h and, after cooling, concentrated in vacuo. Purification by flash chromatography on silica gel (EtOAc/hexane = 20/80) gave 227 mg (74%) as a 2:1 mixture of **30a** and **30b** as determined by ^{1}H NMR from the CO_2CH_3 signal: IR (KBr) 2950, 1730, 1440, 1305, 1150, 1090, 725, 690 cm^{-1}; ^{1}H NMR δ 7.89-7.48 (m, 5 H, ArH), 7.06 (m, 1 H, vinylic H), 3.66 (s, 3 H, OCH_3), 2.54 (m, 3 H), 2.28 (m, 2 H), 2.08 (m, 1 H), 1.70 (m, 1 H). The isomer **30b** is distinguishable in a mixture by ^{1}H NMR δ 3.62 (s, OCH_3).

Anal. Calcd for $C_{14}H_{16}O_4S$: C, 59.98; H, 5.75. Found: C, 60.03; H, 5.82.

1-(Phenylsulfonyl)-4-ethoxycyclohexene (31). A 12 mM solution (100 mL) of 2-(phenylsulfonyl)-1,3-butadiene (1.2 mmol) in CH_2Cl_2 was concentrated on a rotary evaporator to a volume of ca. 10 mL, and ethyl vinyl ether (30 mL) was added. The reaction mixture was heated at reflux temperature for 45 h, and then concentrated at reduced pressure. Purification by flash chromatography on silica gel (eluents: EtOAc/hexane = 10/90 and 20/80) afforded 173 mg (54%) of **31** as a colorless oil: IR (neat) 2985, 2930, 2878, 1450, 1310, 1290, 1155, 1090, 725, 690, 630 cm^{-1}; ^{1}H NMR δ 7.90-7.47 (m, 5 H, ArH), 6.94 (m, 1 H, HC=C), ~3.55 (m, 1 H, HCOEt), 3.48 (two q, J = 6.9 Hz, 2 H, OCH_2Me), 2.67-2.49 (m, 1 H), 2.40-2.15 (m, 3 H), 1.95-1.80 (m, 1 H), 1.78-1.62 (m, 1 H), 1.15 (t, J = 6.9 Hz, 3 H, CH_3); ^{13}C NMR δ 139.45, 139.28, 136.00, 133.19, 129.10, 127.93, 71.65, 63.52, 31.81, 26.83, 21.10, 15.48.

Anal. Calcd for $C_{14}H_{18}O_3S$: C, 63.13; H, 6.81. Found: C, 62.90; H, 6.70.

***cis*-1-Cyano-5-carbomethoxy-6-methylcyclohexene (32).** **25** (310 mg, 1.06 mmol) in MeOH (4 mL), acetic acid (58 μL, 1.0 mmol), and KCN in H_2O (0.4 mL) were mixed together and heated at 50 °C for 31 h. Ether (10 mL) and brine (5 mL) were added and the layers were separated. The aqueous phase was extracted with ether (10 mL). The combined organic phases were washed with aqueous 2 M NaOH (2 × 3 mL), H_2O (3 mL), and finally with brine (3 mL). After drying ($MgSO_4$) and removal of the solvent, the crude product was purified by flash chromatography on silica gel (EtOAc/hexane = 25/75), affording 97 mg (53%) of **32** as an oil: IR (neat) 2960, 2225, 1740, 1440, 1235, 1210, 1170 cm^{-1}; ^{1}H NMR δ 6.59 (m, unresolved, 1 H, HC=CCN), 3.72 (s, 3 H, CO_2CH_3), 2.82 (m, 1 H, HCMe), 2.69 (ddd, J = 12.2, 5.3, 3.2 Hz, 1 H, $HCCO_2Me$), 2.35-2.17 (m, 2 H, allylic H), 2.02-1.88 (m, 1 H, homoallylic H), 1.84-1.68 (m, 1 H, homoallylic H), 1.09 (d, J = 6.9 Hz, 3 H, CH_3); ^{13}C NMR δ 173.27, 144.07, 118.74, 117.28, 51.76, 42.45, 32.45, 25.55, 17.82, 15.48.

Anal. Calcd for $C_{10}H_{13}O_2N$: C, 67.02; H, 7.31. Found: C, 67.02; H, 7.44.

1-Carbomethoxy-2-methyl-1,3-cyclohexadiene (33). To a solution of **25** (330 mg, 1.12 mmol) in MeOH (5 mL) was added a solution of NaOMe in MeOH (prepared from 85 mg of Na (3.7 mmol) and 2.5 mL of MeOH). After the solution was refluxed for 6 h, $NaHCO_3$ (300 mg, 3.6 mmol) was added, and the resulting mixture was allowed to stir at room temperature overnight, followed by silica gel filtration (elution with ether). The solvent was removed by distillation at ambient pressure. The product was bulb-to-bulb distilled, yielding 123 mg (72%) of pure **33**[42] as a colorless oil: ^{1}H NMR δ 6.10 (m, J = 9.0, 4.5, 4.5 Hz, 1 H, H-4), 5.90 (m, J = 9.0, 1.5, 1.5 Hz, 1 H, H-3), 3.75 (s, 3 H, CO_2CH_3), 2.49-2.37 (m, 2 H), 2.22-2.07 (m, 2 H), 2.14 (s, 3 H, CH_3).

Acknowledgment. Financial support from the Swedish Natural Science Research Council and the Swedish Board of Technical Development is gratefully acknowledged.

Registry No. 1, 102860-22-0; **2**, 109802-71-3; **3**, 109802-72-4; *trans*-**4**, 109802-73-5; *cis*-**4**, 109802-96-2; *trans*-**5**, 109802-74-6; *cis*-**5**, 109802-97-3; **6**, 109802-75-7; **7**, 109802-76-8; **8**, 109802-77-9; **9**, 109802-78-0; **10a**, 109802-79-1; **10b**, 109802-98-4; **11**, 102860-24-2; **12**, 109802-80-4; **13**, 97663-39-3; **14**, 59356-67-1; *trans*-**15**, 109802-81-5; *cis*-**15**, 109802-99-5; **16**, 109802-82-6; *trans*-**17**, 109802-83-7; *cis*-**17**, 109803-00-1; **18**, 82736-46-7; **19**, 109802-84-8; **20**, 109802-85-9; **21**, 109802-86-0; **22**, 109802-87-1; **23**, 109802-88-2; (*E*)-**24**, 87040-04-8; (*Z*)-**24**, 109803-01-2; **25**, 109862-70-6; **26**, 109802-89-3; **27**, 670-80-4; **28**, 109802-90-6; **29**, 109802-91-7; **30a**, 109802-92-8; **30b**, 109803-02-3; **31**, 109802-93-9; **32**, 109802-94-0; **33**, 72359-60-5; **34**, 109802-95-1; MeLi, 917-54-4; BuLi, 109-72-8; $NaHC(CO_2Me)_2$, 18424-76-5; Me_2NH, 124-40-3; $Pd(PPh_3)_4$, 14221-01-3; $Pd(OAc)_2$, 3375-31-3; $Pd(dba)_2$, 32005-36-0; $H_2C(CO_2Me)_2$, 108-59-8; $NaHC(CO_2Me)COMe$, 34284-28-1; $H_2C{=}CHCO_2Me$, 96-33-3; $MeCOCH{=}CH_2$, 78-94-4; $EtOCH{=}CH_2$, 109-92-2; 3-(phenylsulfonyl)-4-(chloromercuri)cyclohexene, 102815-53-2; 3-(phenylsulfonyl)-4-(chloromercuri)but-1-ene, 102815-47-4; 3-(phenylsulfonyl)-4-(chloromercuri)-1-pentene, 109803-03-4; 5-(chloromercuri)-4-(phenylsulfonyl)pent-2-ene, 102815-50-9.

