Synthetic Intermediates Potentially Useful for the Synthesis of Tetrodotoxin and Derivatives. III.[1] Synthesis of a Key Lactone Intermediate from Shikimic Acid

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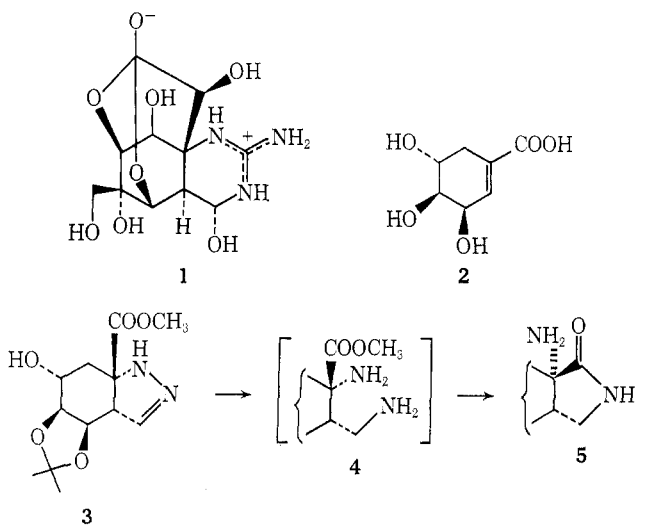
Toward the goal of synthesizing from shikimic acid a pyrazoline intermediate in which the two-carbon angular substituent is tied back through formation of a lactone to the carbocyclic ring (see lactone **60**), diazo ketone **9** was prepared. This substance together with those epoxypyrazolines obtained by the reaction of diazomethane with amides **16** and **17** and ester **18** all failed in their mission. Reaction of pyrazolines **27** and **3**, however, with methanesulfonyl chloride led to novel mesylate derivatives **32** and **33**, the latter affording the oxygen-bridged cyclopropane **36** upon reaction with hot acetic anhydride. The synthetic goal was realized through chain extension of intermediate **3** in which the pyrazoline ring was already in place, a sequence which avoided the undesirable formation of epoxy derivatives at the α position on the side chain (see below). In order for the final ring closure to a lactone to take place, it was found necessary to reduce the α-keto function of amide **45**, producing alcohol **59**. This last substance upon treatment with hot pyridine–water smoothly cyclized to the desired key lactone intermediate **60**.

We describe in this paper further progress toward the synthesis of the Japanese puffer fish (*Fugu*) and California newt neuropoison tetrodotoxin (**1**)[2] (Scheme I) and

SCHEME I

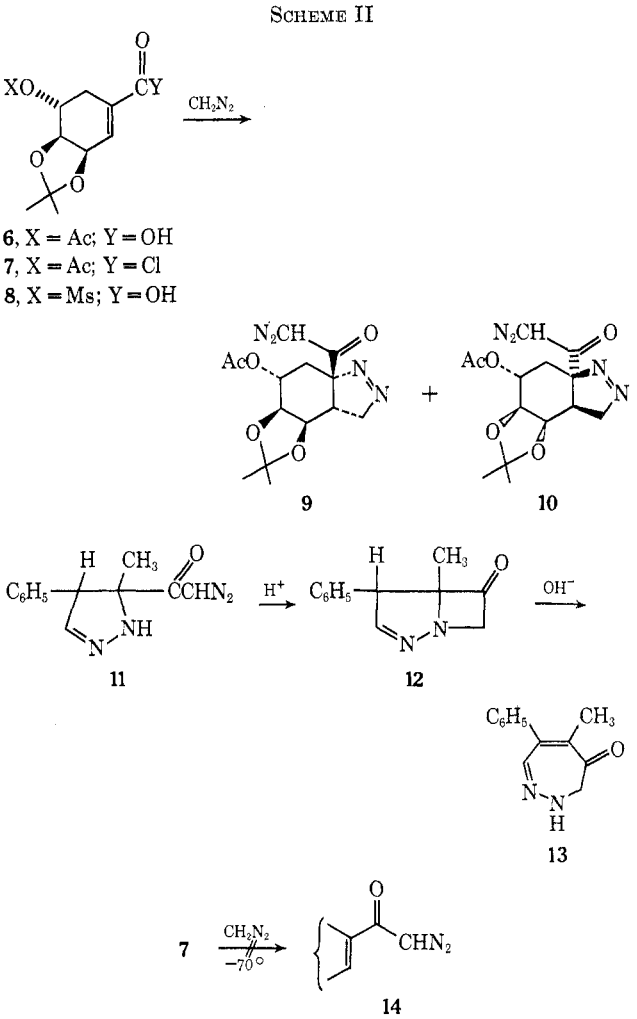


closely related structural derivatives utilizing the readily available natural shikimic acid (**2**) as a starting point. In particular, the chemistry leading to the synthesis of key lactone intermediate **60** is herewith disclosed.

In part II[1] of this series we described the synthesis of pyrazoline **3** from shikimic acid and outlined a plan for the conversion of the pyrazoline ring of **3** into a cyclic guanidine moiety by way of reduction to the 1,3-diamine **4** and subsequent condensation with cyanamide or nitroguanidine. Progress toward this goal, however, became quickly thwarted when attempts to obtain the diamine **4** resulted in a mixture which probably contained the lactam **5**. It became clear that conversion of the pyrazoline ring to the cyclic guanidine must necessarily be accomplished after the side chain is "tied back" to the carbocyclic ring through formation of a lactone or two-thirds ortho ester.

Since in our plan the carboxy group of shikimic acid (**2**) was destined to become the two-carbon angular substituent of tetrodotoxin, it was necessary to convert the carboxy carbon atom into a two-carbon appendage which might then be tied back. It appeared that the reaction of diazomethane with a suitably protected acid chloride would not only provide a two-carbon functionalized appendage but moreover introduce the required pyrazoline ring in the same step. To this end acid **6**[1] (Scheme II) was converted into the acid chlo-

SCHEME II



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(1) Part II: J. F. W. Keana and C. U. Kim, *J. Org. Chem.*, **35**, 1093 (1970).

(2) R. B. Woodward, *Pure Appl. Chem.*, **9**, 49 (1964), and references cited therein.

ride **7** with thionyl chloride and then allowed to react with excess diazomethane. Column chromatography afforded pure oily pyrazolines **9** in 65% yield and **10** in 25% yield.[3,4]

Although simple diazo ketones can be transformed into a variety of functional groups, often in high yield,[5] all attempts to convert the α-diazo ketone function of pyrazoline **9** into an α-halo ketone, a ketoaldehyde, or a keto acid utilizing conventional methods[5] consistently met with failure. It is likely that the pyrazoline ring became involved in a manner analogous to that observed by Moore[6] where the action of acid on pyrazoline **11** led to heterocycle **12**, base treatment of which produced **13**.

The sequence was then attempted stepwise since Moore,[7] for example, was able to add successfully only 1 equiv of diazomethane to α-methylcinnamoyl chloride to obtain the corresponding α,β unsaturated diazo ketone in good yield. However, our acid chloride **7** or the corresponding 5-mesyloxy derivative led to a mixture of diazoketopyrazolines and starting acid chloride even when deficiencies of diazomethane were employed at −70°. Apparently once the unsaturated diazo ketone is formed it reacts with more diazomethane at a much faster rate than does starting acid chloride **7**, and thus it was not possible in our series to prepare the unsaturated diazo ketone **14**.

At this point it occurred to us that the elegant general α-ketoamide synthesis recently developed by Ugi[8] utilizing the reaction between acid chlorides and isocyanides might be applicable to α,β-unsaturated acid chlorides. Thus acid chloride **7** was allowed to react with methyl isocyanide, affording an adduct tentatively represented as imidoyl chloride **15** (Scheme III) in near quantitative yield. The adduct could be hydrolyzed quantitatively to ketoamide **16**. In a completely analogous sequence, mesylate **17** (see below) was also prepared from acid **8**.

Having introduced the desired side chain, we then allowed diazomethane to react with ketoamide **16**, a reaction which led not to the desired pyrazoline **19** but instead to a mixture of epoxypyrazolines **20** and **23** in which diazomethane had added to the α-keto carbonyl group as well, probably nonstereoselectively. Formation of the epoxides could not be suppressed even by reaction of **16** at −70° with 1 equiv of diazomethane. Chromatographic separation was difficult, affording only minor pyrazoline **23** in nearly pure form in 14% yield.[3] It could be estimated from the nmr spectrum of the mixture that major pyrazoline **20** was produced in about 50% yield.

(3) The stereochemical assignment of the newly formed pyrazoline ring as either α or β is partially or entirely based on the following considerations (see part II[1] of this series). The isomer resulting from cis addition of diazomethane to the least hindered side of the double bond (side opposite the acetonide moiety) would be expected to predominate. This isomer and its Δ^2 analog invariably had the longer retention time upon chromatography over silica gel than did the other. Secondly, if the Δ^1-pyrazoline ring is cis to the acetonide moiety the chemical shift difference between the two singlets observed for the acetonide moeity is about 4 Hz, whereas this difference is about 8 Hz if the Δ^1-pyrazoline ring is trans to the acetonide moeity.[1]

(4) Complete spectral data on all pertinent compounds are found in the Experimental Section. All compound names and structures, excepting tetrodofoxin (**1**), are given without regard to absolute configuration.

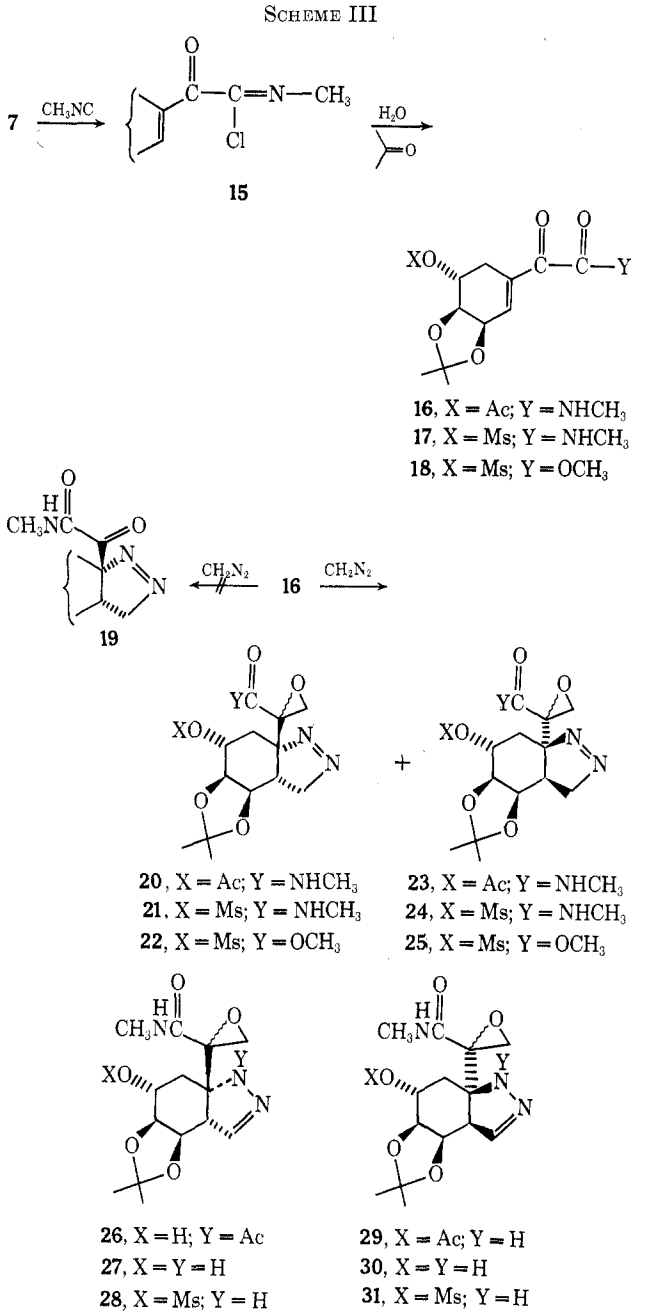
(5) For a review of α-diazo ketone reactions, see F. Weygand and H. J. Bestmann, *Angew. Chem.*, **72**, 535 (1960).

(6) J. A. Moore, W. F. Holton, and E. L. Wittle, *J. Amer. Chem. Soc.*, **84**, 390 (1962); J. A. Moore and L. J. Pandya, *J. Org. Chem.*, **29**, 336 (1964).

