(69.7 mg, 0.307 mmol), Bu_3SnH (182 μL, 0.676 mmol), and AIBN (10.0 mg, 0.061 mmol) in PhH (10 mL) was heated at reflux for 54 min. After cooling, the solvent was evaporated and the residue was purified by flash chromatography (5% EtOAc/hexane) to provide 35.0 mg (85%) of dihydrocinnamaldehyde (**40**), identical with an authentic sample (Aldrich) by ^1H NMR and GC comparison.

Methyl 4-Oxo-6-phenylhexanoate (47). A solution of Bu_3SnH (520 μL, 0.1.93 mmol) in PhH (4 mL) was added via syringe pump over 2.5 h to a refluxing solution of methyl selenide **36** (86.3 mg, 0.380 mmol), methyl acrylate (240 μL, 2.66 mmol), and AIBN (13.0 mg, 0.08 mmol) in PhH (6 mL). After the addition was complete, the reaction was heated an additional 45 min and cooled to room temperature. After solvent removal, the residue was applied to a silica gel plug and the nonpolar tin-containing products eluted with 10% EtOAc/hexane. Subsequent elution with ether gave the crude keto ester **47**, which was purified by flash chromatography (20% EtOAc/hexane) to provide 81.5 mg (97%) of pure **47**: IR (thin film) 2953, 1738, 1718, 1437, 1365, 1207, 1174 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28-7.24 (2 H, m), 7.18-7.14 (3 H, m), 3.65 (3 H, s), 2.88 (2 H, t, J = 7.7 Hz), 2.76 (2 H, t, J = 7.7 Hz), 2.69 (2 H, J = 6.3 Hz), 2.56 (2 H, t, J = 6.3 Hz); HRMS m/e calcd for $C_{13}H_{16}O_3$ (M^+) 220.1099, obsd 220.1100; LRMS m/e 220 (M^+), 188, 160, 146, 133.

(1*R,4*R**,8*R**)-1,4-Dimethyl-5-isopropylidenetricyclo[6.3.0.0^{4,8}]undec-2-en-11-one (52).** To a solution of carboxylic acid **30** (17.1 mg, 0.069 mmol) in $CDCl_3$ (1.5 mL, distilled under N_2 from P_2O_5) was added oxalyl chloride (6.6 μL, 0.075 mmol). The solution was allowed to stand at room temperature for 23 h (^1H NMR analysis indicated the starting material was completely consumed). The solvent was removed, and the residue was purified by flash chromatography (8% EtOAc/hexane) to afford 6.9 mg (44%) of the tricyclic diene **52**: IR (thin film) 2972, 2872, 1729, 1451, 1051, 779 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.74 (1 H, d, J = 5.6 Hz), 5.30 (1 H, d, J = 5.6 Hz), 2.37 (1 H, ddd, J = 17.5, 13.8, 8.7), 2.16-2.04 (2 H, m), 1.97-1.85 (2 H, m), 1.81-1.31 (2 H, m), 1.65 (3 H, s), 1.64 (3 H, s), 1.36 (3 H, s), 1.12 (3 H, s); HRMS m/e calcd for $C_{16}H_{22}O_1$ (M^+) 230.1671, obsd 230.1671; LRMS m/e 230 (M^+), 162, 148, 133, 120, 106.

(1*R,4*R**,5*S**,8*R**)-1,4-Dimethyl-5-(methylethyl)tricyclo[6.3.0.0^{4,8}]undecan-11-one (55).** To a solution of ketone **52** (17.0 mg, 0.074 mmol) in EtOAc (2 mL) was added 10% Pd/C (6 mg). The suspension was then shaken at 25 °C under 3.5 atm H_2 for 24 h. The reaction mixture was filtered through a pad of Celite, the solvent was evaporated, and the residue was purified by flash chromatography (5% EtOAc/hexane) to yield 9.6 mg (56%) of ketone **55** as a clear, sweet-smelling oil: IR (thin film) 2957, 2867, 1737, 1465, 1367, 1253, 1113, 1070 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.28 (1 H, dd, J = 18.8, 10.2 Hz), 2.12-1.99 (2 H, m), 1.92-1.87 (2 H, m), 1.76 (1 H, dd, J = 13.1, 5.8 Hz), 1.71-1.59 (2 H, m), 1.53-1.48 (1 H, m), 1.37 (1 H, ddd, J = 13.1, 13.1, 6.3 Hz), 1.29-1.21 (3 H, m), 1.07 (3 H, s), 1.01-0.90 (1 H, m), 0.96 (3 H, d, J = 8.4 Hz), 0.95 (3 H, s), 0.87 (3 H, d, J = 6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 227.40, 68.28, 62.76, 59.82, 59.26, 38.90, 38.19, 35.32, 35.19, 31.31, 29.15, 28.18, 27.93, 23.44, 22.78, 17.64; HRMS m/e calcd for $C_{16}H_{26}O_1$ (M^+) 234.1984, obsvd 234.1984; LRMS m/e 234 (M^+), 191, 177, 163, 149, 109.

Hydrogenation of Ketones 28/29. The above mixture of ketones **28/29** (11.0 mg, 0.047 mmol, ratio of 1:4.5) was dissolved in MeOH (2 mL) and rhodium on alumina (8.9 mg, 5% Rh content) was added. The suspension was stirred at 25 °C under a balloon of H_2 for 24 h, and then the reaction mixture was filtered through a pad of Celite. Solvent evaporation afforded 10.4 mg (94%) of the ketones **55/56**. The diastereomer ratio was not easily determined by ^1H NMR integration due to overlap of signals, nor could the ratio be determined by GC as both ketones overlapped as a single, sharp peak. The major product was clearly identical with ketone **55** by comparison of the ^1H and ^{13}C NMR data. Additionally, the IR and MS data for the mixture of **28/29** was essentially identical with that for ketone **55**.

Acknowledgment. We thank the National Institutes of Health (Grant No. GM 33378 and Career Development Award to D. P.C.), ICI Pharmaceuticals, the Dreyfus Foundation, and the American Chemical Society (through a Cope Scholar award to D.P.C.) for funding of this work. We also thank Dr. Richard Soll (Wyeth-Ayerst) for carrying out the hydrogenation of **52**.

Total Synthesis of (+)-Ikarugamycin. 1. Stereocontrolled Construction of the Decahydro-*as*-indacene Subunit

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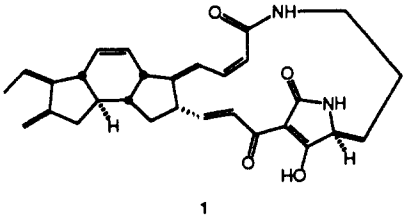
Contribution from the Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210. *Received April 27, 1990*

Abstract: A concise synthesis of the carbotricyclic decahydro-*as*-indacene portion of ikarugamycin is described. Anionic oxy-Cope rearrangement of alcohol **15** leads directly to **18** under the proper workup conditions. Ensuing ketone reduction, ketal hydrolysis, and K_2CO_3-promoted double bond isomerization provides **20**. Dissolving metal reduction of this intermediate generates the pivotal hydroxy ketone **12**. The six contiguous stereocenters in **12** are shown to be capable of substantive purposeful variation. The stereochemical assignments rest on ^1H NMR data and X-ray crystallographic analysis of the *p*-nitrobenzoate of **25**.

Ikarugamycin (**1**), an architecturally unusual macrocyclic antibiotic first isolated in 1972 from a sample of Japanese soil,[1] has also been produced in the culture broths of *Streptomyces phaeochromogenes* var. *ikaruganensis* Sakai. Interest in this substance arose quickly because of its powerful and specific antiprotozoal and antiamoebic activity against such strains as *Tetrahymena pyriformis W*, *Entamoeba histolytica*, and *Trichomonas vaginalis*. In addition, **1** is bacteriocidal against select gram-positive organisms. Unfortunately, however, ikarugamycin is not active against yeast or fungi, is quite toxic to mice (the lethal dose is 6 mg/kg), and causes hemolysis at low concentrations (3.5 mcg/mL) in rabbit blood.



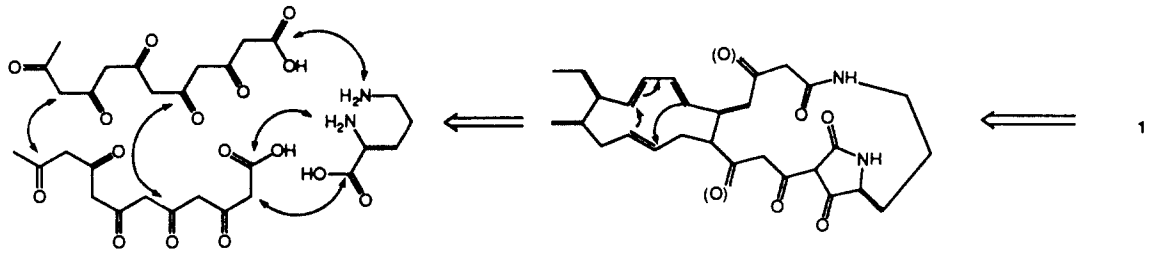
1

Nonetheless, **1** merits serious consideration as a synthetic target because of its unusual bioactivity spectrum and its infrequently encountered combination of structural features. The uncommon *trans,anti,cis*-decahydro-*as*-indacene subunit is endowed with *eight* consecutive stereogenic centers. The macrocyclic lactam to which this building block is fused contains the ninth asymmetric carbon.

(1) Jomon, K.; Kuroda, Y.; Ajisaka, M.; Sakai, H. *J. Antibiot.* **1972**, *25*, 271.

0002-7863/90/1512-9284$02.50/0

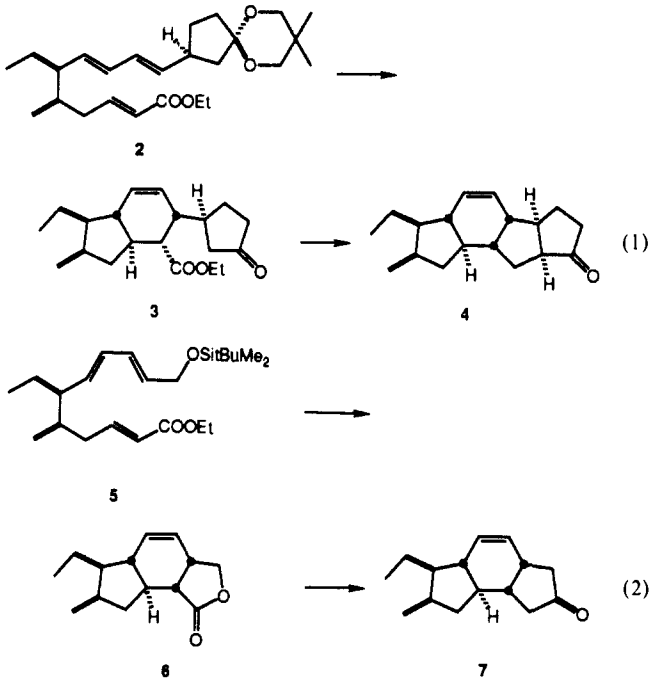
Scheme I



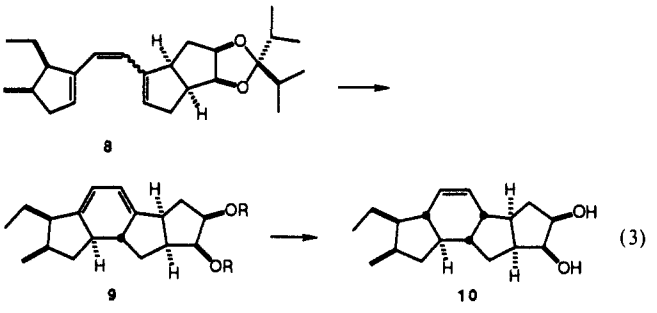
An acylated tetramic acid is also embedded therein. Ikarugamycin belongs to the acetogenin class of natural products and is related to the antibiotic capsimycin.[2] In light of the substantive therapeutic value of many tetramic acids, e.g., tirandimycin[3] and streptolydigin,[4] a route to **1** that would permit access to various structural analogues would carry heightened serviceability and added attractiveness.

