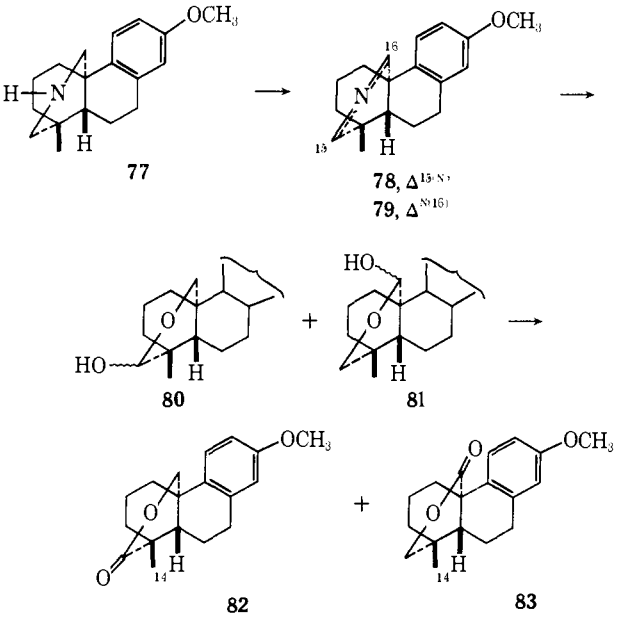


74, HCl salt

75, $R_1 = R_2 = CH_3$
76a, $R_1 = H$; $R_2 = CF_3CO$
b, $R_1 = CH_3$; $R_2 = CF_3CO$
c, $R_1 = CH_3$; $R_2 = H$

desired ester **76c** as an oil in 92% crude overall yield based on the hydrochloride **74**.

Prior to execution of the final step, *i.e.*, conversion of the piperidine ring into the δ-lactone, we tested the applicability of the method reported by ApSimon, *et al.*,[10] using the tetracyclic anisole base **77**[5a] as a model compound. Compound **77** was first dehydrogenated with 2 equiv of lead tetraacetate in benzene in the presence of anhydrous potassium carbonate at room temperature giving a mixture of two isomeric azomethine bases **78** and **79**, mp 112–120°. This mixture was treated with sodium nitrite in a solvent system of acetic acid, water, and dioxane in the presence of sodium acetate according to the literature,[10] yielding a mixture of the isomeric hemiacetals, **80** and **81**, which without separation was oxidized with chromium trioxide to a lactone mixture. The mixture was separated by preparative tlc giving the desired lactone **82**, mp 187–188°, and the isomer **83**, mp 196–198°, in 24 and 16% overall yields (three steps), respectively. Structural differentiation of the two isomeric lactones **82** and **83** was made by comparison of their nmr spectra, in which the 14-methyl signal of **82** appears at τ 8.70 in $CDCl_3$ or 8.69 in pyridine-d_5, whereas that of **83** appears at τ 8.98 in $CDCl_3$ or 9.20 in pyridine-d_5. This shows that the 14-methyl in **82** is deshielded by the neighboring lactonic carbonyl group, in accordance with the result obtained by Wenkert, *et al.*,[32] in a series



77

78, $\Delta^{15(N)}$
79, $\Delta^{(N)16}$

80

81

82

83

of diterpene acid derivatives, and it also shows that no remarkable change in the chemical shift occurs in **82** by changing the solvent, in accordance with the view of Hanson.[33] Some variation, in which the dehydrogenation step was replaced by a two-step process consisting of N-bromination with *N*-bromosuccinimide followed by dehydrobromination with sodium methoxide, was also attempted, affording **82** and **83** in 30 and 15% yield, respectively. As expected, the desired lactone **82** was formed preferentially in both cases.

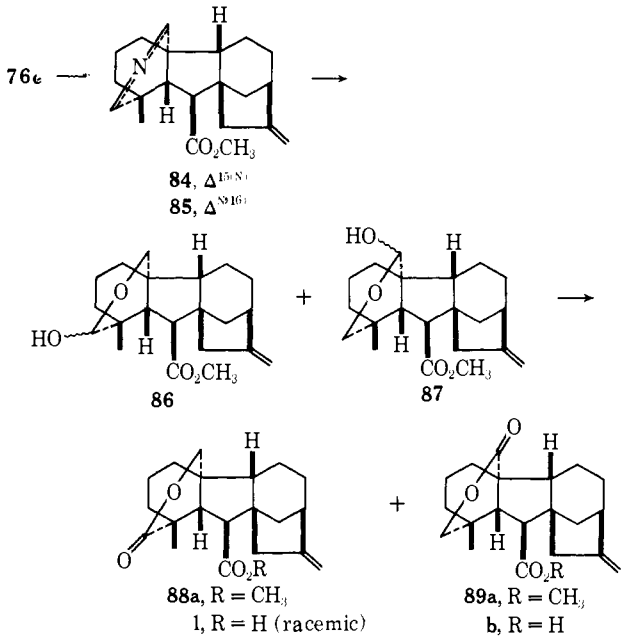
The above reaction sequence was now applied to the pentacyclic base **76c**. The use of *N*-bromosuccinimide

(31) P. W. Brian, H. G. Hemming, and D. Lowe, *Nature (London)*, 193, 946 (1962).

(32) E. Wenkert, A. Afonso, P. Beak, R. W. J. Carney, and P. W. Jeffs, *J. Org. Chem.*, 30, 713 (1965).

(33) J. R. Hanson, *J. Chem. Soc.*, 5036 (1965).

for the dehydrogenation process was avoided, since an excess of this reagent would give rise to migration of the exo double bond. Compound **76c** was thus



treated with 1.3 equiv of lead tetraacetate in dry benzene and tetrahydrofuran in the presence of dry potassium carbonate at 5° yielding a mixture of the isomeric azomethines **84** and **85**, formation of which was evident from an azomethine band at 1663 cm^{-1} in the ir spectrum. The mixture was treated with nitrous acid as described above giving a mixture of the hemiacetals, **86** and **87**, which, without purification, was oxidized with dipyridine–chromium oxide complex[20] in methylene chloride at room temperature for 20 min affording a mixture of the two isomeric lactones, **88a** and **89a**. This was separated by preparative tlc giving the pure *dl*-gibberellin A_{15} methyl ester **88a**, mp 168–170°, and the less polar isomeric lactone ester **89a**, mp 114–116°, both in 5% overall yield over the six-step transformation, based upon the amino acid hydrochloride **74**. Contrary to our expectation, no preferential formation of **88a** to **89a** was observed. The physical properties of the specimen of **88a** were rigorously compared with those of an authentic specimen[34] of gibberellin A_{15} methyl ester and it was found that they had indistinguishable ir (in chloroform) and mass spectra, together with identical glc and tlc behavior in several solvent systems with and without silver nitrate. The less polar lactone ester **89a** exhibited a parent peak of *m/e* 344 in the mass spectrum and bands at 1728, 1656, 1162, 1156, and 884 cm^{-1} in the ir spectrum, all these data being compatible with the isomeric structure. Moreover, while gibberellin A_{15} methyl ester shows the 14-methyl signal at τ 8.85 in the nmr spectrum in deuteriochloroform, compound **89a** shows it at τ 9.20, the observed shift toward a higher field[33] clearly indicating that the compounds are isomeric at the lactone ring. This spectral evidence coupled with the mode of the reaction used allowed the assignment of structure **89a** to this isomer. On carrying out the final step of the synthesis, it was thought that, owing to its hindered nature, hydrolysis of the ester group using alkali might not be effected without any side reactions and that a demethylation reaction with lithium iodide in refluxing collidine[35] would be preferable in the present case. However, some disadvantage was also presumed in this method, since iodine is usually generated in this procedure, and it is well known that iodine can give rise to migration of the double bond from exo to endo and to rearrangement of the bridged ring system.[5b,13,36] For prevention of such side reactions, it was decided to use triphenylphosphine as a coreagent to reduce the iodine generated. As expected, the ester **88a** was smoothly demethylated by refluxing a γ-collidine solution with lithium iodide and triphenylphosphine for 1 hr yielding *dl*-gibberellin A_{15} (**1**), mp 236–237°, without any significant migration of the double bond. This acid was proved to be a racemic form of gibberellin A_{15} by comparing the identity of the ir (in chloroform), the mass spectrum, and tlc with those of an authentic specimen.[34] The isomeric lactone ester **89a** was treated analogously to give the isomeric acid **89b**, mp 197–198°. The ir bands at 1727, 1713, 1656, 1147, and 885 cm^{-1} and the parent peak of *m/e* 330 in the mass spectrum supported the assigned isomeric structure of **89b**.

As accounted for so far, all the steps, in which selectivity is required both sterically and positionally, were well controlled, except that the conversion of the E-piperidine ring into the δ-lactone ring at the final stage, contrary to our expectation, did not proceed regioselectively. Moreover, the present synthesis confirms the correctness of the structure **1** postulated for gibberellin A_{15}.[37]

Bioassay of the synthetic *dl*-gibberellin A_{15} **1** and the isomeric lactone **89b** was carried out by the courtesy of Professor Isogai using rice (Tanginbozu) seedling assay[40,41] and the results are summarized in Table III.

Table III. Biological Activities of *dl*-GA_{15} **1** and the Isomeric Lactone **89b** on Rice Seedling Growth Test[a]

Concn, *M*	Natural GA_{15}	Synthetic *dl*-GA_{15}(**1**)	Isolactone (**89b**)	Control
3×10^{-6}	63.7	40.0	25.7	24.5
1.5×10^{-6}	41.9			
3×10^{-7}	31.2	27.0	22.8	
1.5×10^{-7}	30.6			

[a] Average lengths (millimeters) of 15-sec leaf sheathes are given.

As expected, the racemic gibberellin A_{15} showed half of the activity of the natural product. The isomeric lactone **89b** showed no activity.

(34) The authors are very grateful to Dr. J. R. Hanson for kindly providing us with the authentic specimen of gibberellin A_{15}.

(35) F. Elsinger, J. Schreiber, and A. Eschenmoser, *Helv. Chim. Acta*, **43**, 113 (1960).

(36) (a) A. Yoshikoshi, M. Kitadani, and Y. Kitahara, *Tetrahedron*, **23**, 1175 (1967); (b) A. V. Simclin, E. P. Serebryakov, V. F. Kucherov, and Y. S. Rakovskii, *Khim. Prir. Soedin.*, 163 (1969).

(37) After completion of the work, we noticed a paper of Cross and Gatfield,[38] who succeeded in partial synthesis of gibberellin A_{15} norketone from 7-hydroxykaurenolide. We were informed also of a successful transformation of enmein to gibberellin A_{15} from Professor T. Okamoto of Tokyo University, Department of Pharmaceutical Science (private communication).[39] These two syntheses also verify the gibberellin A_{15} structure.

(38) B. E. Cross and I. L. Gatfield, *Chem. Commun.*, 33 (1970).

(39) M. Somei and T. Okamoto, *Chem. Pharm. Bull.*, **18**, 2135 (1970).

(40) *Cf.* Y. Komoda, Y. Isogai, and T. Okamoto, *Sci. Pap. Coll. Gen. Educ., Univ. Tokyo*, **18**, 221 (1968).

(41) *Cf.* A. Crozier, C. C. Kuo, R. C. Durley, and R. P. Pharis, *Can. J. Bot.*, **48**, 867 (1970).

