Total Synthesis of Spinosyn A. 1. Enantioselective Construction of a Key Tricyclic Intermediate by a Multiple Configurational Inversion Scheme

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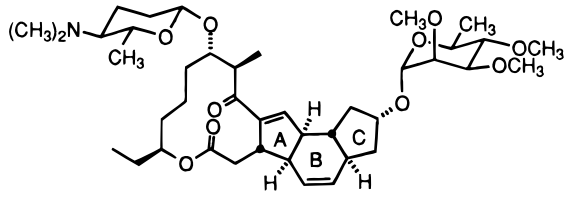
Received November 24, 1997

Abstract: The condensation of (+)-7,7-dimethoxynorbornen-2-one with the cerium reagent derived from enantiopure bromide (+)-**11** gives rise to an exo carbinol, which readily undergoes highly stereocontrolled anionic oxy-Cope rearrangement. Conversion of the resulting ketone into **20** proceeds with clean epimerization at C-11 (spinosyn numbering) to properly set the absolute configuration at that site. Reduction of **20** with lithium in liquid ammonia serves to introduce two additional stereogenic centers of the perhydro-*as*-indacene core. In addition, the protocol makes possible the convenient incorporation of a functionalized two-carbon appendage at C-3 and ultimate generation of a cyclohexene double bond after stereochemical inversion at C-7. This scheme leads to **34**, a tricyclic compound subsequently shown to be an advanced precursor to the powerful insecticide spinosyn A.

The macrocyclic lactone class of natural products, encompassing hundreds of compounds possessing varied biological activity, is often regarded as one of the more challenging areas of total synthesis as a consequence of the substantive structural variation among its members.[2,3] In 1991, impressive insecticidal inhibitory properties, most notably against Lepidoptera larvae, were reported for a multifactored complex produced by the newly discovered species *Saccharopolyspora spinosa*.[4] This soil microbe is responsible for producing a polar, nine-component mixture whose constituents differ in the level of N, O, and C methylation of the sugar and aglycone components. The most prevalent member was initially shown by spectroscopic means, including X-ray crystallography, to be **1**.[5] The absolute stereochemical assignment to spinosyn A (**1**)[6] as well as its eventual common name[7] materialized later.

The revolutionary discovery of the insecticidal potency of this macrolide has been met with intense degradative[8] and synthetic scrutiny.[9] Although **1** does contain D-(+)-forosamine[10] and tri-*O*-methyl-D-rhamnose as unique appendages, its perhydro-*as*-indacene core is recognized to be present in a relatively small number of antibiotics such as ikarugamycin (**2**)[11,12] and capsimycin (**3**).[13] Despite this similarity, noteworthy differences exist. Thus, the absolute configuration of the perhydro-*as*-



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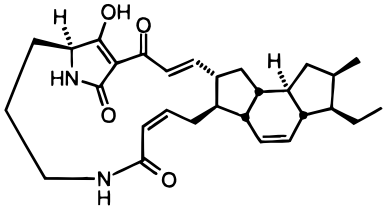

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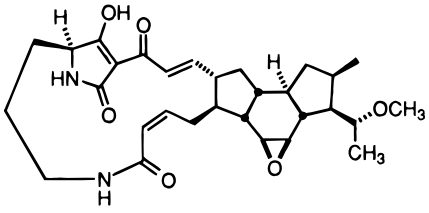

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(2) Omura, S.; Ed. *Macrolide Antibiotics: Chemistry, Biology, and Practice*; Academic Press: Orlando, FL, 1984.

(3) Campbell, W. C., Ed. *Ivermectin and Abamectin*; Springer-Verlag: New York, 1989.

(4) Boeck, L. D.; Chio, E. H.; Eaton, T. E.; Godfrey, O. W.; Michel, K. H.; Nakatsukasa, W. M.; Yao, R. C. Eur. Pat. Appl. 375316, 1990; *Chem. Abstr.* **1991**, *114*, 80066.

(5) Kirst, H. A.; Michel, K. H.; Martin, J. W.; Creemer, L. C.; Chio, E. H.; Yao, R. C.; Nakatsukasa, W. M.; Boeck, L. D.; Occolowitz, J. L.; Paschal, J. W.; Deeter, J. B.; Jones, N. D.; Thompson, G. D. *Tetrahedron Lett.* **1991**, *32*, 4839.

(6) Kirst, H. A.; Michel, K. H.; Mynderase, J. C.; Chio, E. H.; Yao, R. C.; Natsukasa, W. M.; Boeck, L. D.; Occolowitz, J. L.; Paschal, J. W.; Deeter, J. B.; Thompson, G. D. In *Synthesis and Chemistry of Agrochemicals III*; Baker, D. R., Fenyes, J. G., Steffens, J. J., Eds.; ACS Symposium Series No. 504; American Chemical Society: Washington, DC, 1992; pp 214−215 and references therein.

(7) The names initially adopted for **1** (LY232105, A83543A, and lepicidin A) have been recently abandoned in favor of spinosyn A (Kirst, H. A.; communication dated June 7, 1994).

(8) Martynow, J. G.; Kirst, H. A. *J. Org. Chem.* **1994**, *59*, 1548.

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Published on Web 03/10/1998

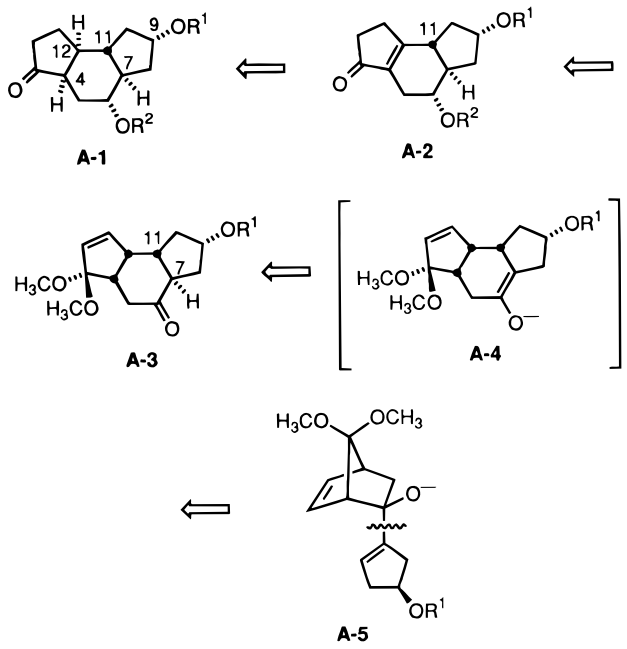
indacene subunit in **1** is opposite to that of **2** and **3**. Furthermore, the tricyclic ring system of the latter two are fused to a 16-membered lactam into which a tetramic acid moiety is embedded, rather than to a 12-membered lactone. Finally, the pattern and type of substituents positioned around the structural core of **1** are entirely different from those of **2** and **3**, neither of which carry saccharide substituents. An inference which can be drawn from this combination of facts is that significant differences in biogenetic origin are at play.

Retrosynthetic Analysis. A distinctive feature of virtually all of the preparations of 5,6,5-*cis*-*anti*-*trans*-decahydro-*as*-indacenes except for those developed in this laboratory[12b−d] and by Whitesell[14] is the utilization of an intramolecular Diels−Alder cycloaddition as the key step for structural assembly. The success realized by us in synthesizing ikarugamycin (**2**) through application of an anionic oxy-Cope pathway prompted examination of the feasibility of elaborating **1** by this means also. Under these circumstances, the substantial thermodynamic preferences resident in these tricyclic networks require proper consideration.[12c,15,16]

A particularly attractive feature of the oxy-Cope approach is the ability to elaborate the entire tricyclic core of **1** carrying an appropriate array of functionality in a single step. The first retrosynthetic plan to have been considered is outlined in Scheme 1. Following coupling of the proper antipodes of two building blocks to generate **A-5**, the only geometrically feasible boatlike [3.3] sigmatropic transition state was expected to generate enolate anion **A-4**. In earlier ground-breaking work,[12b−d] it was learned that protonation of enolates configured in this way under equilibrating conditions would result in the introduction of a trans-fused ring arrangement for thermodynamic reasons. The direct acquisition of **A-3** in this manner properly sets the absolute configuration at C-7 and C-11 (spinosyn A numbering). Complete inversion of stereochemistry at C-4 and C-12 as in **A-1** was expected to materialize cleanly following upon migration of the double bond to an intraring site as in **A-2** and subsequent dissolving metal reduction.[12b−d] This maneuver would serve to complete the plan for setting the absolute configuration of the core.

The promise offered by Scheme 1 was briefly thwarted when the unexpected discovery was made that the conditions required for the **A-3** to **A-2** conversion were sufficiently basic to effect a $\beta \rightarrow \alpha$ configurational change at C-11. When ancillary studies confirmed that **A-2** was less thermodynamically stable than its cis isomer, it became clear that purposeful adjustments of absolute configuration were necessary in order to accommodate these thermodynamic facets of the problem. Herein, we describe

Scheme 1



how advantage can effectively be taken of these inherent thermodynamic biases to arrive at an advanced precursor of spinosyn A (**1**). The ensuing paper describes a body of new chemistry, including the degradation of **1** to **34** and completion of the total synthesis.[17]

Results and Discussion

Resolution of 7,7-Dimethoxynorborn-5-en-2-one. The immediate goal was to obtain both antipodes of ketone **5**. Since the racemate is produced by oxidation of **4a**,[18,19] attempts were initially directed to enzyme-catalyzed kinetic resolution[20] of the chloroacetate derivative **4b**. However, the enantioselectivity uncovered for hydrolysis of **4b** by several lipases proved to be very low. With lipase derived from *P. fluorescens*, for example, the percent ee after 40% reaction was only 3%. Consequently, Johnson's sulfoximine protocol[21] was used instead (Scheme 2). The sterically enforced endo directionality of nucleophilic attack on (±)-**5** results in the production of only the two diastereomers **6** and **7**, which are readily amenable to chromatographic separation and individual thermolysis to regenerate (+)-**5** and (−)-**5**, respectively. The absolute configurational assignments to these enantiomers are based reliably on an X-crystallographic analysis of (+)-**6** (Figure 1), which allowed for direct correlation of the known stereochemistry at sulfur with that resident in the norbornenyl substructure.