(7) J. A. Moore, *ibid.*, **20**, 1607 (1955).

(8) I. Ugi and U. Fetzer, *Chem. Ber.*, **94**, 1116 (1961).

SCHEME III

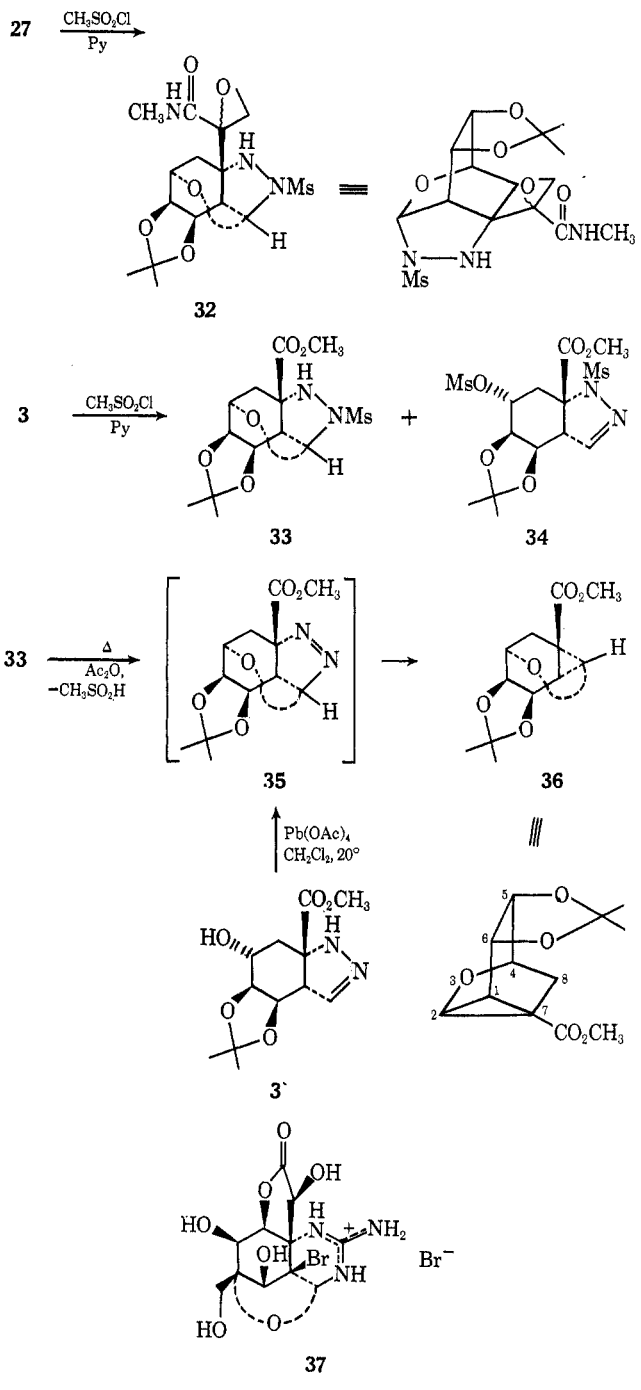


Experience gained in the one-carbon side chain pyrazoline series[1] suggested that pyrazolines **20** and **23** might well suffer isomerization to the Δ^2-pyrazoline series and with, in the case of pyrazoline **20**, concommitant OAc → NAc migration upon treatment with toluenesulfonic acid in refluxing benzene. Indeed, when the mixture was so treated and the resulting products chromatographed, *N*-acetate **26**, mp 195–196°, was isolated in 24% yield, based on starting ketoamide **16**. The structure of **26** followed from the ir spectrum which showed a new sharp strong band at 1620 cm^{-1} (=N—NAc)[1] and the nmr spectrum which displayed a three-proton singlet at δ 2.23 (NAc).[1] In order for a OAc → NAc migration to occur, the C-6 acetoxy group and the pyrazoline ring must be cis to one another. Minor pyrazoline **29** could not be obtained in pure form from this chromatography.

In another series of experiments the mixture of pyrazolines **20** and **23** was treated with sodium methoxide

in methanol, cleaving the acetates and isomerizing the double bond into the 2 position. Chromatographic separation of this mixture afforded first pure minor pyrazoline **30**,[3] mp 176–177°, in 13% yield followed by oily predominant isomer **27** in 26% yield. This latter material was converted into crystalline mesylate derivative **32**, mp 183–185° (Scheme IV), the structure of which for some time remained a mystery.

SCHEME IV



Elemental analysis and mass spectral data revealed that **32** was a monomesylate derivative of **27**. The nmr spectrum of **32** displayed the C-3 proton as a doublet (J = 4.0 Hz) at δ 5.60. The C-3 proton in all the Δ^2-pyrazolines of our series appeared at δ 6.6–7.0; thus **32** was not simply the *N*- or *O*-mesylate of Δ^2-pyrazoline **27**. The *O*-mesylate **28**, prepared by another route (see below), displayed the expected one-proton doublet (J = 1.5 Hz) at δ 6.72 for the C-3 proton. The ir spectrum of **32** was not revealing since other functional groups in the substance masked the crucial OH and C=N regions.

Confirming evidence was obtained from a study of the mesylation of pyrazoline **3**.[1] Treatment of **3** with methanesulfonyl chloride in pyridine followed by a chromatography led to a crystalline monomesylate derivative, mp 126–128°, which was assigned structure **33** and an oily dimesylate derivative **34**. Mesylate **33**, like **32**, displayed in its nmr spectrum a one-proton doublet (J = 3.0 Hz) at δ 5.60 assigned to H-3. The ir spectrum displayed weak absorption at 3400 cm^{-1} (NH or OH) but no absorption at ~1650 cm^{-1} (C=N). Dimesylate **34**, on the other hand, displayed H-3 as the expected doublet (J = 1.5 Hz) at δ 6.90 and showed as well weak C=N absorption at 1650 cm^{-1}.

Treatment of monomesylate **33** with methanesulfonyl chloride in pyridine led quantitatively to starting material, clearly indicating that **33** was not an intermediate on the way to dimesylate **34**. It is our interpretation that initial mesylation on the oxygen atom of **3** (or **27**) is competitive with attack on the pyrazoline ring. Once the simple *O*-mesylate is produced, the hydroxyl is now protected and the substance suffers further rapid attack on N-1 to produce dimesylate **34**. However, if initial attack occurs on the pyrazoline ring, it is the less hindered N-2 which is attacked with concomitant addition of the juxtaposed (in several conformations) C-6 hydroxy group to the C=N group, affording monomesylate **32** (or **33**). An analogous transannular addition of a suitably juxtaposed hydroxy group to a C=N linkage was observed in the instance of bromoanhydrotetrodoic lactone hydrobromide (**37**) by Woodward.[2]

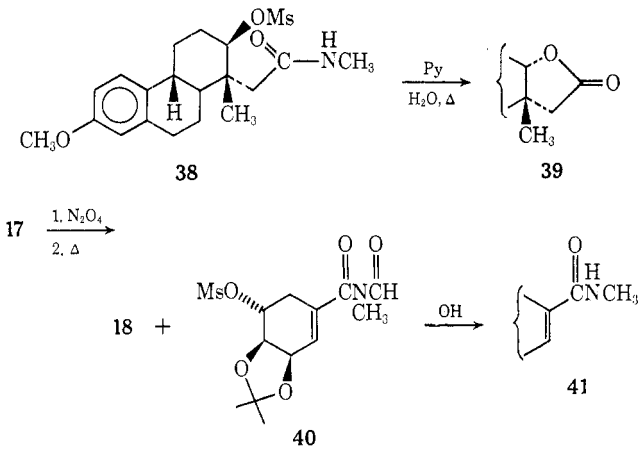
Mesylate **33** also resisted the action of acetic anhydride in pyridine, but when treated with refluxing acetic anhydride a most interesting elimination ensued, producing in high yield a crystalline ester, mp 105–106°, assigned structure **36** on the basis of elemental analysis and spectral data.[4] It seems reasonable that the first step toward **36** might be a thermal elimination of methanesulfinic acid to produce Δ^1-pyrazoline **35** which then suffers rapid loss of nitrogen, producing cyclopropane **36**. It is well known that Δ^1-pyrazolines in which the nitrogen atoms are attached to carbon atoms capable of providing good stabilization for a free radical at that site readily thermally eliminate nitrogen to afford the corresponding cyclopropane.[9] Cyclopropane (**36**) had been obtained earlier by us (unpublished) when ester **3** was treated with lead tetraacetate in dichloromethane with the aim of producing a Δ^1-3-acetoxy derivative.[10] It is not possible to conclude with certainty from the above discussion that the mesylate groups in **32** and **33** are in fact located on N-2 rather than N-1; however, since *N*-acetate **44** (see below), for example, shows no tendency toward addition of the C-6 hydroxy group to the C=N linkage, it is likely that structures **32** and **33** are correct for the substances described.

Because of the low yields and difficult chromatographic separations encountered in the C-6 acetate series above we formulated a new plan which envisioned an intramolecular displacement of the mesylate group

(9) See, *inter alia*, R. Crawford and G. Erickson, *J. Amer. Chem. Soc.*, **89**, 3907 (1967); D. E. McGreer and W. Wu, *Can. J. Chem.*, **45**, 461 (1967).
(10) J. P. Freeman, *J. Org. Chem.*, **29**, 1379 (1964).

in mesylate **21** by the oxygen atom of the amide carbonyl group, a process related to that effected recently by Ireland[11] with the conversion of mesylate **38** to lactone **39** (Scheme V). This scheme eventually proved successful in modified form (see below).

SCHEME V



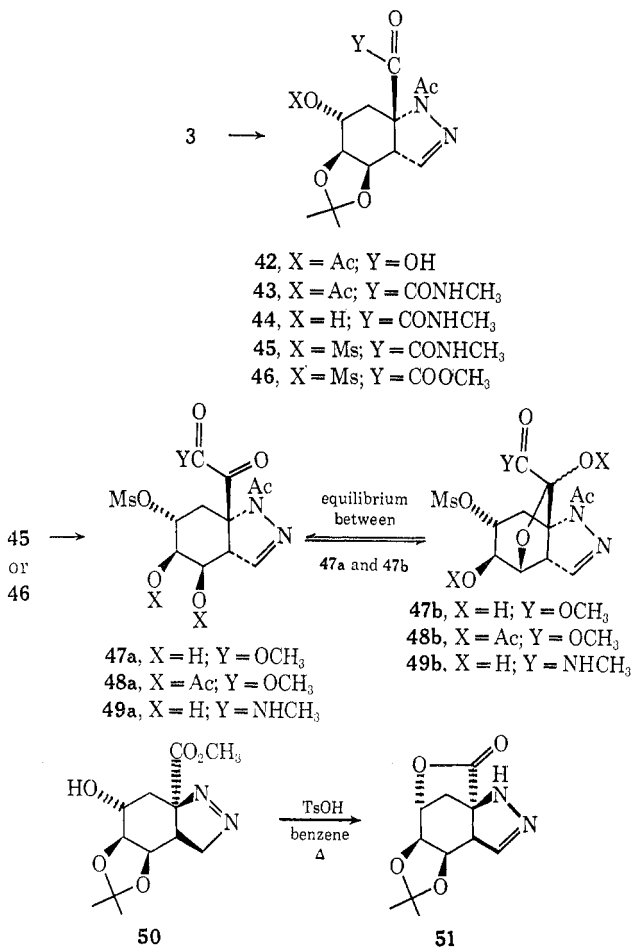
Reaction of diazomethane with mesylate ketoamide **17** (see above) produced, after chromatography, an inseparable oily mixture of pyrazolines **21** and **24** which was isomerized to the readily separable Δ^2-pyrazoline series through refluxing benzene containing toluenesulfonic acid. The oily predominant isomer (by nmr) could be isolated in 18% yield after rechromatography and was assigned structure **28**.[3] The minor isomer **31**, obtained in 10% yield, was characterized only by spectra. The low yield of pure pyrazoline **28** precluded extensive study on the cyclization to a lactone. The substance was subjected to the action of refluxing dimethylformamide, sodium hydride in tetrahydrofuran, and sodium methoxide in methanol, none of which led to useful material.