(42) Trost, B. M.; Verhoeven, T. R.; Fortunak, J. M. *Tetrahedron Lett.* **1979**, *25*, 2301.

A Novel Synthesis of Ikarugamycin: The Carbocyclic Portion

James K. Whitesell* and Mark A. Minton

Contribution from the Department of Chemistry, University of Texas at Austin, Austin, Texas 78712. *Received March 2, 1987*

Abstract: The tetracyclic glycol **2**, a potential intermediate for the synthesis of ikarugamycin (**1**), was synthesized. Key transformations involved were the following: the preparation with resolution of the enantiomeric esters **3**; their separate elaboration and ultimate recombination to form the trienes **17**; photocyclization of **17** with ground-state conformational bias to form diene **18**; and dissolving metal reduction of **20** with internal proton delivery to form predominantly monoene **22**.

In 1972 two Japanese groups described the isolation[1] and detailed, degradative structure elucidation[2] for the novel antimicrobial and amoebicide ikarugamycin (**1**). The interest of several synthetic groups, including this one, was attracted by the unusual carbocyclic portion of this unique natural product[3] and the obvious facility with which the three, linearly fused carbocyclic rings might be constructed by an intramolecular Diels-Alder reaction.[4] An alternate route could be devised that would take advantage of certain symmetry elements present in the carbocyclic moiety. In particular, we have depicted in Scheme I a retrosynthetic analysis which first disconnects the tetramic acid moiety at the two obvious junctions of the carbon-carbon π systems and then proceeds (with inversion of one stereochemical center) to the tetracyclic intermediate **2**.

Progression on to the natural product would involve the following: (1) cleavage of the glycol moiety with differentiation of the two resulting aldehyde functions; (2) inversion at the only

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

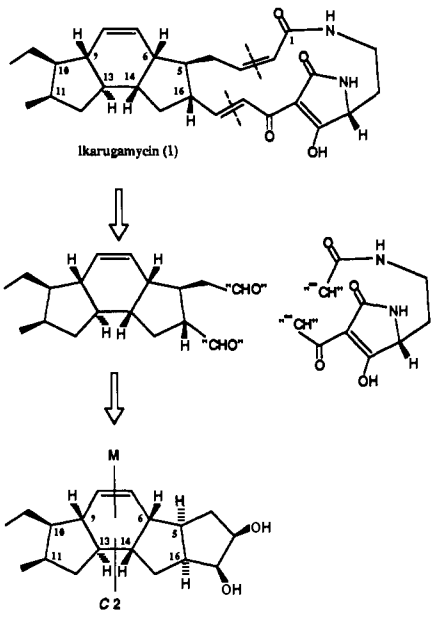
(2) Ito, S.; Hirata, Y. *Tetrahedron Lett.* **1972**, 1181, 1185, 2557. Ito, S.; Hiratar, Y. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1813.

(3) A second natural product, capsimycin, with the same skeleton as ikarugamycin has been reported, see: Seto, H.; Yonehara, H.; Aizawa, S.; Akutsu, H.; Clardy, J.; Arnold, E.; Tanabe, M.; Urano, S. *Koen Yoshishu - Tennen Yuki Kagobutsu Toronkai Koen Yoshishu, 22nd* **1979**, 394. Aizawa, S.; Akutso, H.; Satomi, T.; Nagatsu, T.; Taguchi, R.; Seino, A. *J. Antibiot.* **1979**, *32*, 193.

(4) Boeckman, R. K., Jr.; Napier, J. J.; Thomas, A. J.; Sato, R. I. *J. Org. Chem.* **1983**, *48*, 4152. Kurth, M. J.; Burns, D. H.; O'Brien, M. J. *J. Org. Chem.* **1984**, *49*, 731. For a novel alternate route, see: Paquette, L. A.; Romine, J. L.; Lin, H.-O. *Tetrahedron Lett.* **1987**, *28*, 31.

0002-7863/87/1509-6403$01.50/0

Scheme I



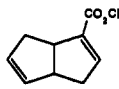
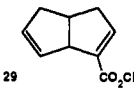
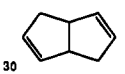
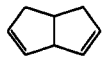
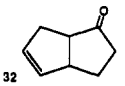
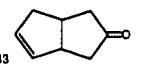
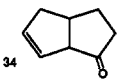
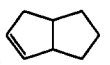
2

stereochemical center (C-16) rendered acidic by an adjacent carbonyl group to the more stable, trans relationship of the side chains; (3) attachment of the macrocyclic tetramic acid moiety. The rationale for the inversion of stereochemistry as well as formation of the superfluous, additional ring present in **2** will become clear shortly.

Within intermediate **2** there are two pseudosymmetry elements that relate stereochemical centers. A correspondence in a mirror image sense can be made between the following centers in pairs: 5 and 10; 6 and 9; 11 and 16. On the other hand, the spatial orientations of groups about centers 13 and 14 are the same, and thus the centers form a small package of C_2 symmetry within the molecule. Each of these local pseudosymmetry elements presents opportunities for unique approaches to the synthesis of the carbocyclic portion of ikarugamycin. Thus, a substantial portion of the mirror symmetric relationship would naturally evolve by deriving centers 5 and 6 from a material whose mirror image was used for elaboration to centers 9 and 10. In particular, the diene ester **3** whose preparation[5] and resolution[6] have previously been described, could serve admirably in this regard. On the other hand, the local C_2 symmetry relating the environment about centers 13 and 14 is reminiscent of the products of photochemically induced cyclization of substituted hexatrienes.[7]

Thus, elaboration of each of the resolved enantiomers of **3** proceeded along the routes illustrated in Schemes II and III to afford phosphonium salt **13** and aldehyde **16**. Certain aspects of each of the separate routes are worthy of note. In particular, the Woodward oxidation of the diene esters proceeded to give a slight preference (1.2:1) for the exo glycol as opposed to the endo. Lack of "normal" selectivity for attack at the more hindered face of the alkene in this oxidation is rare[8] and appears to be related to the catercornered positioning of the double bond with an sp^2 center in the bicyclo[3.3.0]octane system. Thus, Woodward oxidation of alkenes **29**, **31**, **33**, **34**, and **35** (Table I) each of which lacks such an arrangement proceeded as expected to generate a preponderance of the endo glycol. Further, formation of the exo glycol was highly favored in the oxidation of two of these alkenes with

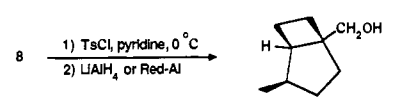
Table I. Cis Hydroxylation of Bicyclo[3.3.0]octenes

		Conditions (endo/exo)						
		I_2 AgOAc	I_2 TlOAc	NBA AgOAc	BrOAc AgOAc	NCS AgOAc	ClOAc AgOAc	OsO_4 NMO
alkene	reference	17	18	19	20		21	22
 3		1:1.2	1:1	3:2	2.5:1	slow rx	2:1	1:2
 29		4:1						
 30		1:1.7						1:7
 31		3:1						1:20
 32		2:3						1:1.8
 33		3.7:1						
 34		7:1						
 35		7:1		7.5:1		7:1		1:20

[a] Reference.

