Total Synthesis of Illudinine, Illudalic Acid, and Illudacetalic Acid

R. B. Woodward* and Thomas R. Hoye[1]

Department of Chemistry, Harvard University, Cambridge, Massachussetts 02138. *Received April 13, 1977*

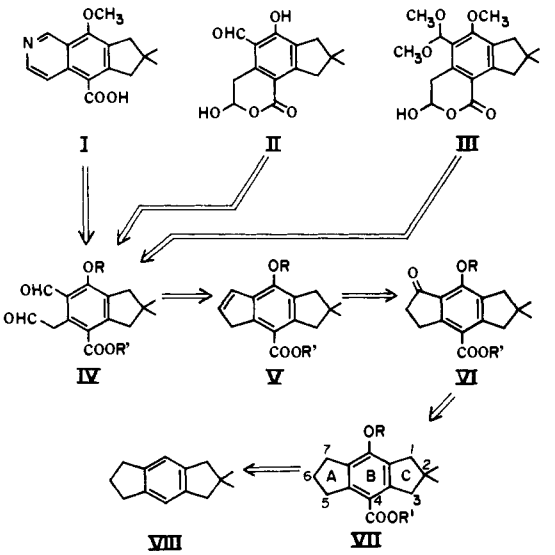
Abstract: Illudinine, illudalic acid, and illudacetalic acid—originally assigned structures I, II, and III, respectively—have each been synthesized from indan in 15 steps. During the course of the work, the structure of natural illudacetalic acid was revised from the simple acetal III to the mixed acetal **29**, and this change was verified by establishing the identity of synthetic **29** with the natural material. Salient features of the synthesis include the preparation of the hydrocarbon VIII, functionalization of the aromatic ring to give VII, selective oxidation of VII to the C-7 ketone VI, elaboration of the cyclopentanone ring into the dialdehyde IV, and conversion of IV to the natural products I, II, and **29**.

Illudinine (I), illudalic acid (II), and illudacetalic acid (III) are three of the many fungal metabolites[2a] isolated from the Basidiomycete (a major class of true fungi), *Clitocybe illudens* (now *Omphalotus olearus* and commonly known as "Jack-O'Lantern").[2b] Although the isolation of illudalic acid as "a fourth crystalline compound" [3] accompanying illudin M was first described in 1952, its structure along with that of illudinine was reported by Anchel and coworkers in 1969.[4] The subsequent isolation and structure determination of illudacetalic acid were communicated in 1972.[5]

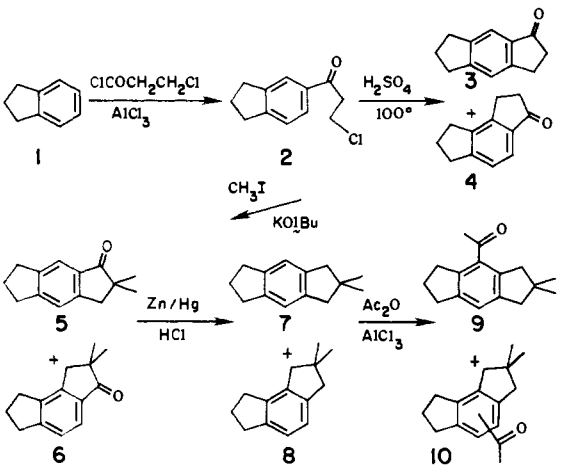
Contemplated chemical syntheses of these metabolities are rendered challenging by the diversity of functional groups, which flank their aromatic nuclei. Of paramount importance in devising a synthetic route to these compounds is the realization that all should be available from the generalized common precursor IV, as suggested in Scheme I. Special note should be made of the removal of the ketone carbonyl in VI, which necessitates a selective oxidation of one of the four benzylic methylene groups in precursor VII. It was hoped that bimolecular attack of any oxidant at one of the benzylic positions in the *s*-hydrindacene[6] VII would occur preferentially on the less-encumbered, normethylcyclopentene ring (ring A), and oxidation involving electron-deficient carbonium ion or radical intermediates should occur predominatly at the benzylic site ortho to the electron-supplying methoxy (R = CH_3) and meta to the electron-withdrawing carbomethoxy (R′ = CH_3) groups rather than vice-versa.

An attempted synthesis based upon this analysis would therefore have to accomplish four major objectives if it were to be successful: (i) construction of the carbon skeleton (i.e., preparation of 2,2-dimethyl-*s*-hydrindacene (VIII)); (ii) functionalization of the aromatic ring (ring B) in VIII with appropriately protected oxygen and carboxyl substituents (i.e., conversion of VIII to VII); (iii) elaboration of ring A via ketone and olefin intermediates to the ultimate precursor of the natural products (i.e., preparation of IV from VII); and (iv) conversion of dialdehyde IV to illudinine (I), illudalic acid (II), and illudacetalic acid (III). Such an accomplishment is now described.

Scheme I



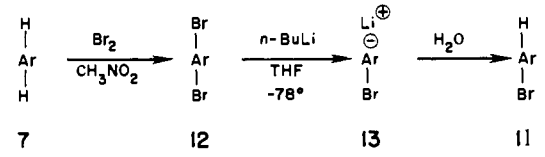
Scheme II



i. Preparation of 2,2-Dimethyl-*s*-hydrindacene (VIII). As outlined in Scheme II, Friedel-Crafts acylation of indan with β-chloropropionyl chloride[7] gave the chloro ketone **2** in 84% yield. Cyclization of **2** in concentrated sulfuric acid at 100 °C for 4 h[7] led to a mixture of linear (*s*-) and nonlinear (*as*-) hydrindacen-1-ones (**3** and **4** respectively) in 85% yield. Although the desired linear isomer could be obtained pure by fractional crystallization, it was found to be more expedient to continue the sequence using the isomeric mixture and to tackle the problem of separation at a later, more convenient time. The hydrindacenones **3** and **4** were converted to their 2,2-dimethyl derivatives **5** and **6** by alkylation with excess methyl iodide and potassium *tert*-butoxide. Clemmensen reduction of the mixture containing these hindered ketones required 20 h of refluxing in an ethanolic solution of concentrated hydrochloric acid in the presence of excess amalgamated zinc. Short-path distillation gave a hydrocarbon fraction containing compounds **7** and **8** and a portion of recovered starting ketones **5** and **6**. Although the hydrocarbon isomers could not be completely re-

solved by gas chromatography, acylation of the mixture with acetic anhydride and aluminum chloride in nitromethane afforded after Kugelrohr distillation a crude product mixture (98%), NMR analysis of which allowed determination of the relative amounts of **7** and **8** (and, by inference, the **5**:**6** and **3**:**4** ratios as well). Broad singlets at δ 6.97 and 7.38, which integrated for 0.82 and 0.18 protons, respectively, could be assigned as the absorptions due to the aromatic protons in the methyl ketones **9** and **10**. Careful spinning-band distillation of the hydrocarbon fraction provided a forerun of unmethylated hydrindacenes (25%), the nonlinear isomer **8** (19%), and pure 2,2-dimethyl-*s*-hydrindacene (**7**) (44%) as a low-melting, crystalline solid. The yield of **7**, based upon the presumption that the starting mixture of ketones contained only 75% **5** and **6** and corrected for the recovered portion of those two ketones, was 67%. Inasmuch as 2,2-dimethyl-*s*-hydrindacene (**7**) was also compound VIII in the introductory analysis, the first portion of the synthesis, construction of the carbon skeleton, was complete.

ii. Functionalization of the Aromatic Ring (conversion of VIII into VII). It was obvious that any successful conversion of the hydrocarbon **7** (VIII) to a form of compound VII would at some point involve a symmetry-destroying differentiation of the two equivalent, unsubstituted, aromatic carbon atoms. As an initial approach to this problem, numerous electrophilic aromatic substitution reactions designed to monofunctionalize the benzenoid ring were examined. These met with varying degrees of success, but did not lead to any overly interesting observations, until the bromination of substrate **7** was studied. Although conditions for the efficient preparation of the monobromo derivative **11** were not found, treatment of **7** with 2 full equiv of bromine in chloroform caused formation of the dibromide **12** in 80% yield. Higher yields could not be obtained with excesses of bromine. After isolation by column chromatography, the dibromide **12** was a white crystalline solid, which held some promise for further use in the synthesis, since the possibility existed of invoking a selective reaction at one of the two bromine atoms as an alternative to electrophilic monosubstitution for differentiating carbons 4 and 8 in the *s*-hydrindacene skeleton. The feasibility of this approach to desymmetrization was convincingly demonstrated by formation of the monoanion **13** upon treatment of **12** with 1 equiv of *n*-butyllithium in tetrahydrofuran at −78 °C. Quenching of the blood-red solution of **13** with water efficiently produced the monobromide **11**. Since the dibromide had been established