At this point it was decided to explore the reactions of the two-carbon side chain α-keto ester series. The action of dinitrogen tetroxide[12] on mesylate amide **17** followed by a period of heating in benzene smoothly led to methyl ester **18**, obtainable in an overall yield of 70% from the acetonide of shikimic acid (**2**) without purification of any intermediates. Also produced in 15% yield along with ester **18** was *N*-methylformamide **40**. Treatment of **40** with sodium hydroxide in methanol afforded *N*-methylamide **41**, mp 130–131°, in 60% yield. The origin of **40** is not clear at this time.

Not surprisingly, ester **18** behaved toward diazomethane in a manner analogous to that of ketoamide **17**. Chromatography of the resulting mixture of pyrazolines **22** and **25** afforded the predominant (by nmr) pure oily pyrazoline **22** in 38% yield. Unfortunately, attempted hydrolysis of **22** with cold methanolic sodium hydroxide led only to poorly resolved mixtures in which the epoxide appeared to have suffered ring opening and the pyrazoline ring perhaps a comparable fate. Thus we were led to explore yet another synthetic permutation, the ultimately successful one toward our goal, namely, one in which the angular carbomethoxy group of a suitable intermediate was chain-extended after the pyrazoline ring had been introduced and protected.

This last approach began with pyrazoline **3**, readily available from shikimic acid in 75% overall yield. Treatment (Scheme VI) of **3** with aqueous sodium hydroxide in methanol afforded the corresponding acid which, without purification, was converted into diacetate **42** in 83% overall yield by acetic anhydride in pyridine. The action of thionyl chloride on acid **42** led to the corresponding acid chloride which was immediately allowed to react with methyl isocyanide.[8] The resulting adduct was hydrolyzed in aqueous acetone to afford after chromatography pure oily amide **43** in 56% overall yield from ester **3**.

SCHEME VI



In order to introduce a good leaving group at the 6 position the OAc of diacetate **43** was selectively hydrolyzed by treatment with 1.1 equiv of aqueous sodium hydroxide in methanol at 0°, producing alcohol **44**, mp 118–122°. The reaction of **44** with methanesulfonyl chloride in pyridine led to mesylate **45** as a white foam. We were now in a position to attempt an intramolecular displacement of the mesylate group (see above). The reaction proved unsuccessful once again, perhaps for the following reasons: (a) the strain involved with formation of the lactone bridge which would contain two sp^2-hybridized carbon atoms; (b) the unfavorable interaction of the bridge with the nearby cis acetonide moiety; (c) an extremely unfavorable position of equilibrium between the two chair conformers of amide **45**, only one of which can cyclize.

(11) R. E. Ireland, D. A. Evans, D. Glover, G. M. Rubottom, and H. Young, *J. Org. Chem.*, **34**, 3717 (1969).
(12) E. H. White, *J. Amer. Chem. Soc.*, **77**, 6008 (1955).

The amide **45** was next converted into ester **46**, mp 153–154°, by the action of dinitrogen tetroxide[11] followed by heat. It was hoped that mild basic hydrolysis of **46** would lead to the corresponding acid which might undergo cyclization to the desired lactone. However, as in the case of ester **22** above, mild hydrolysis attempts on ester **46** led only to bad mixtures, the nmr spectra of which were not promising.

It was possible that removal of the acetonide grouping might allow cyclization to proceed. Toward this goal ester **46** was treated with methanolic hydrogen chloride, affording diol **47**, a substance which readily led to triacetate **48** (see below) by treatment with acetic anhydride in pyridine. Diol **47** was recovered unchanged from treatment with toluenesulfonic acid in refluxing benzene, conditions which readily afforded lactone **51** from ester **50**.[1] From the fact that diol **49**, prepared from amide **47** by the action of methanolic hydrogen chloride, displayed only weak ir absorption at ~1730 cm^{-1} due to the α-keto grouping and that diol **54** (see below) displayed no absorption in this region, it appeared that the failure of the above cyclization attempt likely resulted from existence of both diols **47** and **49** largely in the hemiketal forms **47b** and **49b**, respectively. In this regard it is possible that the structure of triacetate **48** is **48b** rather than **48a**. Spectra do not permit a clear distinction to be made.

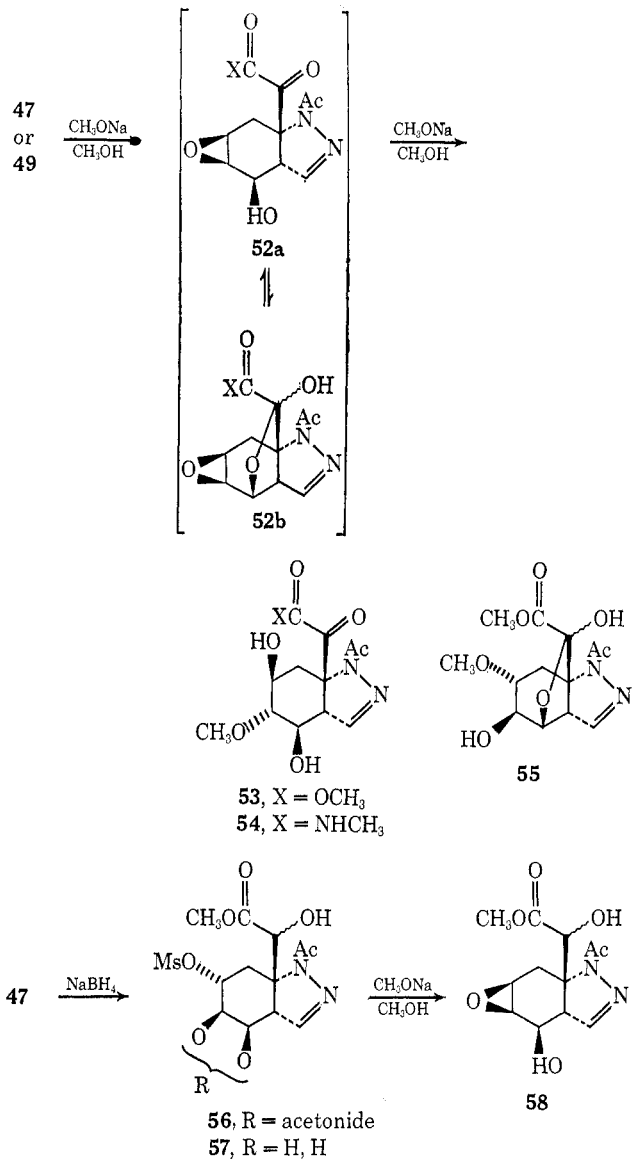
The probable existence of the hemiketal forms suggested an alternative route toward stereospecific inversion of the maverick oxygen function at C-6 *via* an epoxide intermediate. Indeed, treatment of diol **47** with sodium methoxide in methanol smoothly led undoubtedly (see below) *via* epoxide **52** (Scheme VII) to diol **53**, mp 212–216°, in 74% overall yield from diol **47**. Treatment of **53** with acetic anhydride in pyridine afforded the corresponding oily triacetate. Diol **49** in an analogous manner led to amide **54**.

Diol **53** appeared to be stereochemically homogeneous and was assigned the indicated stereochemistry based on the following considerations. Epoxide intermediate **52** would be expected to be opened by methoxide ion in a trans diaxial manner and if the ring opening takes place by attack of methoxide on the hemiketal form **52b**, then diol **53** should be produced stereospecifically. Chemical evidence in support of the 1,3-diol structure **53** was found in the observed resistance of **53** toward formation of an acetonide under conditions which readily converted shikimic acid (**2**) into its acetonide. This is negative evidence, however, and resistance to acetonide formation could be a result of an unusually stable hemiketal form **55** of the isomeric 1,2-diol.

Diol **53** was next subjected to the action of toluenesulfonic acid in refluxing toluene, conditions more vigorous than those used to prepare lactone **51**.[1] Starting **53** was recovered quantitatively. This experiment would suggest that diol **53** exists largely in the hemiketal form and thus formation of a lactone is not feasible. It now appeared necessary that the keto grouping on the side chain in all these intermediates must be reduced to the corresponding alcohol, analogous to the situation in tetrodotoxin, before formation of a lactone or two-thirds ortho ester may proceed.

Reduction of ester **46** with 1.5 equiv of sodium borohydride in ethanol at 0° (conditions which minimized overreduction to the corresponding diol[13]) produced

SCHEME VII

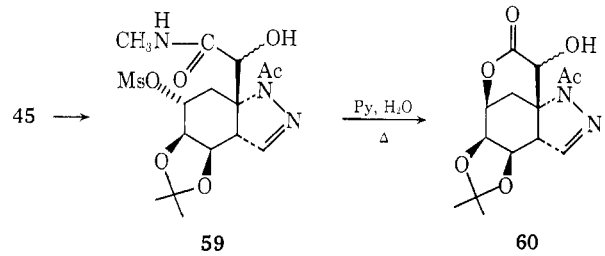


alcohol **56** in 50% yield. The action of methanolic hydrogen chloride on **56** led to triol **57** which, without purification, was treated with sodium methoxide in methanol to give epoxide **58**, an isolable substance which was characterized. Epoxide **58** was subjected to the action of toluenesulfonic acid in refluxing benzene–tetrahydrofuran, conditions which unexpectedly led only to recovered starting material.

Reduction of mesylate amide **45**, on the other hand, proceeded with sodium borohydride in ethanol in high yield to alcohol **59** which was probably a mixture of stereoisomers at the newly introduced center of asymmetry. This time treatment of **59** with refluxing pyridine–water[11] led smoothly to lactone **60** in near quantitative yield. The structure of the long sought after lactone **60** followed from elemental analysis, the mass spectrum which displayed a prominent parent ion at *m/e* 310.1154, the nmr spectrum which showed no mesylate or methylamide groupings, and the ir spectrum which displayed strong absorption at 1750 cm^{-1}, ex-

(13) See, *inter alia*, V. Boekelheide and R. J. Windgassen, *J. Amer. Chem. Soc.*, **81**, 1456 (1959); J. E. G. Barnett and P. W. Kent, *J. Chem. Soc.*, 2743 (1963).

pected for a six-membered lactone. With the lactone **60** in hand the stage is at last set for final elaboration to a toxin derivative.



Experimental Section[14]

4β,5β-Dihydroxy-6α-acetoxy-8β-diazoacetyl-4,5,6,7,8,9β-hexahydro-3(*H*)-indazole 4,5-Acetonide (9) and 4β,5β-Dihydroxy-6α-acetoxy-8α-diazoacetyl-4,5,6,7,8,9α-hexahydro-3(*H*)-indazole 4,5-Acetonide (10).—Acid chloride **7** was prepared by treatment of acid **6**[1] with excess boiling thionyl chloride followed by removal of the excess reagent under vacuum. A solution of 3.00 g (10.9 mmol) of crude acid chloride **7** (reddish oil) in 20 ml of ether was added dropwise to a solution of 2.0 g (47 mmol) of diazomethane in 90 ml of ether at 0°. The solution was allowed to stir for 60 min at 25° and then evaporated *in vacuo* affording 3.8 g of a yellow oil. Chromatography over 80 g of silica gel and elution with chloroform afforded 890 mg (25%) of **10** as a yellow oil. Although molecular distillation of **10** at *ca.* 10^{-5} mm in a 110° oil bath failed to afford an acceptable analytical specimen (see analysis), the mass, nmr, and ir spectra were completely consistent with those expected for **10**: nmr δ 1.25 (s, 3, acetonide methyl), 1.35 (s, 3, acetonide methyl), 1.8–3.3 (m, 3, H-7, 9), 1.90 (s, 3, acetate), 3.8–5.2 (m, 5, H-3, 4, 5, 6), 5.83 (s, 1, $-CHN_2$); ir ($CHCl_3$) 3000 (w), 2130 (s), 1635 cm^{-1} (s); uv max (EtOH) 322 mμ (ε 372); mass spectrum *m/e* 307 (loss of a methyl[15]), 297, 279, 269, 177.

Anal. Calcd for $C_{14}H_{18}N_4O_5$: C, 52.17; H, 5.63. Found: C, 51.43; H, 5.58.

Continued elution with the same solvent system afforded 2.3 g (65%) of **9** as a yellow oil: nmr δ 1.25 (s, 3, acetonide methyl), 1.42 (s, 3, acetonide methyl), 1.89 (s, 3, acetate), 2.0–3.1 (m, 3, H-7, 9), 3.8–5.2 (m, 5, H-3, 4, 5, 6), 5.83 (s, 1, $-CHN_2$); ir ($CHCl_3$) 3000 (w), 2130 (s), 1745 (s), 1645 cm^{-1} (s); uv max (EtOH) 325 mμ (ε 370); mass spectrum *m/e* 322 (parent ion), 307 (loss of a methyl), 280, 279, 177.