The Consequences of Coupling to (−)-5. As a prelude to the requisite coupling reaction, the readily available 4(*R*)-(*tert*-butyldimethylsiloxy)-2-cyclopenten-1-one (**8**)[22] was reduced with L-Selectride, and the enolate anion resulting from 1,4-addition was captured with N-phenyltriflimide to afford the enol triflate **9** (Scheme 3).[23] Treatment of **9** with hexamethylditin

(11) Isolation: (a) Jomon, K.; Kuroda, Y.; Ajisaka, M.; Sakai, H. *J. Antibiot.* **1972**, *25*, 271. (b) Ito, S.; Hirata, Y. *Tetrahedron Lett.* **1972**, 1181, 1185, 2257. (c) Ito, S.; Hirata, Y. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 227, 1813.

(12) Total synthesis: (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. *J. Am. Chem. Soc.* **1989**, *111*, 8037. (c) Paquette, L. A.; Romine, J. L.; Lin, H. S.; Wright, J. *J. Am. Chem. Soc.* **1990**, *112*, 9284. (d) Paquette, L. A.; Macdonald, D.; Anderson, L. G. *J. Am. Chem. Soc.* **1990**, *112*, 9292. (e) Roush, W. R.; Wada, C. K. *J. Am. Chem. Soc.* **1994**, *116*, 2151.

(13) (a) Aizawa, S.; Akutsu, H.; Satomi, T.; Nagatsu, T.; Taguchi, R.; Seino, A. *J. Antibiot.* **1979**, *32*, 193. (b) Seto, H.; Yonehara, H.; Aizawa, S.; Akutsu, H.; Clardy, J.; Arnold, E.; Tanabe, M.; Urano, S. *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu* **1979**, 394; *Chem. Abstr*. **1980**, *92*, 211459u.

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(15) Jurecek, F.; Hanus, V.; Sedmera, P.; Antropiusova, H.; Mach, K. *Tetrahedron* **1979**, *35*, 1463.

(16) For a preliminary account of a portion of this investigation, consult Paquette, L. A.; Gao, Z.; Ni, Z.; Smith, G. F. *Tetrahedron Lett.* **1997**, *38*, 1271.

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(21) Johnson, C. R.; Zeller, J. R. *J. Am. Chem. Soc.* **1982**, *104*, 4021.

(22) Paquette, L. A.; Earle, M. J.; Smith, G. F. *Org. Synth.* **1996**, *73*, 36.

(23) Review: Ritter, K. *Synthesis* **1993**, 735.

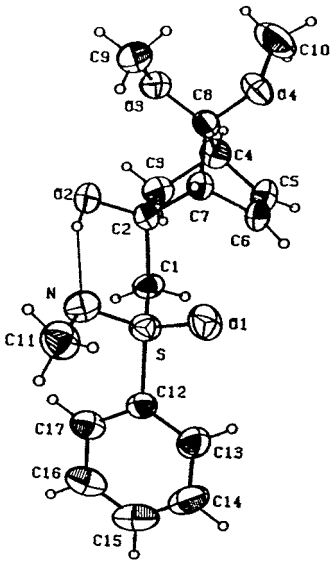
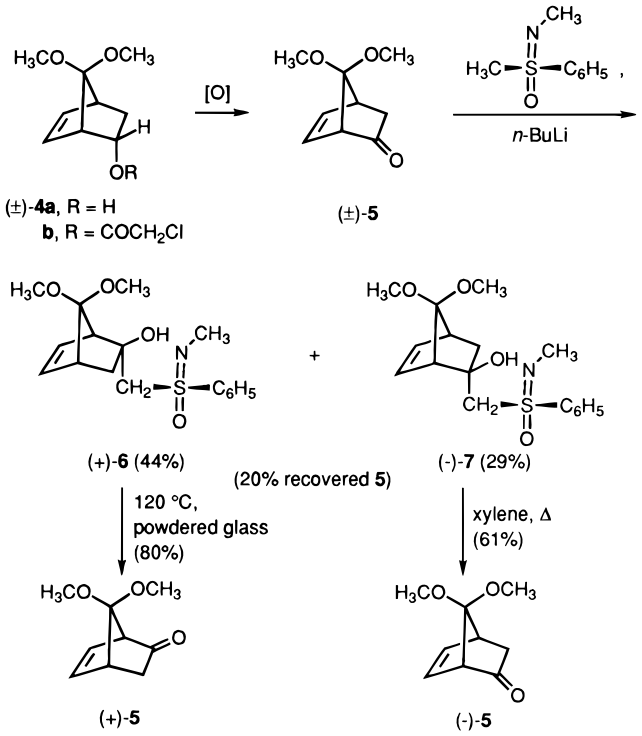


Figure 1. Computer-generated perspective drawing of **6** as determined by X-ray crystallography.

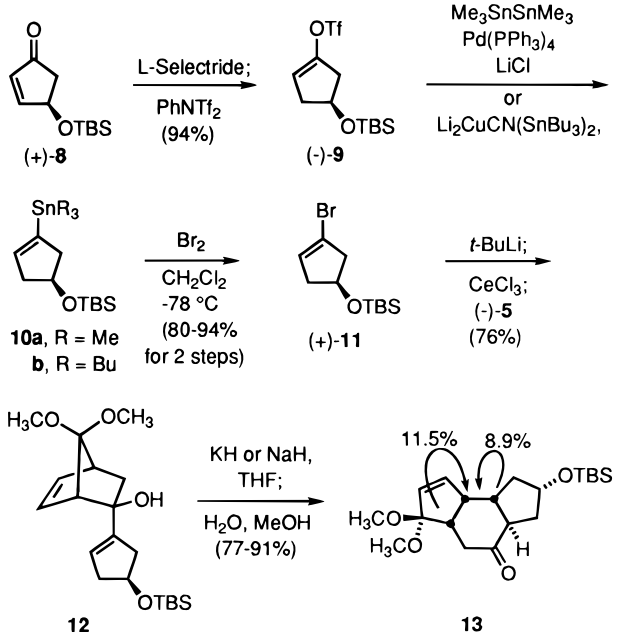
Scheme 2



in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium[24] gave rise to vinylstannane **10a**, brominative substitution[25,26] of which delivered **11** in 80% overall yield. Somewhat greater efficiency (94%) was realized when **9** was reacted with a stannyl cyanocuprate to generate **10b** in advance of conversion to **11**.

As a consequence of the ease of deprotonation of (−)-**5**, recoruse was made to cerium trichloride-mediated coupling[27] with lithiated (+)-**11**. Under these circumstances, 1,2-addition

Scheme 3



occurred from the endo direction to deliver (−)-**12** in 76% yield. When this carbinol was treated with potassium hydride in THF, the oxy-Cope rearrangement was complete within 3 h at room temperature. Although a reaction efficiency of 90% was realized, the isomerization was found to vary appreciably in both rate and yield with the source of KH. On some occasions, decomposition to unidentified compounds was unaccountably observed. No parallel complications unfolded during the use of sodium hydride in THF at reflux (4 h), a fact which led to wholesale adoption of this procedure as this study progressed. It is noteworthy that the addition of 18-crown-6 was unnecessary in either instance as a consequence of the substantial strain release that accompanies dismantling of the norbornene ring. To allow for complete equilibration to (+)-**13**, the highly alkaline aqueous quench solution was allowed to stir for at least 30 min prior to isolation. The stereochemical assignment to this ketone was supported by the determination of NOE effects.

Reduction of the carbonyl functionality in (+)-**13** with diisobutylaluminum hydride proceeded stereoselectively from the β-direction as revealed after acetal hydrolysis by the NOE effects exhibited by (−)-**14** (Scheme 4). Arrival at this intermediate set the stage for base-promoted migration of the cyclopentenone double bond to the intracyclic site. It was soon recognized that this necessary chemical change, best effected with potassium carbonate in hot methanol, also brought about complete configurational inversion at the tertiary allylic site. Equilibration studies performed on **15** and its congeners **16a** and **16b** gave no indication of any return to the respective trans-fused isomer, a feature which we attribute to the thermodynamic bias intrinsic to this particular decahydro-*as*-indacene network.

Establishment of Proper Absolute Configuration. The contrasting thermodynamic preferences that distinguish **13** from **15** are noteworthy in that they demand inversion of the absolute configuration of *both* stereogenic centers at the conjoined B/C rings in order to accommodate ultimate access to spinosyn A. This challenge was easily met and required only that (+)-**5** be involved initially. The advance to diastereomer **20** was accomplished in a fashion entirely parallel to that developed earlier (Scheme 5). Note that the change in configuration of the MOM substituent at C-6 does not alter the overwhelming preference for adoption of a cis B/C ring junction.