Experimental Section

All melting points were measured on a Yazawa hot-stage apparatus and are uncorrected. Unless otherwise stated, ultraviolet spectra were taken in 95% ethanol with a Hitachi EPS-2 spectrometer and infrared spectra in chloroform by use of a Koken DS-201B spectrophotometer. All nmr spectra were taken on deuterated chloroform solutions with a Varian A-60 spectrometer. Unless otherwise specified, the extracts were dried on anhydrous sodium sulfate. Column chromatography was performed according to the method by Reichstein and Shoppee[42] using Woelm alumina (activity II). Dipole moments were measured in the same way as described previously.[5a]

Oxidation of 4 with *tert*-Butyl Chromate. To a solution of 1.024 g of the tetracyclic mesylate **4** in 30 ml of dry carbon tetrachloride was added 14 ml of *tert*-butyl chromate solution[43] and 8 ml of acetic anhydride. The solution was refluxed for 4 hr, cooled, and mixed with a solution of 8 g of oxalic acid in 56 ml of water. The mixture was stirred for 2 hr at room temperature, and extracted with carbon tetrachloride. The carbon tetrachloride extract was washed successively with water, 2 *N* sodium carbonate, and water, then dried and evaporated to leave 1.014 g of a residue which was chromatographed on alumina (3.0 g). Fractions eluted with petroleum ether–benzene (2:1–1:1) were crystallized from acetone–ether to give 358 mg of the starting material **4**, mp 140–141°. Fractions eluted with benzene and benzene–chloroform (9:1) were crystallized from methylene chloride–ether to furnish 81 mg (8%) of the 7-oxo compound **13a**: mp 174–175.5°; ν_{max} 1684, 1607, 1494, 1344, and 1158 cm^{-1}; λ_{max} 222 (ϵ 22,200), 254 (ϵ 8600), and 320 nm (ϵ 3100). *Anal.* Calcd for $C_{19}H_{25}O_4NS$: C, 62.79; H, 6.93; N, 3.85. Found: C, 62.68; H, 6.89; N, 3.78.

Oxidation of 4 with Lead Tetraacetate. To a solution of 273 mg of the tetracyclic mesylate **4** in 1.4 ml of acetic acid was added 800 mg of lead tetraacetate. The mixture was heated at 102° for 6.5 hr, cooled, mixed with 0.5 ml of glycerol, diluted with ice–water, and extracted with methylene chloride. The methylene chloride extract was washed successively with 2 *N* sodium carbonate and water, dried, and evaporated to leave 287 mg of a residue, which was dissolved in 30 ml of methanol. To the solution was added a solution of 230 mg of potassium carbonate in 2 ml of water. The mixture was refluxed for 25 min, concentrated *in vacuo*, diluted with ice–water, and extracted with methylene chloride. The methylene chloride extract was worked up to leave 243 mg of a residue, which was chromatographed on alumina (8 g). Fractions eluted with petroleum ether–benzene (1:1) and benzene were crystallized from ether to give 70 mg of the starting material **4**, mp 139–140°. Fractions eluted with benzene–chloroform (4:1–2:1) were crystallized from methylene chloride–ether to afford 23 mg (8%) of the 7-hydroxy compound **13b**, mp 173–174°. An analytical sample melts at 175–176°: ν_{max} 3592, 1610, 1494, 1335, and 1154 cm^{-1}. *Anal.* Calcd for $C_{19}H_{27}O_4NS$: C, 62.44; H, 7.44; N, 3.84. Found: C, 62.81; H, 7.19; N, 3.84.

Preparation of the Diol 14. To a suspension of 1.006 g of the cyanoaldehyde **3**[5a] in 30 ml of methanol was added 3.5 ml of 31.5% formalin and 5 ml of 6 *N* potassium hydroxide.[44] The suspension was stirred at room temperature for 23 hr, poured into ice–water, and extracted with methylene chloride–methanol (9:1). The organic extract was washed with water, dried, and evaporated to leave 1.089 g of a residue, which was crystallized from methylene chloride–methanol to give 815 mg of the diol **14**, mp 196–199°, and 200 mg of a second crop, mp 183–188°. The total yield was 92%. An analytical sample melts at 203–205°: ν_{max} 3618, 2234, 1610, and 1501 cm^{-1}. *Anal.* Calcd for $C_{18}H_{23}O_3N$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.51; H, 7.58; N, 4.85.

Preparation of Compound 5. A. By Alkaline Cyclization. To a solution of 6.18 g of the diol **14**, dissolved in a mixture of 200 ml of absolute diglyme and 50 ml of pure tetrahydrofuran, was added 6.2 g of lithium aluminum hydride powder under nitrogen with water cooling. The resulting mixture was vigorously stirred at a bath temperature of 110° for 8 hr, cooled, and diluted with 150 ml of tetrahydrofuran. The excess of the hydride was destroyed by slow addition of 70 ml of water–tetrahydrofuran (2:5). The precipitates were filtered off and washed with methylene chloride–methanol (4:1). The filtrate was concentrated under reduced pressure to obtain an almost dry residue, which was dissolved in the washings and shaken with water. The organic layer was dried and the solvent was removed to give 5.48 g of the crude hydroxylamine **15**. In another run an analytical sample of **15**, mp 217–218°, was obtained on crystallization from methylene chloride–methanol: ν_{max} 3632, 1611, and 1501 cm^{-1}. *Anal.* Calcd for $C_{18}H_{27}O_3N$: C, 70.79; H, 8.91; N, 4.59. Found: C, 71.03; H, 8.47; N, 4.09.

The crude hydroxylamine **15** was mesylated by treatment with 12.3 g of methanesulfonyl chloride and 80 ml of pyridine at 0° for 1 hr and then at room temperature for 16 hr. The reaction mixture was worked up in the usual manner to give 9.95 g of the crude trimesylate **16**.

This was dissolved in 100 ml of pure tetrahydrofuran, cooled to 0°, and mixed with 972 mg of a 50% suspension of sodium hydride in mineral oil. After stirring the mixture for 40 min at room temperature, an additional 972 mg of the suspension was introduced into the mixture. It was stirred further for 40 min, poured into 500 ml of water, and extracted with chloroform. The washed and dried organic layer, on removal of the solvent under reduced pressure, produced 9.10 g of foams, which were chromatographed on 250 g of neutral alumina (Woelm II). Fractions eluted with benzene–chloroform (9:1–4:1) were combined and crystallized from chloroform–ether to yield 4.005 g of the dimesylate **17**, mp 198–200°. An analytical sample, recrystallized from methylene chloride–ether, melts at the same temperature: ν_{max} 1611, 1503, 1341, 1172, 1155, 955, and 943 cm^{-1}. *Anal.* Calcd for $C_{20}H_{29}O_6NS$: C, 54.14; H, 6.59; N, 3.15. Found: C, 54.42; H, 6.49; N, 3.19.

A fraction eluted with chloroform was recrystallized twice from chloroform–ether to give 565 mg of the ether dimesylate **18**, mp 206–209°. In another experiment, a sample recrystallized from methylene chloride–ether, mp 201–203°, was analyzed: ν_{max} 3362, 1611, 1502, 1347, 1174, 970, and 957 cm^{-1}. *Anal.* Calcd for $C_{20}H_{29}O_7NS_2$: C, 52.27; H, 6.36; N, 3.06. Found: C, 52.28; H, 6.28; N, 3.19.

To a solution of 5.027 g of the dimesylate **17** in 260 ml of pure tetrahydrofuran was added 2.613 g of powdered lithium aluminum hydride under nitrogen and the resulting mixture was heated under reflux with stirring for 1 hr, cooled to 0°, and mixed with 8 ml of water to destroy the excess of the reagent. The precipitate was filtered off and washed well with chloroform. The filtrate was concentrated under reduced pressure to dryness and the residue was dissolved in the washings, shaken with water, and dried, and the solvent was removed under reduced pressure. The residue was crystallized from acetone–ether to give 3.535 g of the compound **5**, mp 168–169°. A pure sample melts at 170–170.5°: ν_{max} 3621, 1611, 1502, 1337, and 1154 cm^{-1}. *Anal.* Calcd for $C_{19}H_{27}O_4NS$: C, 62.45; H, 7.45; N, 3.83. Found: C, 62.50; H, 7.50; N, 3.98.

B. By Acid Cyclization. A mixture of 961 mg of the diol **14**, 65 mg of *p*-toluenesulfonic acid monohydrate, and 50 ml of acetone was refluxed for 3.5 hr. The mixture was cooled, poured into ice–2 *N* sodium carbonate (10 ml), and extracted with methylene chloride. The methylene chloride extract was washed with water, dried, and evaporated to leave 1.114 g of a residue, which was crystallized from methanol to give 835 mg of the acetonide **19**, mp 123–125°. An analytical sample melts at 126–128°: ν_{max} 2236, 1610, 1502, and 1120 cm^{-1}. *Anal.* Calcd for $C_{20}H_{27}O_3N$: C, 72.92; H, 8.26. Found: C, 72.64; H, 8.19.

A mixture of 487 mg of the acetonide **19**, dissolved in 5 ml of pure tetrahydrofuran and 25 ml of absolute diglyme, and 359 mg of lithium aluminum hydride was stirred under a nitrogen atmosphere at 100–105° for 5 hr. The excess of the hydride was decomposed with water at 0° and the resulting mixture was diluted with 2 *N* sodium hydroxide solution and extracted with ether–chloroform (3:1). The organic solution was washed successively with water, ice-cold 10% tartaric acid solution, and water and then dried, and the solvent was removed under reduced pressure to give 36 mg of a neutral substance, which was not investigated further. The acid washings were combined, made alkaline by addition of 2 *N* sodium hydroxide solution, and extracted with chloroform. The organic solution was washed with water and dried, and the solvent was removed under reduced pressure to produce 455 mg of the crude compound **20** as a basic fraction. Though the residue was considered to be almost pure on the basis of its thin-layer chromatogram, attempts to crystallize it failed.

To a solution of 450 mg of the crude compound **20** in 10 ml of tetrahydrofuran were added a solution of 448 mg of methanesulfonyl chloride in 3.0 ml of tetrahydrofuran and a solution of 313

(42) T. Reichstein and C. W. Shoppee, *Discuss. Faraday Soc.*, 305 (1949).

(43) K. Heusler and A. Wettstein, *Helv. Chim. Acta*, **35**, 284 (1952).

(44) D. Bertin, H. Fritel, and L. Nedelec, *Bull. Soc. Chim. Fr.*, 1068 (1962).

mg of sodium hydroxide in 3.0 ml of water at the same rate over a period of 40 min under ice cooling and vigorous stirring. The mixture was stirred at room temperature for 2 hr, poured onto ice water, and extracted with ether–chloroform (3:1). The organic solution was washed with ice-cold 10% tartaric acid solution and water and dried, and the solvent was removed under reduced pressure to afford 532 mg of a neutral substance, which was crystallized from acetone–ether to yield 372 mg of compound **21**, mp 155.5–157°. Chromatography of the mother liquors on 8 g of neutral alumina gave an additional 73 mg of **21**. A pure sample melts at 156–157°: ν_{max} 3288, 1610, 1576, 1327, and 1152 cm^{-1}. *Anal.* Calcd for $C_{22}H_{33}O_5NS$: C, 62.39; H, 7.85; N, 3.31. Found: C, 62.50; H, 7.89; N, 3.29.

A mixture of 100 mg of compound **21**, 250 mg of *p*-toluenesulfonic acid monohydrate, and 5.0 ml of absolute ether was heated under reflux and nitrogen atmosphere with stirring for 3.5 hr, cooled, poured onto water, and extracted with ether–chloroform (3:1). The organic solution was washed with 2 *N* potassium carbonate solution and water and dried, and the solvent was distilled under reduced pressure. The residue obtained was chromatographed on 4 g of neutral alumina. Fractions eluted with benzene–chloroform (2:1) were recrystallized from ether containing a small amount of acetone to afford 38 mg of the compound **5**, mp 169–170°, which was identified as the sample described in A by comparison of ir spectra and mixture melting points.