Molecular distillation (10^{-5} mm at 110°) of **35** afforded the analytical specimen as a yellow hard oil.

Anal. Calcd for $C_{14}H_{18}N_4O_5$: C, 52.17; H, 5.63. Found: C, 51.78; H, 5.33.

Methyl Isocyanide.—The procedure of Casanova[16] was followed exactly. From 15.0 g (0.25 mol) of *N*-methylformamide (Aldrich Chemical Co.) and 129 g (1.00 mol) of quinoline there was obtained 3.86 g (36%, based on *N*-methylformamide) of methyl isocyanide. This substance was dried and redistilled prior to use.

(3′β,4′β-Dihydroxy-5′α-acetoxycyclohexene-1′-yl)glyoxylic Acid *N*-Methylamide 3′,4′-Acetonide (16).—Following the procedure of Ugi,[8] to a solution of 121 mg (2.95 mmol) of methyl isocyanide in 2 ml of dry tetrahydrofuran at 0° was added a solution of 500 mg (1.83 mmol) of acid chloride **7** in 2 ml of dry tetrahydrofuran under nitrogen. The solution was allowed to stir for 10 hr at 25° and then the solvent was evaporated, affording 570 mg (~100%) of imidoyl chloride **15** as a dark oil, suitable for further reactions: nmr δ 1.45 (s, 6, two methyls of acetonide), 2.00 (s, 3, acetate), 2.2–2.8 (m, 2, H-6′), 3.50 (s, 3, methyl of imine), 4.0–5.4 (s, 3, H-3′, 4′, 5′), 7.00 (broad s, 1, H-2′); ir ($CHCl_3$) 3000 (w), 1750 (s), 1680 (s), 1650 cm^{-1} (s).

A solution of 1.45 g (4.60 mmol) of **15** in 12 ml of acetone–water (1:1) was stirred for 60 min at 0° and then 386 mg of sodium bicarbonate was added. The solution was extracted with 15 ml of chloroform three times. Removal of dried solvent afforded 1.36 g (~100%) of **16** as a slightly yellow oil, suitable for further reactions. Molecular distillation at *ca.* 10^{-5} mm in a 80–90° oil bath afforded the analytical specimen as a colorless hard oil: nmr δ 1.35 (s, 6, two methyls of acetonide), 2.00 (s, 3, acetate), 2.0–2.8 (m, 2, H-6′), 2.87 d, *J* = 5.0 Hz, 3, amide methyl), 4.0–5.2 (m, 3, H-3′, 4′, 5′), 7.0–7.4 (broad, 1, –NH), 7.60 d, *J* = 1 Hz, 1, H-2′); ir ($CHCl_3$) 3500 (w), 3000 (w), 1745 (s), 1700 (s), 1680 (s), 1540 cm^{-1} (m); mass spectrum *m/e* 297 (parent ion), 282 (loss of a methyl), 237 (loss of *N*-methylamide).

Anal. Calcd for $C_{14}H_{19}NO_6 \cdot {}^1/_2H_2O$: C, 54.90; H, 6.53; N, 4.58. Found: C, 54.81; H, 6.29; N, 4.48.

(3′β,4′β-Dihydroxy-5′α-mesyloxycyclohexene-1′-yl)glyoxylic Acid *N*-Methylamide 3′,4′-Acetonide (17).—Acid **8**[1] was converted into the corresponding acid chloride by treatment with excess boiling thionyl chloride followed by removal of the excess reagent under vacuum. To a solution of 4.0 g (12.3 mmol) of the acid chloride in 3 ml of dry tetrahydrofuran at 0° was added a solution of 2.6 g (65 mmol) of methyl isocyanide in 2 ml of tetrahydrofuran under nitrogen. The solution was allowed to stir for 12 hr at 25° and then all the solvent was removed *in vacuo*, affording ~4.5 g of dark oil which was treated with 10 ml of acetone–water (1:1) at 0° for 30 min. Then 1.01 g (12.0 mmol) of sodium bicarbonate was added and all was extracted with chloroform (three 20-ml portions). Removal of the dried chloroform afforded 3.7 g of an orange-colored oil which was chromatographed over 5.0 g of silica gel. Elution with ether afforded ~2.5 g (68%) of **17** as a slightly yellow foam: nmr δ 1.45 (s, 3, acetonide methyl), 1.48 (s, 3, acetonide methyl), 2.2–3.0 (m, 2, H-6′), 2.90 (d, *J* = 5.0 Hz, 3, amide methyl), 3.15 (s, 3, mesylate), 4.0–5.2 (m, 3, H-3′, 4′, 5′), 7.0–7.5 (broad, 1, –NH), 7.5–7.7 (m, 1, H-2′); ir ($CHCl_3$) 3460 (m), 1700 (s), 1680 (s), 1570 cm^{-1} (s); mass spectrum *m/e* 333 (parent ion), 318 (loss of a methyl), 275 (loss of *N*-methylamide).

Molecular distillation of **17** at ~10^{-5} mm in a 120° oil bath afforded the analytical specimen as a hard oil.

Anal. Calcd for $C_{13}H_{19}NO_7S \cdot {}^1/_2H_2O$: C, 45.62; H, 5.85; N, 4.10. Found: C, 45.56; H, 5.46; N, 3.69.

A benzene solution of **17** was refluxed (water separator) for 60 min. Evaporation of the benzene afforded a colorless oil which was exposed to high vacuum to produce a white foam which was dried at 56° (~0.1 mm) for 20 hr to give the analytical specimen.

Anal. Calcd for $C_{13}H_{19}NO_7S$: C, 46.84; H, 5.70. Found: C, 46.63; H, 5.32.

2-[4′β,5′β-Dihydroxy-6′α-acetoxy-4′,5′,6′,7′,8′,9′α-hexahydro-3′(*H*)-indazole-8′α-yl]acrylic Acid *N*-Methylamide 2,3-Epoxide 4′,5′-Acetonide (23).—A solution of 400 mg (1.35 mmol) of α-ketoamide **16** in 1 ml of methanol was added to a solution of 170 mg (4.0 mmol) of diazomethane in 10 ml of ether at 0°. The solution was allowed to stir for 30 min at 0° and then all solvent was removed *in vacuo*, affording 460 mg of a yellow oil which was chromatographed over 8.0 g of silica gel. Elution with 0.2% methanol in chloroform afforded 69 mg (14%) of almost pure (by nmr) minor isomer **23** as a colorless oil followed by 370 mg of an oily mixture of **23** and **20** (~3:7 by nmr). Pyrazoline **23** displayed the following: nmr δ 1.37 (s, 3, acetonide methyl), 1.43 (s, 3, acetonide methyl), 2.10 (s, 3, acetate), 2.0–2.6 (m, 2, H-7′), 2.78 (d, *J* = 4 Hz, 3, methyl of amide), 2.7–3.2 (m, 3, H-9′ and epoxide methylene), 3.0–5.3 (m, 5, H-3′, 4′, 5′, 6′), 6.0–6.7 (broad, 1, –NH); ir ($CHCl_3$) 3500 (m), 1735 (s), 1680 (s), 1540 cm^{-1} (m); mass spectrum *m/e* 338 (loss of a methyl[15]), 310. The analytical specimen of **23** was obtained by molecular distillation (10^{-5} mm) at 100–110° as a colorless hard oil.

Anal. Calcd for $C_{16}H_{23}N_3O_6$: C, 54.38; H, 6.56. Found: C, 54.81; H, 6.47.

2-[1′-Acetyl-4′β,5′β,6′α-trihydroxy-4′,5′,6′,7′,8′,9′β-hexahydro-1′(*H*)-indazole-8′β-yl]acrylic Acid *N*-Methylamide 2,3-Epoxide 4′,5′-Acetonide (26).—A solution of 2.7 g (9.1 mmol) of α-ketoamide **16** in 1 ml of methanol and 3 ml of ether was added dropwise to a solution of 1.2 g (28.6 mmol) of diazomethane in 50 ml of ether at 0°. The solution was allowed to stir for 30 min at 0°; then all the solvent was removed *in vacuo*, affording 3.5 g of a yellow oil which was chromatographed over 40 g of silica gel. Elution with 0.3% methanol in chloroform afforded ~1.4 g of a colorless oily mixture of **20** and **23** by nmr.

The mixture was dissolved in 10 ml of benzene containing 40 mg of *p*-toluenesulfonic acid and then refluxed for 2 hr under nitrogen. Removal of the benzene afforded a reddish oil which was chromatographed over 7 g of silica gel. Elution with 2% methanol in chloroform afforded ~250 mg (24, based on **16**) of

(14) The preamble of the Experimental Section of part II[1] applies here. The drying agent used throughout was anhydrous magnesium sulfate.

(15) Acetonides frequently do not show a parent ion. See J. A. McCloskey and M. J. McClelland, *J. Amer. Chem. Soc.*, **87**, 5090 (1965).

(16) J. Casanova, R. E. Schuster, and N. D. Werner, *J. Chem. Soc.*, 4280 (1963).

26 as a yellow oil which, by scratching in ether, crystallized slowly. Recrystallization from chloroform–ether afforded 60 mg of **26** as white needles: mp 195–196°; nmr δ 1.34 (s, 3, acetonide methyl), 1.42 (s, 3, acetonide methyl), 2.0–3.0 (m, 2, H-7′), 2.21 (s, 3, methyl of –NAc), 2.69 (d, J = 4.5 Hz, 3, methyl of amide), 2.80 (d, J = 4 Hz, 1, epoxide proton), 3.00 (d, J = 4 Hz, 1, epoxide proton), 3.7–5.0 (m, 4, H-4′, 5′, 6′, 9′), 6.85 (d, J = 1.5 Hz, 1, H-3′), 6.6–6.8 (broad, 1, –NH); ir ($CHCl_3$) 3500 (m), 3020 (m), 1675 (s), 1620 (m), 1550 cm^{-1} (m); mass spectrum m/e 353 (parent ion), 338 (loss of methyl), 295 (loss of –(O=)C-NHCH$_3$), 253 (loss of –(O=)C—C(=O)NHCH$_3$).

Anal. Calcd for $C_{16}H_{23}N_3O_6 \cdot {}^1/_4CHCl_3$: C, 50.90; H, 6.14; N, 10.95. Found: C, 51.00; H, 6.40; N, 10.35.

Recrystallization of **26** from ethyl acetate gave white needles, mp 195°, which were also analyzed.

Anal. Calcd for $C_{16}H_{23}N_3O_6$: C, 54.38; H, 6.56. Found: C, 54.49; H, 6.20.

2-[4′β,5′β,6′α-Trihydroxy-4′,5′,6′,7′,8′,9′α-hexahydro-1′(*H*)-indazole-8′α-yl]acrylic Acid *N*-Methylamide 2,3-Epoxide 4′,5′-Acetonide (30) and 2-[4′β,5′β,6′α-Trihydroxy-4′,5′,6′,7′,8′,9′β-hexahydro-1′(*H*)-indazole-8′β-yl]acrylic Acid *N*-Methylamide 2,3-Epoxide 4′,5′-Acetonide (27).—A solution of 980 mg (3.30 mmol) of α-ketoamide **16** in 2 ml of dry tetrahydrofuran was added to a solution of 148 mg (3.30 mmol) of diazomethane in 7 ml of ether at −78°. The solution was allowed to stir for 15 min at −78°; then all the solvent was removed *in vacuo*, affording 1.16 g of a yellow oil. The oil was dissolved in 10 ml of dry methanol containing 216 mg (4.00 mmol) of sodium methoxide and the solution was stirred for 14 hr at 25° under nitrogen. The solution was acidified with 2% hydrochloric acid at 0° and then a small portion of sodium bicarbonate was added until pH 9 ~ 10. Removal of solvent afforded a residue which was digested with several 20-ml portions of chloroform. Removal of the chloroform gave 778 mg of a yellow oil which was chromatographed over 15 g of silica gel. Elution with 1% methanol in chloroform afforded 133 mg (13%) of crystalline **30**. Recrystallization from chloroform and ether afforded 54 mg of white needles: mp 175–176°; nmr δ 1.32 (s, 3, acetonide methyl), 1.47 (s, 3, acetonide methyl), 1.4–2.3 (m, 2, H-7′), 2.68 (d, J = 4.0 Hz, 1, epoxide proton), 2.95 (d, J = 4.0 Hz, 1, epoxide proton), 2.84 (d, J = 5.0 Hz, 3, methyl of amide), 3.5–4.9 (m, 4, H-4′, 5′, 6′, 9′), 6.82 (d, J = 1.0 Hz, 1, H-3′), 6.5–6.8 (broad, 1, –NH), 7.5–7.8 (broad, 1, –NH); ir ($CHCl_3$) 3450 (m), 3350 (w), 1675 (s), 1580 cm^{-1} (m); mass spectrum m/e 311 (parent ion) 295 (loss of a methyl), 253, 211 (loss of –(O=)C—C(=O)NH—CH$_3$). The analytical specimen was prepared by recrystallization of **30** from ethyl acetate to give white needles, mp 176–177°.