OsO_4. On the other hand, significantly less selectivity was exhibited in the oxidation of alkenes **3**, **30**, and **32** by both the Woodward procedure and with OsO_4. Modifications to the Woodward procedure led to improved ratios of endo to exo glycols but had a detrimental effect on chemical yield. Also anomalous was the behavior of **3** toward ozone. When treated with 1 equiv of ozone followed by reductive workup with sodium borohydride only unchanged ester was recovered. With 2 equiv of ozone no recognizable products were obtained. By comparison the model olefin **35** gave the expected ring-opened diol in 87% yield with 1 equiv of ozone.

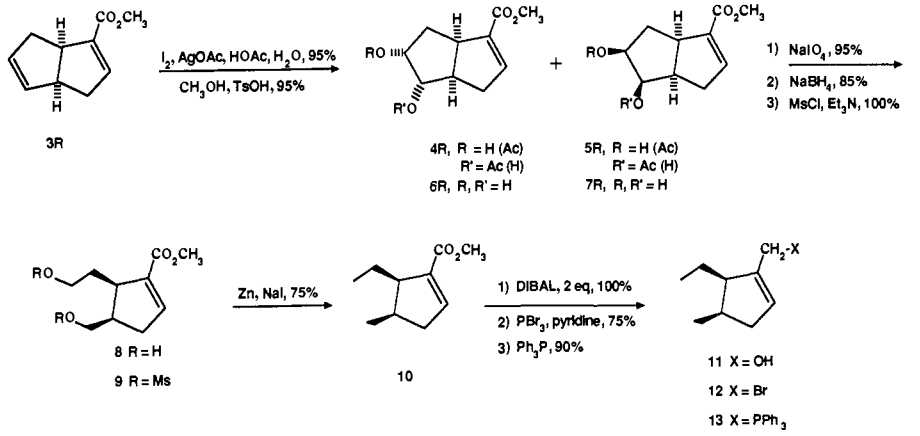
Both glycols in the *R* series (Scheme II) were used for cleavage to the dialdehyde. The desired endo glycol for the *S* series was separated from the exo, and the latter was recycled to the olefin by formation of the dimesylate and subsequent reduction with zinc and sodium iodide (73% overall). Indeed, this zinc reduction of the primary mesylates to methyl groups in the conversion of **9** to **10** was found to be far superior to other techniques, especially hydride reagents, and while the sequence employed has literature precedent,[9] it is a much under-utilized and generally superior method, especially for primary sulfonates. In the present case, reduction of the ditosylate of **8** with lithium aluminum hydride or Red-Al afforded mostly the bicyclic product **36**, the result of addition of hydride to the β carbon of the unsaturated ester and concomitant internal alkylation.



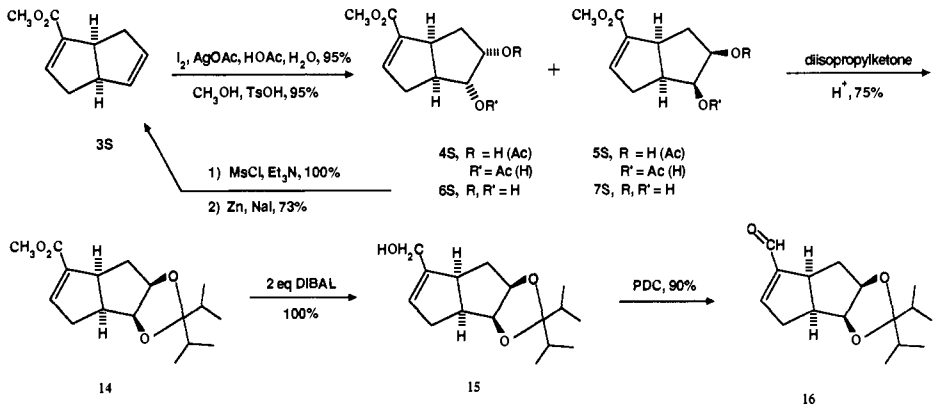
36

(5) Whitesell, J. K.; Minton, M. A.; Flanagan, W. G. *Tetrahedron* **1981**, *37*, 4451.
(6) Whitesell, J. K.; Minton, M. A.; Felman, S. W. *J. Org. Chem.* **1983**, *48*, 2193.
(7) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Verlag Chemie: Weinheim, 1970; pp 51–53.
(8) We are aware of only one other example of delivery of oxygen from the more accessible face on a Woodward oxidation, see: Angyal, S. J.; Kondo, Y. *Aust. J. Chem.* **1980**, *33*, 1013.
(9) Fujimoto, Y.; Tatsuno, T. *Tetrahedron Lett.* **1976**, 3325. Kocovsky, P.; Cerny, V. *Coll. Czech. Chem. Commun.* **1979**, *44*, 246.

Scheme II



Scheme III



The choice of the diisopropyl ketal was mandated by a desire to induce steric bias in the ground state for one of the two possible diastereomeric coils (**A** and **B**, Scheme IV) that would lead to photocyclization.[10] This ketal formed with surprising facility by the straightforward process illustrated. Formation of the phosphorane from **13** with butyllithium and coupling with **16** led to a 2:1 mixture of cis and trans trienes **17** in a combined yield of 75%.

Photocyclization of the mixture of trienes **17** led in 65% yield to a 4:1 mixture of the two possible conrotatory closure products, **18** and **19** (the trans triene is rapidly interconverted with the cis under the reaction conditions). The major product **18** had the desired sterochemistry at carbons 13 and 14,[11] presumably the result of conformational bias in the ground state of the cis triene that is preserved for the full lifetime of the singlet state. It is important to note that this is the first application of the NEER, or Non-Equilibration of Excited Rotamers, principle[12] to stereochemical control in synthesis.[13]

Formation of the monoene **2** from the diene resulting from photocyclization required a process that, overall, would introduce hydrogen atoms at C-6 and C-9 in a cis fashion from what would appear to be the more hindered face of the molecule. Thus, we proceeded along a path that would take advantage of the oxygen functionalities on carbons 3 and 17. Hydrolytic cleavage of the ketal gave the diene glycol **20** that underwent dissolving metal reduction with both regio- and stereochemical direction[11] by internal proton delivery from the hydroxyl groups. Once a proton is delivered internally to C-6, subsequent protonation of the simple allylic radical anion cannot proceed in an internal fashion. Presumably, the regiochemistry of the ultimate product is dictated by the facility with which an external proton source can deliver a hydrogen to the secondary rather than the tertiary center.[14] Protection of the glycol unit and hydroboration of the monoene proceeded as expected with delivery of oxygen and hydrogen to the more sterically accessible, back face **24**, and chromium oxidation afforded ketone **25**. Treatment of **25** with base proceeded with essentially complete conversion to the epimer **26** with the required stereochemistry at C-9.[11,15] Conversion of the ketone to the olefin was achieved through reduction of the intermediate enol phosphorodiamidate **27**. Cleavage of the ketal of **28** afforded the desired intermediate **2**.