Compound 22. A mixture of 83 mg of compound **5**, 151 mg of purified lead tetraacetate, and 10.0 ml of absolute benzene was refluxed under nitrogen with stirring for 3 hr, cooled, poured into water, and extracted with ether. The ethereal solution was shaken successively with 10% potassium iodide solution, 10% sodium thiosulfite solution, and water. The dried solution, on removal of the solvent, yielded 87 mg of foams, which were chromatographed on 4 g of neutral alumina. Elution with benzene/benzene–chloroform (19:1) produced 26.5 mg of forms, which were crystallized from acetone–ether to give 19.0 mg of the compound **22**, mp 213–218°. Two recrystallizations of the compound from the same solvent yielded a sample, mp 216–217°, which was analyzed: ν_{max} no hydroxyl band, 1728 (weak), 1611, 1569, 1493, 1338, and 1155 cm^{-1}; nmr τ 2.72, 2.84, 3.15, 3.30 (m, aromatic), 5.5–6.5 (m, –C*H*O–), 6.23 (s, –OCH_3), 7.33 (s, NSO_2CH_3). *Anal.* Calcd for $C_{19}H_{25}O_4NS$: C, 62.79; H, 6.93. Found: C, 62.24; H, 7.25. The fractions eluted with benzene–chloroform (2:1–1:1) were recrystallized from acetone–ether to recover 29.1 mg of the starting material, mp 166–168°, identified by comparison of ir spectra, thin-layer chromatograms, and melting points.

Preparation of the Hydroxyenone 25. To a stirred solution of 4.00 g of lithium tips in 160 ml of liquid ammonia, which had been distilled over sodium and cooled to −70°, a solution of 2.000 g of the compound **5**, dissolved in 25 ml of pure tetrahydrofuran, and 25 ml of absolute *tert*-butyl alcohol was added slowly over a period of 10 min and the resulting mixture was stirred at −70° for 2 hr. In order to decompose the excess of lithium, 30 ml of absolute methanol was added to the mixture. The ammonia was distilled off and the residue was diluted with water and extracted with ether. The washed ether solution, on removal of the solvent, yielded 1.575 g of the crude compound **23** as a crystalline residue, which was used for the following reaction without purification. In another experiment, the crude material was recrystallized three times from methylene chloride–methanol to produce an analytical sample melting at 178–180°: ν_{max} 3628, 3370 (weak), 1696 (medium), 1670 (medium), 1022, and 1012 m^{-1}; nmr τ 5.49 (1 H, m, OC=C*H*–) and 6.45 (3 H, s, OCH_3). *Anal.* Calcd for $C_{18}H_{27}O_2N$: C, 74.70; H, 9.40; N, 4.84. Found: C, 74.40; H, 9.67; N, 4.88.

A solution of 1.63 g of methanesulfonyl chloride in 12 ml of tetrahydrofuran and 13.1 ml of 10% sodium hydroxide solution were added at the same rate to an ice-cold stirred mixture of 1.575 g of the above-described residue suspended in 40 ml of tetrahydrofuran over a period of 15 min, resulting in the formation of a clear solution. This was stirred at room temperature for 2 hr, allowed to stand overnight, diluted with water, and extracted with ether–methylene chloride (3:1). The organic solution was washed successively with water, 10% tartaric acid solution, and water and dried, and the solvent was distilled off to leave a neutral residue, which was recrystallized from methylene chloride–ether to give 1.733 g of the compound **24**, mp 165–167° (with bubbling). A sample recrystallized twice from methylene chloride–methanol and melting at 165–168° (with bubbling) was analyzed: ν_{max} 3625, 3540, 1696 (medium), 1667 (medium), 1336, and 1154 cm^{-1}. *Anal.* Calcd for $C_{19}H_{29}O_4NS$: C, 62.10; H, 7.96; N, 3.81. Found: C, 62.18; H, 8.23; N, 3.79.

To a boiling solution of 1.500 g of the compound **24** in 30 ml of tetrahydrofuran and 90 ml of methanol, 24 ml of 4 *N* hydrochloric acid was added dropwise. The resulting mixture was heated under reflux with stirring for 30 min and cooled, and the solvent was removed under reduced pressure to almost dryness. The resulting crystalline mass was dissolved in methylene chloride and the acid was removed by washing with water. The residue, obtained on removal of the solvent, was crystallized from methylene chloride–acetone to produce 1.225 g of the hydroxyenone **25**, mp 210–211°. One recrystallization of the crystals from the same solvent gave an analytical sample with the same mp: ν_{max} 3628, 1671, 1638, 1340, and 1148 cm^{-1}; λ_{max} 243.4 (ϵ 15,000) and 313 nm (ϵ 92). *Anal.* Calcd for $C_{18}H_{27}O_4NS$: C, 61.17; H, 7.70; N, 3.96. Found: C, 61.19; H, 8.03; N, 4.14.

Oxidation of the Hydroxyenone 25 with Lead Tetraacetate. A stirred mixture of 1.89 g of lead tetraacetate, 630 mg of precipitated calcium carbonate, 215 mg of iodine, and 75 ml of dried cyclohexane was heated in the dark until it started to boil. To the resulting mixture was added 300 mg of the hydroxyenone **25** in powdered form and the resulting suspension was heated under reflux and irradiation with a 500-W lamp with vigorous stirring. After 30 min the mixture became pale violet; it was cooled and filtered through a Celite layer. The Celite was washed well with methylene chloride–methanol. The filtrate and washings were combined, washed with 20% sodium thiosulfite solution and water, dried, and, on removal of the solvent, produced 318 mg of a residue which showed a positive Beilstein test and was reduced by treatment with 6 ml of acetic acid and 1.2 g of zinc powder at room temperature for 30 min. Working up the reaction mixture in the usual manner gave 284 mg of residue, which was crystallized from methylene chloride–acetone–ether and then from methylene chloride–methanol to give 147 mg of crystals, mp 213–215°, which were proved to be identical with the starting hydroxyenone **25** based on mixture melting point and the thin-layer chromatogram. The mother liquors were chromatographed on 4 g of neutral alumina. Fractions eluted with benzene–chloroform (9:1) produced 7.3 mg of residue, which on recrystallization from methylene chloride–ether yielded 5.7 mg of the compound **26**: mp 185–186°; ν_{max} no hydroxyl, 1721, 1645 (medium), 1490 (medium), 1329, and 1146 cm^{-1}; λ_{max} 206 nm (ϵ of an end absorption, 1900). The fractions eluted with benzene–chloroform (1:1)/chloroform were crystallized from methylene chloride–methanol to give an additional 36 mg of the starting hydroxyenone **25**, mp and mmp 214–215°.

Hydrocyanation of the Hydroxyenone 25. To an ice-cold solution of 1.37 g of triethylaluminum in 12.5 ml of pure tetrahydrofuran was added under nitrogen atmosphere a solution of 186 mg of hydrocyanic acid in 1.32 ml of pure tetrahydrofuran. The powdered hydroxyenone **25** (522 mg) was introduced into the resulting solution and the mixture was stirred at room temperature to give a solution which was further stirred in a sealed flask for 44 hr. The reaction mixture was poured slowly onto a vigorously stirred mixture of 190 ml of 0.1 *N* sodium hydroxide solution and 200 g of ice and extracted with methylene chloride–methanol (4:1). The washed and dried organic solution gave foams, which were dissolved in chloroform and filtered through a layer of 5 g of acid alumina. The filtrate gave a residue which, on crystallization from methanol–ether, yielded 259 mg of the cyano ketone **28**, mp 229–231°.

In another experiment, sands melting at 204–205° which were obtained by rapid recrystallization of chromatographic fractions from methanol–ether were analyzed: ν_{max} (Nujol) 3479, 2229, 1723, 1341, 1329, 1158, and 1141 cm^{-1}. *Anal.* Calcd for $C_{19}H_{28}O_4N_2S$: C, 59.98; H, 7.42; N, 7.36. Found: C, 60.09; H, 7.72; N, 7.40. Slow recrystallization of the sands from methanol yielded a sample melting at 230–231°: ν_{max} (Nujol) 3400, 2243, 1720, 1337, 1324, 1318, 1155, 1150, and 1143 cm^{-1}. Found: C, 59.56; H, 7.78. The two products are considered to be dimorphous modifications and showed a mmp 230–231°. The alumina was eluted with chloroform–methanol (9:1). The eluates and the mother liquors were combined and chromatographed on 8 g of acid alumina again. Residues eluted with chloroform were recrystallized from methanol–ether to give an additional 54 mg of the cyano ketone **28**, mp and mmp 230–231°. A fraction eluted with chloroform–methanol (49:1), on crystallization from methylene chloride–methanol, produced a crystalline sample: mp 214–217°; ν_{max} 3646, 2236, 1718, 1343, and 1153 cm^{-1}. This showed a single spot on its thin-layer chromatogram at a lower position than **28** did and was presumed to be the *cis*-cyano ketone.

Oxidation of the Cyano Ketone 28 with Lead Tetraacetate. A suspension of 728 mg of lead tetraacetate, 166 mg of iodine, and

243 mg of precipitated calcium carbonate in 30 ml of absolute benzene was heated under reflux in the dark for a while. To the mixture was added 125 mg of the powdered cyano ketone **28**, and the resulting mixture was heated with vigorous stirring under irradiation with a 500-W lamp for 30 min. The decolored reaction mixture was cooled and filtered through a Celite layer. The precipitates were washed with chloroform–methanol (3:1) and the filtrate and the washings were shaken with 10% sodium thiosulfite and water. The organic layer, on removal of the solvent, produced 181 mg of the crude product, which was reduced without purification by treatment with 0.50 g of zinc and 2 ml of acetic acid at room temperature for 15 min. The reduced products were extracted with chloroform after neutralization with potassium carbonate. The extracts were hydrolyzed by stirring with 20 ml of methanol and 4 ml of 2 *N* potassium carbonate at room temperature for 16 hr. Extraction of the products with chloroform yielded 66 mg of foams, which were chromatographed on 3 g of acid alumina. The fractions eluted with chloroform–methanol (99:1) were crystallized from methylene chloride–methanol–ether to yield 16.5 mg of the compound **29**, mp 285–286° dec. One recrystallization of the crystals from the same solvent gave an analytical sample: mp 285–287° dec; ν_{max} (Nujol) 3488, 3210, 3073 (weak), 1683, 1325, and 1155 cm^{-1}. *Anal.* Calcd for $C_{19}H_{27}O_5N_2SI$: C, 43.69; H, 5.21; N, 5.36; I, 24.30. Found: C, 44.20; H, 5.68; N, 5.70; I, 24.03.

Ozonolysis of the Hydroxyolefins 34 and 35. A. Direct Preparation of the Tetracyclic Aldehyde 40a. A mixture of 10.00 g of the enone **6**, 12 ml of isopropenyl acetate, and 718 mg of *p*-toluenesulfonic acid monohydrate was refluxed for 4 hr under nitrogen. After cooling, 1 g of sodium acetate was added. The mixture was stirred for 20 min at 3°, concentrated *in vacuo*, diluted with water, and extracted with methylene chloride. The methylene chloride extract was washed with water, dried, and evaporated to leave 12.16 g of a residue. To a suspension of 11.90 g of this residue in 760 ml of 95% ethanol was added a mixture of 12 g of sodium borohydride and 100 ml of 70% aqueous alcohol at room temperature. After refluxing for 10 min, 5% aqueous sodium hydroxide was added. The mixture was refluxed for 10 min, concentrated *in vacuo*, diluted with ice–water, and extracted with chloroform–methanol (4:1). The organic extract was worked up to leave 11.08 g of a crude mixture of isomeric olefins, **34** and **35**. Through a cold (−73°) solution of 312 mg of this crude mixture of olefins in 20 ml of methylene chloride–methanol (99:1), oxygen containing ozone was bubbled until the solution acquired a pale violet color. To the mixture was added 900 mg of zinc dust and 2 ml of acetic acid. The suspension was stirred at 3° for 30 min and then at room temperature for 1 hr, and filtered to remove the solid. The filtrate was neutralized with an aqueous sodium bicarbonate solution and partitioned between methylene chloride and 70 ml of 20% aqueous sodium bisulfite. The aqueous layer was basified with 70 ml of 10% sodium hydroxide with ice-bath cooling, and extracted with methylene chloride. The methylene chloride extract was worked up to leave 143 mg of a residue, which was crystallized from methylene chloride–methanol–ether to afford 116 mg of the tetracyclic aldehyde **40a**, mp 227–230°, in 38% overall yield based on **6**. An analytical sample melts at 234–235.5°: ν_{max} (KBr) 3478, 3408, 2740, 1713, 1319, and 1148 cm^{-1}. *Anal.* Calcd for $C_{18}H_{29}O_5SN$: C, 58.20; H, 7.87; N, 3.77. Found: C, 57.93; H, 7.79; N, 3.64.