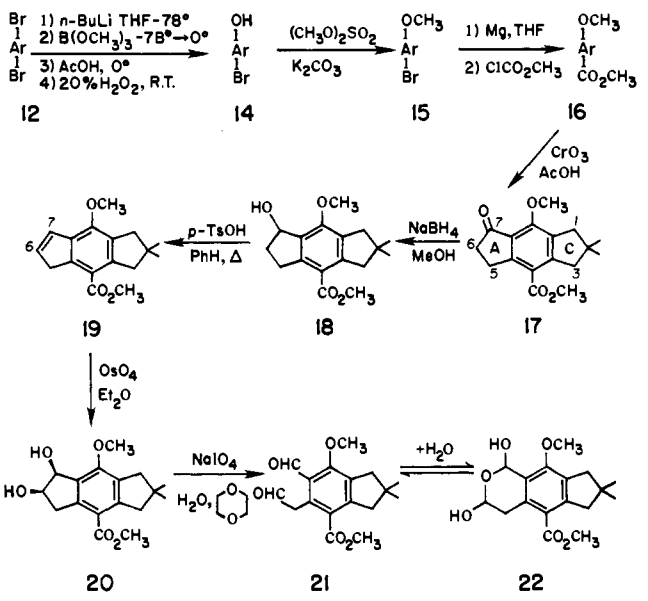


as a viable synthetic intermediate, its preparation in high yield was desirable. When the hydrocarbon **7** was treated at room temperature with exactly 2 equiv of bromine in nitromethane solution, the dibromide **12** precipitated in 95% yield.

Attention was now focused (Scheme III) on the introduction of the C-7 oxygen substituent, which would eventually be needed for the preparation of VII. Trimethyl borate, $B(OCH_3)_3$, has been shown to react with aryl carbanions to produce intermediate organoboranes, which subsequently can be oxidized to the corresponding hydroxy derivatives.[8] Use of this method in the present instance involved the inverse addition of the carbanion **13** to trimethyl borate in tetrahydrofuran at −78 °C. Acetic acid was added, followed by excess 20% aqueous hydrogen peroxide to provide the phenol **14** in 56% yield (74% on a smaller scale).

Thought was next given to the problem of replacing the remaining bromine atom in **14** with a carboxyl group, and the

Scheme III



use of a second carbanionic reaction seemed promising. It was, of course, necessary to protect the hydroxyl group of **14**, and the methyl ether was chosen as a suitable derivative. Thus, methoxy bromide **15** could be prepared in 96% yield after distillation by heating the phenol in acetone in the presence of dimethyl sulfate and potassium carbonate. Efficient generation of the anion corresponding to this bromide by metal–halogen exchange with an alkyllithium reagent in an analogous fashion to that used with the dibromo compound proved not possible.

The conversion of **15** to the corresponding Grignard reagent was then investigated, and it was eventually discovered that treatment of the bromide with 2 equiv of magnesium in a refluxing tetrahydrofuran solution containing 1 equiv of ethylene dibromide was necessary to prepare the magnesium bromide derivative. Addition at room temperature of an excess of methyl chloroformate initiated an exothermic reaction, which produced crystalline 4-carbomethoxy-2,2-dimethyl-8-methoxy-*s*-hydrindacene (**16**) in 98% yield. With the preparation of **16**, the second phase of the synthesis—functionalization of the aromatic ring to a compound of type VII—had been completed.

iii. Elaboration of VII to the Dialdehyde IV. The next objective in accordance with the original synthetic plan was to elaborate the unsubstituted cyclopentene ring (ring A) in VII to the crucial dialdehyde intermediate IV. In anticipation of the possible problems associated with selective oxidation of C-7 in VII, this conversion was considered to be potentially one of the most difficult portions of the synthesis. After numerous attempts to effect this oxidation through the use of reagents such as *o*-chloranil, DDQ, sulfuryl chloride, *N*-bromosuccinimide, and lead tetraacetate; success was finally achieved by employing the classical reagent, chromium trioxide, in acetic acid at room temperature, under conditions of high dilution.[9] Optimum conditions routinely gave a product mixture—readily separable by column chromatography—consisting of the desired 7-oxo derivative **17** (36%) as the major isomer, along with the hindered C-1 ketone (14%), recovered starting material (13%), the 5-oxo derivative (8%), and the C-1,C-7 diketone (6%). It was therefore concluded that the steric factors played a less important role in determining the site of attack by chromium trioxide (ratio of ring A to ring C ketones ~2.5:1) than the electronic influences (ratio of C-1 and C-7 to C-5 ketones ~7:1). Attempts to magnify the steric ef-

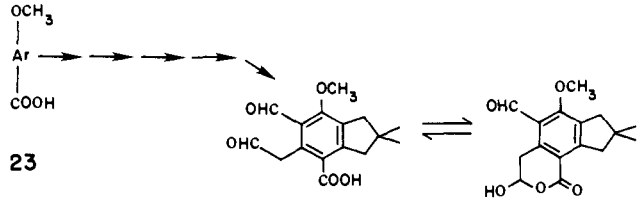
fects by using the presumably much more hindered *tert*-butyl chromate[10] as the oxidizing agent were thwarted by its lower reactivity even under several sets of more forcing conditions.

The net yield of **17** from **16** was substantially improved, when it was discovered that the two undesired monoketones could each be efficiently converted back to the methoxy methyl ester **16**. The 1-oxo derivative was first reduced with sodium borohydride, and the resulting crude alcohol was catalytically (10% Pd/C) hydrogenolyzed in acetic acid containing a small amount of perchloric acid to give **16**. The C-5 ketone could be reduced to **16** directly under the same hydrogenation conditions. Based then on the unrecovered starting material in the actual oxidation, and taking into account the just-described recycling reductions, the overall yield of 4-carbomethoxy-*s*-hydrindacen-7-one (**17**) from **16** was 52%.

With the thought of converting compound **17** regiospecifically into the 6,7 olefin **19**, this ketone was reduced with sodium borohydride in methanol at 0 °C to give the acid-labile alcohol **18** in 96% yield. Reaction of this alcohol with *p*-toluenesulfonic acid in refluxing dry benzene for 10 min provided the tetrahydroindacene **19** as a white crystalline solid in quantitative yield.

Oxidative cleavage of the carbon-carbon double bond in **19** by ozonolysis[11] or one-step, osmium tetroxide catalyzed, sodium metaperiodate cleavage[12] met with only limited success. However, reaction of the olefin with a full equivalent of osmium tetroxide produced the cis diol **20** (NMR (d_5-py) δ 4.73 (H-6, br dd, J = 5 and 6 Hz), 5.52 (H-7, d, J = 5 Hz)) in 98% yield. Subjection of this diol to sodium metaperiodate generated the dialdehyde **21** in quantitative yield. Solution spectral data of the powdery white solid were consistent with this structure (IR (CCl_4) 1730 (s), 1695 (w) cm^{-1}; NMR ($CDCl_3$) δ 9.74 (1 H, t, J = 1 Hz), 10.48 (1 H, s)). However, the elemental analysis, being 4% below the theoretical amount of carbon consistent with formula **21**, suggested that the solid material was actually the hydrated bishemiacetal **22**. This was confirmed by solid-phase IR analysis (KBr, 3400 (s), 1705 (s) cm^{-1}). Thus, in relatively nonpolar solution ($CDCl_3$) the free dialdehyde predominated, whereas the stable bishemiacetal was by far the favored form in the solid state.

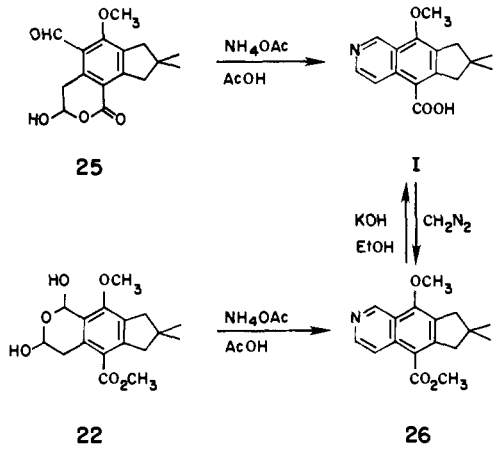
Since compound **21** is of the general structure IV, its availability meant that at least one solution to the third stage of the synthesis had been achieved. A second example of IV was the carboxylic acid **24** (IV, R = CH_3; R′ = H), which had been prepared earlier from the methoxy acid **23** by the exact sequence of reactions that had been used to produce **21** from the ester **16**. The yields were usually slightly lower for the reactions in the carboxylic acid series (19% overall yield for the five steps as compared with 49% yield for the methyl ester series). As expected, the dialdehyde **24** existed as the cyclized lactol **25** both in the solid state and in solution (IR (KBr or



23 24 25

CCl_4) 3350 (w), 1720 (s), 1680 (s) cm^{-1}; NMR ($CDCl_3$) δ 5.86 (1 H, dd, J = 4 and 4 Hz), 10.53 (1 H, s)). In fact, the lactol **25** was a known compound, having been reported[5] as the product of acid hydrolysis of natural illudacetalic acid (III).

iv. Conversion of Dialdehyde IV to Illudinine (I), Illudalic Acid (II), and Illudacetalic Acid (III). With equivalents of the dialdehydes **21** (IV, R,R′ = CH_3) and **24** (IV, R = CH_3; R′ = H) readily available, the final stage of the synthesis of the title natural products I, II, and III was commenced. The first and perhaps most obvious of these conversions involved reaction of the lactol **25** (the equivalent of **24**) with ammonia in an attempt to prepare illudinine (I). To this end **25** was reacted with excess ammonium acetate in acetic acid to give a low yield (36%) of crude illudinine as a glass. A much more efficient route to I involved reaction of the bishemiacetal **22** (the

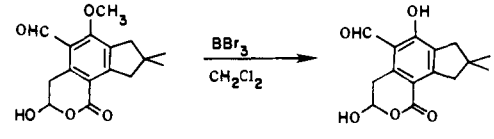


25 I 22 26

equivalent of **21**) under the conditions just described to give crystalline illudinine methyl ester (**26**) in 94% yield which was identical with samples prepared by treatment of both synthetic and natural[4] illudinine with diazomethane. Saponification of **26** to I proceeded smoothly and quantitatively.