The structure and stereochemistry of **1** were elucidated by Ito and Hirata[5,6] who postulated that it derives biosynthetically from the combination of two hexaacetate units and the amino acid L-ornithine (Scheme I). Ensuing reduction, dehydration, and intramolecular Diels–Alder cycloaddition complete hypothetical generation of the framework.

The impetus for two routes to the linearly fused decahydro-*as*-indacene component of **1** have stemmed from this biogenetic proposal. Boeckman's assembly and cyclization of *E,E* triene ester **2** followed by conversion of major stereoisomer **3** (> 5:1) to tetracyclic ketone **4** was reported in 1983 (eq 1).[7] Kurth's approach relied on the thermal activation of **5** to set proper stereochemistry as in **6** (major diastereomer) and ultimately **7** (eq 2).[8]



A highly imaginative, but equally lengthy, alternative means for constructing the carbotricyclic portion of **1** has been devised by Whitesell and Minton (eq 3).[9] Following the elaboration of optically active **8**, this triene was photocyclized to **9** by taking advantage of existing ground-state conformational biases. The target monoene **10** was arrived at 10 steps later.



In 1987, Mehta described a more expedient approach to the less than adequately functionalized racemic ketone **11**.[10]

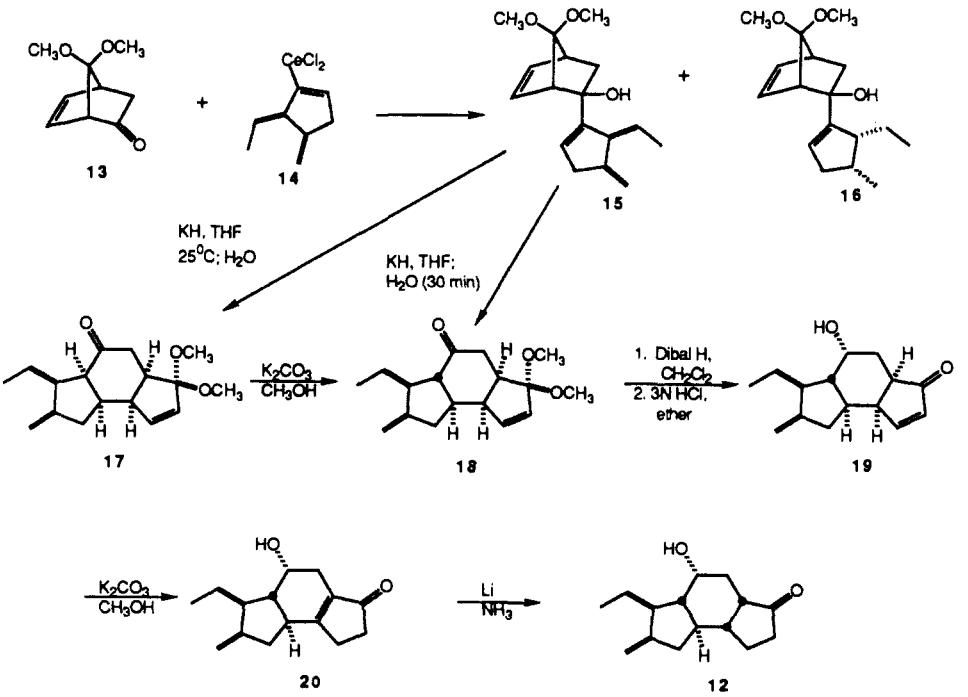
Any scheme that contemplates reaching (+)-ikarugamycin[11] must deal minimally with proper control of relative stereochemistry while holding the realistic prospect for operating within the appropriate enantiomeric series. Whereas the above tactics allow adequately for this requirement, synthetic directness is not well served. In this paper, we provide the complete details surrounding development of an ultra-short route to **12**[12] that is highly convergent[13] and builds complexity rapidly by capitalizing on diastereoselective coupling[14] in advance of anionic oxy-Cope rearrangement.[15]

Synthetic Construction

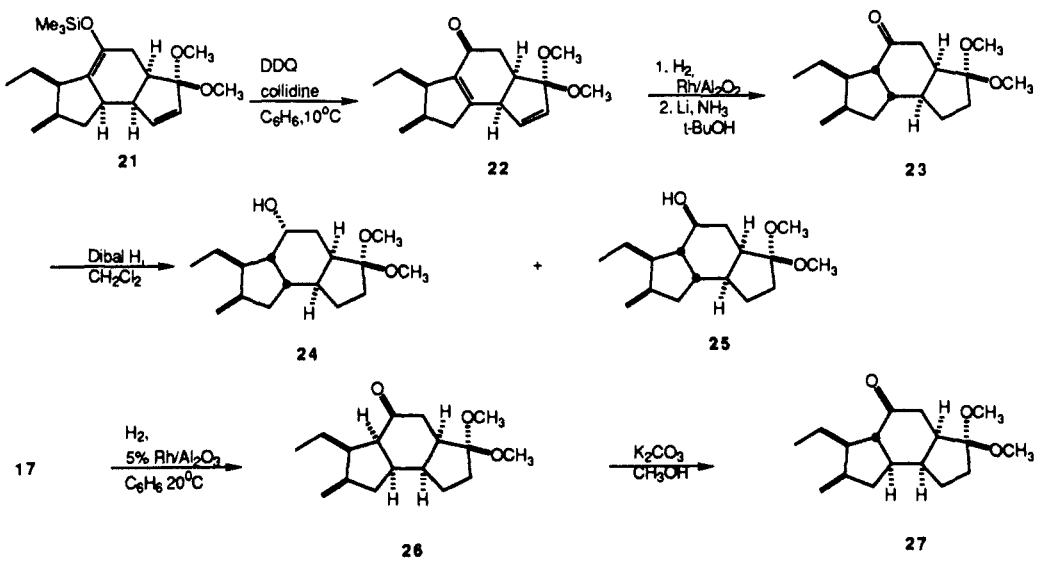
The readily available[16,17] chiral bicyclic ketone (±)-**13** is now recognized to be capable of appreciable levels of double diastereoselection when treated with chiral (racemic) vinyl organocerium reagents.[17] In a directly relevant example, the addition

(2) Aizawa, S.; Akutse, H.; Satomi, T.; Nagatsu, T.; Taguchi, R.; Mogami, M.; Komuro, H.; Seino, A. *J. Antibiot.* **1979**, *32*, 193.
(3) (a) Mackellar, F. A.; Grostic, M.; Olson, E.; Wunk, R.; Branfman, A. R.; Rinehart, K. L. *J. Am. Chem. Soc.* **1971**, *93*, 4993. (b) Duchamp, D. J.; Branfman, A. R.; Button, A. C.; Rinehart, K. L. *Ibid.* **1973**, *95*, 4077.
(4) Rinehart, K. L.; Beck, J. R.; Borders, D. B.; Kinstle, T. H.; Krauss, D. *J. Am. Chem. Soc.* **1963**, *85*, 4038.
(5) Ito, S.; Hirata, Y. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 227, 1813.
(6) Ito, S.; Hirata, Y. *Tetrahedron Lett.* **1972**, *13*, 1181; 1185; 2257.
(7) Boeckman, R. K., Jr.; Napier, J. J.; Thomas, E. W.; Sato, R. I. *J. Org. Chem.* **1983**, *48*, 4152.
(8) Kurth, M. J.; Burns, D. H.; O'Brien, M. J. *J. Org. Chem.* **1984**, *49*, 731.
(9) Whitesell, J. K.; Minton, M. A. *J. Am. Chem. Soc.* **1987**, *109*, 6403.
(10) Mehta, G.; Murthy, A. N.; Reddy, D. S. K. *Tetrahedron Lett.* **1987**, *28*, 1467.
(11) (a) Boeckman, R. K., Jr.; Weidner, C. H.; Perni, R. B.; Napier, J. J. *J. Am. Chem. Soc.* **1989**, *111*, 8036. (b) Paquette, L. A.; Macdonald, D.; Anderson, L. G.; Wright, J. *Ibid.* **1989**, *111*, 8037.
(12) Paquette, L. A.; Romine, J. L.; Lin, H.-S. *Tetrahedron Lett.* **1987**, *28*, 31.
(13) (a) Velluz, L.; Valls, J.; Mathieu, J. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 778. (b) Velluz, L.; Valls, J.; Nomine, G. *Ibid.* **1965**, *4*, 181. (c) Bertz, S. H. *J. Am. Chem. Soc.* **1982**, *104*, 5801.
(14) Paquette, L. A. In *Organic Synthesis: Modern Trends*; Chizhov, O.; Ed.; Blackwell Scientific Publications: Boston, 1988; 1.
(15) For recent reviews, see: (a) Paquette, L. A. *Synlett.* **1990**, 67. (b) Paquette, L. A. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 609.
(16) (a) Jung, M. E.; Hudspeth, J. P. *J. Am. Chem. Soc.* **1978**, *100*, 4309. (b) Jung, M. E.; Hudspeth, J. P. *Ibid.* **1977**, *99*, 5508.
(17) (a) Paquette, L. A.; Learn, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 7873. (b) Paquette, L. A.; Learn, K. S.; Romine, J. L.; Lin, H.-S. *Ibid.* **1988**, *110*, 879.

Scheme II



Scheme III



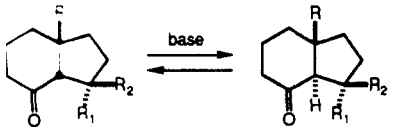
of **14**[18] has been shown to proceed with customary endo stereoselectivity to deliver **15** and **16** in a relative ratio of 92:8 (Scheme II). The ease of chromatographic separation of the two alcohols makes feasible the acquisition of **15** in large amounts.