This novel synthetic approach to ikarugamycin has succeeded in preparing a suitable precursor to the carbocyclic portion that

(10) Ongoing studies dealing with the conformational properties of trienes implicate totally different, steric interactions as being responsible for the selectivity observed. For example, a model system having having only a simple cyclopentenyl ring for the right hand portion resulted resulted in the same sense and level of cyclization bias. Molecular mechanics calculations on this model system are consistent with an approximately 1 Kcal/mol energy difference between the diastereomeric coils that would lead directly to cyclization, with bias in the same direction as experimentally observed. These results will be communicated separately, along with additional observations on this photochemical transformation.

(11) Carbon-13 NMR spectroscopic analysis was used initially to assign stereochemistry in all intermediates. Confirmation of the stereochemical bias for all critical transformations was ultimately obtained by a single-crystal, X-ray structure determination carried out on ketone **26**. We are grateful to Dr. V. M. Lynch for this analysis, the full details of which will be detailed separately.

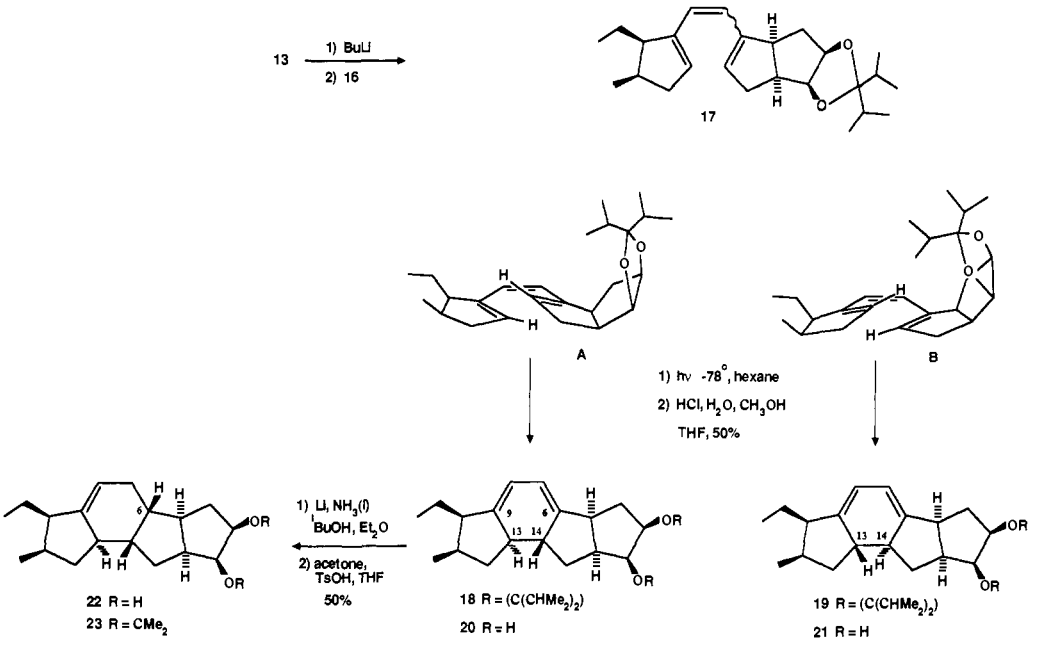
(12) For a leading reference to the NEER principle, see: Jacobs, H. J. C.; Gielen, J. W. J.; Havinga, E. *Tetrahedron Lett.* **1981**, *22*, 4013.

(13) Historically, the first observation of stereochemical control in triene cyclizations was in the vitamin D field, see: Reference 12 and Denny et al. (Denny, M.; Liu, R. S. H. *Nouv. J. Chim.* **1978**, *2*, 637.). Malatesta, V.; Willis, C.; Hackett, P. A. *J. Am. Chem. Soc.* **1981**, *103*, 6781. Dauben, W. G.; Phillips, R. B. *J. Am. Chem. Soc.* **1982**, *104*, 335.

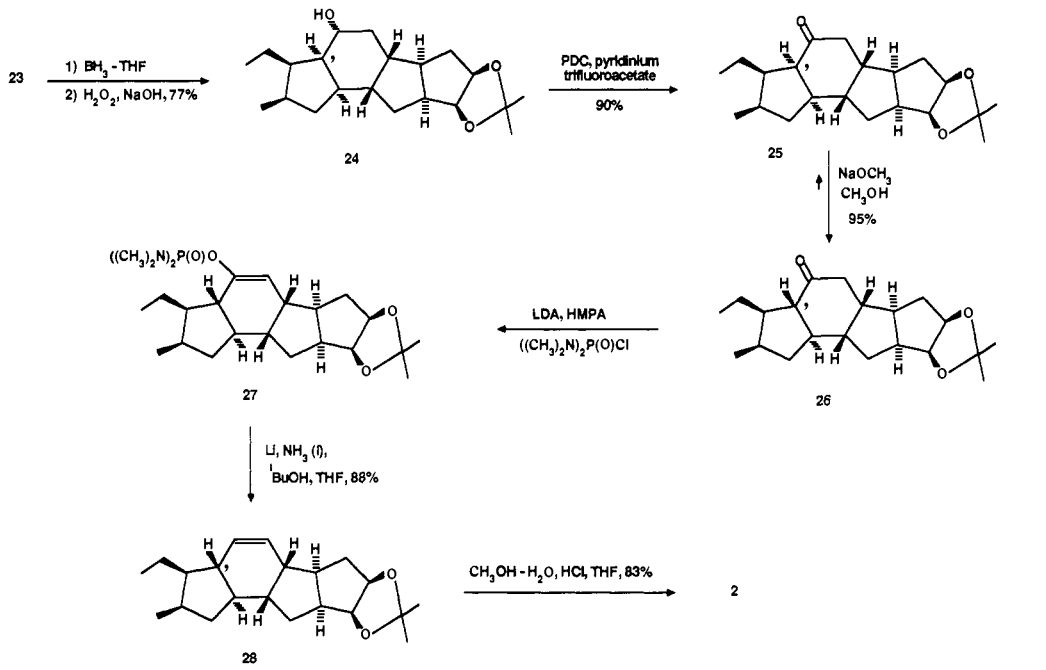
(14) A small amount (10%) of the 1,4-reduction product with the same stereochemistry at C-6 but the opposite stereochemistry at C-9 to that desired was also formed.

(15) The thermodynamic preference for the trans fusion at this ring junction was anticipated, see: Circero, B. L.; Weisbuch, F.; Dana, G. *J. Org. Chem.* **1981**, 46, 914.

Scheme IV



Scheme V



incorporates all of the stereochemical and functional features necessary for completion of the synthesis. Several novel approaches to the control of stereochemistry have been employed, in particular the following: the use of each of the enantiomers of the diene acid to form the appropriate portions of **2**; the use of the hexatriene–cyclohexadiene photoconversion to introduce the requisite stereochemical features at carbons 13 and 14 as mandated by the ground-state, conformational bias; and the internal delivery of a proton during a dissolving metal reduction to fix the stereochemistry at C-6. At this stage our efforts converge with those of Boeckman[16] who has now successfully addressed the challenge of constructing the macrocyclic tetramic acid moiety of ikarugamycin.

Experimental Section

^{13}CMR assignments were confirmed by off-resonance decoupling where appropriate. For convenience spectral assignments for all compounds in Schemes IV and V follow the numbering used for the final product **2**. Only mass spectral peaks of $m/z > 100$ and $> 10\%$ relative intensity are reported.