Anal. Calcd for $C_{14}H_{21}N_3O_5$: C, 54.01; H, 6.80; N, 13.50. Found: C, 54.02; H, 6.80; N, 13.04.

Continued elution with 3% methanol in chloroform afforded 260 mg (26%, based on α-ketoamide **16**) of **27** as a slightly yellow oil (see next experiment): nmr δ 1.32 (s, 3, acetonide methyl), 1.48 (s, 3, acetonide methyl), 2.0–2.8 (m, 2, H-7′), 2.79 (d, J = 5.0 Hz, 3, methyl of amide), 2.80 (d, J = 4.5 Hz, 1, epoxide proton), 3.17 (d, J = 4.5 Hz, 1, epoxide proton), 3.3–5.0 (m, 4, H-4′, 5′, 6′, 9′), 5.0–5.5 (broad, 1, –NH), 6.72 (d, J = 2.0 Hz, 1, H-3′), 6.7–6.9 (broad, 1, –NH); ir ($CHCl_3$) 3450 (m), 3350 (w), 1675 (s), 1570 cm^{-1} (m); mass spectrum m/e 311 (parent ion), 253, 225, 211.

2-[4′β,5′β,6′α-Trihydroxy-2′-methanesulfonyl-3′α→6′α-oxa-2′,3′,4′,5′,6′,7′,8′,9′β-octahydro-1′(*H*)-indazol-8′β-yl]acrylic Acid *N*-Methylamide 2,3-Epoxide 4′,5′-Acetonide (32).—A solution of 160 mg (0.540 mmol) of pyrazoline **27** and 137 mg (1.20 mmol) of methanesulfonyl chloride in 1.5 ml of dry pyridine was allowed to stir for 14 hr at 25° under nitrogen. Removal of pyridine and excess of methanesulfonyl chloride by high vacuum gave a reddish viscous oil which was dissolved into 5 ml of chloroform and washed with 2% hydrochloric acid at 0°. Removal of the dried chloroform afforded 134 mg of a yellow oil which was chromatographed over 3.0 g of silica gel. Elution with chloroform gave 88 mg (42%) of crystalline **32**: mp 180–184°; nmr δ 1.37 (s, 3, acetonide methyl), 1.67 (s, 3, acetonide methyl), 2.3–2.8 (m, 2, H-7′), 2.82 (d, J = 4.5 Hz, 3, methyl of amide), 2.84 (d, J = 5 Hz, 1, epoxide proton), 2.97 (d, J = 5 Hz, 1, epoxide proton), 3.05 (s, 3, mesylate), 3.1–4.8 (m, 4, H-4′, 5′, 6′, 9′), 5.60 (d, J = 4.0 Hz, 1, H-3′), 6.2–6.9 (broad, 1, –NH), 6.55 (broad s, 1, –NH); ir ($CHCl_3$) 3500 (w), 3320 (w), 1680 (s,)1750 cm^{-1} (m); mass spectrum m/e 389 (parent ion), 374 (loss of a methyl), 310, 294, 281. Recrystallization from ethyl acetate afforded the analytical specimen of **32**, mp 183–185°, as white needles.

Anal. Calcd for $C_{15}H_{23}N_3O_7S$: C, 46.27; H, 5.91; N, 10.79. Found: C, 46.30; H, 6.04; N, 10.69.

2-Mesyl-4β,5β,6α-trihydroxy-3α→6α-oxa-8β-carbomethoxy-2,3,4,5,6,7,8,9β-octahydro-1(*H*)-indazole 4,5-Acetonide (33) and 1-Mesyl-4β,5β-dihydroxy-6α-mesyloxy-8β-carbomethoxy-4,5,6,7,-8,9β-hexahydro-1(*H*)-indazole 4,5-Acetonide (34).—A solution of 102 mg (0.380 mmol) of alcohol **3** in 1 ml of pyridine was cooled to 0° and then 130 mg (1.14 mmol) of methanesulfonyl chloride was added under nitrogen. The solution was allowed to stir for 15 hr at 25° and then almost all the solvent was removed by high vacuum affording a residue which was dissolved in 5 ml of chloroform and washed with 3% hydrochloric acid at 0°. Removal of dried chloroform afforded 88 mg of a yellow oil which was chromatographed over 3.0 g of silica gel. Elution with chloroform–carbon tetrachloride (1:1) afforded 48 mg (37%) of crystalline **33**. Recrystallization from ethyl acetate–ether afforded 21 mg of **33** as white needles: mp 126–128°; nmr δ 1.33 (s, 3, acetonide methyl), 1.44 (s, 3, acetonide methyl), 1.5–2.2 (m, 2, H-7), 3.09 (s, 3, mesylate), 3.0–3.2 (m, 1, H-9), 3.80 (s, 3, methyl ester), 4.0–4.8 (m, 3, H-4, 5, 6), 5.1–5.3 (broad s, 1, NH), 5.60 (d, J = 3 Hz, 1, H-3); ir ($CHCl_3$) 3400 (w), 3000 (w), 1745 (s), 1340 cm^{-1} (s); mass spectrum m/e 348 (parent ion), 333 (loss of a methyl), 289 273.

Anal. Calcd for $C_{13}H_{20}N_2O_7S$: C, 44.83; H, 5.75; N, 8.05. Found: C, 44.87; H, 5.59; N, 8.44.

Continued elution with chloroform afforded 18 mg of **34** as a slightly yellow oil: nmr δ 1.32 (s, 3, acetonide methyl), 1.50 (s, 3, acetonide methyl), 1.4–1.7 (m, 2, H-7), 3.10 (s, 3, mesylate), 3.20 (s, 3, mesylate), 3.0–3.2 (m, 1, H-9), 3.88 (s, 3, methyl ester), 4.0–5.2 (m, 3, H-4, 5, 6), 6.90 (d, J = 1.5 Hz, 1, H-3); ir ($CHCl_3$) 3000 (w), 1745 (s) 1350 cm^{-1} (s); mass spectrum m/e 426 (parent peak), 411 (loss of a methyl), 367, 333.

Anal. Calcd for $C_{14}H_{22}N_2O_9S_2$: C, 39.43; H, 5.16. Found: C, 39.50; H, 5.11.

3-Oxa-(5*S*,6*R*)-dihydroxy-7-carbomethoxytricyclo[2.2.2.0^{2,7}]-octane 5,6-Acetonide (36).—Following Freeman's procedure,[10] 150 mg (0.550 mmol) of **3** in 1 ml of methylene chloride was added at 25° to a solution of 267 mg (0.605 mmol) of lead tetraacetate in 2 ml of methylene chloride under nitrogen. The solution was allowed to stir for 60 min at 25° and then 1.5 ml of water was added. The organic layer was filtered through Celite 535 and washed with 4 ml of water followed by 2 ml of 10% aqueous sodium bicarbonate. Removal of the dried solvent afforded 130 mg of crude crystalline **36** which was chromatographed over 3.0 g of silica gel. Elution with carbon tetrachloride afforded 75 mg (56%) of **36** as white needles, mp 105–106°. Recrystallization from carbon tetrachloride–hexane produced the analytical specimen as white needles: mp 105–106°; nmr δ 1.30 (s, 3, acetonide), 1.50 (s, 3, acetonide), 2.0–2.4 (m, 3, H-1, 8), 3.70 (s, 3, methyl ester), 3.8–4.2 (m, 1, H-4), 4.2–4.7 (m, 3, H-2, 5, 6); ir (CCl_4) 3000 (m), 1745 cm^{-1} (s); mass spectrum m/e 240 (parent ion), 224 (loss of an oxygen), 208.

Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 59.59; H, 6.70.

In another experiment, a solution of 63 mg (0.18 mmol) of **33**, mp 124–128°, in 2 ml of acetic anhydride was heated at reflux for 60 min under nitrogen. Removal of acetic anhydride by high vacuum afforded a reddish oil which was chromatographed over 3.0 g of silica gel. Elution with carbon tetrachloride–chloroform (1:1) afforded 36 mg of crude crystals. Recrystallization from carbon tetrachloride–hexane afforded 12 mg of **36** as white needles, mp 104–106°, identical with the product of the lead tetraacetate reaction with **3** (see above) as evidenced by ir, nmr, and mixture melting point behavior.

2-[4′β,5′β-Dihydroxy-6′α-mesyloxy-4′,5′,6′,7′,8′,9′β-hexahydro-1′(*H*)-indazole-8′β-yl]acrylic Acid *N*-Methylamide 2,3-Epoxide 4′,5′-Acetonide (28).—A solution of diazomethane (9 mmol) in 15 ml of ether was added to a solution of 1.2 g (3.6 mmol) of amide **17** in 5 ml of tetrahydrofuran at 0°. The solution was allowed to stir for 30 min at 0° and then all the solvent was removed *in vacuo*, affording 1.4 g of a yellow oil. This oily mixture was refluxed in benzene with 10 mg of *p*-toluenesulfonic acid for 60 min under nitrogen to give 1.3 g of a crude oily mixture of **28** and **31**. A 980-mg sample (2.52 mmol) of the isomerized oily mixture was chromatographed over 20 g of silica gel. Elution with chloroform afforded ~100 mg (10%, based on amide **17**) of an unisomerized oily mixture of **21** and **24**. Continued chloroform elution afforded 100 mg (10%) of pure (by nmr) oily pyrazoline **31**: nmr δ 1.39 (s, 3, acetonide methyl), 1.55 (s, 3, acetonide methyl), 1.8–2.2 (m, 2, H-7′), 2.79 (d, J = 5 Hz, 3, methyl of

amide), 2.8–3.2 (m, 3, probably H-9′ and epoxide proton), 3.10 (s, 3, mesylate), 3.7–4.7 (m, 3, H-4′, 5′, 6′), 5.6–5.8 (broad, 1, -NH), 6.7 (d, J = 1.0 Hz, 1, H-3′), 6.7–6.9 (broad, 1, -NH); ir ($CHCl_3$) 3450 (m), 3000 (w), 1675 (s), 1570 cm$^-$ (m).

Elution with 1% methanol in chloroform afforded ~150 mg of an oily mixture of **28** and **31** followed by 220 mg (22%) of almost pure desired pyrazoline **28**. Rechromatography of this fraction over 3.0 g of silica gel afforded 107 mg of pure oily **28**: nmr δ 1.37 (s, 3, acetonide methyl), 1.52 (s, 3, acetonide methyl), 2.0–2.8 (m, 2, H-7′), 2.83 (d, J = 5.0 Hz, 3, methyl of amide), 2.85 (d, J = 5 Hz, 1, epoxide proton), 3.10 (s, 3, mesylate), 3.18 (d, J = 5 Hz, 1, epoxide proton), 3.6–3.8 (m, 1, H-9′), 4.0–5.1 (m, 3, H-4′, 5′, 6′), 5.7–6.2 (broad, 1, -NH), 6.5–7.0 (broad, 1, -NH), 6.72 (d, J = 1.5 Hz, 1, H-3′); ir ($CHCl_3$) 3450 (m), 1670 (s), 1575 cm^{-1} (m). The mass spectrum of pure **28** displayed no peaks above m/e 150.

Oily **28** was digested with hexane and evaporated to give a foam which was crushed to a powder, dried at 56° in high vacuum, and analyzed.

Anal. Calcd for $C_{15}H_{23}N_3O_7S$: C, 46.27; H, 5.91. Found: C, 46.02; H, 5.89.

Dinitrogen Tetroxide.—Following the procedure of White,[12] nitrogen dioxide, prepared from air and nitric oxide (Matheson), was trapped at −78° affording the dinitrogen tetroxide as a pale blue solid.