(24) Wulff, W. D.; Peterson, G. A.; Bauta, W. E.; Chan, K.-S.; Faron, K. L.; Gilbertson, S. R.; Kaesler, R. W.; Yang, D. C.; Murray, C. K. *J. Org. Chem.* **1986**, *51*, 277.
(25) Crisp, G. T.; Scott, W. J. *Synthesis* **1985**, 335.
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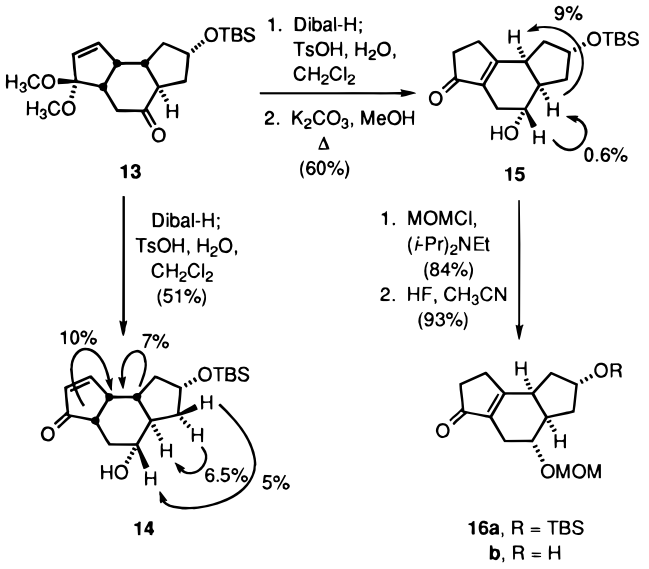
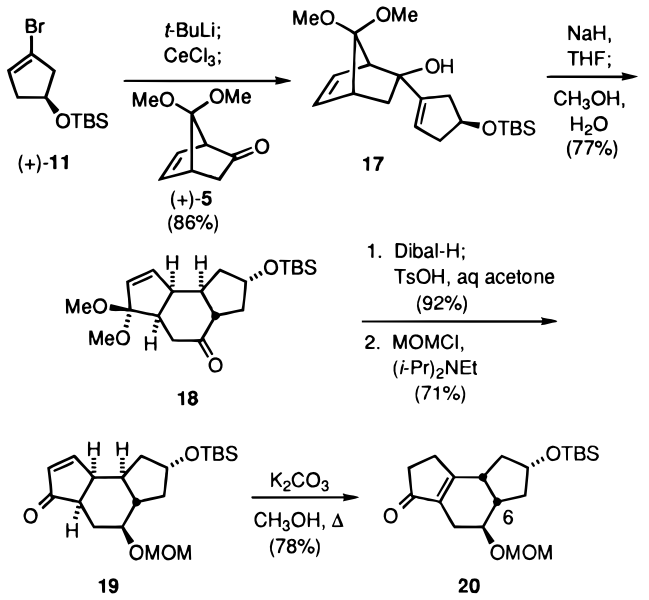
Scheme 4



Scheme 5



The dissolving metal reduction of **20** exhibits considerable sensitivity to preexisting stereochemistry and results in the exclusive formation of **21** (Scheme 6). As a consequence of the clustering of many of the proton signals from this ketone into a rather narrow chemical shift range, the stereochemical assignment was based on several alternative considerations, including (a) the customary adherence to thermodynamic control at the β-enone carbon, which would set C-11 and C-12 in a trans relationship; (b) the recognized greater stability of cis,-anti,cis isomers relative to their cis,anti,trans counterparts,[12c,15] which would position H-4 and H-12 cis to each other; (c) the distinctive appearance of the NMR spectra of **21** relative to those recorded for **14**, and (d) ultimate arrival at spinosyn A.[17]

The critical side chain extension was now undertaken. Exposure of **21** to conventional Wadsworth−Emmons conditions involving the sodium salt of trimethyl phosphonoacetate[28] gave rise to an inseparable 2.5:1 *E/Z* mixture of α,β-unsaturated ester (85%). As foreshadowed by precedent, the deprotonation of these isomers with LDA followed by quenching with aqueous NH_4Cl solution at −78 °C furnished the desired β,γ-isomer cleanly in 93% yield. Exposure of **22** to lithium aluminum hydride[29] then made available the primary carbinol **23**, which was transformed under basic conditions[30] into the *p*-methoxybenzyl derivative. Although we were now positioned to effect the hydroboration−oxidation of **24**, initial probe experiments involving use of the borane·THF complex[31a] proved disappointing in terms of regiochemistry, stereochemistry, and efficiency.[31b] Dramatically, the presence of lithium borohydride[32a] caused **25** to predominate heavily (72%) over the unwanted tertiary C-3 isomer (11%). This observation,[32b] in combination with a substantial difference in polarity between these isomers, was responsible for the ultimate adoption of this protocol.

The protection of the hydroxyl group in **25** as the *tert*-butyldiphenylsilyl derivative proceeded smoothly, thereby making possible selective removal of the MOM functionality with *B*-bromocatecholborane.[33,34] This course of action was followed in order to permit subsequent oxidation of **27** and epimerization of this ketone to deliver the targeted intermediate **29**. That configuration had been inverted from β to α in order to generate the more stable trans B/C arrangement was evident from relevant spectral changes. With arrival at **29**, the absolute configuration at all four stereogenic centers of the tricyclic core had been properly secured.

Functionalization of the ABC Subtarget. Reduction of **29** with DIBAL-H provided a conveniently separable 3:2 mixture of α- and β-alcohols. Dehydration of the α-isomer with the Martin sulfurane[35] followed immediately by selective removal of the TBS group under aqueous acetic acid conditions led to the isolation of **30** (Scheme 7). While the α-alcohol leads predominantly to the indicated product (TLC, NMR analysis, etc.) in relatively rapid fashion (<1 h at 25 °C), the β-alcohol reacts much more slowly (>15 h at 25 °C) and inefficiently and gives rise to a different product in low (15−20%) yield. This dichotomy may be steric in origin. Thus, the E_2 elimination pathway normally adopted by adducts of the sulfurane to secondary alcohols[35] can be readily accommodated in the α-series (see **A**). For the β-isomer, steric crowding precludes extensive population of that conformation (**B**) which projects the leaving group axially. When it does so, elimination to give the more highly substituted cyclohexene isomer would be kinetically favored as is observed. The latter product was not fully characterized due to our inability to separate it from contaminants derived from decomposition of the sulfurane.

Protection of the C-9 hydroxyl in **30** as the pivalate provided a sufficiently stable setting for the steps required to unmask the TBDPS ether and to transform **32** into ketone **33**. The

(28) Wadsworth, W. D., Jr.; Emmons, W. D. *Org. Synth.* **1965**, *45*, 44.
(29) For example: Hori, K.; Hikaga, N.; Inagaki, A.; Mori, S.; Nomura, K.; Yoshii, E. *J. Org. Chem.* **1992**, *57*, 2888.
(30) Evans, D. A.; Rieger, D. L.; Jones, T. K.; Kaldor, S. W. *J. Org. Chem.* **1990**, *55*, 6260.
(31) (a) Brown, H. C.; Vander Jagt, D. L.; Rothberg, I.; Hammer, W. J.; Kawakami, J. H. *J. Org. Chem.* **1985**, *50*, 2179. (b) Under these circumstances, four isomers were produced in a 40:12:9:39 ratio and isolated in a combined 60% yield. The first of these products was subsequently identified as **25**. All four gave the same molecular ion peak in high resoluton MS.
(32) (a) Arase, A.; Nunokawa, Y.; Masuda, Y.; Hoshi, M. *J. Chem. Soc., Chem. Commun.* **1991**, 205 and references therein. (b) This effect can be attributed to the in situ generation of a different borane species. For a summary of past observations, consult Banfi, L.; Narisano, E.; Riva, R. *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; J. Wiley and Sons, Inc.; Chichester, England; 1995; Volume 5, pp 3046−3049.
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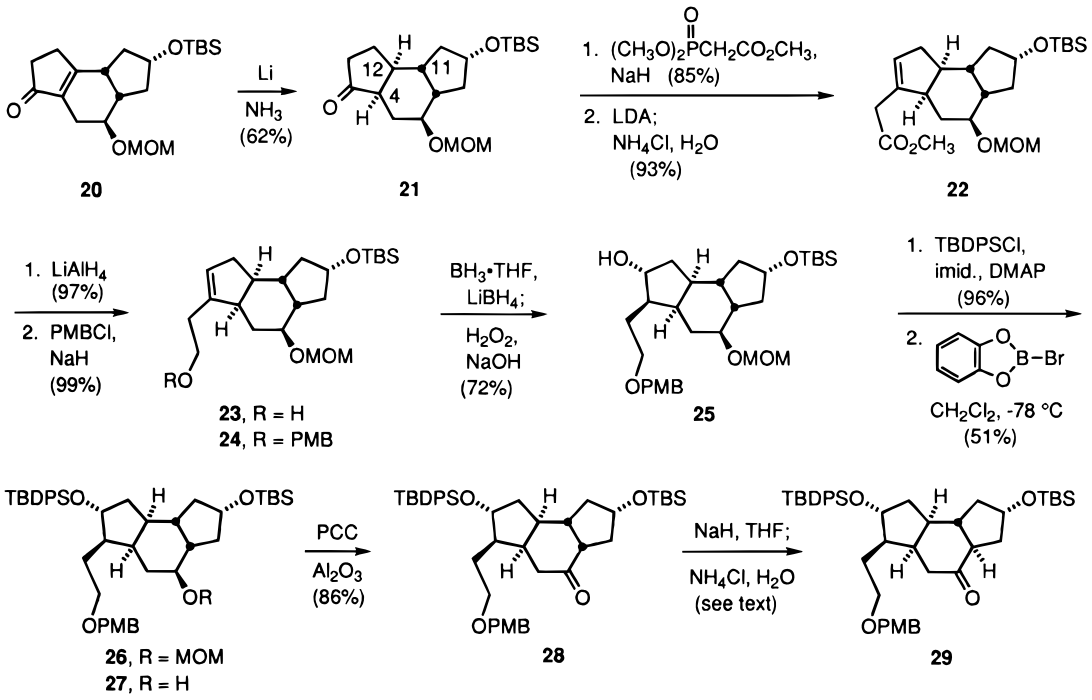
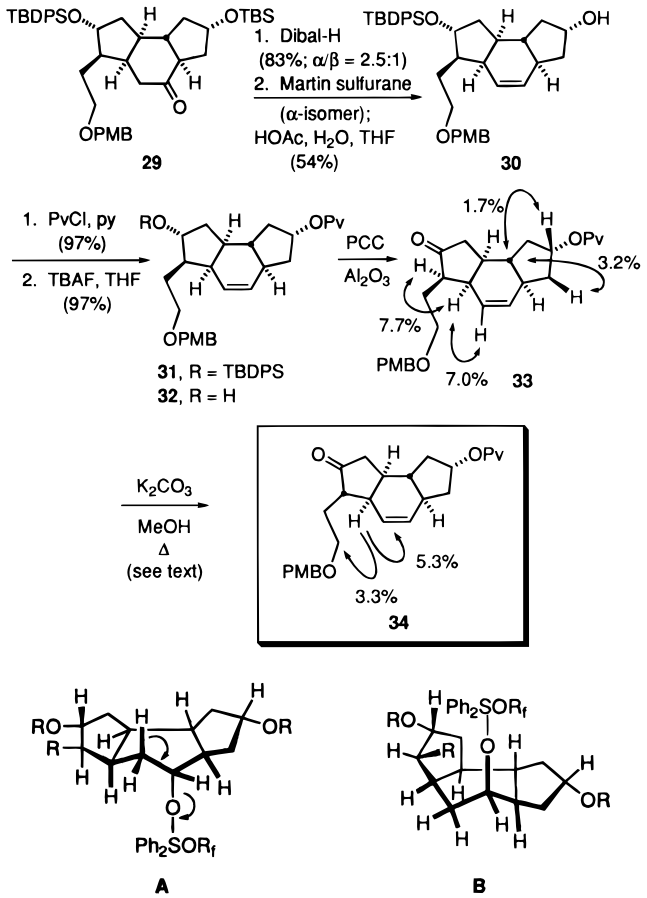
Scheme 6