B. *Via* the Ketoaldehyde 39. In the same way as described in A, 610 mg of an olefinic fraction which was recovered on an insufficient ozonization reaction of the hydroxyolefins **34** and **35** was ozonized again, reduced with zinc and acetic acid, and extracted with methylene chloride. The organic layer was shaken with two portions of 100 ml of 20% sodium hydrogen sulfite solution, washed with water, and dried, and the solvent was removed to produce 440 mg of the nonaldehyde fraction, which was crystallized from methylene chloride–methanol to give 122 mg of the hydroxyolefin **35**, mp 235–236°. This was identified with the authentic sample obtained by reduction of the enone **36** by comparison of their ir spectra and by a mixture melting point. The aqueous layer containing solid sodium hydrogen sulfite adduct was mixed with 50 ml of methylene chloride, cooled to 0°, and then introduced to a solution of 15.5 g of sodium hydroxide in 60 ml of water with vigorous stirring. The alkaline aqueous layer was extracted with methylene chloride. The combined organic layers were washed with water and dried, and the solvent was removed under reduced pressure to give 162 mg of the crude ketoaldehyde **39**: ν_{max} 3620, 3500, 2721, and 1723 cm^{-1}. This showed a spot on its thin-layer chromatogram which was more polar than that of the aldehyde **40a**, and was used for the following reaction without purification.

A mixture of 162 mg of the crude ketoaldehyde **39**, dissolved in 10.0 ml of absolute benzene, and 1.6 g of neutral alumina (Woelm II) was stirred at room temperature for 200 min and then introduced into a column packed with 1.6 g of neutral alumina. Elution with benzene–methylene chloride (1:1)/methylene chloride produced 128 mg of residue. Recrystallization of the residue from methylene chloride–methanol gave 90.5 mg of the aldehyde **40a**, mp 227–229°. Identification with the sample described in A was carried out by comparison of ir spectra, thin-layer chromatograms, and melting points.

Reduction of the Enone 36. A mixture of the enone **36** (101 mg), sodium borohydride (103 mg), and methanol (5 ml) was stirred at room temperature for 1 hr, poured into ice–water, and extracted with methylene chloride. The methylene chloride solution was washed with water, dried, and evaporated to afford 106 mg of a residue, which was crystallized from methanol–methylene chloride to give 61 mg (60%) of the hydroxyolefin **35**, mp 225–227°. An analytical sample melts at 238–239°: ν_{max} 3614, 1337, and 1156 cm^{-1}; τ 9.12 (s, $\rightarrow CCH_3$). *Anal.* Calcd for $C_{18}H_{29}O_3NS$: C, 63.68; H, 8.61; N, 4.13. Found: C, 63.72; H, 8.60; N, 3.94.

Osmium Tetroxide Oxidation of the Hydroxyolefins 34 and 35. To a solution of 100 mg of the hydroxyolefins **34** and **35** was added an ethereal solution of 100 mg of commercial osmium tetroxide of 75.7% purity. The resulting brown solution was kept in a sealed flask at room temperature for 41 hr. The resulting black suspension was diluted with 10 ml of absolute dioxane, cooled to 0°, bubbled with hydrogen sulfide with stirring for 20 min, and filtered through a Celite layer. The precipitates were washed with 30 ml of dioxane and the filtrate and the washings were concentrated under reduced pressure at a low temperature, diluted with water, made alkaline with ice-cold 2 *N* sodium hydroxide solution, and extracted with chloroform. The washed and dried organic solution produced 80 mg of residue, which was chromatographed on 2 g of neutral alumina (Woelm II). The fraction eluted with benzene–chloroform (2:1–1:1) was crystallized from chloroform–ether to give 14 mg of the tetrasubstituted olefin **35**, mp 236–237°. This was identified with an authentic sample by comparison of their ir spectra and melting points. The fraction eluted with chloroform–methanol (99:1) yielded 3.3 mg of a less polar glycol **37**, which showed a spot on its thin-layer chromatogram but was not purified. The residue obtained by elution with chloroform–methanol (49:1–19:1) produced 26.2 mg of a more polar glycol **38**. Attempts to crystallize the latter thin layer chromatographically pure material failed and it was used for the next reaction without further purification.

Periodic Acid Oxidation of the Less Polar Glycol 37. A solution of 3.3 mg of the less polar glycol **37** in 0.4 ml of pure tetrahydrofuran was treated with a solution of 6 mg of periodic acid bishydrate in 0.2 ml of water and the resulting solution was allowed to stand at room temperature for 6 hr, poured into ice water, and extracted with methylene chloride. The organic solution was washed with water and dried, and the solvent was removed under reduced pressure to give 2.0 mg of the crude ketoaldehyde **39** as a semisolid. This showed a spot at a slightly smaller R_f than the starting material on a silica gel chromatogram developed with ethyl acetate–ethanol (9:1), and was identified with the sample described previously by comparison of ir spectra and thin-layer chromatograms.

Perodic Acid Oxidation of the More Polar Glycol 38. To a solution of 26.2 mg of the more polar glycol **38** in 2.6 ml of pure tetrahydrofuran was added a solution of 32 mg of periodic acid bishydrate in 1.3 ml of water and the reaction mixture was kept at room temperature in the dark for 6 days. As about half of the starting material still remained unchanged, an additional 30 mg of the reagent was added to the reaction mixture, which was kept at room temperature for a further 24 hr. The mixture was then poured onto water, and extracted with methylene chloride. The organic solution was washed successively with potassium iodide solution, 10% sodium thiosulfite solution, and water, and then dried. Removal of the solvent gave 21.6 mg of a residue. The residue was separated into aldehydic and nonaldehydic portions by means of sodium hydrogen sulfite adduct formation. The adduct was decomposed in a one-layer method and 9.6 mg of a residue was obtained. This was crystallized from methylene chloride–methanol to produce 8.2 mg of the aldehyde **40a**, mp 230–233°, which was identified with the sample described previously by comparison of thin-layer chromatograms, ir spectra, and melting points.

Acetylation of the Aldehyde 40a. A solution of the aldehyde **40a** (200 mg) in 2 ml of dry pyridine and 1 ml of acetic anhydride was allowed to stand at room temperature overnight. The solution was treated as usual to leave 225 mg of a residue, which was crystallized from methylene chloride–ether to give 213 mg of the monoacetoxyaldehyde **40b**: mp 209–212°; ν_{max} 3594, 2744, 1728, 1718, 1341, and 1153 cm^{-1}. *Anal.* Calcd for $C_{20}H_{31}O_6SN$: C, 58.10; H, 7.56; N, 3.39. Found: C, 57.65; H, 8.04; N, 3.30.

The Compound 40c. A mixture of 1.403 g of the aldehyde **40a**, 15 mg of *p*-toluenesulfonic acid monohydrate, 10.0 ml of ethylene glycol, and 40.0 ml of dry methylene chloride was shaken in a sealed flask at room temperature for 24 hr, poured into dilute sodium carbonate solution, and extracted with methylene chloride–methanol (5:1). The organic layer was washed with water and dried, and the solvent was distilled under reduced pressure. The residue obtained was crystallized from methanol–ether to give 1.327 g of the compound **40c**, mp 174–176°. A pure sample melts at 177–178°: ν_{max} 3503, 1338, 1150, and 1027 cm^{-1}; ν_{max} (dilute CCl_4) 3555 (sh) and 3515 cm^{-1}; τ 5.00 (1 H, d, J = 3.7 Hz, CHC*H*<O_2), 6.05 (4–5 H, A_2B_2, OCH_2CH_2O), 7.27 (3 H, s, SO_2CH_3), and 9.00 (3 H, s CH_3). *Anal.* Calcd for $C_{20}H_{33}O_6NS$: C, 57.81; H, 8.01; N, 3.37. Found: C, 57.92; H, 7.91; N, 3.39.

The Compound 40d. Compound **40c** (50 mg) was acetylated with acetic anhydride in pyridine at room temperature. Working up the reaction mixture and crystallization of the residue from methylene chloride–ether gave 44 mg of the compound **40d**: mp 203–205°; ν_{max} 3549, 1725, 1338, and 1151 cm^{-1}; ν_{max} (dilute CCl_4) 3560 and 1735 cm^{-1}; τ 4.90 (1 H, d d, J = 16 and 8 Hz, C*H*OCOCH$_3$), 5.04 (1 H, d, J = 3.8 Hz, CHC*H*<O_2), 6.05 (4 H, A_2B_2, OCH_2CH_2O), 7.27 (3 H, s, SO_2CH_3), 7.95 (3 H, s, $COCH_3$), and 8.96 (3 H, s, CH_3). *Anal.* Calcd for $C_{22}H_{35}O_7NS$: C, 57.75; H, 7.71; N, 3.06. Found: C, 57.85; H, 7.88; N, 3.11.

The Compound 46. A solution of 1.143 g of **40c** in 11.0 ml of pyridine was treated with pyridine–chromium trioxide complex, prepared from 1.10 g of chromium trioxide and 11.0 ml of pyridine, at room temperature for 19 hr. The reaction mixture was diluted with methylene chloride and filtered, and the precipitate was washed with methylene chloride. The filtrate and washings were mixed with twice their volume of ether and washed with 2 *N* potassium carbonate and water and dried, and the solvent was removed under reduced pressure. The residue was crystallized from methylene chloride–ether containing a small volume of methanol to produce 799 mg of the compound **46**, mp 195.5–196.5°. The crystals (50 mg) were dissolved in benzene–chloroform (1:1) and filtered through a layer of 1 g of alumina. The decolored material was recrystallized from methanol–ether to yield an analytical sample melting at 197.5–198°: ν_{max} 3553, 1716, 1339, and 1150 cm^{-1}; ν_{max} (dilute CCl_4) 3541 and 1725 cm^{-1}. *Anal.* Calcd for $C_{20}H_{31}O_6NS$: C, 58.10; H, 7.56; N, 3.39. Found: C, 58.39; H, 7.82; N, 3.55.

The Acetalenone 43. To an ice-cold, stirred solution of 200 mg of the compound **46** dissolved in 1.00 ml of dry pyridine was added 1.00 ml of a 17.3% solution of thionyl chloride in pyridine, and the resulting mixture was stirred at 0° for 3 min, poured into ice water, and extracted with methylene chloride. The washed and dried organic solution, on removal of the solvent under reduced pressure at low temperature, yielded 193 mg of foams, which were crystallized from methylene chloride–ether containing a small volume of methanol. The crude crystals were recrystallized from acetone to give 72 mg of the acetalenone **43**, mp 198.5–200°. One additional recrystallization of the crystals from acetone–ether raised the mp to 200–201.5°: ν_{max} 1665, 1339, 1158, 1150, and 1129 cm^{-1}; λ_{max} 239 nm (ϵ 13,700); τ 3.78 (1 H, t, J = 1.4 Hz, =C*H*), 4.88 (1 H, d, J = 1.6 Hz, CHC*H*<O_2), 6.14 (4–5 H, m, OCH_2CH_2<O_2), 7.31 (3 H, s, SO_2CH_3), and 9.02 (3 H, s, CH_3). *Anal.* Calcd for $C_{20}H_{29}O_5NS$: C, 60.74; H, 7.39; N, 3.54. Found: C, 60.73; H, 7.63; N, 3.57. Purification of the mother liquors by silica gel layer chromatography developed with ethyl acetate produced an additional 50 mg of the acetalenone **43**, mp 200.5–202°.