The identity of synthetic illudinine (I) with the natural material was established by comparison[13] of IR, NMR, mass, and UV spectra, TLC behavior, melting points, and combustion analysis. Illudinine (I) had been synthesized in fifteen steps with an overall yield of 14%.

Illudalic acid (II) was recognized as being the free phenol of the lactol methyl ether **25**. Accordingly, Lewis acid mediated demethylation of **25** was investigated. Treatment of the aldehyde **25** with boron trichloride—well known for its ability to demethylate selectively anisole derivatives substituted in the ortho position with a carbonyl-containing functional group[14]—repeatedly led to complex reaction mixtures containing numerous products in which the methoxy group had been cleaved to an *o*-hydroxy aldehyde, but from which illudalic acid (II) could not be isolated. However, when **25** was

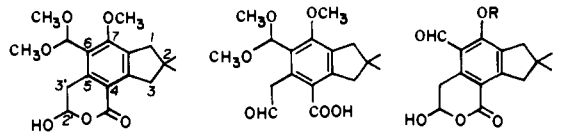


25 II

placed in the presence of 1-2 equiv of boron tribromide in methylene chloride at 0 °C or room temperature, the major product isolated by preparative layer chromatography in consistently low yields of 20-27% was the highly crystalline illudalic acid (II). The identity of this material with the natural product was again established by comparison of IR, NMR, mass, and UV spectra, TLC behavior, melting points, and combustion analysis.

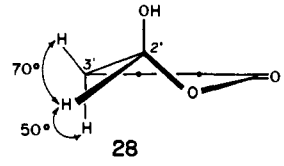
Finally, the preparation of illudacetalic acid (III) was considered. The structure of this acid was initially assigned[5] primarily on the basis of its 60-MHz NMR spectrum which showed among others two singlets at δ 1.11 and 1.16 for the *gem*-dimethyl groups; a broad two-proton signal at 3.25 for H-3′; a pair of singlets at 3.6 and 3.63 for the acetal methoxyls; a one-proton multiplet at 5.1 for H-2′ (seen as a d of d, J = 9 and 4 Hz at 100 MHz (this work)); and a one-proton singlet

at 5.8 for the acetal proton. In addition, the compound dissolved in sodium bicarbonate with evolution of a gas, could be hydrolyzed with acid to the lactol aldehyde **25** as mentioned previously, and had peaks at 2700 and 2560 (broad humps) and 1685 cm^{-1} in its IR spectrum (KBr), which the authors attributed to a tendency of the lactol in III to tautomerize to the open aldehydic acid **27** in the solid phase although they allowed that "it is remarkable that the tautomerism should be suppressed in [**25**], which differs from [III] only by the presence of the free aldehyde group on the aromatic ring".[5]



III 27 25 R=CH_3 II R=H

Several of these pieces of data rendered the assigned structure suspect. For instance, the chemical shift (δ 5.1) and coupling constants (J = 9 and 4 Hz) for the hemiacylal proton on C-2′ in III differed significantly from those of the corresponding protons in the structurally similar lactols **25** (δ 5.86 (dd, J = 4 and 4 Hz)) and illudalic acid (II) (δ 5.95 (dd, J = 4 and 4 Hz)). The broad triplet (doublet of doublets with nearly equal coupling constants) of each of the latter two compounds was consistent with the lactol existing in that half-chair conformation which contained an axial-like hydroxyl group (presumably on the grounds of the anomeric effect) and an equatorial-like C-2′ proton as depicted in **28** (angles esti-



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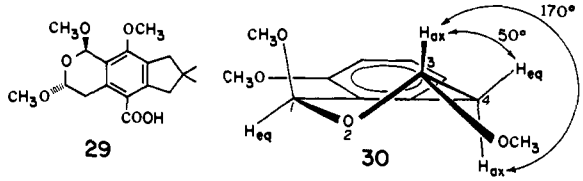
mated from Dreiding models). In addition, the IR spectral data of the natural product were suspiciously lacking a second carbonyl band which should have been observed for the free aldehyde functionality in the ring-opened tautomer **27**—postulation of which was necessitated by the carboxylic acid-like absorptions in the remainder of the IR spectrum.

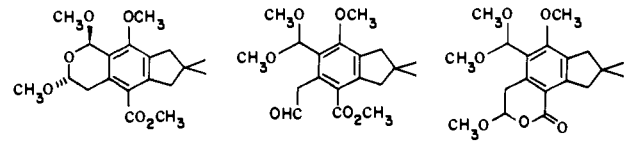
A structure seemingly more consistent with all of the above data for natural illudacetalic acid was the mixed acetal carboxylic acid **29**. It was unarguably more compatible with the IR data, and the NMR exhibited obvious similarities to that of the bishemiacetal **22**. Also, the signal at δ 5.1 as a doublet of doublets with one large and one medium coupling constant (J = 9 and 4 Hz) was readily accommodated by the C-3 proton (now a simple acetal proton) occupying an axial-like position (see **30**). This fact suggested that the two mixed acetal meth-



29 30

oxyls were trans to one another, since it was probable that the C-1 methoxyl would be axial-like both on the basis of the anomeric effect and to relieve as much as possible any peri interaction with the aromatic methoxy group.

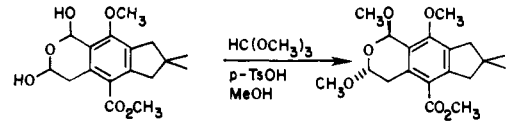
To verify this alternative structure, a small portion of natural illudacetalic acid[13] was esterified with diazomethane—an experiment which was rather surprisingly not reported during the initial structure elucidation studies.[5] The resulting methyl ester exhibited spectral data which were wholly consistent with structure **31** and which immediately ruled out the alternatives **32** or **33**—one or the other of which should have been formed



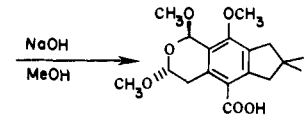
31 32 33

had structure III been correct. Although **29** obviously had the potential of being optically active, polarimetric examination of a chloroform solution of a sample of the natural material[13] showed no measureable rotation at several wavelengths.

The new structure eased rather than complicated the synthetic problems at this point. Reaction of the bishemiacetal methyl ester **22** with excess trimethyl orthoformate in dry methanol containing a trace of *p*-toluenesulfonic acid at room temperature afforded in 95% yield the very same mixed acetal methyl ester **31** which had been obtained from esterification



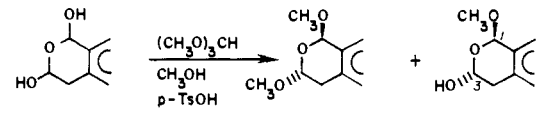
22 31



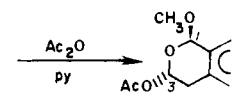
29

of natural illudacetalic acid. This ester was then saponified with sodium hydroxide in refluxing methanol for 20 h to give a 96% yield of illudacetalic acid (**29**) which proved to be extremely difficult to purify. It was hydrolyzed to the aldehydic lactol **25** upon standing in deuteriochloroform to the extent of ~5% after 10 min and ~50% after 2 h. The synthetic compound was shown to be identical with the natural material by comparison of IR, NMR, mass, and UV spectra, TLC behavior, melting points, and combustion analysis.