Scheme 7



stereochemical assignment to **33** was corroborated by multiple NOE experiments. The latter was next exposed to potassium carbonate in methanol at the reflux temperature. Although insufficient quantities of **33** precluded an exhaustive study of this epimerization, it was made clear that migration of the CH_2-CH_2OPMB chain from the sterically congested β interior to the uncluttered α surface could readily be implemented.

Summary. A unified, highly convergent synthesis of (−)-**34** has been realized. The linear sequence from the point where (+)-**11** is conjoined to (+)-**5** is constituted of 21 steps. The route defined herein requires that the absolute configuration at C-11 be properly introduced first. This key issue, which was addressed during the conversion of **19** to **20**, allows for the correct establishment of C-4 and C-12 by reduction under dissolving metal conditions. Finally, reliance is placed on thermodynamically driven epimerization to realize suitable configurational control at C-7. Thus, the protocol is based entirely on the greater stability of the trans fusion of the cyclopentane rings across the "rear" section of the central cyclohexane ring, as well as the energetic preference enjoyed by the overall cis,anti,trans tricyclic arrangement relative to the cis,anti,cis option. Finally, the degradation of spinosyn A to **34** reported in the sequel[17] confirms the assigned structural features. The adaptability of **34** to the total synthesis of **1** to be described subsequently completes the objectives of this investigation.

Experimental Section

General Methods. Melting points are uncorrected. The column chromatographic separations were performed with Woelm silica gel (230−400 mesh). Solvents were reagent grade and in most cases dried prior to use. The purity of all compounds was shown to be >95% by TLC and high field ^{1}H and ^{13}C NMR. The high-resolution and fast-atom-bombardment spectra were recorded at The Ohio State University Campus Chemical Instrumentation Center. Elemental analyses were performed at the Scandinavian Microanalytical Laboratory, Herlev, Denmark or at Atlantic Microlab, Inc., Norcross, GA.

(+)-(*S*)-*S*-[[(1*R*,2*S*,4*R*)-2-Hydroxy-7,7-dimethoxybicyclo[2.2.1]-hept-5-en-2-yl]methyl]-*N*-methyl-*S*-phenylsulfoximine (6) and (−)-(*S*)-*S*-[[(1*S*,2*R*,4*S*)-2-Hydroxy-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-yl]methyl]-*N*-methyl-*S*-phenylsulfoximine (7). A cold (−78 °C) solution of (+)-(*S*)-*N*,*S*-dimethyl-*S*-phenylsulfoximine (1.51 g, 9.19 mmol) in dry THF (40 mL) was treated with *n*-butyllithium (6.2 mL of 1.5 M in hexanes, 9.3 mmol) and stirred for 30 min. A solution of (±)-**5** (1.52 g, 9.05 mmol) in dry THF (10 mL) was added dropwise,

and stirring was maintained at low temperature for 2 h prior to warming to 20 °C. After an additional 3 h of agitation, water (10 mL) was added, the aqueous layer was extracted with ether (2 × 50 mL), and the combined organic phases were washed with water and brine, dried, and concentrated. The residue was chromatographed on silica gel (elution with ethyl acetate) to give 1.33 g (44%) of **6**, 0.85 g (29%) of **7**, and 0.31 g (20%) of recovered **5**.

For **6**: colorless crystals, mp 109−110 °C (from ether); IR ($CHCl_3$, cm^{-1}) 3490; ^1H NMR (300 MHz, $CDCl_3$) δ 7.88−7.84 (m, 2 H), 7.61−7.50 (m, 3 H), 6.18 (dd, J = 6.2, 3.3 Hz, 1 H), 6.09 (ddd, J = 6.2, 3.3, 0.9 Hz, 1 H), 5.92 (s, 1 H), 3.34 (d, J = 13.9 Hz, 1 H), 3.31−3.21 (br s, 1 H), 3.30 (s, 3 H), 3.22 (d, J = 13.9 Hz, 1 H), 3.17 (s, 3 H), 2.86 (br s, 1 H), 2.60 (s, 3 H), 2.01 (dd, J = 12.9, 3.7 Hz, 1 H), 1.41 (d, J = 12.9 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 139.1, 134.9, 133.7, 132.8, 129.3, 129.1, 120.1, 78.6, 64.7, 54.5, 51.9, 49.8, 44.7, 39.5, 29.0; MS m/z ($M^+ - CH_3$) calcd 322.1113, obsd 322.1114; $[\alpha]_D^{22}$ +105 (c 0.56, $CHCl_3$). Anal. Calcd for $C_{17}H_{23}NO_4S$: C, 60.52; H, 6.87. Found: C, 60.94; H, 7.24.

For **7**: colorless crystals, mp 113−4 °C (from ether); IR ($CHCl_3$, cm^{-1}) 3485; ^1H NMR (300 MHz, $CDCl_3$) δ 7.86−7.83 (m, 2 H), 7.55−7.47 (m, 3 H), 6.14 (m, 2 H), 4.80 (br s, 1 H), 3.40 (d, J = 13.8 Hz, 1 H), 3.35 (d, J = 13.8 Hz, 1 H), 3.22 (s, 3 H), 3.22 (d, J = 13.9 Hz, 1 H), 3.16 (s, 3 H), 2.84 (br s, 1 H), 2.59 (s, 3 H), 1.83 (dd, J = 12.9, 3.7 Hz, 1 H), 1.39 (d, J = 12.9 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 139.3, 135.9, 132.38, 132.36, 129.3, 128.9, 120.1, 78.4, 64.6, 53.6, 52.2, 49.5, 44.7, 40.2, 29.1; MS m/z ($M^+ - CH_3$) calcd 322.1113, obsd 322.1120; $[\alpha]_D^{22}$ −29.7 (c 0.62, $CHCl_3$). Anal. Calcd for $C_{17}H_{23}NO_4S$: C, 60.52; H, 6.87. Found: C, 60.58; H, 6.92.

(+)-(1*R*,4*R*)-7,7-Dimethoxybicyclo[2.2.1]hept-5-en-2-one ((+)-5). A 1.50 g (4.6 mmol) sample of **6** was placed in a preheated (120 °C) flask containing 1.53 g of finely powdered glass equipped with a short-path distillation column. After evacuation to 0.1−0.3 Torr, the distillate was collected in a cold (−78 °C) receiver and subjected to flash chromatography on silica gel (elution with hexanes/ethyl acetate 4:1) to give pure (+)-**5** (0.59 g, 80%) as a colorless oil; $[\alpha]_D^{22}$ +596 (c 0.28, $CHCl_3$).

(+)-(1*S*,4*S*)-7,7-Dimethoxybicyclo[2.2.1]hept-5-en-2-one ((−)-5). A solution of **7** (2.40 g, 7.11 mmol) in deoxygenated toluene (150 mL) was heated at reflux for 13 h, cooled, and carefully concentrated at 30 °C and 0.8 Torr. The residue was purified by chromatography on silica gel (elution with hexane) to give (−)-**5** (0.73 g, 61%) of (−)-**6** as a colorless oil; $[\alpha]_D^{22}$ −586 (c 0.27, $CHCl_3$).