The Triol 47. To an ice-cold solution of 200 mg of the aldehyde **40a** in 40 ml of methanol was added 100 mg of sodium borohydride and the resulting solution was stirred at that temperature for 1 hr, concentrated under reduced pressure at low temperature, diluted with water, and extracted with methylene chloride. The residue obtained on removal of the solvent gave 195 mg of the crude triol **47**. Crystallization of the crude material was attempted but failed. Acetylation of the material with acetic anhydride and pyridine at room temperature yielded the corresponding diacetate: mp 181–184°; ν_{max} 3567, 1730, 1337, and 1149 cm^{-1}. *Anal.* Calcd for $C_{22}H_{35}O_7NS$: C, 57.75; H, 7.71; N, 3.06. Found: C, 57.92; H, 7.78; N, 3.01.

The Diol Ketone 48a. A mixture of 152 mg of the crude triol **47**, 4.5 ml of acetone, 1.5 ml of *tert*-butyl alcohol, and 0.75 ml of water was cooled to 7° and 186 mg of *N*-bromosuccinimide was added to the mixture. The resulting mixture was stirred at 6–8° for 2.5 hr, poured into 5% sodium sulfite solution, and extracted with methylene chloride. The washed and dried organic solution, on removal of the solvent, produced foams, which were recrystallized twice from acetone–ether to yield 120 mg of the diol ketone **48a**: mp 208–209°; ν_{max} 3643, 3521, 1714, 1340, and 1151 cm^{-1}. *Anal.* Calcd for $C_{18}H_{29}O_5NS$: C, 58.20; H, 7.87; N, 3.77. Found: C, 58.13; H, 8.03; N, 3.81.

The Diol Ketone Acetate 48b. The diol ketone **48a** (109 mg) was acetylated with acetic anhydride in pyridine at room temperature for 16 hr. The reaction mixture was worked up in the usual way to give 122 mg of foams, which were crystallized from acetone–ether to give 118 mg of the diol ketone acetate **48b**, mp 187–188°. An analytical sample melts at 189–190°: ν_{max} 3587, 3472 (weak), 1739 (sh), 1720, 1342, and 1152 cm^{-1}. *Anal.* Calcd for $C_{20}H_{31}O_6NS$: C, 58.10; H, 7.56; N, 3.39. Found: C, 58.03; H, 7.78; N, 3.68.

The Acetoxyenone 44. An ice-cold solution of 90.5 mg of the diol ketone acetate **48b** in 0.36 ml of pyridine was treated with 0.43 ml of a 20% solution of thionyl chloride in pyridine for 5 min, poured into ice water, and extracted with methylene chloride. The organic solution was washed successively with ice-cold 2 *N* hydrochloric acid, ice-cold 2 *N* sodium carbonate solution, and water, and then dried, and the solvent was removed under reduced pressure to yield 80 mg of yellow foam, which was crystallized from acetone–ether to produce 59.2 mg of the acetoxyenone **44**, mp 129–132°. Recrystallization of the crystals from acetone gave an analytical sample: mp 135–136°; ν_{max} 1736, 1667, 1640 (sh, weak), 1341, 1160, and 1150 cm^{-1}; λ_{max} 238 nm (ϵ 14,300). *Anal.* Calcd for $C_{20}H_{29}O_5NS$: C, 60.74; H, 7.39; N, 3.54. Found: C, 60.55 H, 7.54; N, 3.48.

Alkaline Treatment of the Aldehyde 40a. A. Under a Nitrogen Atmosphere. Into a solution of 300 mg of the aldehyde **40a**, nitrogen was bubbled to remove oxygen and to the oxygen-free solution was added 6 ml of an oxygen-free 2 *N* potassium carbonate solution and the resulting mixture was kept in a sealed flask under nitrogen at 38–43° for 22 hr. Aliquots were taken out after 2.5, 6.3, and 21.5 hr. Each showed an almost identical thin-layer chromatogram on an alumina plate developed with ethyl acetate. The reaction mixture was poured into salt solution and extracted with methylene chloride. The organic layer was washed with water and dried, and the solvent was distilled off under reduced pressure to leave 275 mg of yellow foam, which was crystallized from methylene chloride–ether to produce 131 mg of the nonconjugated enal **49**, mp 173–175°. Recrystallization of the material from methylene chloride–methanol yielded an analytical sample: mp 175–177°; ν_{max} 3590, 2728, 1725, 1338, 1156, and 1148 cm^{-1}; λ_{max} 230 (ϵ 1740) and 301 nm (ϵ 133). *Anal.* Calcd for $C_{18}H_{27}O_4NS$: C, 61.17; H, 7.70; N, 3.96. Found: C, 61.24; H, 7.92; N, 4.05. On acetylation with acetic anhydride in pyridine at room temperature and recrystallization from ether, this product gave the corresponding acetate: mp 160–163°; ν_{max} 2726, 1727, 1339, 1156, and 1150 cm^{-1}; λ_{max} 226 (ϵ 1740) and 306 nm (ϵ 137); τ 0.48 (1 H, d, J = 4 Hz, C*H*=O), 5.1 (1 H, broad m, C*H*OCOCH$_3$), 7.32 (3 H, s, SO_2CH_3), 7.99 (3 H, s, $COCH_3$), and 9.17 (3 H, s, CH_3). *Anal.* Calcd for $C_{20}H_{29}O_5NS$: C, 60.74; H, 7.39; N, 3.54. Found: C, 60.49; H, 7.32; N, 3.69.

B. In the Presence of Air. A solution of 250 mg of the aldehyde **40a** in 37.5 ml of methanol and 7.5 ml of 2 *N* potassium carbonate solution was heated to 45°. After 15 hr of heating in a sealed flask, the reaction mixture was extracted and the residue was considered to consist mainly of the nonconjugated enal **49** and a small amount of the enone **50** (*vide infra*). The reaction was repeated on the residue and after an additional 30 hr of heating, the reaction mixture was diluted with salt solution, extracted with methylene chloride, and purified by column chromatography using 8 g of neutral alumina (Woelm II). Fractions eluted with benzene–chloroform (2:1–1:1) were combined and crystallized from ether containing a small amount of methanol to produce 36 mg of the enone **50**, mp 178–180°. This was recrystallized from methylene chloride–methanol–ether giving a pure sample: mp 180–182°; ν_{max} 3580, 3286, 1701, 1640 (medium), 1340, and 1154 cm^{-1}; λ_{max} 244 (ϵ 8200) and 322 nm (ϵ 45). *Anal.* Calcd for $C_{17}H_{25}O_4NS$: C, 60.16; H, 7.43; N, 4.13. Found: C, 60.50; H, 7.55; N, 4.18. The product was acetylated with acetic anhydride in pyri-

dine at room temperature and recrystallized from acetone–ether to yield the corresponding acetate: mp 184–187°; ν_{max} 1730, 1708, 1642 (medium), 1341, and 1154 cm^{-1}; λ_{max} 242 nm (ϵ 7400); τ 5.0 (1 H, broad m, C*H*OCOCH$_3$), 7.37 (3 H, s, SO$_2$C*H*$_3$), 7.95 (3 H, s, COC*H*$_3$), and 8.70 (3 H, s, C*H*$_3$). *Anal.* Calcd for $C_{19}H_{27}O_5NS$: C, 59.83; H, 7.14; N, 3.67. Found: C, 59.81; H, 7.26; N, 3.89.

Conversion of the Nonconjugated Enal 49 into the Enone 50. A mixture of 5.8 mg of the nonconjugated enal **49**, 1.16 ml of methanol, and 0.23 ml of 2 *N* potassium carbonate was sealed in a ampoule and heated in bath at 35° for 19 hr. The reaction mixture was diluted with salt solution and extracted with methylene chloride. The residue was examined by thin-layer chromatography and consisted mainly of starting material, but also some of the enone **50**. The presence of the enone **50** was also confirmed by the uv spectrum of the residue, which showed an absorption maximum at 244 mμ with ϵ of 3700 corresponding to 45% content.

Wittig Vinylation of the Monacetoxyaldehyde 40b *via* the Hemisuccinate 52b. To a cold (3°) ethereal solution of methylenetriphenylphosphorane, prepared by treating a suspension of 98.6 g of methyltriphenylphosphonium bromide in 710 ml of dry ether with 20.5 g of potassium *tert*-butoxide, was added a solution of **40b** (19.0 g) in 1200 ml of tetrahydrofuran over a period of 5 min under a nitrogen atmosphere. After being stirred at room temperature for 4 hr, the reaction mixture was diluted with water and concentrated *in vacuo*, and then 500 ml of 2 *N* potassium carbonate and 1400 ml of methanol were added. The mixture was refluxed for 45 min, concentrated *in vacuo*, poured into ice–water, and extracted with methylene chloride–ether (1:3). The organic solution was worked up as usual to leave 70.4 g of a residue, to which were added 300 ml of pyridine and 36 g of succinic anhydride. The resulting solution was heated at 87° for 6 hr, cooled, diluted with water, and was then allowed to stand at room temperature for 2 hr. The product was extracted with methylene chloride–ether (3:1). The organic extract was washed successively with 2.8 l. of 2 *N* hydrochloric acid, water, 2 *N* potassium carbonate (400 ml), and water, and then dried and evaporated to give 35.1 g of a neutral material. The alkaline layer was acidified with 2 *N* hydrochloric acid and then extracted with methylene chloride. The methylene chloride solution was washed with water, dried, and evaporated to leave 22.8 g of a residue. In another run an analytical sample of the hemisuccinate **52b**, mp 96–102°, was obtained on crystallization from methylene chloride–methanol–ether: ν_{max} 3516, 3026, 1726, 1641, 1338, 1152, 1025, and 922 cm^{-1}. *Anal.* Calcd for $C_{23}H_{35}O_7SN$: C, 58.83; H, 7.51; N, 2.98. Found: C, 57.92; H, 7.89; N, 3.11. A mixture of 22.8 g of the crude hemisuccinate **52b**, 600 ml of methanol, and 200 ml of 2 *N* potassium carbonate was refluxed for 30 min, concentrated *in vacuo*, and then partitioned between water and methylene chloride. The organic phase was dried, concentrated, and crystallized from methylene chloride–ether to afford 12.67 g of the vinyl alcohol **52a**, mp 187–190°, and 1.07 g of a second crop, mp 182–186°. The total yield was 60%. An analytical sample melts at 196–198°: ν_{max} 3535, 1638, 1335, 1149, 1022, 1007, and 918 cm^{-1}. *Anal.* Calcd for $C_{19}H_{31}O_4SN$: C, 61.76; H, 8.46; N, 3.79. Found: C, 61.89; H, 8.47; N, 3.89.

Oxidation of the Vinyl Alcohol 52a. The vinyl alcohol **52a** (6.71 g) was dissolved in acetone (440 ml). The solution was treated with Jones' reagent[45] (7.5 ml) at 0° for 10 min. The mixture was poured into ice–water and extracted with methylene chloride. The methylene chloride extract was washed with 2 *N* sodium carbonate and saturated sodium chloride solution and then dried and evaporated to leave 6.39 g of a residue which was crystallized from ether–methylene chloride to give 6.14 g (92%) of the vinyl alcohol **53**: mp 208–210°; ν_{max} 3552, 1716, 1639, 1337, 1151, 1010, and 920 cm^{-1}. *Anal.* Calcd for $C_{19}H_{29}O_4SN$: C, 62.10; H, 7.96; N, 3.81. Found: C, 61.83; H, 8.10; N, 4.04.