For structural reasons, [3,3] sigmatropy within **15** must occur via a boat-like transition state. When set in the context of the stereochemistry already predetermined within this alcohol, the oxy-Cope geometry provides for the unequivocal formation of **17**.[17] The configuration of that center α to the carbonyl in **17** is established by virtue of kinetically controlled protonation of the regiospecifically generated enolate anion intermediate from the sterically less demanding direction. When the isomerization reaction mixture is quenched with water, potassium hydroxide is also formed. If the ketonic product is stirred at room temperature in this basic environment for 30 min, epimerization is complete and only **18** is now obtained. Thus, the expenditure of only two synthetic steps is seen to result in elaboration of the intact targeted framework having four stereocenters properly set in trans A/B-locked fashion as demanded by **1**. It remains only to invert stereochemistry at those two carbon atoms that unite rings B and C.

Before proceeding to that phase of the synthesis, additional comment regarding the ready isomerization of **17** to **18** is warranted. Several investigations into the stability of 4-hydrindanones have been reported.[19-21] Clearly apparent from this work is the fact that the thermodynamic preference for cis ring juncture stereochemistry displayed by the parent system (**21a**) can be further enhanced (as in **21b** and **21c**) or almost completely overridden in the opposite direction (e.g., **21d**), depending on the number, location, and stereochemistry of pendant groups (in this case R, R_1, and R_2). Although information about tricyclododecenes and tricyclododecanes related to **17** and **18** is more limited,[22] our extensive knowledge of *cis*-decalin energetics provides an adequate experimental backdrop to assume with reasonable

(18) Barth, W.; Paquette, L. A. *J. Org. Chem.* **1985**, *50*, 2438.

(19) Conia, J. M.; Moinet, G. *Bull. Soc. Chim. Fr.* **1969**, 500.
(20) Lo Cicero, B.; Weisbuch, F.; Dana, G. *J. Org. Chem.* **1981**, *46*, 914.
(21) Kobayashi, M.; Yasuzawa, T.; Kyogoku, Y.; Kido, M.; Kitagawa, I. *Chem. Pharm. Bull. Jpn.* **1982**, *30*, 3431.
(22) Tureck, F.; Hanus, V.; Sedmera, P.; Antropiusova, H.; Mach, K. *Tetrahedron* **1979**, *35*, 1463.



21

a: $R = R_1 = R_2 = H$; 76:24
b: $R = R_1 = H$, $R_2 = CH_3$; 100:0
c: $R_1 = H$, $R = R_2 = CH_3$; 100:0
d: $R = R_2 = H$, $R_1 = CH_3$; 6:94

confidence that like effects should prevail in these tricyclic ketones. Indeed, the thermodynamic bias favoring **18** apparently stems from control exerted by the ethyl and methyl substituents, since they are far less crowded when the ring juncture adopted is trans.

Routinely, **15** and **16** were not purified but rearranged as the mixture. This was made possible because **18** could be selectively crystallized from pentane solution and thereby separated from the minor diastereomer with an overall efficiency of 72%.

In consideration of the ultimate need to introduce a double bond into the six-membered ring of **18**, the issue of ketone carbonyl reduction was viewed as fundamental. Formation of an α-hydroxyl product was thought to best serve our needs because its axial nature would facilitate departure when transformed into a leaving group. Furthermore, recourse to cis elimination was expected to direct olefination to the thermodynamically less-favored disubstituted site. Low-temperature treatment of **18** with Dibal-H in dichloromethane was therefore undertaken in order to capitalize on possible prior coordination of the reducing agent to the β-OCH_3 of the dimethyl ketal. Were this preassociative equilibrium to prove of kinetic significance,[23] the Al–H functionality would be intramolecularly delivered to the β-face of the ketone. Indeed, this reagent proved to be unique in delivering only **19** after acidic hydrolysis. As will be shown subsequently, all other hydride reagents prefer to engage **18** in reduction from its more sterically accessible α-surface.

With ready access to **19**, the stage was now set for stereomodification of the B/C ring juncture. Heating with potassium carbonate in methanol induced essentially quantitative migration of the double bond to the internal site as in **20**. Subsequent dissolving metal reduction resulted in initial trans-locking of the A and C rings, in keeping with anticipated thermodynamic control of this protonation step. Additionally, subsequent kinetic α-protonation of the resulting enolate installed cis B/C stereochemistry. This last phenomenon is again readily understood in steric terms.

Stereochemical Assignments

Four of the six steps deployed in Scheme II serve to establish relative stereochemistry at the six key centers destined to become incorporated into the carbocyclic portion of the antibiotic. As noted above, from the practical point of view, we were also interested in being able to alter stereochemistry at most of these sites for the purpose of analogue production. This goal was amplified upon as shown in Scheme III. The combination of ^1H NMR spectroscopy and X-ray crystallography provided knowledge about the stereochemical course of those reactions of pivotal importance to Schemes II and III.

When the oxy-Cope rearrangement of **15** was carried out at room temperature in the presence of *n*-butyllithium, and chlorotrimethylsilane was subsequently introduced in the absence of aqueous acidic workup conditions, silyl enol ether **21** was obtained. Direct oxidation of this intermediate with DDQ and collidine in cold benzene[24] effected its smooth regiospecific conversion to enone **22**. The four remaining stereogenic centers in **22** were, of course, established during the [3,3]-sigmatropic event and must consequently be identical in relative configuration with their counterparts in **17–19**.

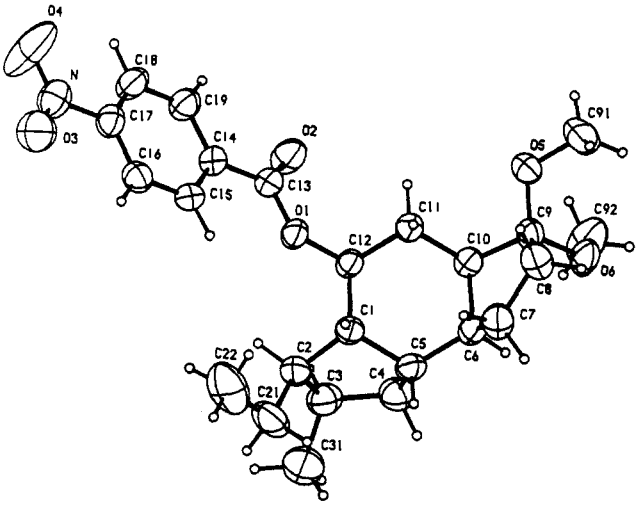
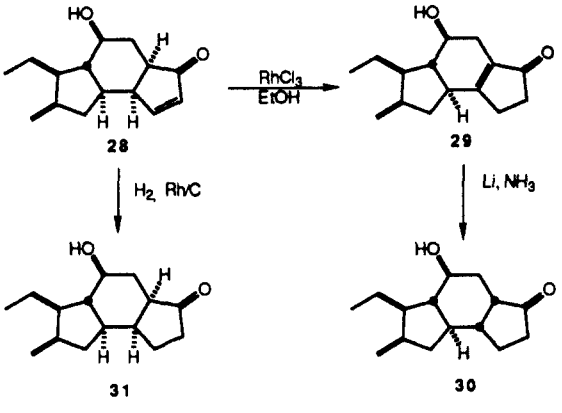


Figure 1. ORTEP drawing of **25**-OPNB.

Scheme IV



Once saturation of the peripheral double bond had been accomplished by means of catalytic hydrogenation, dissolving metal reduction gave rise predominantly to **23**. The IR and ^1H NMR spectra of this tricyclic keto ketal are demonstrably different from those of **26** and **27**, obtained by sequential catalytic reduction and epimerization of **17**. At this point, the two newly introduced tertiary protons in **23** were tentatively given β-configurational status. The resulting cis,anti arrangement comprises an exact parallel to that contained within **12**.

Corroboration of the accuracy of these assignments was achieved by Dibal-H reduction[25] of **23** to a mixture of **24** (52%) and **25** (41%), and conversion of the latter to a nicely crystalline *p*-nitrobenzoate derivative. An ORTEP diagram of **25**-OPNB is depicted in Figure 1.

Ancillary studies involving the reduction of **18** with sodium borohydride afforded a mixture of epimeric alcohols which decomposed partially on attempted chromatographic separation. Direct recourse to hydrolysis of the mixture with 3 N hydrochloric acid in ether gave in 92% overall yield the keto alcohols **19** and **28** in a 1:3 ratio. Use of the bulkier, L-Selectride reagent gave exclusively the equatorial alcohol, thereby permitting extension to the β-hydroxyl series without need for extensive chromatographic purification.

Compound **28** was converted to ketone **29** with rhodium trichloride in hot ethanol[26] and thence via lithium in liquid ammonia

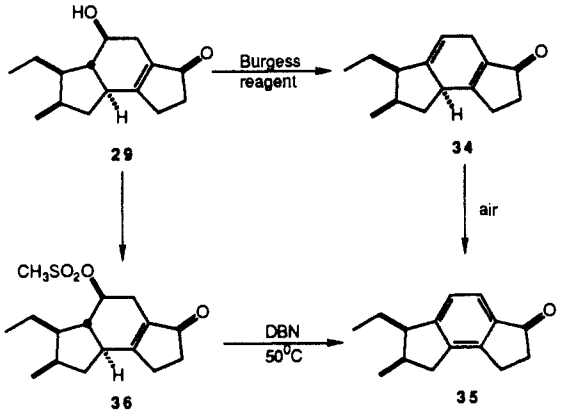
(23) Examination of molecular models of **18** reveals that adoption by the six-membered ring of a boat conformation causes the β-methoxyl oxygen to extend directly over the carbonyl group. For an alternative explanation that is equally consistent with these results, see: Wiberg, K. B.; LePage, T. J. *J. Am. Chem. Soc.* **1988**, *110*, 6642.

(24) Fleming, I.; Paterson, I. *Synthesis* **1979**, 736.

(25) The change in solvent from toluene to dichloromethane serves to increase the relative proportion of the β alcohol.

(26) (a) Andrieux, J.; Barton, D. H. R.; Patin, H. *J. Chem. Soc., Perkin Trans. 1* **1977**, 359. (b) Grieco, P. A.; Nishizawa, M.; Marinovic, N.; Ehmann, W. J. *J. Am. Chem. Soc.* **1976**, *98*, 7102. (c) Grieco, P. A.; Marinovic, N. *Tetrahedron Lett.* **1978**, 2545.

Scheme V

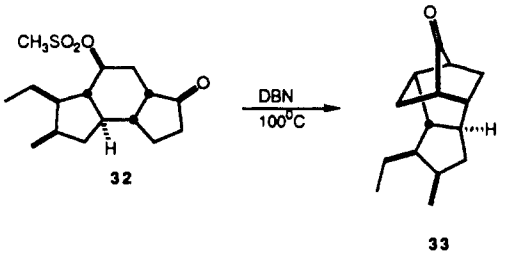


reduction to **30** (Scheme IV). In light of our earlier experiences with this process, we were not apprehensive in assigning trans,-anti,cis stereochemistry to **30**. Its ^1H NMR spectrum is entirely consistent with this conclusion. That the chiral centers newly introduced into **30** are indeed β was confirmed by the hydrogenation of **28** to **31**, a quite different isomer.