Methyl (3′β,4′β-Dihydroxy-5′α-mesyloxycyclohexene-1′-yl)-glyoxylate 3′,4′-Acetonide (18).—To a solution of 760 mg (2.28 mmol) of amide **17** in 10 ml of chloroform containing 450 mg (5.50 mmol) of anhydrous sodium acetate at 0° was added a cold solution of 1.8 g (19.5 mmol) of dinitrogen tetroxide in 10 ml of chloroform. The reaction mixture was allowed to stir for 15 hr at 0° and then 40 ml of cold water was added with good stirring. The chloroform layer was separated and washed with 5% sodium bicarbonate at 0°. Removal of the dried chloroform afforded 850 mg (100%) of crude N-nitroso derivative which was dissolved in 10 ml of dry benzene and heated at reflux for 4 hr. The benzene was removed *in vacuo*, affording 750 mg of a yellow oil, suitable for further reactions. Chromatography of the oil over silica gel and elution with chloroform–carbon tetrachloride (1:1) afforded a colorless foam which was dried at 56° in high vacuum to give the analytical specimen: nmr δ 1.42 (s, 3, acetonide methyl), 1.48 (s, 3, acetonide methyl), 2.5–3.0 (m, 2, H-6′), 3.23 (s, 3, mesylate), 3.92 (s, 3, methyl ester), 4.7–5.1 (m, 3, H-3′, 4′, 5′), 6.9–7.1 (m, 1, H-2′); ir ($CHCl_3$) 3000 (w), 1745 (s), 1690 (s), 1645 cm^{-1} (m); mass spectrum m/e 334 (parent ion), 319 (loss of a methyl), 275 (loss of -(O=)$COCH_3$).

Anal. Calcd for $C_{13}H_{18}O_8S$: C, 46.70; H, 5.38. Found: C, 46.25; H, 5.44.

(3′β,4′β-Dihydroxy-5′α-mesyloxycyclohexene-1′-yl)glyoxylic Acid N-Formyl-N-methylamide 3′,4′-Acetonide (40).—In one experiment, amide **17** was prepared from 1.0 g (4.7 mmol) of the acetonide of shikimic acid without purification of any intermediates. Chromatography of the crude product over 10 g of silica gel afforded ~900 mg (60%, overall) of amide **17** by elution with chloroform–carbon tetrachloride (1:1). Continued elution with the same solvent system afforded 200 mg (18%) of **40** as a colorless oil. Rechromatography over silica gel afforded a colorless foam which was dried at 56° in high vacuum to give the analytical specimen: nmr δ 1.41 (s, 3, acetonide methyl), 1.50 (s, 3, acetonide methyl), 2.6–2.9 (m, 2, H-6′), 3.14 (s, 3, mesylate or amide methyl), 3.17 (s, 3, mesylate or amide methyl), 4.2–5.0 (m, 3, H-3′, 4′, 5′), 6.1–6.3 (m, 1, H-2′), 9.26 (s, 1, formyl proton); ir ($CHCl_3$) 3000 (w), 1730 (m), 1675 cm^{-1} (s); mass spectrum m/e 333 (parent ion), 318 (loss of a methyl), 199.

Anal. Calcd for $C_{13}H_{19}NO_7S \cdot {}^1/_2H_2O$: C, 45.62; H, 5.85; N, 4.10. Found: C, 45.49; H, 5.58; N, 3.84.

(3′β,4′β-Dihydroxy-5′α-mesyloxycyclohexene-1′-yl)glyoxylic Acid N-Methylamide (41).—A solution of 0.19 ml of 1.0 N sodium hydroxide was added to a solution of 63 mg (0.19 mmol) of the amide **40** in 0.5 ml of methanol at 0° under nitrogen. The solution was allowed to stir for 12 hr at 25° and then neutralized with hydrochloric acid at 0°. The neutral solution was extracted with 3 ml of chloroform three times. Removal of the dried chloroform afforded 60 mg of yellow oil which was chromatographed over 2.0 g of silica gel. Elution with chloroform afforded 34 mg (59%) of **41** as white needles. Recrystallization from ether–methylene chloride afforded the analytical specimen as white needles: mp 130–131°; nmr δ 1.42 (s, 3, acetonide methyl), 1.50 (s, 3, acetonide methyl), 2.5–2.9 (m, 2, H-6′), 2.90 (d, J = 5.0 Hz, 3, amide methyl), 3.17 (s, 3, mesylate), 4.1–5.0 (m, 3, H-3′, 4′, 5′), 6.0–6.5 (broad, 1, -NH), 6.5–6.7 (m, 1, H-2′); ir ($CHCl_3$) 3500 (m), 3000 (w), 1680 (s), 1650 (m), 1580 cm^{-1} (m); mass spectrum m/e 305 (parent ion), 290 (loss of a methyl), 248, 230.

Anal. Calcd for $C_{12}H_{19}NO_6S$: C, 47.21; H, 6.23; N, 4.59. Found: C, 47.41; H, 6.28; N, 4.51.

[4′β,5′β-Dihydroxy-6′α-mesyloxy-4′,5′,6′,7′,8′,9′β-hexahydro-3′(*H*)-indazole-8′β-yl]acrylic Acid Methyl Ester 2,3-Epoxide 4′,5′-Acetonide (22).—A solution of diazomethane (6 mmol) in 10 ml of ether was added to a solution of 345 mg (1.03 mmol) of methyl ester **18** in 5 ml of dry tetrahydrofuran at 0°. The solution was allowed to stir for 2 hr at 0°; then all the solvent was removed *in vacuo*, affording 360 mg of a yellow oil which was chromatographed over 10 g of silica gel. Elution with chloroform afforded 150 mg (38%, based on ester **18**) of almost pure pyrazoline **22** as a yellow oil. Rechromatography afforded a colorless oil which was dissolved in small amount of methylene chloride and exposed to high vacuum to give a white foam which was dried in high vacuum at 56° for 3 hr to afford the analytical specimen: nmr δ 1.33 (s, 3, acetonide methyl), 1.47 (s, 3, acetonide methyl), 2.0–2.8 (m, 2, H-7′), 2.9–3.2 (m, 1, H-9′), 3.0 (s, 3, mesylate), 3.04 (d, J = 5 Hz, 1, epoxide proton), 3.28 (s, J = 5 Hz, 1, epoxide proton), 3.75 (s, 3, methyl ester), 4.2–5.0 (m, 5, H-3′, 4′, 6′); ir ($CHCl_3$) 3000 (w), 1745 cm^{-1} (s); mass spectrum m/e 390 (parent ion), 375 (loss of a methyl), 359, 347.

Anal. Calcd for $C_{15}H_{22}N_2O_8S$: C, 46.15; H, 5.64; N, 7.18. Found: C, 46.50; H, 5.53; N, 6.87.

1-Acetyl-4β,5β-dihydroxy-6α-acetoxy-8β-carboxy-4,5,6,7,8,9β-hexahydro-1(*H*)-indazole 4,5-Acetonide (42).—To a solution of 720 mg (2.70 mmol) of ester **3** in 5 ml of methanol was added 3.5 ml of 1.0 N NaOH at 0° under nitrogen. The solution was allowed to stir for 4 hr at 25°; then 240 mg (4.00 mmol) of acetic acid was added. Almost all the solvent was removed by high vacuum affording a slightly yellow viscous oil which was dissolved in 3% methanol in chloroform (15 ml) and dried. Removal of the solvent afforded 782 mg of a clear colorless oil which was dissolved in 5 ml of dry pyridine, cooled to 0° under nitrogen, and then treated with 1.22 g of acetic anhydride. The reaction was allowed to stir for 15 hr at 25°; then almost all the solvent was removed by high vacuum affording a slightly yellow viscous oil which was dissolved in 20 ml of chloroform and washed with 5 ml of 3% hydrochloric acid followed by 5 ml of water. Removal of the dried chloroform afforded 760 mg (83%, based on ester **3**) of **42** as a white foam which was pure enough for further reactions. The analytical specimen was prepared by silica gel column chromatography and elution with chloroform to give a colorless white foam: nmr δ 1.33 (s, 3, acetonide), 1.50 (s, 3, acetonide), 2.00 (s, 3, OAc), 2.31 (s, 3, NAc), 2.5–2.7 (m, 2, H-7), 4.0–5.2 (m, 4, H-4, 5, 6, 9), 6.92 (d, J = 1.5 Hz, 1, H-3), 8.83 (broad s, 1, acid proton); ir ($CHCl_3$) 3500–2300 (broad), 1750 (s), 1670 (s), 1620 cm^{-1} (m); mass spectrum m/e 325 (loss of a methyl[15]), 296 281, 279.

Anal. Calcd for $C_{15}H_{20}N_2O_7 \cdot 1/2H_2O$: C, 51.60; H, 6.03; N, 8.03. Found: C, 51.73; H, 6.29; N, 8.23.

[1′-Acetyl-4′β,5′β-dihydroxy-6′α-acetoxy-4′,5′,6′,7′,8′,9′β-hexahydro-1′(*H*)-indazole-8′β-yl]glyoxylic Acid N-Methylamide 4′,5′-Acetonide (43).—A solution of 740 mg (2.18 mmol) of diacetate **42** in 7 ml of thionyl chloride was heated at reflux for 60 min. Removal of the solvent afforded 764 mg of the corresponding oily acid chloride which was dissolved in 4 ml of dry tetrahydrofuran, cooled to 0° under nitrogen, and then treated with 900 mg (22.0 mmol) of methyl isocyanide in 1 ml of tetrahydrofuran. The reaction was allowed to stir for 12 hr at 25°; then all the solvent was removed *in vacuo*, affording 830 mg of crude adduct as a yellow foam: nmr δ 1.32 (s, 3, acetonide), 1.47 (s, 3, acetonide), 2.00 (s, 3, OAc), 2.18 (s, 3, NAc), 2.2–2.9 (m, 2, H-7′), 3.40 (s, 3, NCH_3), 4.0–5.2 (m, 4, H-4′, 5′, 6′, 9′), 7.10 (d, J = 1.5 Hz, 1, H-3′); ir ($CHCl_3$) 3000 (m), 1740 (s), 1670 (s), 1620 cm^{-1} (m).

A solution of 830 mg of crude adduct in 5 ml of acetone and 5 ml of water was stirred for 10 hr at 0° and then 168 mg of sodium bicarbonate was added. The solution was diluted with 10 ml of water and extracted with 15 ml of chloroform five times. Removal of the dried chloroform afforded 733 mg of yellow oil which was chromatographed over 10 g of silica gel. Elution with chloroform afforded 600 mg (56%, based on ester **3**) of oily α-ketoamide **43**. Oily **43** containing traces of methylene chloride was exposed to high vacuum to give a white foam which was dried at 56° in high vacuum and analyzed: nmr δ 1.32 (s, 3, acetonide), 1.45 (s, 3, acetonide), 2.00 (s, 3, OAc), 2.24 (s, 3,

NAc), 2.2–2.8 (m, 2, H-7′), 2.83 (d, J = 5.0 Hz, 3, amide methyl), 4.2–4.4 (m, 2, H-4′, 6′), 4.75 (m, 1, H-9), 4.8–5.1 (m, 1, H-5′), 7.02 (d, J = 1.5 Hz, 1, H-3), 7.0–7.2 (broad, 1, –NH); mass spectrum m/e 382 (loss of a methyl[15]), 366, 353; ir ($CHCl_3$) 3450 (w), 3000 (m), 1740 (s), 1670 (s), 1620 (m), 1570 cm^{-1} (m).

Anal. Calcd for $C_{17}H_{23}N_3O_7 \cdot {}^1/_2H_2O$: C, 52.29; H, 6.15; N, 10.79. Found: C, 52.23; H, 6.11; N, 10.68.