Additional evidence which supported the assignment of stereochemistry as trans in the revised illudacetalic acid structure **29** was gained as a result of an unexpected course of events. On one particular occasion, when the bishemiacetal **22**



22 31 34



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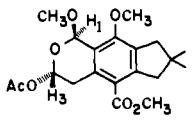
was allowed to react with trimethyl orthoformate in methanol under conditions that were as nearly identical as was controllable with previous experiments which had led to very high yields of the mixed acetal **31**, a second, more polar product, the mixed hemiacetal **34**, was generated in 77% yield. The powdery hemiacetal was characterized as its crystalline acetate **35**, the NMR spectrum of which unambiguously indicated that the

methoxy group was attached to C-1 (H-1 was a sharp singlet at δ 5.70 and 5.72 in **34** and **35**, respectively) and the acetoxy group to C-3 (H-3 was a doublet of doublets, δ 5.40 (J = 9 and 4 Hz) in **34** and δ 6.40 (J = 7.5 and 4.5 Hz in **35**)). These coupling patterns for H-3 again suggested that this proton occupied an axial position in both **34** and **35**, whereas the hydroxy or acetoxy group was equatorial as had been postulated for the C-3 methoxyl in illudacetalic acid (**29**).

Since the protons and substituents attached to both C-1 and C-3 gave rise to signals that were all well separated and distinguishable in the NMR spectrum, the fortuitously arrived at acetate **35** was a compound well suited for examination of possible nuclear Overhauser effects (NOE). The results of this study are summarized in Table I and lead to assignment of trans stereochemistry in **35** with a conformational preference as depicted in **36**.



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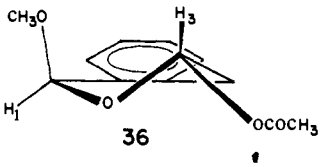

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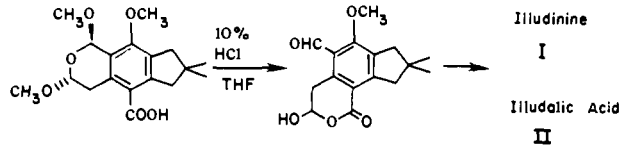
Finally, it should be recalled that illudinine (I) and illudalic acid (II) could both be prepared from the lactol **25**. In fact, by



29 **25**

far the most efficient preparation of this lactol—and the one actually used in practice—was through the acid-catalyzed hydrolysis of synthetic illudacetalic acid (**29**) itself. Thus, the synthesis of the latter natural product was viewed simply as the preparation of another intermediate—a protected dialdehyde—from the standpoint of the synthesis of the former two.

Experimental Section

General Experimental Information. Melting points were determined on a Kofler hot-stage instrument and are uncorrected as are all boiling points. Elemental analyses were performed by Scandinavian Microanalytical Laboratories, Herlev, Denmark. Gas chromatographic separations were carried out on a Varian Aerograph Model 1525-B instrument using columns packed with 5-30% SE-30 on Chromosorb W. Thin layer and preparative layer chromatographic separations were performed on commercially available (Analtech) plates that were used as received. After preparative work compounds were eluted from the absorbents with ethyl acetate. Column chromatography was carried out using activity I Woelm silica gel. Dry benzene, ether, and tetrahydrofuran were distilled under nitrogen or argon from potassium-benzophenone ketyl. Dry *tert*-butyl alcohol and methylene chloride were distilled under nitrogen from calcium hydride. Spinning-band distillations were done on a Perkin-Elmer MFA-200 autoannular still. Routine workup of reaction mixtures is represented by the following—extraction solvent, washing solutions (saturated unless otherwise specified), drying agent—and implies filtration and concentration of the dried organic phase on a rotary evaporator.

All spectral data were obtained from analytically pure samples. Infrared spectra were recorded on a Perkin-Elmer Model 137 instrument. Nuclear magnetic resonance spectra were obtained on a Varian XL-100 instrument in the Fourier transform mode. Mass spectra were determined on an AEI MS-9 double focusing instrument at 70 eV and inlet temperatures of 200-300 °C. Ultraviolet spectra were measured on a Cary Model 14 spectrometer.

5β-Chloropropionylindan (2). Indan (**1**, 64.6 g, 0.547 mol) and β-chloropropionyl chloride (69.6 g, 0.548 mol) were combined and added over a period of 1 h (slight exotherm) to a magnetically stirred solution of $AlCl_3$ (164 g, 1.23 mol) in dry CH_3NO_2 (550 mL) at room temperature. The resulting dark-brown solution was stirred for 4.5 h at room temperature and then poured into a slurry of concentrated HCl (100 mL) and ice (~500 g). Workup (CH_2Cl_2 (3×); 10% HCl, NaCl; $MgSO_4$) gave a gummy brown-black sludge. Continuous extraction for 24 h with low-boiling petroleum ether (bp 30-60 °C, 500 mL) provided crude **2** (102 g, 0.490 mol, 89.6%) as an off-white solid of suitable purity for further reaction. One recrystallization from petroleum ether (bp 60-90 °C) gave white crystals, mp 62-67 °C (lit. 65-66[15] and 68-69 °C[7]). Some workers have experienced skin irritation while handling this compound.[15]

Table I. Results of Nuclear Overhauser Study on **35**

Irradiated proton(s)	Change in integral, %			
	$OCOCH_3$	OCH_3	H-3	H-1
$OCOCH_3$		±0	±0	±0
OCH_3	±0		10	22
H-3	±0	4		±0
H-1	±0	4	−2	

***s*-Hydrindacen-1-one (3).** Chloro ketone **2** (73.9 g, 0.354 mol) was added in small portions with swirling to concentrated H_2SO_4 (290 mL). The resulting dark-red solution was heated (90 °C bath) in an efficient fume hood (HCl evolved) for 4 h, cooled to room temperature, and then cautiously poured onto ice. Workup (benzene (3×); $NaHCO_3$ (2×), NaCl; $MgSO_4$) gave a mixture of ketones **3** and **4** as a cream-colored solid (52.0 g, 0.302 mol, 85.4%, mp 54-75 °C). Repeated recrystallization from petroleum ether (bp 30-60 °C) and sublimation (0.28 mmHg, 55 °C, 15 h) provided an analytical sample of the major isomer **3**: mp 80.0-81.5 °C (lit.[7] 80-81 °C); NMR ($CDCl_3$) δ 2.16 (quintet, 2 H, $CH_2CH_2CH_2$), 2.71 (m, 2 H, CH_2CO), 2.98 (m, 6 H, $ArCH_2$), 7.32 and 7.60 (s, 1 H, ArH); IR (KBr) 1690 cm^{-1}; UV (95% EtOH) λ 256 (ϵ 12 000), 304 (5080); *m/e* (rel intensity) 172 (100). Anal. ($C_{12}H_{12}O$) C, H.

2,2-Dimethyl-*s*-hydrindacen-1-one (5). A solution of ketones **3** and **4** (41.6 g, 0.242 mol), methyl iodide (131 mL, 299 g, 2.10 mol), and dry benzene (150 mL) was added over 2 h to KO-*t*-Bu (prepared from potassium (46.3 g, 1.18 g-atoms) and *tert*-butyl alcohol (455 mL) in benzene (1600 mL)). This mixture was then refluxed for 2 h, cooled to room temperature, and carefully quenched with water (5 mL). Hydrochloric acid (2 N, 600 mL) was then added, and workup (benzene (2×); 10% Na_2SO_3 (2×), $NaHCO_3$, 10% Na_2SO_3, NaCl; $MgSO_4$) yielded a red-orange liquid which was vacuum distilled (bp 106-116 °C (2.2 mmHg)) to provide an orange liquid (45.2 g) comprising a mixture of ketones **5** and **6** as well as a significant amount of starting ketones **3** and **4**. This material could be purified by being stirred in carbon tetrachloride (50 mL) for 0.5 h with decolorizing carbon. Filtration through Celite and concentration under reduced pressure left an oily white solid (mp 25-57 °C) which, after three recrystallizations from petroleum ether (bp 30-60 °C), two sublimations (0.03 mmHg, 30 °C, 2 days), and purification by preparative gas chromatography, gave an analytical sample of **5**: mp 57-61 °C; NMR ($CDCl_3$) δ 1.23 (s, 6 H, CH_3), 2.12 (quintet, 2 H, $CH_2CH_2CH_2$), 2.93 (m, 6 H, $ArCH_2$), 7.26 and 7.60 (s, 1 H, ArH); IR (KBr) 1695 cm^{-1}; UV (95% EtOH) λ 256 (ϵ13 300), 304 (5190); *m/e* (rel intensity) 200 (50). Anal. ($C_{14}H_{16}O$) C, H.