(−)-(*S*)-4-(*tert*-Butyldimethylsiloxy)-1-cyclopenten-1-yl Trifluoromethanesulfonate (9). To a solution of L-Selectride (1.0 M in THF, 14.1 mL, 14.1 mmol) in dry THF (110 mL) at −78 °C was added dropwise a solution of (+)-**8** (3.0 g, 14.1 mmol) and triethylamine (0.2 mL) in THF (50 mL) over 15 min. After 10 additional min, *N*-phenyltriflimide (4.5 g, 12.6 mmol) was added in two portions. The mixture was gradually warmed to room temperature, stirred for 3 h, freed of THF in vacuo, and partitioned between petroleum ether (200 mL) and saturated $NaHCO_3$ solution (100 mL) overnight. The aqueous layer was extracted with petroleum ether (2 × 150 mL), the combined organic layers were washed with brine, dried, and concentrated, and the residue was purified by flash chromatography on silica gel (elution with 1% triethylamine and 1% ethyl acetate in petroleum ether) to give **9** (4.1 g, 94%); IR (neat, cm^{-1}) 1430, 1215, 1148, 1085; ^1H NMR (300 MHz, $CDCl_3$) δ 5.54 (br t, J = 2.2 Hz, 1 H), 4.57 (hept, J = 3.8 Hz, 1 H), 2.82 (br dd, J = 15.3, 7.3 Hz, 1 H), 2.69 (br dd, J = 15.3, 7.3 Hz, 1 H), 2.55 (br d, J = 16.3 Hz, 1 H), 2.34 (br d, J = 16.3 Hz, 1 H), 0.89 (s, 9 H), 0.07 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 146.5, 118.6 (q, J_{C-F} = 320.9, Hz), 115.3, 69.6, 41.2, 39.1, 25.7, 18.0, −4.9; MS m/z ($M^+ - OSO_2CF_3$) calcd 197.1362, obsd 197.1359; $[\alpha]_D^{22}$ −1.69 (c 0.77, $CHCl_3$). Anal. Calcd for $C_{12}H_{21}F_3O_4SSi$: C, 41.60; H, 6.11. Found: C, 41.83; H, 6.20.

(+)-[[(*S*)-3-Bromo-3-cyclopenten-1-yl]oxy]-*tert*-butyldimethylsilane (11). A. Via 10a. A mixture of **9** (4.30 g, 12.4 mmol), hexamethylditin (4.30 g, 13.0 mmol), $Pd(PPh_3)_4$ (0.25 g, 0.02 mmol), and lithium chloride (4.02 g, 94 mmol) in dry THF (100 mL) was refluxed under N_2 for 3.5 h. Petroleum ether (300 mL) was added, the mixture was washed with $NaHCO_3$ solution (100 mL), the aqueous layer was extracted with petroleum ether (2 × 200 mL), and the combined organic layers were washed with brine, dried, and concentrated. The residue was passed through a short column of silica gel (elution with 1% triethylamine in petroleum ether), and the eluent was concentrated and dissolved in CH_2Cl_2 (200 mL). Bromine (0.1 M in CH_2Cl_2, 130 mL, 13.0 mmol) was introduced at −78 °C, and the solution was washed sequentially after 20 min with aqueous ammonia solution (20 mL of 30% ammonium hydroxide was diluted to 200 mL), water, and brine and then dried and concentrated. Purification was effected by chromatography on silica gel (elution with 1% triethylamine and 1% ethyl acetate in petroleum ether) afforded an oil that was distilled in vacuo in a Kugelrohr apparatus to give **11** (2.76 g, 80%); IR (neat, cm^{-1}) 1462, 1365, 1260, 1197; ^1H NMR (300 MHz, $CDCl_3$) δ 5.79−5.76 (m, 1 H), 4.59−4.52 (m, 1 H), 2.91−2.77 (m, 1 H), 2.65−2.49 (m, 2 H), 2.39−2.23 (m, 1 H), 0.89 (s, 9 H), 0.06 (s 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 128.6, 118.0, 71.7, 49.3, 43.0, 25.8, 18.1, −4.78, −4.81; MS m/z ($M^+ - Br$) calcd 197.1362, obsd 197.1340; $[\alpha]_D^{22}$ +18.5 (c 0.96, C_6H_6). Anal. Calcd for $C_{12}H_{21}BrOSi$: C, 47.64; H, 7.64. Found: C, 47.54; H, 7.62.

B. By Way of Stannane 10b. Diisopropylamine (1.11 g, 11.0 mmol) was cooled to −78 °C and treated sequentially with *n*-butyllithium (6.87 mL of 1.6 M, 11.0 mmol), dry THF (20 mL), and tri-*n*-butyltin hydride (2.76 g, 9.5 mmol). After 30 min in the cold, copper(I) cyanide (0.40 g, 4.5 mmol) was introduced, the suspension was warmed slightly until the solid dissolved to give a yellow-green solution, and the mixture was returned to −78 °C prior to the dropwise addition of **9** (1.04 g, 3.0 mmol) dissolved in dry THF (5 mL). After 1 h, a saturated solution of $NaHCO_3$ (50 mL) was added, and the product was extracted into petroleum ether, dried, and concentrated. Flash chromatography on the residue on silica gel (elution with 0.5% triethylamine in petroleum ether) removed some but not all of the tin impurities. This material (0.88 g, 1.81 mmol) in CH_2Cl_2 (10 mL) at −78 °C was added to a solution of bromine in CH_2Cl_2 (7.24 mL of 0.25 M, 1.81 mmol) until the color of bromine just persisted. After the workup described above, there was isolated 0.44 g (94%) of **11**.

(1*S*,2*R*,4*S*)-2-[(*S*)-4-(*tert*-Butyldimethylsiloxy)-1-cyclopenten-1-yl]-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-ol (12). Cerium chloride heptahydrate (0.89 g, 2.4 mmol) was dried at 140 °C under vacuum for 2 h. After being cooled to room temperature, dry THF (10 mL) was added. The slurry was stirred overnight and cooled to −78 °C prior to introduction of the lithium reagent. A solution of (+)-**11** (0.56 g, 2.0 mmol) in dry THF (10 mL) at −78 °C was treated dropwise with *tert*-butyllithium (1.7 M in hexanes, 2.5 mL, 4.2 mmol), stirred for 30 min, transferred via cannula to the cerium chloride slurry, and stirred at −78 °C for another 30 min. To this solution was added (−)-**5** (0.32 M in THF, 4.67 mL, 1.5 mmol), and the mixture was stirred at −78 °C for 2 h, warmed to room temperature over 2 h, and agitated overnight. After being returned to −78 °C, the reaction mixture was treated with 10% acetic acid (20 mL) and diluted with petroleum ether (50 mL). The aqueous layer was extracted with petroleum ether (50 mL), and the combined organic layers were washed with brine, dried, and evaporated. The residue was purified by flash chromatography on silica gel (elution with 20% ethyl acetate in petroleum ether) to afford **12** (0.42 g, 76%), mp 34.5−36 °C; IR ($CHCl_3$, cm^{-1}) 3480; ^1H NMR (300 MHz, C_6D_6) δ 5.97 (ddd, J = 6.1, 3.4, 1.0 Hz, 1 H), 5.91 (ddd, J = 6.1, 3.4, 0.8 Hz, 1 H), 5.26 (t, J = 1.9 Hz, 1 H), 4.57−4.51 (m, 1 H), 4.43 (s, 1 H), 3.23 (ddd, J = 13.0, 5.8, 1.4 Hz, 1 H), 2.98 (s, 3 H), 2.96 (s, 3 H), 2.83 (br s, 1 H), 2.72 (br s, 1 H), 2.62−2.38 (m, 3 H), 1.90−1.79 (m, 2 H), 1.02 (s, 9 H), 0.12 (s, 3 H), 0.10 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 145.6, 135.8, 131.1. 123.0, 121.1, 79.4, 73.3, 54.3, 52.1, 49.0, 46.0, 43.2, 42.6, 39.1, 26.1, 18.3, −4.6, −4.7; MS m/z ($M^+ - OCH_3$) calcd 335.2042, obsd 335.2067; $[\alpha]_D^{22}$ −138 (c 0.49, $CHCl_3$). Anal. Calcd for $C_{20}H_{34}O_4Si$: C, 65.53; H, 9.35. Found: C, 65.26; H, 9.26.

(2*S*,3a*R*,5a*S*,8a*R*,8b*S*)-2-(*tert*-Butyldimethylsiloxy)-2,3,3a,5,5a,6,-8a,8b-octahydro-6,6-dimethoxy-*as*-indacen-4(1*H*)-one (13). A. Use of Potassium Hydride. To a suspension of potassium hydride (prewashed with hexane and dried under vacuum, 14 mg, 0.35 mmol) in dry THF (30 mL) at −40 °C was added **12** (0.10 g, 0.27 mmol) in one portion. The mixture was warmed to room temperature and stirred for 3 h, cooled again in an ice-bath, and treated with water (1 mL) and methanol (1 mL). The reaction mixture was stirred at room-temperature

overnight, diluted with hexane (100 mL), washed with brine, and dried. Purification of the residue by flash chromatography on silica gel (elution with 10% ethyl acetate in petroleum ether) afforded **13** (91 mg, 91%); IR (neat, cm^{-1}) 1719; ^1H NMR (300 MHz, C_6D_6) δ 5.86 (m, 1 H), 5.68 (m, 1 H), 4.06 (m, 1 H), 2.95 (s, 3 H), 2.92 (s, 3 H), 2.63−2.43 (m, 2 H), 2.17−1.92 (m, 2 H), 1.88−1.67 (m, 2 H), 1.51−1.21 (m, 4 H), 0.94 (s, 9 H), 0.03 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 209.4, 134.5, 133.1, 112.4, 73.0, 49.2, 48.5, 48.0, 44.4, 43.5, 41.4, 39.1, 38.0, 34.4, 26.0, 18.2, −4.6, −4.7; MS *m/z* (M^+) calcd 336.2226, obsd 336.2253; $[\alpha]_D^{22}$ +46 (*c* 0.60, $CHCl_3$). Anal. Calcd for $C_{20}H_{34}O_4Si$: C, 65.53; H, 9.35. Found: C, 65.79; H, 9.47.