The Enones 54. To a cold (−73°) solution of 1.00 g of the vinyl ketone **53** in 14 ml of dry methylene chloride and 2 ml of dry pyridine a solution of 1.3 equiv of thionyl chloride (0.254 ml) in 1.8 ml of dry methylene chloride was added with stirring over 15 sec. After the resulting solution had been stirred for 2 min, a cold (−15°) solution of ethylene glycol–water (1:1) was added and the solution was partitioned between water and methylene chloride. The methylene chloride extract was washed successively with 10 ml of 2 *N* hydrochloric acid and water, dried, and concentrated to *ca.* 50-ml volume. The resulting solution was chromatographed on alumina (30 g). Fractions eluted with methylene chloride were crystallized from acetone–ether to afford 680 mg of the enone **54**, mp 214–216°, and 176 mg of a second crop, mp 203–208°. The total yield was 90%. An analytical sample melts at 216.5–218.5°: ν_{max} 1670, 1643, 1340, 1160, and 1150 cm^{-1}; λ_{max} 245 nm (ϵ 12,700). *Anal.* Calcd for $C_{19}H_{27}O_3SN$: C, 65.31; H, 7.79; N, 4.01. Found: C, 64.73; H, 7.89; N, 4.30.

Hydrocyanation of the Enone 54. To a solution of 1.00 g (11.5 mmol) of the enone **54** in 50 ml of methylene chloride was added 11.8 ml of a solution of diethyl aluminum cyanide in dry benzene (1.22 mmol/ml) at 24° under an argon atmosphere. The resulting solution was allowed to stand at 24° for 3 hr, diluted with 400 ml of dry ether, poured into ice-cold 2 *N* sodium hydroxide, and extracted with methylene chloride–ether (1:3). The organic extract was washed with water, dried, and evaporated to leave a residue which was crystallized from methylene chloride–ether to give 0.816 g of the cyano ketone **55**, mp 202–205°. The resulting mother liquor was evaporated to dryness, and then the residue was dissolved in 25 ml of dry methylene chloride. The solution was treated with 5.9 ml of the benzene solution of diethyl aluminum cyanide (1.22 mmol/ml), and worked up to give 124 mg of the cyano ketone **55**, mp 199–204°. The total yield was 90%. Recrystallization from methylene chloride gave an analytical sample of **55** melting at 212–213°: ν_{max} 2222, 1727, 1642, 1341, 1101, 1020, 996, and 926 cm^{-1}. *Anal.* Calcd for $C_{20}H_{28}O_3SN_2 \cdot 0.5CH_2Cl_2$: C, 58.76; H, 6.98; N, 6.69; Cl, 8.46. Found: C, 59.60; H, 7.23; N, 7.10; Cl, 7.60. Recrystallization from acetone–ether produced another analytical sample, mp 214–215°. *Anal.* Calcd for $C_{20}H_{28}O_3SN_2$: C, 63.81; H, 7.50; N, 7.44. Found: C, 63.65; H, 7.62; N, 7.36.

The Compound 56. A mixture of 381 mg of the cyano ketone **55**, 835 mg of hydrazine dihydrochloride, 4.00 ml of 80% hydrazine hydrate, and 19 ml of triethylene glycol was heated at 90–100° for 1 hr to give a clear solution, to which, after cooling, was added 1.45 g of potassium hydroxide (85% purity). The resulting mixture was heated to raise the temperature to 200–220° over 30 min, then heated at 200–220° for a further 30 min, cooled, poured into water, and extracted with ether–methylene chloride (3:1) to give 323 mg of hard syrup, which was chromatographed on 30 g of neutral alumina. The fractions eluted with petroleum ether–benzene (1:1)–benzene were recrystallized twice from methylene chloride–ether to give 42.4 mg of the compound **56**, mp 165–167°. One recrystallization of the compound from the same solvent gave an analytical sample: mp 170–171°; ν_{max} 2229, 1641, 1338, 1150, and 923 cm^{-1}. *Anal.* Calcd for $C_{20}H_{30}O_2N_2S$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.12; H, 8.55; N, 7.36.

Reduction of the Cyano Ketone 55 with Lithium Tri-*tert*-butoxyaluminum Hydride. To a cold (0°) solution of 30 mg of the cyano ketone **55** in 1.5 ml of tetrahydrofuran was added 115 mg of lithium tri-*tert*-butoxyaluminum hydride. The reaction mixture was stirred at room temperature for 3.5 hr, and the excess of reagent was destroyed with water. The resulting mixture was extracted with methylene chloride–methanol (4:1). The organic extract was washed with saturated sodium chloride solution, dried, and evaporated to leave 34.5 mg of a residue which was crystallized from methylene chloride–methanol–ether to give 25.2 mg (83.4%) of the 7β-hydroxycarbonitrile **58**, mp 200–202°. An analytical sample melts at 201–202°: ν_{max} 3594, 1641, 1336, and 1150 cm^{-1}. *Anal.* Calcd for $C_{20}H_{30}O_3N_2S$: C, 63.47; H, 7.99; N, 7.40. Found: C, 63.44; H, 7.89; N, 7.70.

Conversion of 58 into the Imino Lactone 59. A mixture of 15.2 mg of the 7β-hydroxycarbonitrile **58**, 1.9 ml of dry benzene, and 20.5 mg of *p*-toluenesulfonic acid monohydrate was refluxed for 3 hr and then partitioned between cold 2 *N* sodium carbonate and ether–methylene chloride (3:1). The organic phase was washed with saturated sodium chloride, dried, and evaporated to leave 14.8 mg of a residue which was crystallized from methylene chloride–ether to give 14.5 mg (95%) of the imino lactone **59**, mp 186–190°. An analytical sample melts at 188–190°: ν_{max} (CCl_4) 3065, 1692, 1636, 1162, and 920 cm^{-1}. *Anal.* Calcd for $C_{20}H_{30}O_3SN_2$: C, 63.47; H, 7.99; N, 7.40. Found: C, 63.18; H, 7.85; N, 7.56.

Regeneration of the Cyano Ketone 55 from the Imino Lactone 59. To a solution of 586 mg of the imino lactone **59** in 59 ml of dry *tert*-butyl alcohol, 1.03 g of potassium *tert*-butoxide was added. The mixture was refluxed for 1.5 hr, poured into ice–water, and extracted with ether–methylene chloride (3:1). The organic extract was washed successively with 2 *N* hydrochloric acid and water, and worked up to leave 593 mg of crude 7β-hydroxycarbonitrile **58** which was dissolved in 35 ml of acetone. The solution was treated

(45) K. Bowden, I. M. Heilbron, E. R. H. Jones, and C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

with Jones' reagent (0.59 ml) at 0° for 15 min, poured into ice–water, and extracted with methylene chloride. The methylene chloride extract was washed successively with 2 *N* sodium carbonate and water, dried, and evaporated to leave 568 mg of a residue which was crystallized from methylene chloride–ether to give 368 mg of the cyano ketone **55**, mp 208–210°, and 41 mg of second crop, mp 200–206°, in 70% overall yield based on **59**.

Reduction of the Cyano Ketone 55 with Aluminum Isoproxide. The cyano ketone **55** (4.036 g) was dissolved in 440 ml of dry toluene containing 3.20 g of aluminum isoproxide, and the mixture was gently refluxed for 1 hr under removal of toluene (100 ml) as an azeotropic distillate. The cooled solution was diluted with cold 2 *N* hydrochloric acid, and the mixture was extracted with methylene chloride. The methylene chloride extract was washed with water, dried, and evaporated to dryness under reduced pressure. The residue (4.028 g) was dissolved in 480 ml of dry benzene and 4.63 g of *p*-toluenesulfonic acid monohydrate was added. The solution was refluxed for 1 hr under removal of benzene (140 ml) as an azeotropic distillate. The cooled reaction mixture was poured into 2 *N* sodium carbonate and extracted with ether–methylene chloride (3:1). The organic phase was washed with 600 ml of 2 *N* hydrochloric acid and with water, dried, and evaporated to leave 3.27 g of a neutral residue which was crystallized from methylene chloride–ether to give 1.696 g of the 7α-hydroxycarbonitrile **57**, and 0.940 g of second crop, mp 112–117°. Chromatography of the mother liquor gave an additional 0.233 g of **57** melting at 115–118°. The yield of **57** was 71%. An analytical sample melts at 161–162° (dimorphism): ν_{max} 3596, 2233, 1639, 1338, 1151, and 924 cm^{-1}. *Anal.* Calcd for $C_{20}H_{30}O_3N_2S$: C, 63.47; H, 7.99; N, 7.40. Found: C, 63.17; H, 7.94; N, 7.48. The acidic aqueous layer was made alkaline with sodium carbonate and extracted with methylene chloride. The organic extract was washed with water, dried, and evaporated to give 0.62 g of crude imino lactone **59**.

The Tetrahydropyranyloxyaldehyde 60b. To the 7α-hydroxycarbonitrile **57** (2.253 g) was added 12.6 ml a solution of diisobutylaluminum hydride in dry tetrahydrofuran (1.9 mmol/ml) at 0° under a nitrogen atmosphere. After being stirred for 40 min at 0°, the reaction mixture was diluted with cold 2 *N* sodium hydroxide (50 ml) and extracted with methylene chloride. The organic extract was washed with water, dried, and evaporated to leave 2.43 g of a residue which was dissolved in tetrahydrofuran (164 ml) and in methanol (52 ml), and a solution of sodium acetate (11.8 g) in a mixture of acetic acid (24.0 g) and water (20 ml) was added. The reaction mixture was refluxed for 10 min, concentrated *in vacuo*, diluted with saturated sodium chloride solution, and extracted with methylene chloride. The organic extract was dried and evaporated to leave 2.01 g of crude hydroxyaldehyde **60a**. The crude hydroxyaldehyde **60a** (2.01 g) was dissolved in dry benzene (60 ml) containing dihydropyrane (1.54 ml) and *p*-toluenesulfonic acid (90 mg). The mixture was refluxed for 1 hr, poured into cold 2 *N* sodium carbonate, and extracted with ether–methylene chloride (3:1). The organic extract was washed with water, dried, and evaporated to leave 2.80 g of a residue which was crystallized from methylene chloride–ether to give 1.704 g of the tetrahydropyranyloxyaldehyde **60b**, mp 138–141°. The mother liquor was evaporated to dryness and chromatographed on alumina (30 g). Fractions eluted with petroleum ether–benzene (1:2), benzene, and benzene–methylene chloride (9:1–2:1) were crystallized from the same solvent pair to afford 524 mg of **60b**, mp 137–141°. The total yield was 80.5%. An analytical sample melts at 150–154°: ν_{max} 2721, 1722, 1337, 1150, and 924 cm^{-1}. *Anal.* Calcd for $C_{25}H_{39}O_3NS$: C, 64.49; H, 8.44; N, 3.01. Found: C, 64.27; H, 8.60; N, 3.20.