From the knowledge gained above, we can confidently assign stereochemistry to all of the remaining decahydro-*as*-indacene intermediates. Their number and variety bode well for the accessing isomers of ikarugamycin should this be desired.

Dehydration Studies

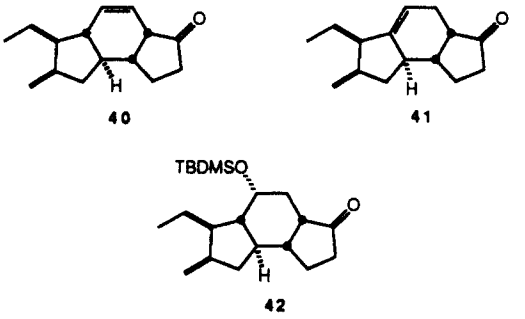
It is instructive to call attention to the interrelationship of configuration and reactivity within this series of molecules, particularly as it relates to chemistry at the hydroxyl-bearing carbon. For example, activation of this center in **30** by conversion to mesylate **32** followed by attempted E_2 elimination served only to produce **33** via 1,5-displacement. In this instance, the ideal stereoalignment that can be realized between the enolate anion and electrophilic center greatly facilitates C–C bond formation.



The presence of an intraring double bond as in **29** denies an opportunity to these same two atoms to be proximal. Not unexpectedly, however, dehydration of this intermediate eventuates in the ultimate aromatization of ring B, an undesirable occurrence. When **29** was heated with the Burgess reagent,[27] diene **34** was obtained in 66% yield, with dehydration occurring in the thermodynamic direction (Scheme V). The formation of Saytzeff product is viewed as the combined result of the cis relationship of the reacting centers and the greater stability offered by trisubstitution. On standing in air, **34** experiences gradual oxidation to give **35**. This process can be hastened simply by warming mesylate **36** with DBN to 50 °C for 5 h. Under these conditions, **35** is produced with 88% efficiency.

As shown in Scheme VI, conversion of **23** to enol phosphoramidate **37** can be achieved with exceptionally good regioselectivity.[28] Its reduction with lithium and *tert*-butyl alcohol in ethylamine[29] at −15 °C afforded **38** in 94% overall yield. This ketal could be smoothly hydrolyzed to the β,γ-unsaturated enone **39**. The important point here is that even though double bond regiochemistry is now conveniently and properly set, the harsh reduction conditions are not likely to prove serviceable in a more elaborate setting later in the sequence.

In order to circumvent potentially troublesome issues such as this, attention was focused on axial alcohol **12**. Indeed, the application of standard Burgess conditions to **12** gave **40** admixed with lesser amounts of **41** in 78% yield. The workability of this process augured well for its successful adaptation at a more advanced stage. Accordingly, **12** was transformed into **42** as a prelude to continued development of the synthetic pathway toward **1**.[30] The presence of the silyl ether functionality was intended to serve as a preventitive measure against possible migration of the double bond if introduced early.



Conclusion

A highly efficient six-step route to racemic **12** is described. The convergent carbonyl regenerative scheme **13** → **15** → **18** proceeds with impressive stereoselectivity. The several stereocenters in this key intermediate are shown to be capable of substantive purposeful variation. The serviceability of **18** as a precursor of **40** has also been demonstrated. Indeed, the synthetic strategy outlined above is shown subsequently to be the underlying foundation of a de novo synthesis of natural (+)-ikarugamycin.[30] Furthermore, the present findings should be helpful in designing further technology for the preparation of numerous other decahydro-*as*-indacene derivatives on demand.

The oxy-Cope protocol utilized herein offers the option for kinetic resolution. The sole requirement is that one of the starting materials be available in optically pure (or highly enantiomerically enriched) form. While this is certainly within the realm of feasibility, we have not pursued this tactic because of a desire to examine the level of enantiomer discrimination in a very different context. The overwhelming success realized in enantioselection at this particular juncture[29] dispelled all notions of returning to resolve either **13** or **14**.

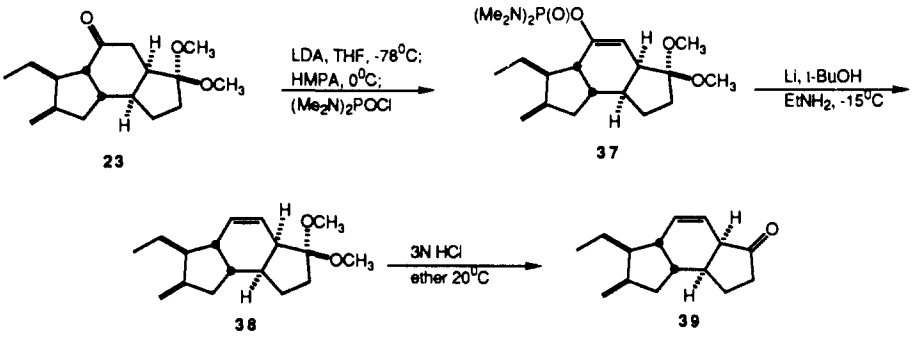
Experimental Section

Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 1320 spectrophotometer. ^1H NMR spectra were recorded at 300 MHz and the ^{13}C NMR data obtained at either 75 or 20 MHz as indicated. Mass spectra were measured on a Kratos MS-30 instrument by Mr. Dick Weisenberger at The Ohio State University Chemical Instrumentation Center. Elemental analyses were performed at the Scandinavian Microanalytical Laboratory, Herlev, Denmark. All MPLC separations were conducted on Merck Lobar columns (Lichroprep Si-60) with the help of a Fluid Metering INC pump and a Waters Associates Model R403 differential refractometer detector. All reactions were performed under an inert atmosphere (nitrogen or argon) unless otherwise indicated. Solvents were reagent grade and dried prior to use.

(3a*R,5a*S**,6*R**,7*R**,8a*R**,8b*S**)-6-Ethyl-3a,4,5a,6,7,8,8a,8b-octahydro-7-methyl-*as*-indacene-3,5-dione 3-(Dimethyl acetal) (18). A. By Anionic Oxy-Cope Rearrangement.** Potassium hydride (236 mg, 5.92 mmol) was preweighed into a 100-mL round-bottomed flask under argon. Tetrahydrofuran (40 mL) was added and the solution was cooled to 0 °C. Alcohol **15**[17] (1.30 g, 4.68 mmol) dissolved in 20 mL of the same solvent was slowly added and the reaction mixture was stirred at room temperature for 2.5 h. The solution was recooled to 0 °C and 10 mL of water was added. After 30 min of continued agitation and extraction

(27) Burgess, E. M.; Penton, H. R., Jr.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26.
(28) Compare ref 9 for comparable use of enol phosphonate reduction.
(29) Ireland, R. E.; Thompson, W. J.; Srouji, G. H.; Etter, R. *J. Org. Chem.* **1981**, *46*, 4863.
(30) Paquette, L. A.; Macdonald, D.; Anderson, L. G. *J. Am. Chem. Soc.*, following paper in this issue.

Scheme VI



with ether (3 × 40 mL), the combined organic phases were washed with brine (2 × 40 mL) and dried. Concentration gave a residue which was crystallized from pentane to give 832 mg (64%) of **18** as white needles. The mother liquor was subjected to MPLC on Florisil (elution with 7% ethyl acetate in petroleum ether) to recover an additional 104 mg of **18** (total yield, 72%): mp 85–87.5 °C; IR (KBr, cm^{-1}) 2960, 2940, 2910, 2870, 1720, 1460, 1365, 1340, 1150, 1040, 985; ^1H NMR (300 MHz, C_6D_6) δ 5.92 (dd, J = 1.9, 6.3 Hz, 1 H), 5.67 (dd, J = 6.1, 2.6 Hz, 1 H), 2.97 (s, 3 H), 2.95 (s, 3 H), 2.85–2.78 (m, 1 H), 2.58 (dd, J = 17.3, 2.8 Hz, 1 H), 2.45–2.39 (m, 1 H), 2.28–2.19 (m, 1 H), 2.10 (dd, J = 17.3, 6.6 Hz, 1 H), 1.98–1.86 (m, 2 H), 1.61–1.51 (m, 1 H), 1.48–1.39 (m, 2 H), 1.22–1.10 (m, 1 H), 1.03 (t, J = 7.2 Hz, 3 H), 0.83 (d, J = 7.1 Hz, 3 H), 0.79 (t, J = 10.5 Hz, 1 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 209.29, 134.79, 133.09, 112.43, 55.56, 49.13, 48.50, 45.16, 43.63, 43.08, 39.68, 38.08, 36.38, 36.14, 24.14, 15.98, 12.39; MS m/z (M^+) calcd 278.1882, obsd 278.1843.

B. By Epimerization of 17. Ketone **17**[17] (87 mg, 0.31 mmol) and 6.5 mg of potassium carbonate were dissolved in 8 mL of methanol. The reaction mixture was stirred at 25 °C for 48 h. After removal of the solvent by rotary evaporation, the residue was dissolved in ethyl acetate, filtered, washed with brine, and dried. Concentration gave 68 mg (78%) of **18**, spectroscopically identical with the material prepared in A.

(3a*R,5*R**,5a*S**,6*R**,7*R**,8a*R**,8b*S**)-6-Ethyl-4,5,5a,6,7,8,8a,8b-octahydro-5-hydroxy-7-methyl-*as*-indacen-3(3a*H*)-one (19).** Ketone **18** (535.5 mg, 1.9 mmol) was dissolved in dichloromethane (25 mL) under an argon atmosphere. The solution was cooled to −78 °C and 2.5 mL of diisobutylaluminum hydride (1 M in hexanes) was added dropwise with stirring for 3 h. The reaction mixture was quenched by the addition of 1 mL of 3 N hydrochloric acid and allowed to warm to room temperature. The solvent was removed in vacuo, and the residue was partitioned between 3 N hydrochloric acid (3 mL) and ether (3 mL). After the mixture was stirred at room temperature for 12 h, the aqueous phase was separated and extracted with ether. The combined organic layers were washed with saturated sodium bicarbonate solution and brine prior to drying. Concentration gave 426 mg (94.5%) of **19** as a colorless crystalline solid: mp 153–154 °C (from ether); IR (KBr, cm^{-1}) 3445, 2950, 2880, 1710, 1455, 1355, 1335, 1185, 1085, 1025, 965, 795; ^1H NMR (300 MHz, C_6D_6) δ 6.94 (m, 1 H), 6.05 (d, J = 5.9 Hz, 1 H), 3.41 (br s, 1 H), 2.56 (br s, 1 H), 2.04–1.92 (m, 4 H), 1.68–1.52 (m, 3 H), 1.38–1.23 (m, 4 H), 0.91 (t, J = 7.2 Hz, 3 H), 0.79–0.75 (m, 1 H), 0.70 (d, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 211.36, 161.59, 135.23, 73.14, 49.86, 48.44, 45.41, 43.15, 41.30, 34.72, 33.36, 32.97, 22.20, 17.30, 13.27; MS m/z (M^+) calcd 234.1620, obsd 234.1616. Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.77; H, 9.54.