Methyl (1*R*)-(−)-*cis*,*endo*- and -*exo*-6,7-Dihydroxy-*cis*-bicyclo-[3.3.0]oct-2-ene-2-carboxylate (6*R* and 7*R*).[17] Iodine (26.4 g, 0.105 mol, 1 equiv) was added in small portions over 1.25 h to a vigorously stirred suspension of 17.2 g (0.105 mol) of **3*R***[23] and 36.7 g (0.22 mol, 2 equiv)

(16) Boeckman, R. K.; Perni, R. B. *J. Org. Chem.* **1986**, *51*, 5486.

(17) Ellington, P. S.; Hey, D. G.; Meakins, G. D. *J. Chem. Soc. C* **1966**, 1327.

(18) Cambie, R. C.; Rutledge, P. S. *Org. Synth.* **1979**, *59*, 169.

(19) Jasserand, D.; Girard, J. P.; Rossi, J. C.; Granger, R. *Tetrahedron Lett.* **1976**, 1581.

(20) Wilson, M. A.; Woodgate, P. D. *J. Chem. Soc., Perkin Trans. 2* **1976**, 141.

(21) de la Mare, P. B. D.; Wilson, M. A.; Rosser, M. J. *J. Chem. Soc. Perkin Trans. 2* **1973**, 1480.

(22) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973. VanRheenen, V.; Cha, D. Y.; Hartley, W. M. *Org. Synth.* **1978**, *58*, 43.

of dry silver acetate in 1 L of acetic acid. Most of the previous portion of iodine had dissolved before the next was added. Thirty min after addition was complete 18.9 mL (1.05 mol, 10 equiv) of water was added, and the mixture was stirred in the dark overnight. After 15 h at room temperature the mixture was heated at 70 °C for 2 h. The mixture was cooled and vacuum filtered before acetic acid was removed on a rotary evaporator connected to a vacuum pump. The residual oil was taken up in ether, filtered again, neutralized with aqueous sodium bicarbonate, washed with brine, and concentrated leaving 24.0 g (100%) of viscous yellow oil consisting of a mixture of monoacetates **4*R*** and **5*R***.

A solution of 21.8 g (90.7 mmol) of the monoacetate mixture and 1.7 g (9.1 mmol, 0.1 equiv) of *p*-toluenesulfonic acid monohydrate in 190 mL of methanol was refluxed overnight. The solution was cooled and stirred for 1 h with 0.80 g (9.5 mmol) of sodium bicarbonate. Methanol was removed, and the residue was taken up in ethyl acetate and filtered through silica gel to remove salts. The mixture of (−)-diols (1.2:1 exo:endo) was purified but not separated by preparative HPLC by using ethyl acetate to yield 17.2 g (95%) of a hygroscopic, crystalline mixture of **6*R*** and **7*R***. (For spectral data see the *S* series, below.)

Methyl (1*S*)-(+)-*cis*,*endo*-6,7-Dihydroxy-*cis*-bicyclo[3.3.0]oct-2-ene-2-carboxylate (7*S*). Woodward oxidation[17] of **3*S*** was carried out extactly as described above for **3*R***, except that the (+)-diols obtained were separated during HPLC purification by using recycling techniques. From 15.7 g (95.5 mmol) of **3*S***[23] there were obtained 7.6 g of endo diol **7*S*** and 9.6 g of exo diol **6*S***. Analytical samples were obtained as pale yellow hygroscopic waxy solids by molecular distillation at 120–125 °C, 0.04–0.05 mmHg.

Endo diol 7*S*: $[\alpha]^{23}_D$ +37.5° (*c* 1.0, absolute EtOH); IR 3580, 3040, 2940, 1710, 1625, 1415, 1355, 1240, 1090, 1015, 680; ^{1}HMR (500 MHz) 6.72 (q, 1 H, *J* = 2, C3-H), 4.10 (ddd, 1 H, *J* = 4, 6.5, 8, C7-H), 4.02 (dd, 1 H, *J* = 4, 6, C6-H), 3.72 (s, 3 H, OCH_3), 3.32 (m, 1 H, C1-H), 2.88 (dq, 1 H, *J* = 3, 20, C4-H_{endo}), 2.85 (dddd, 1 H, *J* = 3.5, 6.5, 10, 10, C5-H), 2.50 (ddm, 1 H, *J* = 2.5, 10.5, 20, C_4-H_{exo}), 2.35 (br, 2 H, OH), 2.28 (ddd, 1 H, *J* = 6.5, 9, 13.5, C_8-H_{exo}), 1.65 (ddd, 1 H, *J* = 7, 8, 13.5, C8-H_{endo}) (assignments of endo and exo resonances were confirmed by 2D-NOE); ^{13}CMR (20 MHz) 165.7 (CO), 144.0 (C3), 138.7 (C2), 75.3 (C6), 74.4 (C7), 51.3 (OCH_3), 46.2 (C1), 43.0 (C5), 36.1 (C8), 32.6 (C4).

Exo diol 6*S*: mp 68–70 °C; $[\alpha]^{21}_D$ +46.7° (*c* 1.07, absolute EtOH); IR 3585, 3035, 2940, 1715, 1630, 1420, 1360, 1240, 1090, 1035, 1010, 890, 680; ^{1}HMR (360 MHz) 6.64 (q, 1 H, *J* = 2, C3-H), 4.02 (td, 1 H, *J* = 4, 5.5, C7-H), 3.73 (s + m, 4 H, OCH_3 + C6-H), 3.52 (m, 1 H, C1-H), 3.41 (br, 2 H, OH), 2.80 (ddt, 1 H, *J* = 2.5, 10, 19, C4-H_{exo}), 2.76 (m, 1 H, C5-H), 2.33 (dm, 1 H, *J* = 19, C4-H_{endo}), 2.13 (ddd, 1 H, *J* = 6, 9.5, 13.5, C8-H_{exo}), 1.77 (dt, 1 H, *J* = 5, 13.5, C8-H_{endo}); ^{13}CMR (20 MHz) 165.4 (CO), 142.3 (C3), 139.2 (C2), 80.8 (C6), 73.9 (C7), 51.4 (OCH_3), 46.0 (C5 or C1), 45.8 (C1 or C5), 37.3 (C4), 36.1 (C8).

The unwanted exo isomer was recycled to the starting olefin **3*S*** by conversion to the dimesylate and reductive elimination. Thus, 8.3 mL (107 mmol, 2.2 equiv) of methanesulfonyl chloride was added dropwise over 30 min to a stirred, ice-cold solution of 9.6 g (48.5 mmol) of diol **6*S*** and 20.2 mL (145 mmol, 3 equiv) of triethylamine in 285 mL of dichloromethane. After stirring at 0 °C for 2 h, the mixture was poured into ice water. The organic layer was washed with cold 2 N HCl, water, and 1 N sodium bicarbonate. Concentration provided 17.7 g (100%) of dimesylate as a viscous orange oil which very slowly crystallized.