Formyl Olefination of the Tetrahydropyranyloxyaldehyde 60b. To a suspension of sodium hydride (60 mg; 52.9% oil dispersion) in dry tetrahydrofuran (2 ml) a solution of the diethyl β-(cyclohexylamino)vinylphosphonate (350 mg) in dry tetrahydrofuran (5 ml) was added with stirring and ice cooling in an argon atmosphere, and the mixture was stirred for 20 min. A solution of the tetrahydropyranyloxyaldehyde **60b** (477.6 mg) in dry tetrahydrofuran (5.5 ml) was then added, and the mixture was stirred at room temperature overnight. The reaction mixture was poured into ice–water and extracted with ether–methylene chloride (2:1). The organic extract was washed with water, dried, and evaporated to leave 663.4 mg of a residue which was dissolved in benzene (30 ml). The resulting solution was mixed with a solution of oxalic acid (700 mg) in water (45 ml). The mixture was stirred at room temperature overnight. Working up in the usual way gave crude tetrahydropyranyloxyformylolefin (544 mg) which was dissolved in tetrahydrofuran (16 ml). The solution was treated with 10% perchloric acid (614 ml) at room temperature for 1.5 hr. The reaction mixture was poured into ice–water and extracted with ether–methylene chloride (2:1). The organic extract was worked up to leave 478.6 mg of a residue which was crystallized from methylene chloride–ether to give the hydroxyformylolefin **61a**, mp 191–194°. The mother liquor was chromatographed over alumina (5 g). Fractions eluted with benzene–chloroform (1:1–1:2) afforded 42.6 mg of **61a**, mp 143–147° (dimorphism). The yield of **61a** was 87%. An analytical sample melts at 194–197°: ν_{max} 3620, 2732, 1689, 1630, 1337, 1150, and 920 cm^{-1}; τ 4.00 (q, J = 6.7, 16.2 Hz), 3.33 (d, J = 16.2 Hz), and 0.48 (d, J = 6.7 Hz). *Anal.* Calcd for $C_{22}H_{33}O_4NS$: C, 64.84; H, 8.16; N, 3.44.

Preparation of the Vinyl Hemiacetal 63. To a solution of 54 mg of crude hydroxyaldehyde **60a** in 1 ml of dry pyridine was added 54 mg of *p*-toluenesulfonyl chloride. The solution was allowed to stand at room temperature overnight. A few pieces of ice were then added. The mixture was let stand at room temperature for 1 hr, diluted with cold 2 *N* hydrochloric acid (8 ml), and extracted with ether–methylene chloride. The organic extract was washed with water, dried, and evaporated to leave 49 mg of a residue which was purified by preparative tlc (silica gel, benzene–AcOEt (1:1)) to give 23 mg of the vinyl hemiacetal **63**, mp 179–181°. Recrystallization from methylene chloride–ether afforded an analytical sample: mp 181–183°; ν_{max} 3574, 1638, 1334, and 1149 cm^{-1}. *Anal.* Calcd for $C_{20}H_{31}O_4NS$: C, 62.97; H, 8.19; N, 3.67. Found: C, 62.82; H, 8.14; N, 3.72.

The Diacetoxy Derivative 65 *via* the Tosylate 61b. To a solution of 314 mg of the hydroxyformylolefin **61a** in 3 ml of dry pyridine was added 320 mg of *p*-toluenesulfonyl chloride. The mixture was allowed to stand at room temperature overnight. A few pieces of ice were then added. The mixture was let stand at room temperature for 1 hr, poured into cold 2 *N* hydrochloric acid (32 ml), and extracted with ether–methylene chloride (2:1). The organic extract was washed successively with water, 2 *N* sodium carbonate, and water, and evaporated to leave 438 mg of amorphous tosylate **51b**; ν_{max} 2726, 1690, 1637, 1599, 1358, 1336, 1168, 1150, and 914 cm^{-1}, the tlc of which proved it to be pure. To a solution of 100 mg of the above tosylate **61b** in 0.8 ml of dry methylene chloride and 30 mg of zinc chloride, 2 ml of acetic anhydride was added at 0° with stirring. Stirring was continued for 1 hr. The reaction mixture was poured into ice–water and extracted with methylene chloride. The methylene chloride extract was washed with water, dried, and evaporated to leave 110 mg of a residue, which was crystallized from ether to give 93 mg (79%) of the diacetoxy derivative **65**, mp 111–123°. Recrystallization from methylene chloride–ether afforded an analytical sample: mp 118–126°; ν_{max} 1763, 1600, 1348, 1340, 1174, 1151, 957, and 916 cm^{-1}. *Anal.* Calcd for $C_{33}H_{45}O_9NS_2$: C, 59.70; H, 6.83; N, 2.11. Found: C, 59.52; H, 6.94; N, 2.08.

(±)-1α,4aα-[(*N*-Mesyl)methanoiminomethano]-1β-methyl-8-methylene Gibbane-10-carboxylic Acid (73a). Dry ozone was bubbled into a cold (−73°) solution of 1.200 g of the diacetoxy derivative **65** in 60 ml of dry methylene chloride until a blue-violet color developed. The solution was allowed to stand for 5 min. The excess of ozone was expelled by dry argon at −73°. To the cold (−73°) reaction mixture was added 600 mg of zinc dust. To the suspension were added 12 ml of acetic acid and 600 mg of zinc dust at 0° under stirring. Stirring was continued for 1 hr at room temperature. The zinc dust was removed by filtration and washed with methylene chloride. The filtrate was washed with water, dried, and evaporated to leave 1.141 g of crude 10β-formyl derivative **66**, ν_{max} 2722 and 1724 cm^{-1}, which was dissolved in 2.4 ml of tetrahydrofuran. To the cold (−13°) solution was added a solution of potassium hydroxide (348 mg) in dry methanol (11.7 ml). The mixture was stirred for 7 min, poured into ice–water, and extracted with ether–methylene chloride (2:1). The organic extract was washed with water, dried, and evaporated to leave 1.043 g of the intermediate **67**, ν_{max} 2706 and 1728 cm^{-1}. To a solution of 1.043 g of the intermediate **67** in 7.5 ml of *N*-methylpyrrolidone, a solution of pyrrolidine (0.29 ml) in dry methanol (2.52 ml) was added at room temperature. The reaction mixture was allowed to stand at room temperature overnight, then warmed at 65° for 1.5 hr, and concentrated *in vacuo* to leave 1.377 g of the intermediate **68**, ν_{max} 1661 cm^{-1}, which was hydrolyzed by heating with 50% aqueous acetic acid (15 ml) at 100° for 1 hr. The mixture was worked up to leave 886 mg of crude hexacyclic formyl hemiacetal **69**: ν_{max} 3390 (br), 2722, and 1723 cm^{-1}; tlc (silica gel G, ethyl acetate–benzene 2:1), four spots attributable to four stereoisomers epimeric both at C_8 and C_{13}. To a solution of 886 mg of the hemiacetal

69 in 68 ml of dry methylene chloride was added Collins reagent[20] (5.0 g) at room temperature. The suspension was stirred at room temperature for 45 min. Insoluble solid was filtered off and the filtrate was separated into acidic and neutral components by methylene chloride and 2 *N* potassium bicarbonate partition. The methylene chloride layer was worked up to leave 791 mg of crude formyl lactone **71**: ν_{max} 2724, 1766, and 1725 cm^{-1}; tlc (silica gel G, methylene chloride–acetone (4:1)), two spots attributable to two stereoisomers epimeric at C_8. To a solution of 791 mg of this crude lactone **71** in 29 ml of methanol was added 11 ml of 2 *N* potassium carbonate. The mixture was stirred at room temperature for 1 hr and concentrated *in vacuo* and the residue was separated into acidic and neutral components by ether–methylene chloride (4:1) and potassium carbonate partition. From the acidic fraction 420 mg of crude carboxylic acid **72a** (ν_{max} 1710 and 1679 cm^{-1}) was obtained. The corresponding methyl ester **72b** was obtained by action of diazomethane. Recrystallization from ether afforded an analytical sample: mp 184–186°; ν_{max} 1730, 1674, and 1608 cm^{-1}; τ 9.19 (3 H, s, CH_3), 7.24 (3 H, s, SO_2CH_3), 6.31 (3 H, s, CO_2CH_3), 3.97 (1 H, s, CH=C), and 0.35 (1 H, s, C=CCHO); λ_{max} 253.5 nm (ϵ 13,050). *Anal.* Calcd for $C_{22}H_{31}O_5NS$: C, 62.69; H, 7.41; N, 3.32. Found: C, 62.54; H, 7.41; N, 3.31. A mixture of 420 mg of the above crude carboxylic acid **72a**, 0.36 ml of 80% hydrazine hydrate, 20 ml of triethylene glycol, and 342 mg of potassium hydroxide pellets (85%) was heated at 130° for 30 min. The temperature was gradually raised to 200° by distilling the low boiling material out over 15 min, and the solution was heated at this temperature for 1 hr. After cooling, the reaction mixture was separated into acidic and neutral components by ether–methylene chloride (4:1) and potassium hydroxide. Careful acidification of the aqueous phase to pH 4 with cold 2 *N* hydrochloric acid, followed by chloroform–methanol (9:1) extraction, washing with water, drying, and removal of the solvent under reduced pressure, afforded the crude *exo*-methylenecarboxylic acid **73** (295 mg) which was crystallized from methanol–methylene chloride to give 235 mg of **73a**, mp 161–164°, in 30% overall yield based on **61a**. An analytical sample melts at 192–194°: ν_{max} (KBr) 3419, 1707, 1619, 1329, 1139, and 926 cm^{-1}. *Anal.* Calcd for $C_{21}H_{31}O_4NS \cdot 0.5H_2O$: C, 62.65; H, 8.01; N, 3.48. Found: C, 62.08; H, 7.90; N, 3.46. From the neutral fraction 4.8 mg of a residue separated. Treatment of the carboxylic acid **73** with diazomethane afforded the methyl ester **73b**. Recrystallization from ether–petroleum ether gave an analytical sample: mp 93–96°; ν_{max} (KBr) 1713, 1658, 1328, 1151, and 874 cm^{-1}. *Anal.* Calcd for $C_{22}H_{30}O_4NS$: C, 64.81; H, 8.16; N, 3.44. Found: C, 65.31; H, 8.81; N, 2.79.

Demesylation of the *N*-Mesylcarboxylic Acid 73. To a solution of 86 mg of lithium in 32 ml of liquid ammonia, a solution of the *N*-methylcarboxylic acid **73** (130 mg) in 1.12 ml of dry tetrahydrofuran and 2.24 ml of dry *tert*-butyl alcohol was added dropwise with stirring at −75° over a period of 4 min. After 25 min, 308 mg of anhydrous ammonium chloride was added to the mixture, and ammonia was evaporated off. The residue was dissolved in 3 ml of water. Careful acidification of the solution with cold (0°) 3 *N* hydrochloric acid at −12° afforded a crystalline precipitate which was filtered off and washed with cold water to give 65 mg (56%) of the amino acid hydrochloride **74**. Recrystallization from methanol–ethyl acetate gave an analytical sample: mp >300° dec; ν_{max} (KBr) 2680, 1713, 1658, 1587, and 871 cm^{-1}. *Anal.* Calcd for $C_{20}H_{30}O_2NCl$: C, 68.25; H, 8.59; N, 3.97. Found: C, 67.96; H, 8.75; N, 3.72.

Model Experiments. Conversion of the Tetracyclic Anisole Base 77 into the Isomeric Lactones, 82 and 83. **A.** To a solution of 136.0 mg of the tetracyclic anisole base **77**[5a] in 7 ml of dry benzene was added 276 mg of potassium carbonate and 443 mg of lead tetraacetate. The suspension was stirred at room temperature for 1 hr, poured into ice–2 *N* potassium carbonate (5 ml), and diluted with 10 ml of ether–methylene chloride (7:1). The precipitate was filtered off and washed with ether–methylene chloride (7:1). The filtrate was washed with water and then evaporated to leave 149 mg of a crude mixture of the two isomeric azomethine bases **78** and **79**, mp 112–120°. The mixture was dissolved in dioxane (15 ml) and to this solution a solution of sodium nitrite (300 mg) and sodium acetate (300 mg) in water (10 ml) was added, followed by a solution of acetic acid (0.6 ml) in dioxane (1 ml), added at room temperature with stirring over 3.5 hr under nitrogen. The reaction mixture was allowed to stand at room temperature overnight, concentrated *in vacuo*, diluted with 2 *N* potassium carbonate (10 ml), and extracted with ether–methylene chloride (6:1). The organic extract was washed successively with water, 2 *N* sulfuric acid (20 ml), and water, then dried and evaporated to leave 142.4 mg of a crude mixture of the isomeric hemiacetals **80** and **81** which was treated with a chromium trioxide (130 mg)–pyridine (1.4 ml) complex at 12° for 3 hr. The reaction mixture was diluted with ice–water, and extracted with ether. The ether extract was washed with water, dried, and evaporated to leave 138.9 mg of a residue which was separated by preparative tlc (silica gel G, benzene–ethyl acetate, 8:1) to give 34.2 mg (24%) of the lactone **82**, mp 187–188°, and 23.5 mg (16%) of the isomer **83**, mp 196–198°, on crystallization from methylene chloride–ether. An analytical sample **82** melts at 187–188°: ν_{max} 1723, 1609, and 1505 cm^{-1}; nmr ($CDCl_3$) τ 8.70 (3 H, s, CCH_3), 8.69 (pyridine-d_5) (3 H, s, CCH_3). *Anal.* Calcd for $C_{18}H_{22}O_3$: C, 75.49; H, 7.74. Found: C, 75.05; H, 7.77.