(5*R,5a*S**,6*R**,7*R*,8a*S**)-6-Ethyl-1,4,5,5a,6,7,8,8a-octahydro-5-hydroxy-7-methyl-*as*-indacen-3(2*H*)-one (20).** Enone **19** (563 mg, 2.41 mmol) was dissolved in methanol (35 mL) and 34 mg (0.26 mmol) of potassium carbonate was added. The solution was heated to 60 °C with vigorous stirring for 2.5 h. After the solution was cooled to room temperature, the solvent was removed by rotary evaporation, and the residue was partitioned between ethyl acetate (60 mL) and water (20 mL). The aqueous layer was extracted with ethyl acetate, and the combined organic layers were washed with brine, dried, and concentrated. Chromatography on Florisil (elution with 45% ethyl acetate in petroleum ether) gave 550 mg (98%) of **20** as a colorless oil: IR (neat, cm^{-1}) 3400, 2960, 2920, 2870, 1730, 1685, 1635, 1440, 1400, 1380, 1270, 1240, 1040; ^1H NMR (300 MHz, C_6D_6) δ 3.72 (q, J = 4.9 Hz, 1 H), 2.64 (q, J = 8.3 Hz, 2 H), 2.33 (s, 2 H), 2.13–2.11 (m, 2 H), 2.09–1.77 (m, 4 H), 1.42–1.15 (m, 5 H), 0.88 (t, J = 7.3 Hz, 3 H), 0.73 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 207.45, 175.01, 134.78, 68.69, 49.15, 47.38, 39.25, 37.61, 35.06, 34.30, 28.02, 27.38, 22.83, 14.84, 12.88; MS m/z (M^+) calcd 234.1620, obsd 234.1628.

(3a*R,5*S**,5a*R**,6*R**,7*S**,8a*S**,8b*S**)-6-Ethyldecahydro-5-hydroxy-7-methyl-*as*-indacen-3(2*H*)-one (12).** Enone **20** (59.1 mg, 0.25 mmol) dissolved in 1 mL of tetrahydrofuran was added dropwise over 10 min to a solution of lithium metal (4.7 mg, 0.67 mmol) in 6 mL of ammonia at −78 °C. After being stirred for an additional 35 min, the reaction mixture was quenched by the addition of saturated ammonium chloride solution (1 mL). Ether (30 mL) was added, and the ammonia was allowed to evaporate. The residue was diluted with ether, washed with brine, dried, and concentrated. Purification by MPLC on Florisil (elution with 37% ethyl acetate in petroleum ether) gave 49.7 mg (83%) of ketone **12** as a white solid: mp 76–79 °C (from ether); IR (neat, cm^{-1}) 3420, 2950, 2920, 2860, 1730, 1455, 1405, 1145, 1120, 720, 695; ^1H NMR (300 MHz, C_6D_6) δ 3.25 (br s, 1 H), 2.03–1.82 (m, 3 H), 1.78–1.22 (series of m, 14 H), 0.92 (t, J = 7.3 Hz, 3 H), 0.77 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 218.69, 69.79, 49.29, 47.95, 46.61, 39.83, 38.36, 37.31, 34.93, 33.38, 30.21, 25.42, 22.60, 15.88, 13.27; MS m/z (M^+) calcd 236.1776, obsd 236.1772.

(3a*R,6*R**,7*R**,8b*R**)-6-Ethyl-3a,4,6,7,8,8b-hexahydro-7-methyl-*as*-indacene-3,5-dione 3-(Dimethyl acetal) (22).** To a magnetically stirred solution of **15** (250 mg, 0.91 mmol), dry TMEDA (0.5 mL), and triphenylmethane (1.5 mg), in dry tetrahydrofuran (15 mL) at −20 °C under argon, was added dropwise *n*-butyllithium in hexane (0.71 mL of 1.55 M, 1.10 mmol) to generate a pink color. The reaction mixture was allowed to warm to room temperature, stirred for 11 h, and recooled to −40 °C. Chlorotrimethylsilane (171 μL, 1.35 mmol) was introduced, and the solution was returned to 20 °C. After solvent evaporation, the residue was dissolved in 60 mL of ether–petroleum ether (1:1) and washed with 5% sodium bicarbonate solution (15 mL) and brine (15 mL). The organic layer was dried and concentrated in vacuo at room temperature to give **21** as a pale yellow oil that was used directly.

To a magnetically stirred solution of DDQ (510 mg, 2.25 mmol) in anhydrous benzene at 4 °C under argon was added dropwise dry collidine (0.32 mL, 2.43 mmol). After 30 min at 20 °C, this solution was cooled to 4 °C and a solution of **21** in dry benzene (2 mL) was introduced dropwise. After 1 h at 4 °C, the mixture was filtered through a short pad of neutral alumina (grade III, elution with 20% ethyl acetate in petroleum ether). The colorless filtrate was concentrated in vacuo, and the residue was purified by MPLC on neutral alumina (grade III, elution with 5% ethyl acetate in petroleum ether) to give 112 mg (45% overall) of dienone **22** as a colorless solid: mp 62.7–63.2 °C (from petroleum ether); IR (KBr, cm^{-1}) 2955, 2930, 2875, 2830, 1670, 1380, 1350, 1155, 1085, 1070, 1045, 992, 980; ^1H NMR (300 MHz, C_6D_6) δ 5.79 (dd, J = 6.0, 1.8 Hz, 1 H), 5.68 (dd, J = 6.0, 2.8 Hz, 1 H), 3.03 (s, 3 H), 2.96 (s, 3 H), 3.10–2.90 (m, 2 H), 2.75 (dd, J = 16.5, 4.0 Hz, 1 H), 2.55 (td, J = 7.0, 4.0 Hz, 1 H), 2.28 (dd, J = 16.5, 7.0 Hz, 1 H), 2.24–2.10 (m, 1 H), 2.03–1.80 (m, 2 H), 1.80–1.65 (m, 1 H), 1.60–1.45 (m, 1 H), 0.90 (t, J = 7.5 Hz, 3 H), 0.90 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 193.64, 158.87, 140.16, 135.02, 132.58, 111.50, 49.53, 46.22, 45.43, 45.02, 42.64, 37.13, 36.22, 21.72, 15.02, 11.85 (one carbon not observed); MS m/z (M^+) calcd 276.1730, obsd 276.1728. Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 74.02; H, 8.78.

(3a*R,6*R**,7*R**,8b*S**)-6-Ethyl-1,2,3a,4,6,7,8,8b-octahydro-7-methyl-*as*-indacene-3,5-dione 3-(Dimethyl acetal).** A magnetically stirred suspension of 5% rhodium on alumina (24 mg) and dienone **22** (25.6 mg, 0.093 mmol) in benzene (15 mL) was hydrogenated for 50 min. Filtration through Celite and evaporation of the filtrate gave pure dihydro derivative (26.0 mg, 100%) as a colorless solid: mp 67.8–68.2 °C (from petroleum ether); IR (KBr, cm^{-1}) 2955, 2930, 2875, 2825, 1670, 1460, 1387, 1125, 1043; ^1H NMR (300 MHz, C_6D_6) δ 3.05–2.88 (m, 1 H), 2.93 (s, 3 H), 2.90 (s, 3 H), 2.58–2.43 (m, 2 H), 2.40–2.28 (m, 2 H), 2.28–2.10 (m, 1 H), 2.02–1.30 (series of m, 8 H), 0.92 (t, J = 7.5 Hz, 3 H), 0.89 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 194.22, 161.61, 141.98, 110.72, 49.42, 47.98, 46.43, 45.52, 42.43, 39.59, 37.61, 36.12, 33.99, 26.71, 21.67, 15.18, 12.40; MS m/z (M^+) calcd 278.1880, obsd 278.1902. Anal. Calcd for $C_{17}H_{26}O_2$: C, 73.34; H, 9.41. Found: C, 73.45; H, 9.43.

(3a*R,5a*S**,6*R**,7*R**,8a*S**,8b*R**)-6-Ethyldecahydro-7-methyl-*as*-indacene-3,5-dione 3-(Dimethyl acetal) (23).** To a magnetically stirred solution of lithium (8.9 mg, 1.28 mmol) in liquid ammonia (15 mL) at −78 °C under argon was added dropwise a solution of the dihydro derivative of **22** (57.0 mg, 0.205 mmol) and *tert*-butyl alcohol (15 μL, 0.1 mmol) in 2 mL of anhydrous tetrahydrofuran. The resulting mixture was stirred at −78 °C for an additional hour and then allowed to reflux for 75 min. Excess isoprene and solid ammonium chloride (15 mg) were introduced and the ammonia was allowed to evaporate. After customary extractive workup with ether, the residue was subjected to MPLC on silica gel (elution with 8% ethyl acetate in petroleum ether). There was isolated 41.1 mg (72%) of **23** and 14.0 mg (24%) of the cis,syn,cis ketone. For **23**: colorless oil; IR (neat, cm^{-1}) 2958, 2932, 2870, 1710, 1122, 1048, 1040; ^1H NMR (300 MHz, C_6D_6) δ 2.99 (s, 3 H), 2.93 (s, 3 H), 2.52–2.27 (m, 4 H), 2.23–2.12 (m, 2 H), 2.08–1.95 (m, 1 H), 1.90–1.73 (m, 3 H), 1.65–1.50 (m, 2 H), 1.38–1.18 (m, 4 H), 0.91 (t, J = 7.4 Hz, 3 H), 0.68 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 212.67, 111.42, 53.96, 49.31, 48.57, 45.72, 45.18, 42.32, 40.66, 40.46, 37.95, 34.01, 31.74, 26.91, 22.89, 15.18, 12.94; MS m/z (M^+) calcd 280.2038, obsd 280.2022. For the cis,syn,cis isomer: colorless oil; IR (neat, cm^{-1}) 2955, 2905, 2870, 1703, 1148, 1120, 1048; ^1H NMR (300 MHz, C_6D_6) δ 2.96 (s, 3 H), 2.94 (s, 3 H), 2.79–2.64 (m, 1 H), 2.39–2.19 (m, 4 H), 2.11–1.74 (m, 6 H), 1.65 (dt, J = 13.3, 8.0 Hz, 1 H), 1.54–1.18 (m, 4 H), 1.10 (t, J = 7.1 Hz, 3 H), 0.84 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 213.03, 111.19, 52.74, 49.93, 49.12, 48.94, 44.36, 41.37, 40.17, 37.19, 36.57, 34.79, 32.42, 25.37, 20.54, 18.62, 14.63; MS m/z (M^+) calcd 280.2038, obsd 280.2033.