2,2-Dimethyl-*s*-hydrindacene (7). A solution of the crude mixture of ketones **3**–**6** (44.5 g, 0.222 mol) in 95% ethanol (235 mL) was added dropwise over 3.5 h to a refluxing mixture of freshly prepared amalgamated zinc dust (195 g), water (65 mL), concentrated HCl (196 mL, added slowly), and 95% ethanol (18.5 mL). After the mixture had been refluxed for an additional 20 h, more concentrated hydrochloric acid (100 mL) was added. Following a final 2-h period of reflux, the reaction mixture was cooled and decanted from the insoluble zinc residues, which then were washed successively with water (500 mL) and ether (100 mL). Workup (ether (3×); H_2O, $NaHCO_3$, NaCl; $MgSO_4$) provided an orange liquid. Vacuum distillation gave a mixture of hydrocarbons containing **7** and **8** (34.3 g, bp 78-86 °C (0.6 mmHg)) and starting ketones **5** and **6** (2.55 g, 0.0128 mol, bp 100-110 °C (0.6 mmHg), 5.8%). The lower boiling fraction was further purified by careful spinning-band distillation (7200 rpm, reflux ratio 100:1, pot temperature 120-125 °C) to provide unmethylated hydrindacenes (bp 60-65 °C (0.6 mmHg), 9.0 g), 2,2-dimethyl-*as*-hydrindacene (**8**, bp 80-81 °C (1.3 mmHg), 4.1 g), 2,2-dimethyl-*s*-hydrindacene (**7**, bp 75-78 °C (0.6 mmHg), 18.7 g), and

2,2-dimethylhydrindacen-1-ones **5** and **6** (bp 76-78 °C (0.35 mm Hg), 1.5 g). This corresponded to a 66.5% yield of pure **7** based upon unrecovered, methylated starting ketones. A center cut from the distillation afforded a low-melting solid which was sublimed (0.4 mmHg, 25 °C, 1 day) to give an analytical sample of **7**: mp 31.5-33.0 °C; NMR ($CDCl_3$) δ 1.16 (s, 6 H, CH_3), 2.06 (quintet, 2 H, $CH_2CH_2CH_2$), 2.69 (s, 4 H, $ArCH_2C(CH_3)_2$), 2.86 (t, 4 H, $ArCH_2CH_2$), 7.05 (s, 2 H, ArH); UV (95% EtOH) λ 258 (sh) (ϵ 664), 262 (sh) (1080), 266 (sh) (1700), 270 (2460), 276 (3420), 280 (3540), 290 (3650); *m/e* (rel intensity) 186 (100). Anal. ($C_{14}H_{18}$) C, H. The unsymmetrical isomer **8** from the spinning-band distillation was purified once more by short-path distillation to give an analytical sample: bp 82 °C (0.95 mmHg); NMR ($CDCl_3$) δ 1.16 (s, 6 H, CH_3), 2.06 (quintet, 2 H, $CH_2CH_2CH_2$), 2.63 and 2.71 (s, 2 H, $ArCH_2C(CH_3)_2$), 2.8 (m, 4 H, $ArCH_2CH_2$), 7.01 (m, 2 H, ArH); UV (95% EtOH) λ 272 (ϵ 1120), 278 (1450), 280 (sh) (1270), 286 (994); *m/e* (rel intensity) 186 (94). Anal. ($C_{14}H_{18}$) C, H.

4,8-Dibromo-2,2-dimethyl-*s*-hydrindacene (12). Hydrocarbon **7** (15.7 g, 0.0844 mmol) was suspended in dry CH_3NO_2 (150 mL), and a solution of bromine (9.70 mL, 28.4 g, 0.178 mol) in CH_3NO_2 (70 mL) was added dropwise over 0.5 h. The reaction mixture, which by then contained a thick precipitate of the dibromide, was stirred for an additional 0.5 h and filtered. The pale-orange solid was washed with 10% $NaHSO_3$ (2 × 100 mL) and water (5 × 100 mL), air dried, and sublimed (0.3 mmHg, 80 °C, 5 days) to provide dibromide **12** (26.7 g). The entire filtrate from the above washings was worked up (CH_2Cl_2; NaCl; $MgSO_4$) to give an oily solid (2.35 g), recrystallization of which from absolute MeOH gave an additional sample of **12** (0.805 g). A portion of the total amount of **12** (27.5 g, 0.0799 mol, 94.7%) was recrystallized from MeOH (4×) and sublimed (0.4 mmHg, 55 °C, 20 h) to provide an analytical sample: mp 83.5-84.0 °C; NMR ($CDCl_3$) δ 1.20 (s, 6 H, CH_3), 2.11 (quintet, 2 H, $CH_2CH_2CH_2$), 2.83 (s, 4 H, $ArCH_2C(CH_3)_2$), 3.02 (t, 4 H, $ArCH_2CH_2$); UV (95% EtOH) λ 225 (sh) (ϵ12 000), 237 (sh) (8860), 267 (sh) (860), 274 (1470), 283 (1510); *m/e* (rel intensity) 346 (51), 344 (100), 342 (52). Anal. ($C_{14}H_{16}Br_2$) C, H, Br.

4-Bromo-2,2-dimethyl-8-hydroxy-*s*-hydrindacene (14). A solution of dibromide **12** (29.1 g, 0.0846 mol) in dry THF (130 mL) was cooled to −78 °C in a dry, 250-mL, pear-shaped flask under a nitrogen atmosphere, and *n*-BuLi (43 mL, 2.1 M solution in hexane, 0.0903 mol) was added to this magnetically stirred solution over a 10-min period.[16] After having been stirred for an additional 15 min at −78 °C, the rose-colored solution of monoanion was cannulated into a magnetically stirred, −78 °C solution of trimethyl borate (10.7 mL, 9.79 g, 0.0942 mol, distilled from and dried over anhydrous LiCl) in dry THF (130 mL). The reaction solution was warmed to 0 °C and stirred for 45 min. Acetic acid (8.0 mL, 8.4 g, 0.14 mol) was added in one portion to the clear solution, and a fluffy white precipitate appeared. A 20% aqueous H_2O_2 solution (28.7 mL, 0.169 mol) was immediately added dropwise over a 10-min interval. This suspension was then warmed to room temperature and vigorously stirred for 45 min. After the addition of water (250 mL), the mixture was worked up (ether; 10% $Fe_2(NH_4)_2(SO_4)_2$ saturated with $(NH_4)_2SO_4$ (3×), $NaHCO_3$, NaCl; $MgSO_4$) to give an oily solid (25.1 g). This crude material was triturated with ice-cold pentane and filtered to give a white powdery portion of bromophenol **14** (12.4 g, mp 143-147 °C). The filtrate contained a pale yellow oil (12.7 g) which was purified by column chromatography on silica gel (450 g, cyclohexane to 3% EtOAc-cyclohexane gradient elution) to give various butyl-containing products and an additional portion of the bromophenol **14** (0.826 g) (total yield of purified **14** 13.2 g, 0.0970 mol, 55.5%). A portion of the solid phenol was sublimed (0.25 mmHg, 110 °C, 15 H), recrystallized from hexanes (3×), and resublimed to give an analytical sample, mp 147-148.5 °C (with softening at ~120 °C); NMR ($CDCl_3$) δ 1.20 (s, 6 H, CH_3), 2.13 (quintet, 2 H, $CH_2CH_2CH_2$). 2.73 (s, 4 H, $ArCH_2C(CH_3)_2$), 2.92 (t, 4 H, $ArCH_2CH_2$), 4.36 (s, 1 H, OH); IR (KBr) 3250 cm^{-1}; UV (95% EtOH) λ 273 (ϵ 589), 284 (379); UV (NaOH added) λ 246 (ϵ 8230), 285 (1710), 294 (1500); *m/e* (rel intensity) 282 (94), 280 (100). Anal. ($C_{14}H_{17}BrO$) C, H, Br.

4-Bromo-2,2-dimethyl-8-methoxy-*s*-hydrindacene (15). Bromophenol **14** (3.65 g, 13.0 mmol) was dissolved in reagent grade acetone (130 mL), K_2CO_3 (2.69 g, 19.5 mmol) and dimethyl sulfate (1.80 g, 14.3 mmol) were added, and the mixture was refluxed with stirring for 16 h. Saturated $NaHCO_3$ solution (30 mL) was added to the cooled reaction mixture which was then stirred for 1 h at room temperature. Water (100 mL) was added and the mixture worked up (CH_2Cl_2 (3×); NaCl; $MgSO_4$) to give a yellow oil which was vacuum distilled to provide bromo ether **15** (3.68 g, 12.5 mmol, 95.9%; bp 108-110 °C (0.11 mmHg)) as a low-melting, white solid. Sublimation (0.2 mmHg, room temperature, 5 days), low-temperature recrystallization from ether-pentane (1×), and resublimation gave an analytical sample: mp 40.5-43.5 °C; NMR ($CDCl_3$) δ 1.21 (s, 6 H, CH_3), 2.11 (quintet, 2 H, $CH_2CH_2CH_2$), 2.73 and 2.83 (s, 2 H, $ArCH_2C(CH_3)_2$), 2.90 and 3.01 (t, 2 H, $ArCH_2CH_2$), 3.80 (s, 3 H, OCH_3); UV (95% EtOH) δ 228 (sh) (ϵ 10 300), 262 (sh) (480), 271 (684), 280 (625); *m/e* (rel intensity) 296 (99), 294 (100). Anal. ($C_{15}H_{19}BrO$) C, H, Br.