[1′-Acetyl-4′β,5′β,6′α-trihydroxy-4′,5′,6′,7′,8′,9′β-hexahydro-1′(*H*)-indazole-8′β-yl]glyoxylic Acid *N*-Methylamide 4′,5′-Acetonide (44).—A solution of 2.1 g (5.3 mmol) of diacetate **43** in 15 ml of methanol was cooled to 0°; then 5.8 ml of 1.0 *N* NaOH was added dropwise by syringe under nitrogen. The reaction was allowed to stir for 30 min at 0°; then four drops of acetic acid was added to neutralize the solution. Almost all the solvent was removed by high vacuum to give a yellow viscous oil which was digested with 30 ml of 10% methanol in chloroform. Removal of the dried solvent afforded 2.1 g of crude alcohol **44** as a yellow oil. A 200-mg sample was chromatographed over 3.0 g of silica gel. Elution with 2% methanol in chloroform afforded 146 mg of slightly yellow crystalline **44**. Recrystallization from chloroform afforded white needles, mp 75–77°, recrystallization of which from benzene afforded fine white needles, mp 92–95° (see analytical results). Sublimation at 0.1–0.2 mm in a 170° oil bath afforded solvent free powder-like crystals: mp 118–122°; nmr δ 1.32 (s, 3, acetonide), 1.47 (s, 3, acetonide), 2.29 (s, 3, NAc), 2.8–3.1 (m, 3, H-7′ and –OH), 2.87 (d, J = 5.0 Hz, 3, amide methyl), 4.0–4.9 (m, 4, H-4′, 5′, 6′, 9′), 7.10 (d, J = 1.5 Hz, H-3′), 7.0–7.3 (broad, 1, –NH); ir ($CHCl_3$) 3800–3100 (broad), 3000 (w), 1730 (m), 1690 (s), 1640 (m), 1620 (m), 1570 cm^{-1} (m); mass spectrum m/e 339 (parent ion), 324 (loss of methyl), 311, 282, 281, 263.

Anal. [White needles (mp 75–77°) from chloroform and dried at 56° in high vacuum for 20 hr.] Calcd for $C_{15}H_{21}N_3O_6 \cdot {}^3/_4CHCl_3$: C, 44.05; H, 4.55; N, 9.80. Found: C, 43.42; H, 5.08; N, 10.02.

Anal. [White needles (mp 92–95°) from benzene and dried at 56° in high vacuum for 20 hr.] Calcd for $C_{15}H_{21}N_3O_6 \cdot {}^1/_3C_6H_6$: C, 55.88; H, 6.34; N, 11.50. Found: C, 56.06; H, 6.20; N, 11.47.

Anal. [Sublimed powder-like crystals (mp 118–122°).] Calcd for $C_{15}H_{21}N_3O_6$: C, 53.06; H, 6.24; N, 12.38. Found: C, 52.39; H, 6.14; N, 12.29.

[1′-Acetyl-4′β,5′β-dihydroxy-6′α-mesyloxy-4′,5′,6′,7′,8′,9′β-hexahydro-1′(*H*)-indazole-8′β-yl]glyoxylic Acid *N*-Methylamide 4′,5′-Acetonide (45).—A solution of 125 mg (0.350 mmol) of alcohol **44** in 1 ml of pyridine was cooled to 0° and then 130 mg (1.15 mmol) of methanesulfonyl chloride was added under nitrogen. The reaction was allowed to stir for 17 hr at 25° and then almost all the solvent was removed by high vacuum affording a viscous reddish oil which was dissolved in 10 ml of chloroform and washed with 1 ml of 3% hydrochloric acid then 1 ml of water. Removal of the dried chloroform afforded 120 mg (80%) of mesylate **45** as a yellow foam, suitable for further reactions. This yellow foam was chromatographed over 3.0 g of silica gel. Elution with chloroform afforded 97 mg (64%) of pure white foam: nmr δ 1.32 (s, 3, acetonide), 1.47 (s, 3, acetonide), 2.30 (s, 3, NAc), 2.3–2.8 (m, 2, H-7′), 2.87 (d, J = 5.0 Hz, 3, amide methyl), 3.05 (s, 3, mesylate), 4.2–5.1 (m, 4, H-4′, 5′, 6′, 9′), 7.08 (d, J = 1.5 Hz, 1, H-3′), 7.0–7.2 (broad, 1, –NH); ir ($CHCl_3$) 3500 (m), 3000 (m), 1730 (m), 1690 (s), 1650 (m), 1620 cm^{-1} (m); mass spectrum m/e 417 (parent ion), 402 (loss of a methyl), 341, 331, 315.

Anal. Calcd for $C_{16}H_{23}N_3O_8S$: C, 46.04; H, 5.51; N, 10.07. Found: C, 46.00; H, 5.64; N, 9.65.

Methyl [1′-Acetyl-4′β,5′β-dihydroxy-6′α-mesyloxy-4′,5′,6′,7′,-8′,9′β-hexahydro-1′(*H*)-indazole-8′β-yl]glyoxylate 4′,5′-Acetonide (46).—To a solution of 230 mg (0.550 mmol) of mesylate **45** in 5 ml of chloroform at 0° was added 500 mg (5.50 mmol) of dinitrogen tetroxide in 5 ml of cold chloroform under nitrogen. The solution was allowed to stir for 18 hr at 0° and then 5 ml of cold water was added. The organic layer was separated and washed with 5% sodium bicarbonate. Removal of dried chloroform afforded 240 mg of the *N*-nitroso derivative as a slightly yellow oil. A solution of the *N*-nitroso derivative in 5 ml of dry benzene was refluxed for 3 hr and then the benzene was removed *in vacuo*, affording 230 mg (100%) of ester **46** as a yellow oil which crystallized upon addition of one drop of methanol. Recrystallization from methanol afforded 160 mg (70%) of white plates: mp 153–154°; nmr δ 1.32 (s, 3, acetonide), 1.45 (s, 3, acetonide), 2.25 (s, 3, NAc), 2.2–2.8 (m, 2, H-7′), 2.98 (s, 3, mesylate), 3.84 (s, 3, methyl ester), 4.0–5.0 (m, 4, H-3′, 4′, 5′, 9′), 6.90 (d, J = 1.0 Hz, H-3′); ir ($CHCl_3$) 3000 (w), 1740 (s), 1690 (m), 1660 (m), 1620 cm^{-1} (m); mass spectrum m/e 418 (parent ion), 403 (loss of a methyl), 367, 361, 331, 315, 289, 273.

Anal. Calcd for $C_{16}H_{22}N_2O_9S$: C, 45.93; H, 5.26; N, 6.69. Found: C, 45.84; H, 5.07; N, 6.92.

Methyl [1′-Acetyl-4′β,5′β-dihydroxy-6′α-mesyloxy-4′,5′,6′,-7′,8′,9′β-hexahydro-1′(*H*)-indazole-8′β-yl)glyoxylate (47).—A solution of 180 mg (0.43 mmol) of mesylate **46**, mp 153–154°, in 4 ml of chloroform–methanol (1:1) was cooled to 0° and then 3 ml of methanol containing ~300 mg of hydrogen chloride was added. The reaction was allowed to stir for 3 hr at 25° and then all the solvent was removed *in vacuo* affording 155 mg of a slightly yellow oil which was chromatographed over 3.0 g of silica gel. Elution with 2% methanol in chloroform afforded 112 mg (69%) of **47** as a pure white foam which was dried at 56° in high vacuum for 20 hr to give the analytical specimen: nmr ($CD_3(O{=})CCD_3$) δ 2.20 (s, 3, NAc), 2.8–3.5 (m, 2 or 3, assignment not clear), 3.18 (s, 3, mesylate), 3.80 (s, 3, methyl ester), 3.7–5.2 (m, 5 or 6, assignment not clear), 7.30 (d, J = 1.0 Hz, 1, H-3′); mass spectrum m/e 291 (loss of (O=)C—C(=O)OCH_3), 249, 231.

Anal. Calcd for $C_{13}H_{18}N_2O_9S \cdot {}^1/_2H_2O$: C, 40.31; H, 4.90; N, 7.23. Found: C, 40.11; H, 4.60; N, 6.99.

Methyl [1′-Acetyl-4′β,5′β-diacetoxy-6′α-mesyloxy-4′,5′,6′,7′-8′,9′β-hexahydro-1′(*H*)-indazole-8′β-yl]glyoxylate (48).—To a solution of 67 mg (0.18 mmol) of mesylate **47** in 1 ml of pyridine at 0° was added 55 mg (0.54 mmol) of acetic anhydride under nitrogen. The reaction was allowed to stir for 12 hr at 25° and then almost all the solvent was removed by high vacuum affording a viscous slightly yellow oil which was dissolved in 5 ml of chloroform and washed with 3% hydrochloric acid at 0°. Removal of the dried chloroform afforded 76 mg of a colorless oil which was chromatographed over 3.0 g of silica gel. Elution with chloroform afforded 62 mg of white foam which was dried at 56° for 12 hr under high vacuum to give the analytical specimen: nmr δ 1.7–2.3 (m, 2, H-7′), 2.08 (s, 6, two OAc), 2.26 (s, 3, NAc), 3.08 (s, 3, mesylate), 3.89 (s, 3, methy ester), 3.9–4.2 (m, 1, H-9′), 4.7–5.8 (m, 3, H-4′, 5′, 6′), 7.05 (d, J = 1.5 Hz, 1, H-3′); ir ($CHCl_3$) 3000 (m), 1730 (s), 1685 (s), 1650 (s), 1610 cm^{-1} (m); mass spectrum m/e 446, 315, 279, 272.

Anal. Calcd for $C_{17}H_{22}N_2O_{11}S$: C, 44.18; H, 4.76; N, 6.06. Found: C, 44.38; H, 4.96; N, 5.76.

[1′-Acetyl-4′β,5′β-dihydroxy-6′α-mesyloxy-4′,5′,6′,7′,8′,9′β-hexahydro-1′(*H*)-indazole-8′β-yl]glyoxylic Acid *N*-Methylamide (49).—To a solution of 50 mg (0.12 mmol) of mesylate **45** in 1 ml of methanol at 0° was added 1 ml of methanol containing ~100 mg of hydrogen chloride. The reaction was allowed to stir for 3 hr at 25° and then all the solvent was removed *in vacuo* affording 40 mg of a yellow foam. Chromatography over silica gel and elution with 2% methanol in chloroform afforded a foam which was dried at 56° in high vacuum and analyzed: nmr (D_2O) δ 1.7–2.2 (m, 2, H-7), 2.25 (s, 3, NAc), 2.70 (s, 3, methyl of amide), 3.20 (s, 3, mesylate), 3.5–4.7 (m, ~4, H-4′, 5′, 6′, 9′), 7.3 (d, J = 1.0 Hz, 1, H-3′); ir (CH_3CN) 1730 (w), 1690 (s), 1660 (s), 1620 cm^{-1} (w); mass spectrum m/e 291 (loss of (O=)-C—C(=O)$NHCH_3$), 249, 231.

Anal. Calcd for $C_{13}H_{19}N_3O_8S \cdot {}^1/_2CHCl_3$: C, 37.07; H, 4.46. Found: C, 37.42; H, 4.49.

Methyl [1′-Acetyl-4′β,6′β-dihydroxy-5′α-methoxy-4′,5′,6′,7′,-8′,9′β-hexahydro-1′(*H*)-indazole-8′β-yl]glyoxylate (53).—To a solution of 117 mg (0.310 mmol) of diol **47** in 3 ml of dry methanol at 0° was added 55 mg (0.93 mmol) of sodium methoxide under nitrogen. The reaction was allowed to stir for 30 min at 0° and then four drops of acetic acid was added (pH 6). Almost all the solvent was removed *in vacuo* affording a slightly yellow oil which was digested with 20 ml of 3% methanol in chloroform and filtered through Celite 535. Removal of the dried solvent afforded 120 mg (containing sodium acetate) of a yellow oil which was chromatographed over 3.0 g of silica gel. Elution with 2% methanol in chloroform afforded 72 mg (74%) of white powder-like crystals. Recrystallization from benzene afforded 44 mg of white needles: mp 212–216° dec; nmr δ 1.4–2.2 (m, 2, H-7′), 2.32 (s, 3, NAc), 2.6–3.2 (broad s, 2 OH, exchangeable with D_2O), 3.50 (s, 3, methoxy group), 3.5–4.8 (m, 4, H-4′, 5′, 6′, 9′), 3.85 (s, 3, methyl ester), 7.20 (d, J = 1 Hz, 1, H-3′); ir ($CHCl_3$) 3500–3100 (broad), 3000 (m), 1750 (s), 1680 (s), 1620 cm^{-1} (m); mass spectrum m/e 255, 213, 195, 194.

Anal. Calcd for $C_{13}H_{18}N_2O_7$: C, 49.68; H, 5.77; N, 8.91. Found: C, 49.35; H, 5.52; N, 8.60.