$[\alpha]^{24}_D$ +33.4° (*c* 1.02, $CHCl_3$); ^{1}HMR (360 MHz) 6.77 (br s, 1 H, C3-H), 4.99 (q, 1 H, *J* = 5, C7-H), 4.74 (dd, 1 H, *J* = 4, 5, C6-H), 3.75 (s, 3 H, OCH_3), 3.65 (m, 1 H, C1-H), 3.12 (s, 3 H, SO_2CH_3), ca. 3.11 (m, 1 H, C5-H), 3.10 (s, 3 H, SO_2CH_3), 2.86 (ddt, 1 H, *J* = 1.5, 9.5, 19.5, C4-H_{exo}), 2.48 (m, 2 H, C_4-H_{endo} & C8-H_{exo}), 2.02 (dt, 1 H, *J* = 5, 14.5, C8-H_{endo}) ^{13}CMR (20 MHz) 164.5 (s, CO), 142.0 (d, C3), 138.0 (s, C2), 85.0 (d, C6), 80.8 (d, C7), 51.6 (q, OCH_3), 44.6 (d, C1 or C5), 44.1 (d, C: or C1), 38.5 (q, SO_2CH_3), 38.4 (q, SO_2CH_3), 36.2 (t, C4), 34.6 (t, C8).

A mixture of 17.7 g (50 mmol) of the above crude dimesylate, 44.9 g (0.30 mol, 6 equiv) of sodium iodide and 19.6 g (0.30 mol, 6 equiv) of zinc dust in 460 mL of DME was refluxed with stirring overnight. After cooling, the mixture was vacuum filtered through Celite. The filter cake was washed well with pentane and water, and then the combined filtrates were poured into 3 L of water and extracted thrice with pentane. The combined pentane layers were washed with 3 L of water followed by a back extraction of the aqueous phase with pentane. This treatment was repeated once more to remove the last traces of DME. Concentration of the pentane layers yielded 6 g (73%) of the ester **3*S*** as a fluid yellow oil, suitable for resubmission to the Woodward oxidation.

Methyl (4*R*)-(−)-*cis*-5-Ethyl-4-methyl-1-cyclopentene-1-carboxylate (10). A mixture of 20.2 g (56 mmol) of the crude dimesylate **9**, 50.8 g (0.34 mol, 6 equiv) of sodium iodide, and 73.9 g (1.13 mol, 20 equiv) of zinc dust in 510 mL of DME was refluxed with stirring for 3 h. After cooling, the mixture was vacuum filtered through Celite and worked up as above. Concentration of the pentane layers yielded 7.1 g (75%) of the volatile ester **10** as a fluid yellow oil, free of the corresponding lactone impurity according to ^{13}CMR analysis. A colorless analytical sample was molecularly distilled at 80–85 °C, 40–42 mmHg.

$[\alpha]^{22}_D$ −18.2° (*c* 1.05, absolute EtOH); IR 2935, 1710, 1620, 1425, 1095; ^{1}HMR (360 MHz) 6.78 (narrow m, 1 H, C2-H), 3.72 (s, 3 H, OCH_3), 2.77 (br q, 1 H, *J* = ca. 6, C5-H), 2.50 (6 or 7 line m, 1 H, *J* = 7.5, C4-H), ca. 2.45 (dddd, 1 H, *J* = 0.5, 3, 8, 17, C3-H), 2.10 (ddt, 1 H, *J* = 2.5, 8.5, 17, C3-H), ca. 1.54 (m, 2 H, C7-H), 1.06 (d, 3 H, *J* = 7, C6-H), 0.86 (t, 3 H, *J* = 7.5, C8-H); ^{13}CMR (20 MHz) 165.9 (s, CO), 143.4 (d, C2), 140.6 (s, C1), 51.1 (q, OCH_3), 47.6 (d, C5), 40.1 (t, C3), 37.5 (d, C4), 21.3 (t, C7), 15.1 (q, C6), 12.1 (q, C8).

Methyl (1*S*)-(+)-*cis*,*endo*-6,7-Dihydroxy-*cis*-bicyclo[3.3.0]oct-2-ene-2-carboxylate Diisopropylketal (14). A solution of 12.6 g (63.5 mmol) of endo diol **7*S***, 27.1 mL (191 mmol, 3 equiv) of diisopropylketone, and 1.21 (6.4 mmol, 0.1 equiv) of *p*-toluenesulfonic acid monohydrate in 225 mL of benzene was refluxed for 28 h under a Soxhlet extractor filled with 4 Å molecular sieves. After having been cooled to room temperature, the solution was stirred 1.75 h with 0.61 g (7 mmol) of sodium bicarbonate. After concentration, the residue was filtered through Florisil and purified by preparative HPLC by using 9:1 Skelly B/ethyl acetate. There were obtained 14.1 g (73%) of the ketal ester **14** as a pale yellow oil as well as a small amount of recovered diol **7*S*** from an ethyl acetate flush of the column. A colorless analytical sample of **14** was obtained by molecular distillation at 85 °C, 0.05 mmHg.

$[\alpha]^{22}_D$ +18.5° (*c* 1.0, absolute EtOH); IR 2940, 1710, 1625, 1415, 1360, 1245, 1200, 1110, 1065, 1020, 680; ^{1}HMR (360 MHz) 6.66 (q, 1 H, *J* = 2, C3-H), 4.76 (dt, 1 H, *J* = 4.5, 7, C7-H), 4.63 (t, 1 H, *J* = 7, C6-H), 3.72 (s, 3 H, OCH_3), 3.40 (m, 1 H, C1-J), 2.96 (dq, 1 H, *J* = 3, 18.5, C4-H_{endo}), 2.86 (qd, 1 H, *J* = 3.5, 8.5, C5-H), 2.47 (ddt, 1 H, *J* = 2, 9.5, 18.5, C4-H_{exo}), 2.23 (ddd, 1 H, *J* = 7, 8, 14.5, C8-H_{exo}), 2.09 (septet, 1 H, *J* = 7, endo-*i*-Pr CH), 2.02 (ddd, 1 H, *J* = 4.5, ca. 5, 14.5, C8-H_{endo}), 1.96 (septet, 1 H, *J* = 7, exo-*i*-Pr CH), 0.95 (d, 6 H, *J* = 7, endo-*i*-Pr CH_3), 0.91 (d, 3 H, *J* = 7, exo-*i*-Pr CH_3), 0.89 (d, 3 H, *J* = 7, exo-*i*-Pr CH_3); ^{13}CMR (20 MHz) 165.3 (s, CO), 143.4 (d, C3), 138.2 (s, C2), 118.2 (s, $(i\text{-Pr})_2CO_2$), 84.3 (d, C6 or C7), 83.1 (d, C7 or C6), 51.2 (q, OCH_3), 50.8 (d, C1), 45.1 (d, C5), 36.6 (t, C8), 34.3 (d, *i*-Pr CH), 33.5 (d, *i*-Pr CH), 32.3 (t, C4), 18.5 (q, *i*-Pr CH_3), 18.3 (q, *i*-Pr CH_3).

Trienes 17. *n*-Butyllithium (4.8 mL of 2.9 M solution in hexane, 14 mmol, 1.05 equiv) was added dropwise over 7 min to a stirred, ice-cold suspension of 6.25 g (13.4 mmol) of phosphonium salt **13** in 100 mL of ether. The resulting deep red solution was stirred 30 min more with ice cooling, and then a solution of 3.73 g (14.1 mmol, 1.05 equiv) of aldehyde **16** in 30 mL of ether was added dropwise over 1.5 h. The reaction was stirred another 20 min at 0 °C, 30 min at room temperature, and finally 30 min at reflux. Water (13 μL, 0.7 mmol) was added, and then ether was distilled under a stream of argon (50 °C bath, dry ice-cooled receiver). The residue was diluted with specially purified Skelly B and filtered through Florisil under argon. Concentration (vacuum replaced with argon) provided 3.9 g (79%) of an approximately 2:1 mixture of cis and trans trienes **17**: UV 287, 274, 264, 256 (sh) (These absorptions are mostly due to the trans triene. Samples richer in cis show only a broad, featureless maximum at 267.).