4-Carbomethoxy-2,2-dimethyl-8-methoxy-*s*-hydrindacene (16). A solution of bromo ether **15** (3.68 g, 12.5 mmol) and $BrCH_2CH_2Br$ (1.04 mL, 2.27 g, 12.1 mmol) in dry THF (41 mL) was added dropwise in 45 min to a stirred, refluxing mixture containing magnesium (617 mg, 25.4 mg-atoms) and dry THF (5 mL). Heating was continued for an additional 1.25 h, and the solution of Grignard anion was allowed to cool to room temperature. The addition of methyl chloroformate (2.79 mL, 3.40 g, 36.0 mmol) in one batch caused the solution to boil briefly. The mixture was stirred for 3 h at room temperature by which time a white precipitate had appeared. Hydrochloric acid (10%, 50 mL) was added and the mixture was worked up (ether (3×); $NaHCO_3$, NaCl; $MgSO_4$) to give the ester **16** (3.34 g, 12.3 mmol, 98.2%) as a golden yellow oil which crystallized upon standing in vacuo. A small portion was purified by low temperature recrystallization from ether-pentane (4×) and sublimation (2 × 0.03 mmHg, 45 °C, 2 days) for elemental analysis: mp 50.5-56.0 °C; NMR ($CDCl_3$) δ 1.16 (s, 6 H, CH_3), 2.07 (quintet, 2 H, $CH_2CH_2CH_2$), 2.75 (s, 2 H, *o*-$CH_3OArCH_2C(CH_3)_2$), 2.93 (t, 2 H, *o*-$CH_3OArCH_2CH_2$), 3.00 (s, 2 H, *o*-$CH_3O_2CArCH_2C(CH_3)_2$), 3.18 (t, 2 H, *o*-$CH_3O_2CArCH_2CH_2$), 3.87 and 3.88 (s, 3 H, OCH_3 and CO_2CH_3); IR (KBr) 1705 cm^{-1}; UV (95% EtOH) λ 253 (ϵ 10 900), 293 (3230); *m/e* (rel intensity) 274 (100). Anal. ($C_{17}H_{22}O_3$) C, H.

4-Carbomethoxy-2,2-dimethyl-8-methoxy-*s*-hydrindacen-7-one (17). To a solution of methyl ester **16** (3.34 g, 12.2 mmol) in glacial AcOH (710 mL) was added in one portion a freshly prepared solution of CrO_3 in aqueous AcOH (27.0 mL; 1.0 M CrO_3 in 19:1 AcOH-water; 270 mmol). The reaction solution was stirred at room temperature for 2 h and then poured into water (4 L). The greenish brown cloudy suspension was worked up (ether [5 × 500 mL]; water (2×), $NaHCO_3$ (2×), NaCl; $MgSO_4$) to give a yellow oil (3.98 g). This material was chromatographed on silica gel (125 g, 10 L of 3-10% EtOAc-hexanes, gradient elution) to give, in order of elution starting material **16** (429 mg, 1.57 mmol, 12.8%), undesired C-1 monoketone (502 mg, 1.74 mmol, 14.3%), desired C-7 monoketone **17** (1251 mg, 4.35 mmol, 35.6%), undesired C-5 monoketone (262 mg, 0.910 mmol, 7.5%), C-1, C-7 diketone (230 mg, 0.757 mmol, 6.2%). Compound **17** was purified by recrystallization from hexanes (2×) and aqueous EtOH (1×) and sublimation (0.05 mmHg, 80 °C, 2 days) to give a white, crystalline, analytical sample: mp 100.5-102.0 °C; NMR ($CDCl_3$) δ 1.16 (s, 6 H, CH_3), 2.68 (m, 2 H, $ArCOCH_2$), 2.79 (s, 2 H, *o*-$CH_3OArCH_2C(CH_3)_2$), 3.10 (s, 2 H, *o*-$CH_3O_2CArCH_2C(CH_3)_2$), 3.36 (m, 2 H, $ArCOCH_2CH_2$), 3.92 (s, 3 H, CO_2CH_3), 4.05 (s, 3 H, OCH_3); IR (KBr) 1700 cm^{-1}; UV (95% EtOH) λ 232 (ϵ 32 700), 264 (10 900), 311 (3470); *m/e* (rel intensity) 288 (100). Anal. ($C_{17}H_{20}O_4$) C, H.

4-Carbomethoxy-2,2-dimethyl-7-hydroxy-8-methoxy-*s*-hydrindacene (18). A solution of the ketone **17** (1.15 g, 3.99 mmol) in absolute MeOH (65 mL) was cooled to 0 °C, and $NaBH_4$ (313 mg, 8.24 mmol) was added in one portion. After having been stirred at 0 °C for 0.5 h, the reaction solution was quenched with water (150 mL), and the mixture was worked up (CH_2Cl_2 (4×); NaCl; $MgSO_4$) to give the alcohol **18** (1.11 g, 3.83 mmol, 95.9%) as a white solid, mp 75-79 °C. Recrystallization from hexanes (2×) gave an analytically pure sample: mp 75-84 °C; NMR ($CDCl_3$) δ 1.14 and 1.16 (s, 3 H, CH_3), 2.81 (s, 2 H, *o*-$CH_3OArCH_2C(CH_3)_2$, 3.02 (s, 2 H, *o*-$CH_3O_2CArCH_2C(CH_3)_2$), 3.86 (s, 3 H, CO_2CH_3), 3.99 (s, 3 H, OCH_3), 5.44 (m, 1 H, HOC*H*); IR (KBr) 3400, 1680 cm^{-1}; UV (95% EtOH) λ 255 (ϵ 10 800), 290 (2920); *m/e* (rel intensity) 290 (100). Anal. ($C_{17}H_{22}O_4$) C, H.

4-Carbomethoxy-2,2-dimethyl-8-methoxy-1,2,3,5-tetrahydro-*s*-indacene (19). *p*-Toluenesulfonic acid (4 mg) was added to a solution of alcohol **18** (1.04 g, 3.59 mmol) in dry benzene (75 mL) under nitrogen, and the mixture was refluxed for 10 min. After cooling to room temperature, the reaction mixture was concentrated to a total volume of 5 mL and passed through a short column of silica gel (7.5 × 0.75

cm, 2:1 hexanes-EtOAc elution). Solvent removal provided the tetrahydroindacene **19** (974 mg, 3.58 mmol, 99.8%) as an off-white solid. A low-temperature recrystallization of a small portion from an ether-pentane mixture followed by sublimation (0.05 mmHg, 55 °C, 1 day) gave an analytically pure sample: mp 78-80 °C; NMR ($CDCl_3$) δ 1.16 (s, 6 H, CH_3), 2.78 (s, 2 H, *o*-$CH_3OArCH_2C(CH_3)_2$), 3.10 (s, 2 H, *o*-$CH_3O_2CArCH_2C(CH_3)_2$), 3.70 (br s, 2 H, $ArCH_2CH{=}C$), 3.90 (s, 3 H, CO_2CH_3), 3.96 (s, 3 H, OCH_3), 6.52 (dt, J = 6 and 2 Hz, 1 H, $ArCH{=}CH$), 7.03 (dt, J = 6 and 2 Hz, 1 H; $ArCH{=}CH$); IR (KBr) 1705 (s), 1580 (w), 1545 (w) cm^{-1}; UV (95% EtOH) λ 248 (ϵ 21 300), 271 (sh) (13 600), 310 (1850), 320 (sh) (1660); *m/e* (rel intensity) 272 (100). Anal. ($C_{17}H_{20}O_3$) C, H.

4-Carbomethoxy-6,7-*cis*-dihydroxy-2,2-dimethyl-8-methoxy-*s*-hydrindacene (20). To a solution of tetrahydroindacene **19** (168 mg, 0.630 mmol) in dry ether (5 mL) was added a solution of OsO_4 (160 mg, 0.630 mmol) in dry ether (5 mL). The reaction mixture turned black and began depositing a precipitate within minutes. After having been stirred at room temperature for 15 h, the mixture was concentrated by removing the ether under a *slow* stream of nitrogen (caution: resulting osmate ester was very fine and light). Pyridine (4 mL), water (4 mL), and $NaHSO_3$ (324 mg, 3.12 mmol) were added. The resulting black solution was stirred at room temperature for 4 h, diluted with water (50 mL), and extracted with CH_2Cl_2 (5 × 15 mL). The combined organic layers were washed with water and brine, and dried (Na_2SO_4), filtered through Celite, and concentrated (initially under reduced pressure and then in vacuo) to afford the crude diol **20** as a white powder (184 mg, 0.602 mmol, 97.5%). Recrystallization of a portion from EtOAc and then from EtOAc-hexanes gave an analytical sample: mp 159-162 °C; NMR ($CDCl_3$) δ 1.14 and 1.16 (s, 3 H, CH_3), 2.80 (s, 2 H, *o*-$CH_3OArCH_2C(CH_3)_2$), 3.30 (br t, 2 H, $ArCH_2CHOH$), 3.87 (s, 3 H, CO_2CH_3), 4.02 (s, 3 H, OCH_3), 4.48 (m, 1 H, $ArCH_2CHOH$), 5.18 (m, 1 H, $ArCHOH$); IR (KBr) 3350, 1705 cm^{-1}; UV (95% EtOH) λ 254 (ϵ 10 600), 287 (2760); *m/e* (rel intensity) 306 (80). Anal. ($C_{17}H_{22}O_5$) C, H.