(3a*R,5a*R**,6*R**,7*R**,8a*S**,8b*S**)-6-Ethyl-1,2,4,5,5a,6,7,8,8a,8b-decahydro-5(*S**)- and -5(*R**)-hydroxy-6-methyl-*as*-indacen-3(3a*H*)-one 3-(Dimethyl acetal) (24 and 25).** To a magnetically stirred solution of ketone **23** (50.0 mg, 0.178 mmol) in 10 mL of dry dichloromethane at −78 °C under argon was added dropwise 0.232 mL of Dibal-H solution (1 M in hexane, 0.232 mmol). The reaction mixture was stirred at −78 °C for 1 h and then quenched at −78 °C with dry methanol (3 mL). The mixture was allowed to warm to room temperature and stirred for an additional hour prior to being passed through a short pad of Celite. The filtrate was concentrated in vacuo, and the residue was subjected to MPLC on silica gel (elution with 40% ethyl acetate in petroleum ether). There was obtained 26.3 mg (52%) of α-alcohol **24** and 20.7 mg (41%) of β-alcohol **25**. For **24**: colorless oil; IR (neat, cm^{-1}) 3480 (br), 2950, 2930, 2870, 2825, 1460, 1450, 1143, 1130, 1118, 1047; ^1H NMR (300 MHz, C_6D_6) δ 3.93 −3.80 (m, 1 H), 3.13 (s, 3 H), 3.11 (s, 3 H), 2.43 (br q, J = 9.2 Hz, 1 H), 2.26–2.04 (m, 2 H), 1.97–1.68 (m, 7 H), 1.60 (ddd, J = 12.4, 7.9, 1.7 Hz, 1 H), 1.50 (td, J = 10.2, 4.8 Hz, 1 H), 1.44–1.08 (m, 4 H), 0.96 (br s, 1 H), 0.92 (t, J = 7.3 Hz, 3 H), 0.75 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 111.66, 67.36, 49.12, 48.94, 46.85, 44.94, 41.79, 41.40, 41.18, 38.24, 34.45, 33.28, 30.29, 27.93, 22.94, 15.04, 13.11; MS m/z ($M^+ - CH_3OH$) calcd 250.1932, obsd 250.1928. For **25**: colorless oil; IR (neat, cm^{-1}) 3420 (br), 2958, 2938, 2905, 2870, 2826, 1460, 1322, 1145, 1115, 1045; ^1H NMR (300 MHz, C_6D_6) δ 3.27 −3.18 (m, 1 H), 3.11 (s, 3 H), 3.07 (s, 3 H), 2.23–1.94 (m, 4 H), 1.94–1.49 (m, 6 H), 1.49–1.12 (m, 7 H), 0.96 (t, J = 7.3 Hz, 3 H), 0.85 (d, J = 7.2 Hz, 3 H); MS m/z (M^+) calcd 282.2204, obsd 282.2218.

To a stirred solution of **25** (19.4 mg, 0.069 mmol) and 8.4 μL of dry pyridine in dry benzene (2 mL) under argon was added 14.0 mg (0.075 mmol) of *p*-nitrobenzoyl chloride, and the mixture was stirred for 40 h, filtered through a short pad of neutral alumina (grade III), and evaporated. The residue was purified by MPLC on silica gel (elution with 5% ethyl acetate in petroleum ether) to give 15.5 mg (52%) of **25**-OPNB as yellowish needles, mp 116.0–116.7 °C (from petroleum ether).

X-ray Crystallographic Analysis of 25-OPNB. A prismatic colorless crystal of **25**-OPNB approximate dimensions 0.25 × 0.40 × 0.55 mm was mounted on the tip of a thin glass fiber. Both X-ray examination of the crystal and data collection were at room temperature by using an Enraf-Nonius CAD4 diffractometer with graphite-monochromated Mo Kα radiation. At room temperature the cell parameters and standard deviations are determined by least-squares fitting from 24 reflections, well distributed in reciprocal space and lying in the 2θ range between 25–30°. Intensity data were collected by ω − 2θ scan mode with 2θ range between 4° and 45°. A total of 4033 independent reflections was measured with 2130 unique data having $I > 3.0\sigma(I)$. Details of the data collection are given in Table I (Supplementary Material). The data were corrected for Lorentz and polarization effects and also absorption.

(3a*R,5a*R**,6*R**,7*R**,8a*R**,8b*R**)-6-Ethyldecahydro-7-methyl-*as*-indacene-3,5-dione 3-(Dimethyl acetal) (26).** A solution of **17** (46 mg, 0.166 mmol) in benzene (15 mL) was treated with 5% rhodium on alumina (46 mg) and hydrogenated at room temperature for 3 h. Filtration of the mixture through Celite and solvent evaporation left an oil; purification of which by MPLC on activity III neutral alumina (elution with 5% ethyl acetate in petroleum ether) gave **26** (35 mg, 75%) as a colorless oil: IR (neat, cm^{-1}) 2955, 2905, 2870, 1703, 1148, 1120, 1048; ^1H NMR (300 MHz, C_6D_6) δ 2.96 (s, 3 H), 2.94 (s, 3 H), 2.79–2.64 (m, 1 H), 2.39–2.19 (m, 4 H), 2.11–1.74 (m, 6 H), 1.65 (dt, J = 13.3, 8.0 Hz, 1 H), 1.54–1.18 (m, 4 H), 1.10 (t, J = 7.1 Hz, 3 H), 0.84 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 213.03, 111.19, 52.74, 49.93, 49.12, 48.94, 44.36, 41.37, 40.17, 37.19, 36.57, 34.79, 32.42, 25.37, 20.54, 18.62, 14.63; MS m/z (M^+) calcd 280.2038, obsd 280.2034.

(3a*R,5a*S**,6*R**,7*R**,8a*R**,8b*R**)-6-Ethyldecahydro-7-methyl-*as*-indacene-3,5-dione 3-(Dimethyl acetal) (27).** To a magnetically stirred solution of **26** (35 mg, 0.125 mmol) in dry methanol (5 mL) at room temperature under argon was added dry, powdered potassium carbonate (19 mg, 0.14 mmol). This mixture was stirred for 24 h, excess methanol was removed in vacuo, and the residue was treated with ether and filtered through a small pad of activity III neutral alumina. After evaporation of the filtrate, the residue was purified by MPLC (silica gel, elution with 13% ethyl acetate in petroleum ether) to give 32 mg (91%) of **27** as a colorless solid: mp 69.5–70.1 °C (from petroleum ether); IR (KBr, cm^{-1}) 2950, 2930, 2865, 2820, 1710, 1460, 1250, 1150, 1110, 1090, 1046; ^1H NMR (300 MHz, C_6D_6) δ 2.95 (s, 6 H), 2.42–2.27 (m, 3 H), 2.19–2.05 (m, 1 H), 2.04–1.80 (m, 4 H), 1.77–1.49 (m, 4 H), 1.48–1.20 (m, 3 H), 1.00 (t, J = 7.4 Hz, 3 H), 0.79 (d, J = 7.1 Hz, 3 H), 0.76–0.68 (m, 1 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 209.44, 112.18, 54.28, 49.80, 48.39, 48.13, 41.17, 41.08, 38.50, 37.87, 32.78, 30.84, 22.99, 19.66, 17.32, 13.24 (one carbon not observed); MS m/z (M^+) calcd 280.2038, obsd 280.2036. Anal. Calcd for $C_{17}H_{28}O_3$: C, 72.82; H, 10.06. Found: C, 72.85; H, 10.17.

(3a*R,5*S**,5a*S**,6*R**,7*R**,8a*R**,8b*S**)-6-Ethyl-4,5,5a,6,7,8,8a,8b-octahydro-5-hydroxy-7-methyl-*as*-indacen-3(3a*H*)-one (28).** Ketone **18** (100 mg, 0.35 mmol) was dissolved in tetrahydrofuran and cooled to −78 °C under nitrogen. L-Selectride (0.35 mL, 1 M in tetrahydrofuran) was added dropwise, and the solution was stirred for 1 h. Methanol (1 mL) was added, and the solution was warmed to room temperature. The solvent was removed in vacuo, and the residue was partitioned between methylene chloride (4 mL) and water (1 mL). The aqueous phase was extracted with methylene chloride and the combined organic layers were washed with brine. Concentration gave an oily residue which was partitioned between 3 N hydrochloric acid (3 mL) and ether (3 mL). After being stirred at room temperature for 12 h, the aqueous phase was extracted with ether, and the combined organic phases were washed with saturated sodium bicarbonate solution and brine prior to drying. Concentration gave an oil which was crystallized from ether to give 67.3 mg (80%) of **28** as a white solid: mp 112–113.5 °C (from ether); IR (KBr, cm^{-1}) 3470, 2960, 2935, 2870, 1710, 1465, 1375, 1315, 1240, 1190, 1085, 1055, 900, 830; ^1H NMR (300 MHz, C_6D_6) δ 6.89 (dd, J = 5.9, 2.6 Hz, 1 H), 5.98 (dd, J = 5.9, 2.1 Hz, 1 H), 3.74 (s, 1 H), 2.63 (m, 1 H), 2.21–2.12 (m, 2 H), 2.02–1.94 (m, 2 H), 1.69–1.51 (m, 4 H), 1.08 (m, 2 H), 0.79 (t, J = 7.3 Hz, 3 H), 0.70 (d, J = 7.1 Hz, 3 H), 0.69–0.64 (m, 1 H), 0.58 (d, J = 2.9 Hz, 1 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 209.97, 161.32, 134.41, 65.42, 46.04, 44.23, 43.58, 41.67, 36.30, 34.91, 34.10, 32.65, 22.28, 17.09, 12.93; MS m/z (M^+) calcd 234.1620, obsd 234.1619. Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.95; H, 9.51.

(5*S,5a*S**,6*R**,7*R**,8a*S**)-6-Ethyl-1,4,5,5a,6,7,8,8a-octahydro-5-hydroxy-7-methyl-*as*-indacen-3(2*H*)-one (29).** Enone **28** (56.8 mg, 0.25 mmol) was placed in a 10-mL round-bottomed flask fitted with a reflux condenser and dissolved in 3 mL of absolute ethanol. Rhodium trichloride trihydrate (17 mg, 0.07 mmol) was added, and the flask was evacuated and flushed thoroughly (3×) with argon. After being heated at reflux for 3 h, the reaction mixture was cooled to room temperature, poured into water (1 mL), and extracted with ether (3 × 25 mL). The combined organic layers were washed with brine (2 × 10 mL) and dried. Concentration gave a brown residue which was filtered through Florisil (5 g, elution with 47% ethyl acetate in petroleum ether) to give 49.4 mg (87%) of **29** as a white solid: mp 97–97.5 °C (from ether); IR (neat, cm^{-1}) 3420, 2960, 2920, 2870, 1680, 1640, 1450, 1390, 1380, 1260, 1080, 1040, 1010; ^1H NMR (300 MHz, C_6D_6) δ 3.81–3.31 (m, 1 H), 2.46–2.34 (m, 2 H), 2.19–1.97 (m, 6 H), 1.76–1.64 (m, 3 H), 1.52–1.28 (m, 4 H), 0.95 (t, J = 7.4 Hz, 3 H), 0.76 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 206.72, 174.88, 135.49, 67.45, 47.45, 43.36, 40.88, 38.10, 35.25, 35.16, 27.49, 27.83, 24.03, 14.90, 13.16; MS m/z (M^+) calcd 234.1620, obsd 234.1622. Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.73; H, 9.47.