^{1}HMR (90 MHz) 6.15 (d, 2 H, *J* = 4.5, trans C7-H and C8-H), 5.85 (br s, 2 H, cis C7-H and C8-H), 5.67 (m, 1 H, trans C13-H or C14-H), 5.53 (m, 3 H, trans C13-H or C14-H and cis C13-H and C14-H), 4.9–4.5 (m, 4 H, C3-H and C17-H), 3.0–0.8 (m, remaining protons); ^{13}CMR (20 MHz) cis 144.3 (s, C9), 143.4 (s, C6), 131.8 (d, C7 or C8), 129.7 (d, C8 or C7), 125.3 (d, C13 or C14), 125.1 (d, C14 or C13), 118.2 (s, $(i\text{-Pr})_2CO_2$), 84.5 (d, C17 or C3), 84.0 (d, C3 or C17), 52.1 (d, C10), 50.8 (d, C5), 45.3 (d, C16), 40.0 (t, C12), 36.3 (d or t, C11 or C4), 36.2 (t or d, C4 or C11), 34.4 (d, *i*-Pr CH), 33.5 (d, *i*-Pr CH), 31.4 (t, C15), 20.5 (t, CH_2 of Et), several peaks ca. 18.4 (q, *i*-Pr CH_3), 15.3 (q, CH_3 at C11), 12.4 (q, CH_3 of Et); trans 147.3 s, C9), 145.1 (s, C6), 130.0 (d, C7 or C8), 129.5 (d, C8 or C7), 126.0 (d, C13), 124.8 (d, C14), 118.9 (s, $(i\text{-Pr})_2CO_2$), 85.2 (d, C17), 83.1 (d, C3), 50.4 (d, C5), 47.0 (d, C10), 45.2 (d, C16), 39.9 (t, C12), 38.2 (d, C11), 37.8 (t, C4), 34.9 (d, *i*-Pr CH), 33.5 (d, *i*-Pr CH), 31.8 (t, C15), 21.0 (t, CH_2 of Et), several peaks ca. 18.4 (q, *i*-Pr CH_3), 15.3 (q, CH_3 at C11), 12.3 (q, CH_3 of Et).

(2*R*)-*cis*,*anti*,*cis*-2,3,5b,6,7,8,8a,9,9a,9b-Decahydro-3-ethyl-2-methyl-1*H*-cyclopent[*b*]-*as*-indacene-*cis*,*endo*-7,8-diol Diisopropylketal (18). A solution of 0.6 g (1.6 mmol) of cis and trans trienes **17** in 120 mL of specially purified Skelly B contained in an ordinary 4-oz glass

(23) We have made a significant improvement in the preparation of *cis*-bicyclo[3.3.0]oct-6-en-2-one, an intermediate in the synthesis[5,6] of **3**. See Supplementary Material for Whitesell, J. K.; Minton, M. A. *J. Am. Chem. Soc.* **1986**, *108*, 6802.

bottle was deoxygenated by bubbling argon through it for 1 h. A septum was wired onto the bottle, which was then immersed in a large unsilvered Pyrex Dewar containing isopropyl alcohol cooled to −75 °C by a refrigeration coil. The Dewar was placed in a Rayonet type RS preparative photochemical reactor and irradiated at 3500 A for 24 h. (The exact time depended on the individual lamps employed and was determined by irradiating a sample for a shorter time, determining the ratio of triene to diene by ^{13}CMR and extrapolating to 90% conversion.) Over irradiation had to be avoided as the ratio of diastereomeric dienes decreased to nearly 1:1 after 110 h, even though some triene was still present (equilibrium being established?). Low temperature was also necessary, as a room temperature run gave a nearly 1:1 ratio of **18** and **19**. After having been warmed to room temperature, concentration (vacuum replaced with argon) gave 0.6 g (100%) of product as a pale yellow oil. At conversions up to 90% the ratio of inseparable diastereomeric dienes **18** and **19** was 4:1 in favor of the configuration corresponding to ikarugamycin.[11] Several samples could be irradiated simultaneously.

(2*R*)-*cis*,*anti*,*cis*-2,3,5b,6,7,8,8a,9,9a,9b-Decahydro-3-ethyl-2-methyl-1*H*-cyclopent[b]-*as*-indacene-*cis*,endo-7,8-diol (20). A solution of 2.2 g (5.9 mmol) of crude dienes **18** and **19** (including some batches with ratios of diastereomers less than 4:1) in 60 mL of methanol, 15 mL of THF, and 2.5 mL of water was acidified with 0.5 mL of 2 N HCl and stirred overnight at room temperature. After 15 h the solution was concentrated (vacuum replaced with argon) and again treated as above. After another 24 h solid sodium bicarbonate was added, and the mixture was concentrated (vacuum replaced with argon) and filtered under argon through silica gel with ethyl acetate. The crude product (1.7 g) was purified by preparative HPLC by using 2:1 Skelly B/ethyl acetate. There were obtained 0.86 g (50%) of **20** as a yellow oil which soon crystallized as well as small quantities of the slower moving diastereomeric diene **21**, the corresponding aromatized material, and another unidentified trienediol as oils.

Major diastereomer 20: ^{1}HMR (360 MHz) 5.68 (m, 1 H, C7-H or C8-H), 5.64 (m, 1 H, J = 2.5, C7-H or C8-H), 4.01 (ddd, 1 H, J = 4, 6.5, 9.5, C3-H), 3.95 (dd, 1 H, J = 4, 6, C17-H), 2.98 (br q, 1 H, J = 8.5, C5-H), 2.66 (qd, 1 H, J = 6, 9.5, C16-H), 2.59 (m, 1 H, C10-H), 2.35–2.18 (m, 3 H, C11-H, C13-H, and C14-H), 2.12 (septet, 1 H, J = 7, C12-H), 2.00 (ddd, 1 H, J = 6.5, 8.5, 12.5, C4-H_{exo}), 1.52 (ddd, 1 H, J = 7.5, 9.5, 12.5, C4-H_{endo}), 1.46–1.27 (m, 3 H, C15-H and CH_2 of Et), 1.12 (dt, 1 H, J = 7.5, 12.5, C15-H), 0.95 (d, 3 H, J = 7, CH_3 at C11), 0.94 (t, 3 H, J = 7.5, CH_3 of Et), ca. 0.9 (m, 1 H, C12-H); ^{13}CMR (20 MHz) 151.2 (s, C9), 148.8 (s, C6), 116.0 (d, C7 or C8), 116.0 (d, C8 or C7), 75.6 (d, C17 or C3), 75.3 (d, C3 or C17), 47.9 (d, C14 or C13), 47.3 (d, C13 or C14), 47.1 (d, C10), 45.6 (d, C16), 43.4 (d, C5), 39.3 (t, C4), 37.8 (t, C12), 37.3 (d, C11), 32.4 (t, C15), 21.8 (t, CH_2 of Et), 15.5 (q, CH_3 at C11), 12.4 (q, CH_3 of Et).