5-Carbomethoxy-1,3-dihydroxy-7,7-dimethyl-9-methoxy-1,3,4,6,7,8-hexahydrocyclopenta[*g*]-2-benzopyran (22). The diol **20** (826 mg, 2.70 mmol) was dissolved in 30% aqueous dioxane (40 mL) and treated with $NaIO_4$ (689 mg, 3.22 mmol). This mixture was stirred for a few minutes at room temperature, and a white precipitate appeared. Stirring was continued for a total period of 2 h. The addition of water (100 mL) caused the mixture to become homogeneous. Workup (CH_2Cl_2 (3×); $MgSO_4$) left an off-white powdery solid (875 mg, 2.71 mmol, 100%). This material could not be crystallized and was purified by being repeatedly slurried with 1:1 hexanes-ether to give an analytical sample of **22**: mp 103-111 °C; NMR (as **21** in $CDCl_3$) δ 1.19 (s, 6 H, CH_3), 1.61 (s, H_2O), 2.88 (s, 4 H, $ArCH_2C(CH_3)_2$, 3.88 (s, 3 H, CO_2CH_3), 3.96 (s, 3 H, OCH_3), 4.21 (br s, 2 H, CH_2CHO), 9.74 (t, 1 H, J = 1 Hz, CH_2CHO), 10.48 (s, 1 H, ArCHO); IR (as **22** in KBr) 3300, 1705 cm^{-1}; UV (as **22** in 95% EtOH) λ 250 (ϵ 7090), 283 (sh) (1500); *m/e* (rel intensity) 304 (10). Anal. ($C_{17}H_{22}O_6$) C, H.

Illudalic Acid Methyl Ether (25) from Illudacetalic Acid (29). Illudacetalic acid (**29**, 117 mg, 0.348 mmol) was dissolved in THF (3 mL), and 10% HCl (10 drops) was added. The reaction mixture was stirred for 1 h at room temperature, diluted with water (25 mL), and worked up (CH_2Cl_2 (3×); Na_2SO_4) to give **25** as a light-yellow foam (100 mg, 0.345 mmol, 99.2%). One sample of this foam crystallized (mp 85-140 °C (lit.[5] 146-149 °C)) but could not be successfully recrystallized for purification: NMR ($CDCl_3$) δ 1.20 (s, 6 H, CH_3), 2.88 (s, 2 H, *o*-CH_3OArCH_2), 3.24 (AB quartet, 2 H, *o*-$COArCH_2C(CH_3)_2$), 3.60 (m, 2 H, CH_2COH), 4.00 (s, 3 H, $ArOCH_3$), 5.87 (t, 1 H, J = 4 Hz, $HCOH$), 10.54 (s, 1 H, ArCHO); IR (KBr) 3350, 1715, 1680 cm^{-1}; UV (95% ETOH) λ 212 (ϵ21 100), 241 (14 400), 305 (sh) (1320); UV (NaOH added) λ 211 (ϵ 28 300), 275 (sh) (2350); *m/e* (rel intensity) 290 (76).

Illudinine Methyl Ester (26). The bishemiacetal **22** (27.8 mg, 0.0864 mmol) was dissolved in glacial AcOH (2 mL) and treated with excess NH_4OAc (160 mg, 2.20 mmol). The reaction was stirred at room temperature for 2.5 h, and water (10 mL) and saturated $NaHCO_3$ solution (25 mL) were added. Workup (CH_2Cl_2 (4×); $MgSO_4$) gave **26** as a pale-yellow oil (23.1 mg, 0.0811 mmol, 93.9%) which crystallized upon being scratched. This material was sublimed (0.2 mmHg, 55 °C, 3 days), recrystallized from hexanes (3×), and resublimed (0.2 mmHg, 75 °C, 1 day) to give an analytical sample: mp 89.5-91.0 °C (lit.[4] 83-84 °C); NMR ($CDCl_3$) δ 1.20 (s, 6 H, CH_3), 3.00 (s, 2 H, *o*-$CH_3OArCH_2C(CH_3)_2$), 3.09 (s, 2 H, *o*-$CH_3O_2CArCH_2C(CH_3)_2$), 4.03 (s, 3 H, CO_2CH_3), 4.10 (s, 3 H, OCH_3), 8.26 (br d, 1 H, J = 6 Hz, ArH_4), 8.58 (br d, 1H, J = 6 Hz, ArH_3), 9.56 (br s, 1 H, ArH_1); IR (KBr) 1700 (s), 1610 (w), 1555 (m) cm^{-1}; UV (95% EtOH) λ 230 (ϵ 47 900), 289 (5370), 298 (5430), 320 (sh) (4590), 332 (5710); UV (HCl added) λ 228 (ϵ23 400), 251 (41 700), 292 (3330), 358 (5160); *m/e* (rel intensity) 285 (100). Anal. ($C_{17}H_{19}NO_3$) C, H, N.

Illudacetalic Acid (29). Crude methyl illudacetalate (**31**), 59.1 mg, 0.169 mmol) was dissolved in MeOH (2 mL) and 1 N NaOH (1 mL) was added. This solution was refluxed for 20 h under a nitrogen atmosphere, cooled to room temperature, diluted with saturated KH_2PO_4 solution (30 mL), and extracted with CH_2Cl_2 (4×). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated to provide illudacetalic acid (**29**, 54.6 mg, 0.162 mmol, 96.2%) as a white foam. This foam crystallized when triturated with methylcyclohexane. Recrystallization from this solvent (3×) gave an analytical sample: mp 115-130 °C (natural, 135-138[13] and 145-147 °C[5]);[17] NMR ($CDCl_3$) δ 1.12 and 1.17 (s, 3 H, CH_3), 2.80 (s, 2 H, *o*-CH_3OArCH_2), 3.00 (AB quartet, 2 H, *o*-$HO_2CArCH_2C(CH_3)_2$), 3.26 (m, 1 H, $CH_2CH(OCH_3)$), 3.62 and 3.65 (s, 3 H, $CHOCH_3$), 3.88 (s, 3 H, $ArOCH_3$), 5.09 (dd, 1 H J = 9 and 4 Hz, $CH_2CH(OCH_3)$), 5.80 (s, 1 H, $ArCHOCH_3$); IR (KBr) 2500-3500, 1680 cm^{-1}; UV (95% EtOH) λ 213 (ϵ 31 800), 244 (7160), 280 (sh) (1700); UV (NaOH added) λ 213 (ϵ16 200), 270 (sh) (1300); *m/e* (rel intensity) 336 (5); TLC (silica gel, EtOAc) R_f 0.28 (streak). Anal. ($C_{18}H_{24}O_6$) C, H.

Methyl Illudacetalate (31). The bishemiacetal **22** (130 mg, 0.404 mmol) was dissolved in dry MeOH (3 mL, distilled from Mg-$(OCH_3)_2$) containing trimethyl orthoformate (0.5 mL) and a small crystal of *p*-TsOH. The reaction mixture was stirred at room temperature for 1 h, diluted with CH_2Cl_2 (5 mL), and filtered through a short column of silica gel (0.5 × 5 cm). Elution with CH_2Cl_2 (50 mL) and evaporation of the solvents under reduced pressure yielded a pale-yellow oil which was purified by plate chromatography on silica gel (2 × 200 × 200 mm, 1:1 hexanes-EtOAc elution) to give methyl illudacetalate (**31**) as a colorless oil (134 mg, 0.383 mmol, 95.3%) which crystallized after being dried in vacuo. An analytical sample, mp 111-114 °C, was prepared by recrystallization from hexanes (2×): NMR ($CDCl_3$) δ 1.10 and 1.15 (s, 3 H, CH_3), 2.79 (s, 2 H, *o*-CH_3OArCH_2), 2.85 (AB quartet, 2 H, *o*-$CH_3O_2CArCH_2C(CH_3)_2$), 3.06 (m, 2 H, $CH_2CH(OCH_3)$), 3.60 and 3.64 (s, 3 H, $HCOCH_3$), 3.86 (s, 6 H, OCH_3 and CO_2CH_3), 5.07 (dd, 1 H, J = 9 and 4 Hz, CH_2CHOCH_3), 5.78 (s, 1 H, $ArCHOCH_3$); IR (KBr) 1710 cm^{-1}; UV (95% EtOH) λ 248 (ϵ 9760), 280 (sh) (3610); *m/e* (rel intensity) 350 (10). Anal. ($C_{19}H_{26}O_6$) C, H.