Methyl [1′-Acetyl-4′β,6′β-diacetoxy-5′α-methoxy-4′,5′,6′,7′,-8′,9′β-hexahydro-1′(*H*)-indazole-8′β-yl]glyoxylate (not shown). —A solution of 46 mg (0.15 mmol) of diol **53** in 1 ml of pyridine was cooled to 0° and then 73 mg (0.72 mmol) of acetic anhydride was added under nitrogen. The reaction was allowed to stir for 12 hr at 25°. Almost all the solvent was removed by high vacuum affording a yellow viscous oil which was dissolved in 5 ml of chloroform and washed with 3% hydrochloric acid at 0°. Removal of dried chloroform afforded 53 mg (90%) of the triacetate as a colorless oil: nmr δ 1.3–1.9 (m, 2, H-7′), 2.17 (s, 6, two OAc), 2.30 (s, 3, NAc), 3.50 (s, 3, methoxy group), 3.85 (s, 3, methyl ester), 4.5–5.3 (m, 4, H-4′, 5′, 6′, 9′), 6.95 (d, J = 1.5 Hz, 1, H-3′); ir ($CHCl_3$) 3000 (m), 1750 (s), 1690 (s), 1620 cm^{-1} (m). Chromatography over silica gel and elution with chloroform afforded a pure white foam which was dried at 56° in high vacuum for 20 hr and analyzed.

Anal. Calcd for $C_{17}H_{22}N_2O_9 \cdot {}^1/_4CHCl_3$: C, 48.36; H, 5.19; N, 6.54. Found: C, 48.17; H, 5.15; N, 6.28.

[1′-Acetyl-4′β,6′β-dihydroxy-5′α-methoxy-4′,5′,6′,7′,8′,9′β-hexahydro-1′(*H*)-indazole-8′β-yl]glyoxylic Acid *N*-Methylamide (54).—To a solution of 45 mg (0.12 mmol) of diol **49** in 1 ml of methanol at 0° was added 24 mg (0.48 mmol) of sodium methoxide under nitrogen. The reaction was allowed to stir for 30 min at 0° and then two drops of acetic acid was added. Removal of all the solvent afforded a residue which was digested with 10% methanol in chloroform and filtered through Celite 535. Removal of the dried solvent gave a 50-mg residue which was chromatographed over 3.0 g of silica gel. Elution with 2% methanol in chloroform afforded 16 mg of **54** as a white oil. Rechromatography over silica gel and elution with 1% methanol in chloroform afforded the analytical specimen as a colorless oil: nmr δ 1.4–1.9 (m, 2, H-7′), 2.25 (s, 3, NAc), 2.91 (d, J = 5.0 Hz, 3, methyl of amide), 3.0–3.2 (m, 3, H-9′ and two –OH), 3.48 (s, 3, methoxy group), 3.5–4.8 (m, 3, H-4′, 5′, 6′), 6.3–6.7 (broad, 1, –NH), 7.15 (d, J = 1 Hz, 1, H-3′); ir ($CHCl_3$) 3500 (m), 3000 (w), 1685 (s), 1620 (m), 1570 cm^{-1} (m); mass spectrum m/e 313 (parent ion), 279, 255, 213.

Anal. Calcd for $C_{13}H_{19}N_3O_6 \cdot H_2O$: C, 47.13; H, 6.39; N, 12.68. Found: C, 47.39; H, 6.03; N, 12.49.

Methyl 2-Hydroxy-2-[1′-acetyl-4′β,5′β-dihydroxy-6′α-mesyloxy-4′,5′,6′,7′,8′,9′β-hexahydro-1′(*H*)-indazole-8′β-yl]acetate 4′,5′-Acetonide (56).—A solution of 80 mg (0.19 mmol) of **46** in 1 ml of tetrahydrofuran was added at 0° to a solution of 2.80 mg (0.075 mmol) of sodium borohydride in 1 ml of ethanol. The solution was allowed to stir for 60 min at 0° and then almost all the solvent was removed *in vacuo*. The white oily residue was treated with 1 ml of ice-cold 5% hydrochloric acid and extracted with 5 ml of chloroform three times. Removal of the dried solvent afforded 80 mg of colorless oil which was chromatographed over 3.0 g of silica gel. Elution with chloroform afforded 41 mg (50%) of **56** as a colorless oil. Rechromatography over silica gel and elution with chloroform afforded a white foam which was dried at 56° in high vacuum to give the analytical specimen: nmr δ 1.32 (s, 3, acetonide), 1.48 (s, 3, acetonide), 2.2–2.9 (m, 2, H-7′), 2.30 (s, 3, *N*-acetate), 2.99 (s, 3, mesylate), 3.72 (s, 3, methyl ester), 4.2–4.9 (m, 5, H-2, 4′, 5′, 6′, 9′), 6.90 (d, J = 1.5 Hz, 1, H-3′); ir ($CHCl_3$) 3600–3200 (broad), 3000 (m), 1745 (s), 1725 (s), 1645 (s), 1610 cm^{-1} (m); mass spectrum m/e 420 (parent ion), 405 (loss of a methyl), 363, 361, 331.

Anal. Calcd for $C_{16}H_{24}N_2O_9S$: C, 45.71; H, 5.71. Found: C, 45.57; H, 5.81.

Methyl 2-Hydroxy-2-[1′-acetyl-4′β-hydroxy-4′,7′,8′,9′β-tetrahydro-1′(*H*)-indazole-8′β-yl]acetate 5′β,6′β-Epoxide (58).—To a solution of 40 mg (0.09 mmol) of **56** in 0.5 ml of methanol at 0° was added 1 ml of methanol containing 50 mg of hydrogen chloride. The solution was allowed to stir for 3 hr at 25° and then all the solvent was removed *in vacuo* affording 38 mg of triol **57** as a colorless hard oil: nmr (CD_3OD) δ 1.3–1.7 (m, 2, H-7′), 2.30 (s, 3, *N*-acetate), 2.8–3.0 (m, ~2, assignment not clear), 3.12 (s, 3, mesylate), 3.5–4.6 (m, ~5, assignment not clear), 3.77 (s, 3, methyl ester), 7.10 (d, J = 1.0 Hz, 1, H-3′).

The triol was dissolved in 1 ml of methanol at 0° and then 16 mg (0.30 mmol) of sodium methoxide was added under nitrogen. The solution was allowed to stir for 20 min at 0° and then one drop of acetic acid was added to neutralize the solution. Almost all the solvent was removed *in vacuo* affording a yellow oily residue which was digested with 10 ml of 3% methanol in chloroform and filtered through Celite 535. Removal of the solvent afforded 40 mg of a slightly yellow oil which was chromatographed over 3.0 g of silica gel. Elution with 1% methanol in chloroform afforded 27 mg of **58** as a colorless hard oil: nmr 1.5–2.4 (m, 2, H-7′), 2.30 (s, 3, *N*-acetate), 3.0–4.2 (m, 6 or 7, assignment not clear), 3.79 (s, 3, methyl ester), 7.0–7.2 (m, 1, H-3′); ir ($CHCl_3$) 3600–3300 (broad), 3000 (s), 1750 (s), 1680 (s), 1620 cm^{-1} (s); mass spectrum m/e 284 (parent ion), 253, 242, 225, 207, 195. The exact molecular weight as determined by high resolution mass spectrometry was 284.0995 (calcd for $C_{12}H_{16}N_2O_6$: 284.1004).

2-Hydroxy-2-[1′-acetyl-4′β,5′β-dihydroxy-6′α-mesyloxy-4′,5′,-6′,7′,8′,9′β-hexahydro-1′(*H*)-indazole-8′β-yl]acetic Acid *N*-Methylamide 4′,5′-Acetonide (59).—A solution of 110 mg (0.264 mmol) of amide **45** in 1 ml of tetrahydrofuran was added at 0° to a solution of 33 mg (0.39 mmol) of sodium borohydride in 2 ml of ethanol. The solution was allowed to stir for 3 hr at 25° and then almost all the solvent was removed *in vacuo* affording a yellow viscous oil which was treated with 3% hydrochloric acid at 0°. The acidic solution was extracted with 5 ml of chloroform three times. Removal of dried chloroform afforded 112 mg of **59** as a slightly yellow oil which was chromatographed over 3.0 g of silica gel. Elution with 1% methanol in chloroform afforded 80 mg (73%) of pure **59** as a white foam: nmr δ 1.37 (s, 3, acetonide), 1.50 (s, 3, acetonide), 1.9–2.7 (m, 2, H-7′), 2.32 (s, 3, *N*-acetate), 2.81 (d, J = 5.0 Hz, 3, amide methyl), 3.02 (s, 3, mesylate), 4.1–5.2 (m, 4, H-4′, 5′, 6′, 9′), 6.55 (s, 0.6, H-2), 6.75 (s, 0.4, H-2), 7.05 (d, J = 1.0 Hz, 1, H-3′), 7.0–7.2 (broad, 1, –NH–); ir ($CHCl_3$) 3500 (w), 3400–3100 (broad), 3000 (w), 1680 (s), 1620 (m); mass spectrum m/e 404 (loss of a methyl[15]), 361, 350, 341, 331, 323. Rechromatography over silica gel afforded a white foam which was dried at 56° for 20 hr to give the analytical specimen.

Anal. Calcd for $C_{16}H_{25}N_3O_8S$: C, 45.82; H, 5.97. Found: C, 45.31; H, 6.12.

2-Hydroxy-2[1′-acetyl-4′β,5′β,6′β-trihydroxy-4′,5′,6′,7′,8′,-9′β-hexahydro-1′(*H*)-indazole-8′β-yl]acetic Acid 1→6′β-Lactone 4′,5′-Acetonide (60).—A solution of 34 mg (0.08 mmol) of **59** in 1 ml of pyridine containing 100 mg of water was heated at 100–110° for 12 hr under nitrogen. Almost all the solvent was removed by high vacuum affording a reddish residue which was dissolved in 10 ml of chloroform and washed with 3% hydrochloric acid at 0°. Removal of the dried solvent afforded 25 mg of **60** as a colorless oil. Chromatography over silica gel and elution with chloroform afforded lactone **60** as a white foam: nmr δ 1.33 (s, 3, acetonide), 1.55 (s, 3, acetonide), 2.31 (s, 3, *N*-acetate), 2.6–3.2 (m, 2, H-7′ and OH), 3.7–4.8 (m, 4, H-4′, 5′, 6′, 9′), 5.50 (s, 1, H-2), 6.90 (d, J = 1.0 Hz, 1, H-3′); ir ($CHCl_3$) 3600–3300 (broad), 3000 (m), 1750 (s), 1680 (s), 1620 cm^{-1} (m); mass spectrum m/e 310 (parent ion), 295 (loss of a methyl), 265, 252, 235.

Anal. Calcd for $C_{14}H_{18}N_2O_6 \cdot H_2O$: C, 51.22; H, 6.14. Found: C, 51.71; H, 6.17.

The exact molecular weight as determined by high resolution mass spectrometry was 310.1154 (calcd for $C_{14}H_{18}N_2O_6$: 310.1160).

Registry No.—**9,** 26681-48-1; **10,** 26681-49-2; **15,** 26681-50-5; **16,** 26681-51-6; **17,** 26681-52-7; **18,** 26681-53-8; **22,** 26681-54-9; **23,** 26681-55-0; **26,** 26681-56-1; **27,** 26681-57-2; **28,** 26681-58-3; **30,** 26681-59-4; **31,** 26681-60-7; **32,** 26681-61-8; **33,** 26681-62-9; **34,** 26681-63-0; **36,** 26681-64-1; **40,** 26731-47-5; **41,** 26681-20-9; **42,** 26681-21-0; **43,** 26681-22-1; **44,** 26681-23-2; **45,** 26681-24-3; **46,** 26731-48-6; **47a,** 26681-25-4; **47b,** 26681-36-7; **48a,** 26681-26-5; **48b,** 26681-37-8; **49a,** 26681-27-6; **49b,** 26681-38-9; **53,** 26681-28-7; **54,** 26681-29-8; **56,** 26681-30-1; **57,** 26681-31-2; **58,** 26681-32-3; **59,** 26681-33-4; **60,** 26681-34-5; methyl (1′-acetyl-4′β,6′β-diacetoxy-5′α-methoxy-4′,5′,6′,7′,8,′9′β-hexahydro-1′(*H*)-indazole-8′β-yl)glyoxylate, 26681-35-6.

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