An analytical sample of **83** melts at 196–198°: ν_{max} 1724, 1610, and 1504 cm^{-1}; nmr ($CDCl_3$) τ 8.98 (3 H, s, CCH_3), 9.20 (pyridine-d_5) (3 H, s, CCH_3). *Anal.* Calcd for $C_{18}H_{22}O_3$: C, 75.49; H, 7.74. Found: C, 75.22; H, 7.77.

B. To a solution of the tetracyclic anisole base **77**[5a] (103 mg) in tetrahydrofuran (0.55 ml) and methanol (0.55 ml) was added a mixture of *N*-bromosuccinimide (77 mg, 1.1 equiv), lithium chloride (100 mg), sodium acetate (62.5 mg), acetic acid (19 mg), and water (0.5 ml) at 0°. The mixture was stirred for 2.5 hr at 0°, poured into ice–water, and extracted with methylene chloride. The methylene chloride extract was washed with water, dried, and evaporated to leave 138 mg of a residue which was mixed with sodium methoxide (55 mg) and dry methanol (2 ml). The mixture was refluxed for 1 hr, cooled, poured into ice–water, and extracted with methylene chloride. The methylene chloride extract was worked up to leave 103 mg of a crude mixture of azomethine bases **78** and **79**. This mixture was mixed with dioxane (10 ml), sodium nitrite (200 mg), sodium acetate (200 mg), water (6.6 ml), and acetic acid (0.4 ml) at 0° with stirring. The reaction solution was allowed to stand at 0° overnight, poured into ice–water, and extracted with methylene chloride. The methylene chloride extract was washed successively with 2 *N* sodium carbonate, water, 2 *N* hydrochloric acid, and water, then dried and evaporated to leave 109 mg of a residue which was dissolved in acetone (4 ml). The solution was oxidized with Jones' reagent (0.35 ml) at 0° for 5 min, poured into ice–water, and extracted with methylene chloride. The methylene chloride extract was worked up to leave 99 mg of a residue which was purified by preparative tlc (silica gel, benzene–CH_2Cl_2 (9:1)) to afford 33 mg (30%) of the lactone **82** and 16 mg (15%) of the isomer **83**.

(±)-Gibberellin A_{15} Methyl Ester 88a. To a cold (−8°) solution of the hydrochloric acid salt **74** (26 mg) in dry pyridine (0.3 ml) was added a solution of trifluoroacetic anhydride (100 mg) in dry methylene chloride (1 ml) over a period of 2 min under argon. The reaction mixture was stirred for 35 min, and then at room temperature for 8 min, then poured into ice–2 *N* hydrochloric acid (2 ml), and extracted with methylene chloride. The methylene chloride extract was washed with water, dried, and evaporated to leave 29.8 mg of crude trifluoroacetylamide **76a**, ν_{max} 1687 and 881 cm^{-1}.

The above trifluoroacetylamide (30.4 mg) was esterified with diazomethane to give 29.8 mg of crude ester **76b**, ν_{max} 1732, 1688, and 881 cm^{-1}. To a solution of 29 mg of the ester **76b** in 3 ml of methanol was added 0.75 ml of 3 *N* potassium carbonate. The mixture was refluxed for 1.5 hr under argon, concentrated to half of the initial volume, and partitioned between cold 4 *N* sulfuric acid (4 ml) and ether. The aqueous acidic layer was made alkaline with 2 *N* sodium carbonate, and extracted with methylene chloride. The methylene chloride extract was worked up to leave 21.4 mg of basic ester **76c** (92% crude overall yield based on **74**): ν_{max} 1731 and 880 cm^{-1}. To a cold (5°) solution of this basic ester **76c** (11.0 mg) in 0.6 ml of dry benzene–dry tetrahydrofuran (9:1) was added anhydrous potassium carbonate (12 mg) and lead tetraacetate (19.2 mg) under nitrogen. The suspension was stirred for 30 min, poured into ice–water, and extracted with ether–methylene chloride. The organic extract was washed with water, dried, and evaporated to leave 11.2 mg of a crude mixture of the isomeric azomethines **84** and **85**, ν_{max} 1732 and 1663 cm^{-1}, which, without purification, was dissolved in dioxane (1.7 ml). To the solution was added a solution of sodium nitrite (30 mg) and sodium acetate (30 mg) in water (1.13 ml). To the mixture a solution of acetic acid (57 μl) in dioxane (0.11 ml) was added at room temperature with stirring over 2 hr under argon. The reaction mixture was allowed to stand at 3° overnight, concentrated *in vacuo*, diluted with 2 *N* potassium carbonate (0.6 ml), and extracted with ether–methylene chloride (4:1). The organic extract was washed successively with water, 0.5 *N* sulfuric acid, and water, and then dried and evaporated to

leave 10.6 mg of a crude mixture of the hemiacetals, **86** and **87**, ν_{max} 3554 and 1731 cm^{-1}, which was dissolved in 1 ml of dry methylene chloride. To the solution was added 53 mg of Collins' reagent[20] under nitrogen. The suspension was stirred for 25 min, poured into ice–water, and extracted with ether–methylene chloride (4:1). The organic extract was washed with 2 *N* sulfuric acid (1 ml) and water, dried, and evaporated to leave 9.6 mg of a crude mixture of isomeric lactones, **88a** and **89a**. Preparative tlc of the above mixture on silica gel (doubly developed with *n*-hexane–methanol (10:1)) furnished 0.9 mg of *dl*-gibberellin A_{15} methyl ester **88a** and 1.2 mg of the isomeric lactone ester **89a**. Crystallization of the former component from ether–pentane gave 0.6 mg of *dl*-gibberellin A_{15} methyl ester A_{15} **88a**, mp 168–170°. Its ir (in chloroform), mass spectrum, tlc (silica gel G, ethyl acetate–benzene (9:1)), and glc (1% OV-1 and 1% QF-1) data were identical with those of an authentic sample. Crystallization of the latter component from ether–pentane gave 0.6 mg of the isomeric lactone ester **89a**: mp 114–116°; ν_{max} 1728, 1656, 1162, 1156, and 884 cm^{-1}; mass, molecular ion *m/e* 344; nmr τ 9.20 (3 H, s, CH_3).

***dl*-Gibberellin A_{15} 1.** A mixture of 1.7 mg of the *dl*-gibberellin A_{15} methyl ester **88a** and 4 mg of triphenylphosphine, 8 mg of anhydrous lithium iodide, and 0.4 ml of dry γ-collidine was refluxed for 50 min under argon. The reaction mixture was cooled, acidified with 1.6 ml of 3 *N* hydrochloric acid, and extracted with ether–methylene chloride (3:1). The organic layer was extracted successively with 2 *N* sodium hydroxide (0.8 ml) and water. After acidification (to pH 3) of the aqueous sodium hydroxide extract with dilute hydrochloric acid, the aqueous layer was extracted with chloroform–methanol (9:1). The organic extract was washed with water, dried, and evaporated to leave 1.7 mg of a residue, which was crystallized from acetone–pentane to furnish 0.6 mg of *dl*-gibberellin **1**, mp 236–237°. This sample showed an ir spectrum (in chloroform), mass spectrum, and tlc (Woelm silica gel, benzene–ethyl acetate (4:1), isopropyl ether–acetic acid (95:5)) completely identical with those of an authentic sample of **1** (the naturally occurring optically active compound).

The Lactone Acid 89b. A mixture of 2.7 mg of the isomeric lactone ester **89a**, triphenylphosphine (4.0 mg), anhydrous lithium iodide (8 mg), and dry γ-collidine (0.4 ml) was treated as above to afford 2.1 mg of an acidic residue, which was crystallized from acetone–pentane to furnish 0.8 mg of the lactone acid **89b**, mp 187–189°. Recrystallization raised the melting point to 197–198°: ν_{max} 1727, 1713, 1656, 1147, and 885 cm^{-1}; mass, molecular ion *m/e* 330.

Bioassay. Preparation of Test Solutions. *dl*-Gibberellin A_{15} **1** (60 μg) was dissolved in water (6 ml) at 70° to give a 3×10^{-5} *M* solution. The isomeric lactone **89b** (60 μg) was also dissolved in water (6 ml) at 70° to give a 3×10^{-5} *M* solution. These solutions were diluted with water to give 3×10^{-6} *M* solutions.

Bioassay Procedures. The rice seedling growth test procedure as follows. Seeds of rice (*Oryza sativa*, var. Norin No. 29) were soaked in EtOH for 10 min and then in a saturated solution of bleaching powder for 1 hr. The sterilized seeds were transferred into a large petri dish containing sterilized water of 1 cm depth. The petri dish was kept at 30° for 48 hr under white fluorescent and incandescent lamps (about 5000 lx). Germinating seeds having 3–5 mm coleoptiles were employed for further use. These seeds were placed in test tubes (3 × 10 cm), 15 to one test tube, containing 1.35 ml of aqueous test solution. After covering the tubes with a polyethylene sheet, they were kept for 5 days under white fluorescent and incandescent lamps (about 5000 lx). The second leaf sheathes of the seedlings were then measured and compared with those of control plants, grown in water alone.

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The Stereochemistry of Addition Reactions of Allenes. V. Stereoselective Bromination of 1,2-Cyclononadiene

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Abstract: Bromine addition to partially resolved 1,2-cyclononadiene has been found to give a mixture of *optically active* normal and transannular monoadducts. In carbon tetrachloride the major product is *cis*-2,3-dibromocyclononene; the minor product is *cis*-1,4-dibromocyclononene formed by a 1,5-hydride shift. In methanol, the major products are *cis*-1-bromo-4-methoxycyclononene and *cis*-2-bromo-3-methoxycyclononene formed in the ratio of 3:2, respectively. Induction of asymmetry in the normal 2,3 adducts and in the transannular 1,4 adducts is discussed in terms of the involvement of dissymmetric transition states and reaction intermediates. Absolute configuration of each of the derived 1,4 adducts is assigned by reason of the absolute configuration of the starting allene and the nature of the stereoselective reactions by which they are formed. The 2,3 adducts are evidently formed by a mechanism of trans electrophilic addition.

The dissymmetry inherent in 1,3-disubstituted allenes provides a valuable probe of the stereochemistry of addition reactions to the allenic system. By this approach it has been established that mercuric acetate and halogens react with (*R*)-(−)-2,3-pentadiene in methanol to give monoadducts by way of net trans addition of the attacking reagents to one of the double bonds.[3,4] The orientation of addition is such that the attacking electrophile combines exclusively with the central allenic carbon to form a mixture of cis and trans isomeric adducts in which the trans isomer predominates (83–94%). The intermediacy of dissymmetric bridged ions has been suggested to explain the stereoselectivity observed (eq 1).

Electrophilic additions to other optically active allenes have been reported. Reaction of (+)-2,2-dimethyl-3,4-hexadien-1-ol with 2,4-dinitrobenzene-

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