***trans*-3-Acetoxy-5-carbomethoxy-1,9-dimethoxy-7,7-dimethyl-1,3,4,6,7,8-hexahydrocyclopenta[*a*]-2-benzopyran (35).** A sample of bishemiacetal **22** (58.2 mg, 0.184 mmol) was treated with trimethyl orthoformate (0.5 mL) and *p*-TsOH (one small crystal) in dry MeOH (1 mL) under conditions supposedly identical with those described for the preparation of methyl illudacetalate (**31**). Plate chromatography on silica gel (2 × 200 × 200 mm, 2:1 hexanes-EtOAc elution) of the crude product led to the mixed acetal **31** (5.4 mg, 0.015 mmol, 8.4%) and the mixed hemiacetal **34** (47.4 mg, 0.141 mmol, 76.7%) as a powdery solid: mp 96-110 °C; NMR ($CDCl_3$) δ 1.10 and 1.16 (s, 3 H, CH_3), 2.79 (s, 2 H, *o*-CH_3OArCH_2), 2.85 (AB quartet, 2 H, *o*-$CH_3O_2CArCH_2C(CH_3)_2$), 3.17 (m, 2 H, CH_2CHOH), 3.61 (s, 3 H, $CHOCH_3$), 3.85 and 3.87 (s, 3 H, $ArOCH_3$ and CO_2CH_3), 5.46 (br m, 1 H, $CHOH$), 5.75 (s, 1 H, $ArCHOCH_3$); IR (KBr) 3350, 1705 cm^{-1}; UV (95% EtOH) λ 212 (ϵ 36 400), 247 (8230), 287 (sh) (1600); *m/e* (rel intensity) 336 (7). Precise mass measurement: calcd for $C_{18}H_{24}O_6$, 336.1573; found, 336.1594.

This mixed hemiacetal **34** (44.2 mg, 0.132 mmol) was dissolved in Ac_2O (1 mL) and pyridine (100 μL) and stirred at room temperature for 0.5 hour. The solvents were removed in vacuo, and the colorless oil was purified by plate chromatography on silica gel (2 × 200 × 200 mm, 2:1 hexanes-EtOAc elution). The resulting acetate **35** (28.7 mg, 0.102 mmol, 77.5%) crystallized upon being scratched and was recrystallized from hexanes (2×) to give an analytical sample: mp 106-108.5 °C; NMR ($CDCl_3$) δ 1.11 and 1.16 (s, 3 H, CH_3), 2.13 (s, 3 H, CH_3CO_2), 2.80 (s, 2 H, *o*-CH_3OArCH_2), 2.88 (AB quartet, 2 H, *o*-$CH_3O_2CArCH_2C(CH_3)_2$), 3.15 (m, 2 H, CH_2CHOAc), 3.63 (s, 3 H, $HCOCH_3$), 3.86 and 3.88 (s, 3 H, $ArOCH_3$ and CO_2CH_3), 5.78 (s, 1 H, $ArCHOCH_3$), 6.40 (dd, J = 7 and 5 Hz, 1 H, CHOAc); IR (KBr) 1750, 1710 cm^{-1}; UV (95% EtOH) λ 212 (ϵ 40 500), 247 (8510), 277 (sh) (1830); *m/e* (rel intensity) 378 (1). Anal. ($C_{20}H_{26}O_7$)

C, H.

Illudinine (I). Method A. Illudinine methyl ester (**26**, 23.1 mg, 0.0811 mmol) was dissolved in 95% EtOH (2.5 mL), and 40% aqueous KOH (20 drops) was added. This solution was stirred at room temperature for 20 h, neutralized (to ca. pH 3) with 10% HCl, and poured into pH 7 buffer (35 mL). Continuous extraction of the aqueous mixture with ether (50 mL), drying of the ethereal phase (Na_2SO_4), filtration, and concentration under reduced pressure yielded illudinine (I) as a white solid (22.0 mg, 0.0811 mmol, 100%). Recrystallization of this material from 95% EtOH (2×) gave an analytical sample: mp 218-229 °C dec (natural, 215-224 °C dec[13] and 228-229 °C dec[4]);[17] NMR (TFA-*d*) δ 1.32 (s, 6 H, CH_3), 3.37 (s, 2 H, *o*-CH_3OArCH_2), 3.49 (s, 2 H, *o*-$HOOCArCH_2$), 4.45 (s, 3 H, OCH_3), 8.51 (br s, 1 H, ArH_4), 9.31 (br s, 1 H, ArH_3), 9.80 (br s, 1 H, ArH_1); IR (KBr) 3400 (br), 2400 (br), 1825 (br) (all w), 1680, 1620, 1565 (all m) cm^{-1}; UV (95% EtOH) λ 234 (ϵ 37 400), 288 (4430), 298 (4490), 310 (sh) (3750), 323 (4580); UV (NaOH added) λ237 (ϵ 45 500), 275 (sh) (2470), 287 (3290), 298 (3430), 321 (sh) (2970), 333 (3640); UV (HCl added) λ231 (ϵ 15 100), 251 (34 600), 292 (2720), 359 (4300); *m/e* (rel intensity) 271 (100); TLC (silica gel, 2% AcOH-EtOAc) R_f 0.28. Anal. ($C_{16}H_{17}NO_3$) C, H, N.

Method B. Illudalic acid methyl ether (**25**, 18.1 mg, 0.625 mmol) was dissolved in glacial AcOH (1 mL), and excess NH_4OAc (53.0 mg, 0.686 mmol) was added. The reaction mixture was stirred at room temperature for 3 h and water (10 mL) was added. The solution was extracted with CH_2Cl_2 (4×). Benzene was added to the combined organic extracts, and the solvents were removed under reduced pressure to give illudinine (I) as an impure yellow oil (12.0 mg). Purification by plate chromatography on silica gel (0.5 × 200 × 200 mm, 1% AcOH-EtOAc) led to a poor recovery of purified illudinine (5.4 mg, 0.0199 mmol, 31.9%). It was eventually found that the best method for removing the product from silica gel was to extract with 5% aqueous NaOH, neutralize with excess pH 7 buffer, continuously extract with ether, add benzene to the ether layer, and concentrate to dryness under reduced pressure.

Method C. Illudacetalic acid (**29**, 23.6 mg, 0.0704 mmol) was treated as above (107 mg of NH_4OAc, 1 mL of AcOH). Workup involved diluting the mixture with pH 7 buffer (75 ml) and continuously extracting with ether to give illudinine (I) as a white solid (14.3 mg, 0.0528 mmol, 75.0%).

Illudalic Acid (II). Illudalic acid methyl ether (**25**, 66.8 mg, 0.230 mmol) was dissolved in dry CH_2Cl_2 (2.5 mL) and BBr_3 (55 μL, 120 mg, 0.58 mmol) was added. The reaction mixture was stirred at room temperature for 2.5 h and then quenched with ice and water (10 mL). Workup (CH_2Cl_2 (3×); Na_2SO_4) left an orange oil (67.0 mg), which was purified by column chromatography on silica gel (5 g, 3 L of 5-20% EtOAc-hexanes gradient elution) to give illudalic acid (II, 17.0 mg, 0.0615 mmol, 26.8%) as the major product. Recrystallization from 95% EtOH (3×) gave an analytical sample: mp 190-210 °C dec (natural, 180-200 °C dec[13] and 200 °C dec[4]);[17] NMR ($CDCl_3$) δ 1.19 (s, 6 H, CH_3), 2.73 (s, 2 H, *o*-$HOArCH_2$), 3.25 (s, 2 H, *o*-$COArCH_2$), 3.52 (m, 2 H, $ArCH_2COH$), 4.3 (br s, 1 H, OH), 5.95 (dd, 1 H, J = 4, 4 Hz, $HCOH$), 10.27 (s, 1 H, CHO), 12.42 (s, 1 H, ArOH); IR (KBr) 3300, 1675, 1640, 1630 cm^{-1}; UV (95% EtOH) λ 246 (ϵ 24 500), 270 (sh) (10 500), 331 (1770); UV (NaOH added) λ 258 (ϵ18 300), 280 (sh) (8490), 388 (4800); *m/e* (rel intensity) 276 (70); TLC (silica gel, 2% AcOH-EtOAc) R_f 0.60. Anal. ($C_{15}H_{16}O_5$) C, H.

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References and Notes

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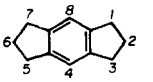

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(16) The initial tetrahydrofuran solution should have been more dilute as the dibromide precipitated about one-fifth of the way through the *n*-butyllithium addition, stirring became sluggish, and the reaction mixture warmed noticeably during the next two-fifths of the alkyllithium addition. The reaction mixture became homogeneous again, but the undesired butylated byproducts were very probably formed during this period of higher temperature.

(17) The acquisition of mixture melting points from samples of the natural and synthetic **29**, I, and II was deemed not worthwhile since the provided samples[13] each had considerably lower melting points than had been originally reported and since the latter two melted with accompanying decomposition.