B. With Sodium Hydride as Base. To a solution of **12** (0.21 g, 0.57 mmol) in THF (60 mL) at 0 °C was added sodium hydride (60%, 53 mg, 1.3 mmol). The mixture was refluxed for 4 h, cooled to −20 °C, and quenched with water (2 mL) and methanol (3 mL). The identical workup delivered 0.16 g (77%) of **13** very reproducibly.

(3a*S*,5*R*,5a*R*,7*S*,8a*S*,8b*R*)-2-(*tert*-Butyldimethylsiloxy)-4,5,5a,6,7,8,-8a,8b-octahydro-5-hydroxy-*as*-indacen-3(3a*H*)-one (14). Ketone **13** (0.11 g, 0.31 mmol) and 4 Å molecular sieves were mixed in CH_2Cl_2 (15 mL), stirred at room temperature for 30 min, and cooled to −78 °C. To this mixture was added dropwise a solution of DIBAL-H (0.62 mL, 0.62 mmol) in CH_2Cl_2 (5 mL). After 10 min, saturated $NaHCO_3$ solution (0.5 mL) was added, and the mixture was stirred and filtered through a pad of Celite and sodium sulfate, which was rinsed with CH_2Cl_2. The filtrate was treated with *p*-toluenesulfonic acid (20 mg) and water (1 mL), stirred for 10 min, washed with water and brine, and then dried. Purification of the residue by flash chromatography on silica gel (elution with 50% ethyl acetate in petroleum ether) gave **14** (51 mg, 51%), mp 103−4 °C (from ether); IR ($CHCl_3$, cm^{-1}) 3660, 1700; ^1H NMR (300 MHz, $CDCl_3$) δ 7.62 (dd, J = 5.9, 2.5 Hz, 1 H), 6.30 (dd, J = 5.9, 2.0 Hz, 1 H), 4.36−4.29 (m, 1 H), 3.61−3.54 (m, 1 H), 3.27−3.21 (m, 1 H), 2.56 (q, J = 6.1 Hz, 1 H), 2.21−2.08 (m, 2 H), 1.94−1.68 (m, 3 H), 1.56−1.36 (m, 4 H), 0.86 (s, 9 H), 0.03 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 212.1, 162.1, 134.4, 74.0, 72.4, 46.2, 43.9, 42.7, 41.3, 40.0, 38.4, 32.8, 25.8, 18.1, −4.77, −4.80; MS *m/z* (M^+) calcd 322.1964, obsd 322.1965; $[\alpha]_D^{22}$ −129 (*c* 0.4, $CHCl_3$). Anal. Calcd for $C_{18}H_{30}O_3Si$: C, 67.03; H, 9.38. Found: C, 66.81; H, 9.37.

(5*R*,5a*R*,7*S*,8a*S*)-7-(*tert*-Butyldimethylsiloxy)-1,4,5,5a,6,7,8,8a-octahydro-5-hydroxy-*as*-indacen-3(2*H*)-one (15). A slurry of **13** (20 mg, 0.05 mmol) and 4 Å molecular sieves (200 mg) in CH_2Cl_2 (10 mL) was stirred for 10 min and cooled to −78 °C. To the mixture was added DIBAL-H (1 M in hexane, 0.11 mL, 0.11 mmol) dropwise. The mixture was stirred at −78 °C for 1 h, quenched with saturated $NaHCO_3$ solution (2 mL), stirred at room temperature for 30 min, and filtered through a Celite pad (CH_2Cl_2 rinse). The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL), and the combined organic layers were treated with *p*-toluenesulfonic acid monohydrate (100 mg, 0.520 mmol), shaken occasionally for 5−10 min, and neutralized with saturated $NaHCO_3$ solution (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic phases were washed with brine, dried, and concentrated. The residue was dissolved in methanol (3 mL), treated with potassium carbonate (50 mg), refluxed for 2 h, and freed of methanol in vacuo. The residue was purified by flash chromatography on silica gel (elution with 50% ethyl acetate in petroleum ether) to afford **15** (11 mg, 60%) as white crystals, mp 104−5 °C (from petroleum ether); IR ($CHCl_3$, cm^{-1}) 3600, 1688, 1640; ^1H NMR (300 MHz, C_6D_6) δ 4.16−4.11 (m, 1 H), 3.32−3.27 (m, 1 H), 2.88−2.85 (m, 1 H), 2.54 (br d, J = 14.0 Hz, 1 H), 2.30−2.24 (m, 1 H), 2.11−1.62 (series of m, 9 H), 1.18−1.10 (m, 1 H), 0.96 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 206.8, 173.9, 135.9, 73.2, 69.9, 43.5, 40.5, 39.8, 35.1, 28.8, 28.2, 26.1, 26.0, 18.2, −4.58, −4.64; MS *m/z* (M^+) calcd 322.1964, obsd 322.1955; $[\alpha]_D^{22}$ −11.2 (*c* 0.25, $CHCl_3$). Anal. Calcd for $C_{20}H_{30}O_3Si$: C, 67.03; H, 9.38. Found: C, 66.75; H, 9.30.

(5*R*,5a*R*,7*S*,8a*S*)-7-(*tert*-Butyldimethylsiloxy)-1,4,5,5a,6,7,8,8a-octahydro-5-(methoxymethoxy)-*as*-indacen-3(2*H*)-one (16a). Hydroxy ketone **15** (50 mg, 0.15 mmol) was dissolved in Hunig's base (2 mL) and cooled to 0 °C. Chloromethyl methyl ether (0.2 mL, 1.5 mmol) was introduced dropwise, and the mixture was stirred at room temperature for 5 h, diluted with CH_2Cl_2 (20 mL) and saturated $NaHCO_3$ solution (10 mL), and stirred for another 30 min. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), the combined organic layers were washed with brine, dried, and concentrated, and the residue was purified by chromatography on silica gel (elution with 50% ethyl acetate in petroleum ether) to give **16a** (48 mg, 84%); IR (neat, cm^{-1}) 1700, 1647; ^1H NMR (300 MHz, C_6D_6) δ 4.56 (d, J = 6.8 Hz, 1 H), 4.42 (d, J = 6.8 Hz, 1 H), 4.14−4.10 (m, 1 H), 3.35−3.21 (m, 1 H), 3.15 (s, 3 H), 2.83 (q, J = 8.8 Hz, 1 H), 2.61 (br d, J = 16.5 Hz, 1 H), 2.45 (quint, J = 8.0 Hz, 1 H), 2.19−2.10 (m, 1 H), 2.06 (t, J = 4.6 Hz, 2 H), 1.92−1.67 (series of m, 4 H), 1.61−1.53 (m, 1 H), 1.17−1.08 (m, 1 H), 0.95 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 206.0, 173.0, 135.6, 95.2, 75.5, 73.1, 55.2, 41.6, 40.3, 40.2, 39.9, 35.0, 28.0, 25.5, 18.2, −4.60, −4.64; MS *m/z* (M^+) calcd 366.2226, obsd 366.2282; $[\alpha]_D^{22}$ −29.4 (*c* 0.47, $CHCl_3$).

(5*R*,5a*R*,7*S*,8a*S*)-1,4,5,5a,6,7,8,8a-Octahydro-7-hydroxy-5-(methoxymethoxy)-*as*-indacen-3(2*H*)-one (16b). To a solution of **16a** (83 mg, 0.23 mmol) in acetonitrile (30 mL) was added a solution of 48% aqueous hydrofluoric acid in acetonitrile (1.38 M, 1.64 mL, 2.26 mmol). The mixture was stirred at room temperature for 0.5 h, quenched with triethylamine (0.5 mL), and concentrated. Purification of the residue by flash chromatography on silica gel (elution on ethyl acetate) afforded **16b** (53 mg, 93%); IR ($CHCl_3$, cm^{-1}) 3550, 1692, 1644; ^1H NMR (300 MHz, C_6D_6) δ 4.53 (d, J = 6.8 Hz, 1 H), 4.40 (d, J = 6.8 Hz, 1 H), 4.13−4.08 (m, 1 H), 3.33−3.21 (m, 1 H), 3.14 (s, 3 H), 2.83 (q, J = 8.6 Hz, 1 H), 2.60 (br d, J = 16.4 Hz, 1 H), 2.45 (quint, J = 8.1 Hz, 1 H), 2.18−2.08 (m, 1 H), 2.05 (t, J = 4.6 Hz, 2 H), 1.92−1.67 (m, 5 H), 1.60−1.51 (m, 1 H), 1.16−1.07 (m, 1 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 206.1, 173.0, 135.5, 95.2, 75.3, 72.0, 55.2, 41.6, 40.1, 39.8, 39.4, 35.0, 30.1, 25.4; MS *m/z* (M^+) calcd 252.1361, obsd 252.1303; $[\alpha]_D^{22}$ −44.7 (*c* 0.3, $CHCl_3$).