(3a*R,5*R**,5a*R**,7*S**,8a*S**,8b*S**)-6-Ethyldecahydro-5-hydroxy-7-methyl-*as*-indacen-3(2*H*)-one (30).** Enone **29** (242.4 mg, 1.04 mmol) dissolved in 1 mL of tetrahydrofuran was added dropwise over 20 min to a solution of lithium metal (18 mg, 2.6 mmol) dissolved in 20 mL of ammonia at −78 °C. After being stirred for an additional 45 min, the reaction mixture was quenched by the addition of saturated ammonium chloride solution (2 mL). Ether (50 mL) was added, and the ammonia

was allowed to evaporate. The residue was diluted with ether, washed with brine, dried, and concentrated. Purification by MPLC on Florisil (elution with 30% ethyl acetate in petroleum ether) gave 175 mg (72%) of **30** as a white solid: mp 96–98 °C (from ether); IR (CH_2Cl_2, cm^{-1}) 3600, 2960, 2930, 2870, 1725, 1450, 1380, 1140, 1050; ^1H NMR (300 MHz, C_6D_6) δ 3.65 (s, 1 H), 2.27–1.74 (m, 7 H), 1.62–1.10 (series of m, 10 H), 0.90 (t, J = 7.3 Hz, 3 H), 0.68 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 219.95, 66.20, 46.69, 46.06, 4474, 40.85, 39.89, 36.44, 34.46, 34.13, 30.01, 24.50, 22.68, 14.78, 13.04; MS m/z (M^+) calcd 236.1776, obsd 236.1771. Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.23. Found: C, 76.21; H, 10.26.

(3a*S,5*R**,5a*R**,7*S**,8a*S**,8b*R**)-6-Ethyldecahydro-5-hydroxy-7-methyl-*as*-indacen-3(2*H*)-one (31).** Enone **28** (50 mg, 0.21 mmol) was dissolved in 5 mL of ethyl acetate and 10 mg of 5% rhodium on carbon was added. The reaction mixture was flushed with hydrogen and stirred at atmospheric pressure for 1.5 h. The catalyst was removed by filtration through a cotton plug, and the mother liquor was concentrated. Washing with pentane gave 51 mg (99%) of **31** as a white solid: mp 120.5–121 °C (from ether); IR (KBr, cm^{-1}) 3500, 2960, 2940, 2935, 2900, 2870, 1740, 1455, 1400, 1375, 1210, 1150, 1100, 1070; ^1H NMR (300 MHz, C_6D_6) δ 3.68 (s, 1 H), 2.44 (m, 1 H), 2.17–1.54 (m, 8 H), 1.37–1.03 (m, 5 H), 0.94 (t, J = 7.3 Hz, 3 H), 0.81 (d, J = 7.1 Hz, 3 H), 0.81–0.59 (m, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 219.19, 65.63, 45.40, 44.85, 43.13, 39.05, 37.74, 35.72, 35.50, 31.73, 27.12, 21.12, 19.69, 17.93, 13.40; MS m/z (M^+) calcd 236.1776, obsd 236.1780.

(3a*R,5*R**,5a*R**,7*S**,8a*S**,8b*S**)-6-Ethyldecahydro-5-hydroxy-7-methyl-*as*-indacen-3(2*H*)-one Methanesulfonate (32).** Alcohol **30** (20 mg, 0.085 mmol) was dissolved in methylene chloride (1 mL) and cooled to 0 °C. Triethylamine (0.047 mL, 0.34 mmol) and methanesulfonyl chloride (0.013 mL, 0.17 mmol) were added and stirring was maintained for 1 h. The reaction mixture was quenched by addition of water (1 mL), and the aqueous phase was extracted with ether. The combined organic layers were washed with brine and dried. Concentration gave an oil which was purified by MPLC on Florisil (elution with 44% ethyl acetate in petroleum ether) to give 23.2 mg (87.2%) of **32** as a white solid: mp 86.5–89 °C (from ether); IR (KBr, cm^{-1}) 3020, 2960, 2940, 2870, 1720, 1500, 1345, 1330, 1170, 1150, 1115, 980, 890, 870, 780; ^1H NMR (300 MHz, C_6D_6) δ 4.72 (s, 1 H), 2.39–2.30 (m, 1 H), 2.15 (s, 3 H), 2.04–1.68 (m, 6 H), 1.51–1.00 (series of m, 9 H), 0.87 (t, J = 7.2 Hz, 3 H), 0.57 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 218.15, 79.09, 65.91, 45.50, 45.25, 40.46, 39.85, 37.92, 35.49, 33.93, 33.62, 27.80, 24.07, 22.05, 14.50, 12.74; MS m/z ($M^+ - SO_3CH_3$) calcd 219.1749, obsd 219.1757.

(1*R,2*R**,3a*R**,5*S**,7*S**,8*R**,8a*S**)-1-Ethyloctahydro-2-methyl-4,7:5,8-dimethanoazulene-6(1*H*)-one (33).** Mesylate **32** (15 mg, 0.048 mmol) was dissolved in 2 mL of 1,5-diazabicyclo[4.3.0]non-5-ene and heated at 100 °C for 3 h under argon. After being cooled to room temperature, the solution was diluted with ether (2 mL) and brine (2 mL) and stirred for 10 min. The aqueous phase was extracted with ether, and the combined organic layers were washed with brine, dried, and concentrated. Purification by MPLC on Florisil (elution with 15% ethyl acetate in petroleum ether) gave 4.5 mg (43%) of **33** as a colorless oil; IR (neat, cm^{-1}) 2960, 2930, 2870, 1720, 1450, 1375, 1365, 1260, 1110, 865; ^1H NMR (300 MHz, C_6D_6) δ 2.47 (q, J = 10.9 Hz, 1 H), 2.25–1.67 (m, 7 H), 1.47–0.89 (series of m, 8 H), 0.84 (t, J = 7.3 Hz, 3 H), 0.60 (d, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 217.21, 54.66, 50.43, 50.00, 47.38, 42.63, 41.56, 40.30, 40.17, 38.34, 29.93, 24.42, 20.26, 14.39, 13.24; MS m/z (M^+) calcd 218.1671, obsd 218.1669.

(6*R,7*R**,8a*S**)-6-Ethyl-1,4,6,7,8,8a-hexahydro-7-methyl-*as*-indacen-3(2*H*)-one (34).** Alcohol **29** (20 mg, 0.085 mmol) was dissolved in 1 mL of dry benzene under nitrogen and 27 mg (0.128 mmol) of Burgess reagent was added. After being heated at reflux for 1 h, the reaction mixture was cooled to room temperature, and 1 mL of water was added. The solution was taken up in ether, washed with brine, and dried. Filtration and concentration gave 12 mg (66%) of **34** as a colorless oil; IR (neat, cm^{-1}) 2960, 2920, 2870, 1695, 1630, 1460, 1440, 1400, 1380, 1340, 1270, 1260, 1240, 1040, 820; ^1H NMR (300 MHz, C_6D_6) δ 5.31 (s, 1 H), 3.03–2.97 (m, 1 H), 2.76–2.64 (m, 2 H), 2.15–2.01 (m, 3 H), 1.98–1.74 (m, 3 H), 1.41–1.25 (m, 3 H), 1.16–1.01 (m, 1 H), 0.87 (t, J = 7.7 Hz, 3 H), 0.81 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 235.95, 205.27, 172.13, 144.97, 115.76, 49.43, 39.75, 35.16, 35.08, 34.67, 27.37, 23.61, 20.79, 15.65, 12.69. The mass spectrum of **34** was identical with that of **35**, dehydrogenation occurring readily at some point during the measurement.

(5*S,5a*S**,6*R**,7*R**,8a*S**)-6-Ethyl-1,4,5,5a,6,7,8,8a-octahydro-5-hydroxy-7-methyl-*as*-indacen-3(2*H*)-one Methanesulfonate (36).** Alcohol **29** (50 mg, 0.214 mmol) was dissolved in 3 mL of dry dichloromethane under argon. The solution was cooled to 0 °C, and triethylamine (0.119 mL, 0.854 mmol) was introduced followed by the addition of methanesulfonyl chloride (0.033 mL, 0.427 mmol). The reaction mixture was stirred at 0 °C for 1 h and quenched with 1 mL of water. The solution was diluted with ether, washed with brine, and dried. Filtration and concentration gave 48 mg (72%) of **36** as an oil: IR (neat, cm^{-1}) 2970, 2940, 2880, 1735, 1690, 1645, 1450, 1400, 1350, 1245, 1175, 950, 920, 860; ^1H NMR (300 MHz, C_6D_6) δ 4.79–4.38 (m, 1 H), 2.50–2.42 (m, 1 H), 2.29–2.24 (m, 2 H), 2.17 (s, 3 H), 2.05 (t, J = 4.9 Hz, 2 H), 1.98–1.81 (m, 4 H), 1.78–1.62 (m, 1 H), 1.39–1.22 (m, 4 H), 0.93 (t, J = 7.3 Hz, 3 H), 0.67 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 205.33, 173.81, 134.29, 78.46, 46.25, 43.48, 40.98, 38.23, 37.49, 35.09, 35.04, 27.54, 24.95, 23.52, 14.76, 12.91; MS m/z (M^+) calcd 312.1395, obsd 312.1390.

***cis*-6-Ethyl-1,6,7,8-tetrahydro-7-methyl-*as*-indacen-3(2*H*)-one (35).** Mesylate **36** (25 mg, 0.08 mmol) was dissolved in 2 mL of 1,5-diazabicyclo[4.3.0]non-5-ene and heated at 50 °C for 5 h under argon. After being cooled to room temperature, the solution was diluted with ether (2 mL) and brine (2 mL), and stirred for 10 min. The aqueous phase was extracted with ether, and the combined organic layers were washed with brine and dried. Purification by MPLC on Florisil (elution with 22% ethyl acetate in petroleum ether) gave 15 mg (88%) of **35** as a colorless oil: IR (neat, cm^{-1}) 2940, 2930, 2880, 1700, 1600, 1440, 1375, 1350, 1270, 1260, 1040; ^1H NMR (300 MHz, C_6D_6) δ 7.78 (d, J = 8.0 Hz, 1 H), 6.91 (d, J = 7.7 Hz, 1 H), 2.64 (q, J = 7.0 Hz, 1 H), 2.56–2.51 (m, 1 H), 2.48–2.15 (m, 6 H), 1.44–1.35 (m, 2 H), 0.87–0.80 (m, 6 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 204.70, 153.66, 150.89, 140.52, 128.84, 123.63, 122.06, 50.15, 37.71, 36.85, 36.44, 24.20, 21.57, 14.84, 12.33; MS m/z (M^+) calcd 214.1358, obsd 214.1359.