Minor diastereomer 21: ^{1}HMR (360 MHz) 5.70 (m, 2 H, C7-H and C8-H), ca. 4.1 (m, 1 H, C3-H), 3.96 (dd, 1 H, J = 4, 6, C17-H), 3.0–0.85 (m, remaining protons except Me), 0.94 (t, 3 H, J = 7.5, CH_3 of Et), 0.79 (d, 3 H, J = 7, CH_3 at C11); ^{13}CMR (90 MHz) 150.5 (s, C9), 148.3 (s, C6), 116.2 (d, C7 or C8), 115.5 (d, C8 or C7), 75.5 (d, C17 or C3), 74.1 (d, C3 or C17), 48.7 (d, C13 or C14), 48.1 (d, C14 or C13), 46.6 (d, C16), 45.0 (d, C10), 42.8 (d, C5), 38.5 (t, C12), 37.7 (t, C4), 34.9 (d, C11), 31.6 (t, C15), 21.2 (t, CH_2 of Et), 14.6 (q, CH_3 at C11), 12.7 (q, CH_3 of Et).

Spectral data for other byproducts will be found in the Supplementary Material.

(2*R*)-*cis*,*anti*,*cis*,*cis*-2,3,5,5a,5b,6,7,8,8a,9,9a,9b-Dodecahydro-3-ethyl-2-methyl-1*H*-cyclopent[*b*]-*as*-indacene-*cis*,*endo*-7,8-diol (22). Ammonia (120 mL) was redistilled from a blue solution with lithium wire into a flask at −78 °C containing 0.7 g (0.1 mol, 40 equiv) of pentane-washed lithium wire and 55 mL of ether under argon. A solution of 0.55 mL of *tert*-butyl alcohol (5.8 mmol, 2.4 equiv) in 3.5 mL of ether was added with stirring, followed by dropwise addition of a solution of 0.65 g (2.4 mmol) of dienediol **20** in 10 mL of ether over 10 min. The dark blue mixture was stirred 4 h at −78 °C and then allowed slowly to warm over several hours to 0 °C and finally to room temperature overnight. The mixture was then cooled in ice and quenched by careful dropwise addition of methanol and then water. After acidification with concentrated HCl the layers were separated, and the aqueous phase was washed twice more with ether. The combined organic layers were washed with water, 1 N sodium bicarbonate, and brine. Concentration and filtration through silica gel with ethyl acetate gave 0.52 g (80%) of yellow, semicrystalline product which was purified by semipreparative HPLC by using 3:1 Skelly B/ethyl acetate. There were obtained 0.3 g (45%) of **22** as well as earlier fractions containing small amounts of the *cis*-1,2-reduced species with opposite regiochemistry and the 1,4-reduced diol corresponding to **2** but with opposite stereochemistry at C9, all as white crystalline solids.

Major 1,2-reduced diol 22: ^{1}HMR (360 MHz) 5.27 (m, 1 H, C8-H), 4.09 (br m, 1 H, C3-H), 3.93 (br m, 1 H, C17-H), 2.53 (qd, 1 H, J = 6, 9, C16-H), 2.30 (dm, 1 H, J = 3, ?, 18, C7-H), 2.23–1.85 (m, 11 H), 1.68 (dd, 1 H, J = 5.5, 10.5), 1.62 (dd, 1 H, J = 9, 12.5), 1.49 (m, 2 H), 1.28 (m, 1 H, J = 7.5, ?, CH_2 of Et), 0.96 (m, 1 H, C12-H), 0.93 (t, 3 H, J = 7.5, CH_3 of Et), 0.70 (d, 3 H, J = 7, CH_3 at C11); ^{13}CMR (22.5 MHz) 146.1 (s, C9), 114.5 (d, C8), 77.2 (d, C17), 74.1 (d, C3), 48.4 (d, C10), 47.3 (d, C5), 45.9 (2C, d, C13 and C16), 43.5 (d, C14), 38.4 (d, C6), 37.7 (t, C12), 36.2 (t, C4), 34.1 (d, C11), 29.4 (t, C15), 27.1 (t, C7), 20.7 (t, CH_2 of Et), 160.0 (q, CH_3 at C11), 12.6 (q, CH_3 of Et).

(2*R*)-(+)-*cis*,*trans*,*anti*,*cis*,*cis*-2,3,3a,5a,5b,6,7,8,8a,9,9a,9b-Dodecahydro-3-ethyl-2-methyl-1*H*-cyclopent[*b*]-*as*-indacene-*cis*,*endo*-7,8-diol (2). A milky "solution" of 55 mg (0.17 mmol) of crude **28** in 2 mL of methanol, 1 mL of THF, and 0.4 mL of water was acidified with 1 drop of concentrated HCl and heated under reflux for 1.5 h. The now homogeneous solution was cooled, neutralized with 1 N sodium bicarbonate, and extracted twice with ether. The combined extracts were washed with brine and concentrated leaving 39 mg (83%) of crude diol **2** as a white crystalline solid. An analytical sample was recrystallized from benzene and Skelly B as very fine needles: mp 132–4 °C; $[\alpha]^{22}_D$ +20.8° (*c* 0.77, absolute EtOH); ^{1}HMR (360 MHz) 5.76 (narrow m, 2 H, C7-H and C8-H), 4.08 (m, 1 H, C3-H), 3.93 (dd, 1 H, J = 4, 6, C17-H), 2.55 (br 5 line m, 1 H, J = ca. 9.5, C16-H), 2.33 (m, 1 H), 2.24 (br pentet, 1 H, J = 7.5), 2.17–2.04 (m, 6 H, includes OH), 2.02 (dd, 1 H, J = 7.5, 8.5), 1.64 (dd, 1 H, J = 9, 12.5), 1.61–1.42 (m, 3 H), 1.39–1.25 (m, 2 H), 1.19 (qd, 1 H, J = 7, 11), 0.93 (t, 3 H, J = 7, CH_3 of Et), 0.88 (d, 3 H, J = 7, CH_3 at C11), 0.69 (td, 1 H, J = 6.5, 12, C12-H); ^{13}CMR (90 MHz) 131.1 (d, C8), 128.4 (d, C7), 76.9 (d, C17), 74.2 (d, C3), 51.6 (d, C5), 48.2, 47.9 (2C), 47.7, 44.6 (all d, C6, C9, C10, C13, C14), 44.6 (d, C16), 38.2 (t, C12 or C4), 37.2 (t, C4 or C12), 33.1 (d, C11), 28.6 (t, C15), 21.6 (t, CH_2 of Et), 17.7 (q, CH_3 at C11), 13.3 (q, CH_3 of Et).

Acknowledgment. The research efforts that led to these results have been supported by the National Institutes of Health (AI-20157 and GM-31750) as well as the Robert A. Welch Foundation (F-626). We thank P. da Silva Jardin, V. D. Tran, and M. K. Fisher for the preparation of intermediates and preliminary photochemical experiments.

Supplementary Material Available: Complete experimental details for all transformations not reported here as well as UV, ^{1}HMR, and ^{13}CMR data for the 4:1 mixture of **18** and **19** and mass spectral and analytical data for **7S**, **6S**, **10**, **14**, **22**, and **2** (21 pages). Ordering information is given on any current masthead page.