(1*R*,2*S*,4*R*)-2-[(*S*)-4-(*tert*-Butyldimethylsiloxy)-1-cyclopenten-1-yl]-7,7-dimethoxybicyclo[2.2.2]hept-5-en-2-ol (17). To a solution of (+)-**11** (1.51 g, 5.4 mmol) in dry THF (50 mL) at −78 °C was added *tert*-butyllithium (1.7 M in pentane, 7.6 mL, 13 mmol) during 10 min. This solution was transferred via cannula to a slurry of dry cerium(III) chloride (7.0 mmol) in THF (30 mL). The resulting deep orange solution was stirred at −78 °C for 30 min, at which point a solution of (+)-**5** (0.60 g, 3.6 mmol) in dry THF (6 mL) was added dropwise at −78 °C. The mixture was warmed to 20 °C overnight and cooled in ice before being quenched with 20% acetic acid (50 mL). The separated aqueous phase was extracted with petroleum ether (2 × 50 mL), and the combined organic fractions were dried and evaporated. The residue was purified by MPLC on silica gel (elution with 20% ethyl acetate in petroleum ether) to give **17** (1.10 g, 86%) as a colorless oil which solidified on standing, mp 68−69 °C; IR ($CHCl_3$, cm^{-1}) 3560, 1155, 1100; ^1H NMR (300 MHz, $CDCl_3$) δ 6.10 (m, 1 H), 5.86 (m, 1 H), 5.28 (m, 1 H), 4.48 (m, 1 H), 4.36 (s, 1 H), 3.33 (s, 3 H), 3.19 (s, 3 H), 2.95−2.92 (m, 1 H), 2.80−2.78 (m, 1 H), 2.57−2.40 (m, 3 H), 2.30−2.21 (m, 1 H), 1.84 (dd, J = 12.9, 0.8 Hz, 1 H), 1.77 (dd, J = 12.9, 3.4 Hz, 1 H), 0.87 (s, 9 H), 0.04 (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 144.4, 135.4, 131.5, 123.5, 120.6, 78.8, 72.9, 54.0, 52.3, 49.5, 45.4, 42.6, 42.0, 38.4, 25.9, 18.1, −4.7, −4.8; MS *m/z* (M^+) calcd 366.2227, obsd 366.2218.

(2*S*,3a*S*,5a*R*,8a*S*,8b*R*)-2-(*tert*-Butyldimethylsiloxy)-2,3,3a,5,5a,6,-8a,8b-Octahydro-6,6-dimethoxy-*as*-indacen-4(1*H*)-one (18). Sodium hydride (60% in mineral oil, 0.33 g, 8.4 mmol) was added in one portion to a solution of **17** (1.80 g, 4.9 mmol), in dry THF (150 mL) at 0 °C. The solution was refluxed for 2 h, cooled to 20 °C, diluted with petroleum ether (200 mL), and extracted with $NaHCO_3$ solution (2 × 100 mL) and brine (2 × 100 mL) prior to drying and concentration. The resulting brown oil was purified by MPLC on Florisil (10% ethyl acetate in petroleum ether as eluent) to yield **18** (1.39 g, 77%) as a colorless oil; IR (film, cm^{-1}) 1720; ^1H NMR (300 MHz, $CDCl_3$) δ 5.98 (dd, J = 6.1, 1.8 Hz, 1 H), 5.68 (dd, J = 6.1, 2.6 Hz, 1 H), 4.13 (m, 1 H), 3.02 (s, 3 H), 2.98 (s, 3 H), 2.89 (m, 1 H), 2.62 (dd, J = 17.4, 2.6 Hz, 1 H), 2.49 (m, 1 H), 2.33−1.96 (m, 5 H), 1.63 (m, 1 H), 1.21 (m, 1 H), 1.00 (s, 9 H), 0.011 (s, 3 H), 0.013 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 212.1, 135,3, 132.4, 112.0, 72.3, 49.5, 48.8, 48.6, 44.0, 43.1, 40.2, 38.9, 38.2, 34.7, 25.8, 18.0, −4.7, −4.8; MS *m/z* (M^+ − OMe) calcd 335.2042, obsd 335.2049.

(3a*R*,5*S*,5a*S*,7*S*,8a*R*,8b*S*)-7-(*tert*-Butyldimethylsiloxy)-4,5,5a,6,7,8,-8a,8b-octahydro-5-(methoxymethoxy)-*as*-indacen-3(3a*H*)-one (19). Diisobutyl aluminum hydride (1 M in hexanes, 5 mL, 5 mmol) was added over 5 min to a solution of **18** (0.33 g, 0.91 mmol) in dry hexanes (50 mL) at −78 °C. After 10 min, saturated potassium sodium tartrate solution (20 mL) was added, and the reaction mixture was allowed to warm to 20 °C, stirred for 6 h, washed with water (50 mL), 10% aqueous acetic acid (3 × 50 mL), and brine (100 mL), and finally dried and evaporated. The residue was purified by MPLC on silica gel (elution with 50% petroleum ether in ethyl acetate) to give the hydroxy ketone (0.27 g, 92%) as a colorless oil; IR ($CHCl_3$, cm^{-1}) 1695; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55 (dd, J = 5.8, 2.5 Hz, 1 H), 6.26 (dd, J = 5.8, 2.0 Hz, 1 H), 4.25 (m, 1 H), 3.68 (m, 1 H), 3.28 (m, 1 H), 2.56 (m, 1 H), 2.34 (m, 1H), 2.23−2.10 (m, 2 H), 1.84−1.72 (m, 2 H), 1.72 (br s, 1 H), 1.55 (m, 1 H), 1.28 (m, 1 H), 1.06 (m, 1 H), 0.87 (s, 9 H), 0.03 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 210.6, 160.9, 134.2, 73.4, 72.3, 46.0, 45.4, 42.5, 41.3, 40.3, 38.3, 33.5, 26.1, 18.3, −4.5, −4.7; MS m/z (M^+) calcd 322.1964, obsd 322.1969.

Methoxymethyl chloride (350 μL, 5 mmol) was added dropwise to a solution of the hydroxy ketone (0.28 g, 0.86 mmol) dissolved in diisopropylethylamine (3 mL) and CH_2Cl_2 (2 mL). After 18 h of stirring, saturated $NaHCO_3$ solution was introduced. After 30 min, the separated organic layer was washed with water and brine prior to drying and solvent evaporation. The residue was purified by MPLC on silica gel (30% ethyl acetate in petroleum ether as eluent) to give **19** (0.23 g, 71%) as a colorless oil; IR ($CHCl_3$, cm^{-1}) 1695; ^1H NMR (300 MHz, $CDCl_3$) δ 7.52 (dd, J = 5.8, 2.4 Hz, 1 H), 6.22 (dd, J = 5.8, 2.1 Hz, 1 H), 4.65 (d, J = 7.0 Hz, 1 H), 4.51 (d, J = 7.0 Hz, 1 H), 4.24 (m, 1 H), 3.61 (m, 1 H), 3.31 (s, 3 H), 3.26 (m, 1 H), 2.51 (m, 1 H), 2.32 (m, 1 H), 2.19−2.03 (m, 2H), 1.83 (m, 1 H), 1.73 (m, 1 H), 1.58 (m, 1 H), 1.31−1.13 (m, 2 H), 0.85 (s, 9 H), 0.02 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 211.0, 161.8, 134.4, 94.5, 78.0, 71.8, 55.1, 45.2, 43.1, 42.6, 41.1, 40.0, 38.1, 29.5, 25.8, 18.0, −4.8, −4.8; MS m/z (M^+) calcd 366.2226, obsd 366.2173. Anal. Calcd for $C_{20}H_{34}O_4Si$: C, 65.53; H, 9.36. Found: C, 65.55; H, 9.29.

(5*S*,5a*S*,7*S*,8a*R*)-7-(*tert*-Butyldimethylsiloxy)-1,4,5,5a,6,7,8,8a-octahydro-5-(methoxymethoxy)-*as*-indacen-3(2*H*)-one (20). A mixture of **19** (0.23 g, 0.61 mmol) and potassium carbonate (20 mg) in methanol (25 mL) was refluxed for 2 h, cooled, and freed of solvent. The residue was dissolved in CH_2Cl_2 (25 mL), rinsed with water (5 mL) and brine (2 × 10 mL), dried, evaporated, and purified by MPLC on silica gel (50% ethyl acetate in petroleum ether as eluent) to give **20** (0.18 g, 78%) as a colorless oil; IR ($CHCl_3$, cm^{-1}) 1690, 1650; ^1H NMR (300 MHz, $CDCl_3$) δ 4.70 (d, J = 6.9 Hz, 1 H), 4.64 (d, J = 6.9 Hz, 1 H), 4.30 (m, 1 H), 3.85 (m, 1 H), 3.36 (s, 3 H), 2.86 (m, 1 H), 2.61−2.07 (series of m, 9 H), 1.59 (m, 1 H), 1.43 (m, 1 H), 0.83 (s, 9 H), 0.02 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 207.7, 175.1, 134.6, 95.2, 74.1, 73.0, 55.5, 41.7, 39.7, 39.5, 38.5, 34.9, 28.2, 25.7, 23.9, 18.0, −4.8, −4.9; MS m/z (M^+) calcd 366.2226, obsd 366.2294. Anal. Calcd for $C_{20}H_{34}O_4Si$: C, 65.53; H, 9.36. Found: C, 65.26; H, 9.32.