(3a*R,5a*R**,6*R**,8a*S**,8b*S**)-6-Ethyl-1,2,5a,6,7,8,8a,8b-octahydro-7-methyl-*as*-indacen-3(3a*H*)-one 3-(Dimethyl acetal) (38).** A solution of **23** (29.2 mg, 0.104 mmol) in anhydrous tetrahydrofuran (1 mL) was added dropwise to a magnetically stirred solution of lithium diisopropylamide [prepared from 97.5 μL of 1.6 M *n*-butyllithium (0.156 mmol) and 29.2 μL of diisopropylamine (0.208 mmol) in 3 mL of dry tetrahydrofuran at 0 °C for 10 min] under argon at −78 °C. The mixture was stirred at −78 °C for 40 min, allowed to warm to 0 °C, treated with 32.6 μL of HMPA, and stirred at 0 °C for 20 min. Following the addition of *N,N,N',N'*-tetramethylphosphorodiamidic chloride (30.9 μL, 0.208 mmol), stirring was maintained for 15 min at 0 °C and overnight at room temperature. Saturated sodium bicarbonate solution (10 mL) was introduced and the mixture was stirred for 30 min, diluted with water, and extracted with ether (4 × 30 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried, and evaporated to leave 47.3 mg of the enol phosphoramidate as a colorless oil.

To a magnetically stirred solution of *tert*-butyl alcohol (18.6 μL) in dry ethylamine (10 mL) at −15 °C under argon was added lithium wire (7.9 mg, 1.14 mmol). The resulting deep blue solution was stirred at −15 °C for 10 min and treated dropwise with a solution of the enol phosphoramidate and *tert*-butyl alcohol (36.0 μL, 0.385 mmol) in 2 mL of dry tetrahydrofuran. After 15 min, the mixture was allowed to warm to 0 °C, stirred for 1 h, and quenched with solid ammonium chloride. Ethylamine was evaporated under reduced pressure, and the product was extracted into ether–petroleum ether (2:1), dried, and concentrated. MPLC purification (silica gel, elution with 2.5% ethyl acetate in petroleum ether) gave 25.9 mg (94%) of **38** as a colorless oil: IR (neat, cm^{-1}) 2955, 2935, 2870, 2825, 1460, 1320, 1140, 1120, 1065, 1044; ^1H NMR (300 MHz, C_6D_6) δ 5.86 (br d, J = 10.3 Hz, 1 H), 5.69 (dt, J = 10.3, 2.9 Hz, 1 H), 3.16 (s, 3 H), 3.10 (s, 3 H), 2.66–2.62 (m, 1 H), 2.43–2.34 (m, 1 H), 2.26–2.04 (m, 3 H), 1.95–1.65 (m, 3 H), 1.55–1.33 (m, 5 H), 1.23–1.06 (m, 1 H), 0.88 (t, J = 7.2 Hz, 3 H), 0.81 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 133.40, 124.22, 112.15, 52.27, 49.92, 47.96, 40.33, 39.73, 39.17, 38.28, 37.11, 34.41, 31.03, 26.34, 22.36, 15.41, 13.24; MS m/z (M^+) calcd 264.2092, obsd 264.2084.

(3a*R,5a*S**,6*R**,7*R**,8a*S**,8b*S**)-6-Ethyl-1,2,5a,6c,7,8,8a,8b-octahydro-7-methyl-*as*-indacen-3(3a*H*)-one (39).** A solution of **38** (24.2 mg, 0.092 mmol) in ether (2 mL) was treated with 3 N hydrochloric acid and stirred vigorously at 20 °C for 16 h. After dilution with 20 mL of ether–petroleum ether (1:1), the organic phase was washed with 1% sodium bicarbonate solution (2 mL) and brine (2 mL), dried, and concentrated. The residue was purified by MPLC on silica gel (elution with 2.5% ethyl acetate in petroleum ether) to give 17.8 mg (89%) of **39** as a colorless oil; IR (neat, cm^{-1}) 2956, 2924, 2866, 1743; ^1H NMR (300 MHz, C_6D_6) δ 5.68 (ddd, J = 10.0, 3.6, 1.9 Hz, 1 H), 5.56 (ddd, J = 10.0, 3.4, 2.7 Hz, 1 H), 2.55–2.45 (m, 1 H), 2.08–1.88 (m, 3 H), 1.88–1.68 (m, 3 H), 1.48–1.03 (m, 7 H), 0.84 (t, J = 7.3 Hz, 3 H), 0.76 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 215.75, 132.58, 121.45, 51.23, 48.11, 40.65, 38.70, 38.37, 36.64, 36.16, 34.06, 25.98, 22.16, 15.79, 13.14; MS m/e (M^+) calcd 218.1668, obsd 218.1673.

(3a*R,6*S**,7*S**,8a*S**,8b*S**)-6-Ethyl-1,3a,4,6,7,8,8a,8b-octahydro-7-methyl-*as*-indacen-3(2*H*)-one (40).** Alcohol **12** (25 mg, 0.12 mmol) was dissolved in 2 mL of benzene under nitrogen. Burgess reagent (25 mg,

0.12 mmol) was added, and the solution was brought to reflux for 1 h. After being cooled to room temperature, the reaction mixture was partitioned between water (2 mL) and ether (5 mL). The aqueous phase was extracted with ether, and the combined organic layers were washed with brine, dried, and concentrated. Purification by MPLC on Florisil (elution with 25% ethyl acetate in petroleum ether) gave 22 mg (78%) of **40** and its isomer **41** (ratio 4:1) as an oil: IR (neat, cm^{-1}) 2950, 2920, 2850, 1740, 1450, 1375, 1260, 1100; ^1H NMR (300 MHz, C_6D_6) δ 5.70-5.68 (m, 1 H), 5.58-5.57 (m, 1 H), 5.33-5.31 (m, 1 H), 2.77 (m, 1 H), 2.49-2.24 (m, 2 H), 2.12-1.71 (series of m, 13 H), 1.59-1.29 (series of m, 13 H), 0.89-0.81 (m, 6 H), 0.77-0.71 (m, 6 H); MS m/z (M^+) calcd 218.1670, obsd 218.1683.

(3a*R,5*S**,5a*R**,7*S**,8a*S**,8b*S**)-5-(*tert*-Butyldimethylsiloxy)-6-ethyldecahydro-7-methyl-*as*-indacen-3(2*H*)-one (42).** Alcohol **12** (130.4 mg, 0.55 mmol) and imidazole (150 mg, 2.2 mmol) were dissolved in 2.5 mL of dimethylformamide under argon. *tert*-Butyldimethylsilyl triflate (0.22 mL, 1.1 mmol) was added dropwise, and the solution was stirred at 25 °C for 1 h. A second equivalent of the triflate was added to the reaction mixture was stirring for 1 h before it was quenched with saturated sodium bicarbonate solution (1.5 mL). Water (1.5 mL) was added, and the solution was extracted with ether. The combined organic layers were washed with brine and dried prior to concentration. Purification by MPLC on silica gel (elution with 8% ethyl acetate in petroleum ether) gave 184.4 mg (95.4%) of **42** as a white solid: mp 46-48 °C (crystallized on standing at 0 °C); IR (neat, cm^{-1}) 2960, 2930, 2860, 1740, 1460, 1410, 1380, 1360, 1255, 1090, 1060, 840, 770; ^1H NMR (300 MHz, C_6D_6) δ 3.53-3.51 (m, 1 H), 2.08-1.99 (m, 2 H), 1.92-1.24 (series of m, 14 H), 0.98 (s, 9 H), 0.92 (t, J = 7.3 Hz, 3 H), 0.79 (d, J = 7.1 Hz, 3 H), 0.09 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 217.49, 70.45, 49.70, 47.53, 45.31, 40.35, 37.82, 37.60, 35.79, 33.22, 29.66, 26.39, 26.16 (3C), 22.65, 18.30, 15.96, 13.29, -4.19, -4.67; MS m/z (M^+) calcd 335.2406, obsd 335.2434.

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Supplementary Material Available: Tables listing the experimental X-ray diffraction data, bond distances, bond angles, least-squares planes, positional parameters, and refined temperature factor expressions for **25**-OPNB (12 pages). Ordering information is given on any current masthead page.

Total Synthesis of (+)-Ikarugamycin. 2. Elaboration of the Macrocyclic Lactam and Tetramic Acid Substructures and Complete Assembly of the Antibiotic

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Abstract: The antibiotic ikarugamycin (**5**) has been synthesized in a triply convergent and enantioselective manner. The previously prepared ketone **1** was first converted to acetylenic ester **2**, an intermediate in which all eight of the stereogenic centers present in the carbotricyclic segment of **5** have been set in their proper absolute configuration. Very high levels of kinetic resolution were achieved during 1,4-addition of vinylmagnesium bromide to aldimine **9**. Following coupling of **2** to the ornithine segment **20**, the aldehyde group was unmasked and condensation was effected with phosphonate **23**. After arrival at **3**, the acyl ketene was liberated thermally and macrocyclization occurred smoothly. The total synthesis was completed by partial hydrogenation of the triple bond, dehydrative removal of the hydroxyl group in ring B, Dieckmann cyclization to form the tetramic acid, and deblocking of the amide nitrogen. The spectral properties of the synthetic material were identical with those of the natural product.

In the preceding paper,[2] we developed a concise, stereocontrolled approach to **1**, a tricyclic ketone which was intended to become the decahydro-*as*-indacene subunit of ikarugamycin (**5**).[3] The appendage of functionalized sidechains onto ring C as in **2** was expected to proceed with the proper stereoselectivity by analogy to the established behavior of related linear triquinane systems.[4] The reactive centers present in **2** were to be selected in order to permit convenient introduction of the ornithine segment (see **3**) as well as those additional trigonal carbons that would ultimately allow for construction of the macrocyclic lactam as in **4**. The final issues at this stage of inception were to involve dehydrative removal of water to set the cyclohexene double bond[2] and Dieckmann cyclization to generate the tetramic acid ring system.[5]

Several additional tactical issues central to the projected synthesis in Scheme I derive from precedent developed by others in other contexts. The impact of this prior art on the retrosynthetic analysis will be made known at appropriate points below. This full account of our total synthesis of (+)-ikarugamycin elaborates upon findings announced in preliminary form[6] alongside a communication by Boeckman and co-workers in which an alternate route to the same antibiotic was described.[7] In both undertakings, the complex target was approached in a manner that delayed to the final stages the assembly of its sensitive and highly polar acyl tetramic acid unit in order to avoid the difficulties in manipulation and purification often associated with this class of compounds.

(1) NSERC Postdoctoral Fellow, 1987-1989.

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