(3a*R*,5*S*,5a*S*,7*S*,8a*S*,8b*S*)-7-(*tert*-Butyldimethylsiloxy)decahydro-5-(methoxymethoxy)-*as*-indacen-3(2*H*)-one (21). A solution of **20** (0.20 g, 0.53 mmol) in dry THF (5 mL) containing *tert*-butyl alcohol (40 μL, 0.41 mmol) was added dropwise over 3 min to a solution of liquid ammonia (20 mL) containing lithium wire (40 mg, excess) at −33 °C. After 3 min, isoprene (0.5 mL) was introduced followed by solid ammonium chloride (2 g) and saturated NH_4Cl solution (5 mL). The reaction mixture was allowed to warm to 20 °C over 4 h and the aqueous residue was extracted with ether (3 × 10 mL). The combined organic phases were washed with water (10 mL) and brine (2 × 10 mL) prior to drying. The solvent was evaporated, and the residue was purified by MPLC on silica gel (20% ethyl acetate in petroleum ether as eluent) to give **21** (0.12 g, 62%) as a colorless oil; IR ($CHCl_3$, cm^{-1}) 1740; ^1H NMR (300 MHz, $CDCl_3$) δ 4.71 (d, J = 6.8 Hz, 1 H), 4.60 (d, J = 6.8 Hz, 1 H), 4.26 (m, 1 H), 3.65 (m, 1 H), 3.35 (s, 3 H), 2.43−1.81 (series of m, 11 H), 1.71−1.64 (m, 1 H), 1.49−1.37 (m, 2 H), 0.88 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 220.4, 95.4, 75.7, 72.6, 55.4, 46.5, 42.1, 41.9, 39.4, 37.8, 35.9, 26.9, 25.9, 25.5, 18.0, −4.8; MS m/z (M^+) calcd 368.2383, obsd 368.2335. Anal. Calcd for $C_{20}H_{36}O_4Si$: C, 65.18; H, 9.85. Found: C, 65.24; H, 9.84.

Methyl (3a*R*,5*S*,5a*S*,7*S*,8a*S*,8b*S*)-7-(*tert*-Butyldimethylsiloxy)-1,-3a,4,5,5a,6,7,8,8a,8b-decahydro-5-(methoxymethoxy)-*as*-indacene-3-acetate (22). A solution of trimethyl phosphonoacetate (0.68 g, 3.73 mmol) in dry THF (20 mL) was added via cannula to a flame-dried flask containing 0.14 g (3.3 mmol) of sodium hydride. After 20 min of stirring, this solution was added to a solution of **21** (0.46 g, 1.24 mmol) in THF (15 mL) at 30−40 °C, kept at this temperature for 1 h, and then refluxed for 3 h. The reaction mixture was quenched by the careful addition of 5 mL of water. The separated aqueous layer was extracted with ether (50 mL x 4), and the combined extracts were washed with aqueous $NaHCO_3$ solution (10 mL) and brine (10 mL) prior to drying and concentration. The residue was purified by chromatography on silica gel (elution with hexanes−ethyl acetate, 8:1) to provide 0.45 g (85%) of α,β-unsaturated esters as an oily liquid.

A solution of diisopropylamine (1.5 mL, 10.6 mmol) in dry THF (20 mL) was cooled to −15 °C, treated with a solution of *n*-butyllithium in hexanes (6.3 mL, 1.6 M, 10.1 mmol), stirred for 15 min at −15 °C, and cooled to −78 C. To this solution was added a solution of the above esters (430 mg, 1.0 mmol) in THF (20 mL). Stirring was maintained for 30 min before quenching with saturated NH_4Cl solution (5 mL). The mixture was extracted with ether (4 × 15 mL), and the combined ether extracts were washed with aqueous $NaHCO_3$ solution (5 mL) and brine (5 mL). The ethereal solution was dried and evaporated to leave a crude product which was purified by chromatography on silica gel (hexanes−ethyl acetate 8:1 as eluent) to yield 0.40 g (93%) of **22** as a colorless oil; IR (film, cm^{-1}) 1743; ^1H NMR (300 MHz, $CDCl_3$) δ 5.47 (br s, 1 H), 4.74 (d, J = 6.8 Hz, 1 H), 4.64 (d, J = 6.8 Hz, 1 H), 4.29 (m, 1 H), 3.68 (s, 3 H), 3.56 (m, 1 H), 3.38 (s, 3 H), 3.10 (m, 2 H), 2.76 (m, 1 H), 2.40 (m, 1 H), 2.25 (m, 1 H), 2.08−2.01 (m, 5 H), 1.81 (m, 1 H), 1.65 (m, 1 H), 1.34 (m, 1 H), 1.01 (m, 1 H), 0.87 (s, 9 H), 0.03 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 171.9, 139.6, 126.6, 95.2, 77.7, 72.9, 55.3, 51.7, 44.3, 42.5, 41.7, 40.5, 40.0, 39.8, 36.7, 35.2, 31.7, 25.9, 18.1, −4.8; MS m/z ($M^+ - H$) calcd 423.2536, obsd 423.2533. Anal. Calcd for $C_{23}H_{40}O_5Si$: C, 65.05; H, 9.49. Found: C, 65.17; H, 9.47.

(3a*R*,5*S*,5a*S*,7*S*,8a*S*,8b*S*)-7-(*tert*-Butyldimethylsiloxy)-1,3a,4,5,-5a,6,7,8,8a,8b-decahydro-5-(methoxymethoxy)-*as*-indacene-3-ethanol (23). To a suspension of lithium aluminum hydride (0.11 g, 2.8 mmol) in dry ether (20 mL) was added a solution of **22** (0.40 g, 0.95 mmol) in 20 mL of ether at 0 °C. The mixture was stirred for 10 min, quenched with wet ether (20 mL), treated with saturated Rochelle salt solution (10 mL), agitated vigorously, and extracted with ether. The combined ethereal phases were washed with $NaHCO_3$ solution and brine, dried, and concentrated. The crude product was purified by chromatography on silica gel (elution with hexanes−ethyl acetate 1:1) to give 360 mg (97%) of **23** as a colorless oil; IR (film, cm^{-1}) 3439; ^1H NMR (300 MHz, $CDCl_3$) δ 5.42 (m, 1 H), 4.73 (d, J = 6.8 Hz, 1 H), 4.64 (d, J = 6.8 Hz, 1 H), 4.65 (m, 2 H), 4.60 (m, 2 H), 3.95 (m, 1H), 3.66 (m, 2 H), 2.70 (m, 2 H), 2.5−1.8 (series of m, 7 H), 1.7−1.0 (series of m, 6 H), 0.88 (s, 9 H), 0.04 (s, 6 H); MS m/z (M^+) calcd 396.2699, obsd 396.2708.

***tert*-Butyl[[(2*S*,3a*S*,4*S*,5a*R*,8a*S*,8b*S*)-1,2,3,3a,4,5,5a,8,8a,8b-decahydro-6-[2-[(*p*-methoxybenzyl)oxy]ethyl]-4-(methoxymethoxy)-*as*-indacen-2-yl]oxy]dimethylsilane (24).** A solution of **23** (0.29 g, 0.73 mmol) in DMF/THF (1.1 v/v, 8 mL) was added to a flask containing sodium hydride (37 mg of 60% mineral oil dispersion, 0.92 mmol) at −20 °C. After 15 min at 0 °C, *p*-methoxybenzyl chloride (0.27 g, 1.7 mmol) was introduced in one portion, and the reaction mixture was allowed to stir overnight at room temperature, warmed to 40 °C, stirred for 2 h, cooled in an ice−water bath, and quenched with water (2 mL). Diethylamine (2.0 mL) was added to destroy the excess *p*-methoxybenzyl chloride. The mixture was stirred at 0 °C for an additional 1 h and diluted with ether (50 mL). The ethereal solution was washed with water and brine. After drying and concentration, the crude product was chromatographed on silica gel (hexanes−ethyl acetate 8:1 as eluent) to provide 0.37 g (99%) of **24** as a colorless oil; IR (film, cm^{-1}) 1248, 1172, 1100, 1040; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27 (m, 2 H), 6.89 (m, 2 H), 5.30 (br s, 1 H), 4.73 (d, J = 6.8 Hz, 1 H), 4.64 (d, J = 6.8 Hz, 1 H), 4.45 (m, 2 H), 4.21 (m, 1 H), 3.81 (s, 2 H), 3.80 (s, 3 H), 3.55 (m, 1 H), 3.38 (s, 3 H), 2.51−2.17 (series of m, 2 H), 2.11−1.99 (m, 8 H), 1.81 (m, 1 H), 1.65 (m, 1 H), 1.28 (m, 1 H), 1.01 (m, 1 H),

0.88 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 159.2, 144.4, 130.6, 129.4, 129.2, 122.9, 113.8, 95.3, 78.0, 72.9, 72.5, 68.6, 55.2, 44.7, 43.0, 41.9, 40.4, 40.1, 39.9, 36.8, 32.2, 29.6, 25.9, 18.1, −4.8; MS *m*/*z* (M^+) calcd 516.3271, obsd 516.3254.

(2*R*,3*R*,3a*R*,5*S*,5a*S*,7*S*,8a*S*,8b*S*)-7-(*tert*-Butyldimethylsiloxy)-dodecahydro-3-[2-[(*p*-methoxybenzyl)oxy]ethyl]-5-(methoxymethoxy)-*as*-indacen-2-ol (25). To a cooled (−30 °C) mixture of **24** (31 mg, 0.06 mmol) and lithium borohydride (26 mg, 1.2 mmol) in THF (1.0 mL) was added dropwise a solution of BH_3·THF (1 M solution in THF, 1.2 mL, 1.2 mmol, 20 equiv) in THF. The reaction mixture was stirred at −20 to −30 °C for 4.5 h, quenched with careful addition of 0.2 mL of water at −20 °C, and allowed to warm to 20 °C. To this white slurry was added 0.2 mL of premixed 1:1 (v/v) of 3 N sodium hydroxide and 30% hydrogen peroxide at room temperature. The mixture was stirred for an additional 1 h, diluted with 5 mL of water, and extracted with ethyl acetate (5 × 15 mL). The combined extracts were washed with $NaHCO_3$ solution and brine, dried, and freed of solvent. The crude product was purified on a silica gel column (hexanes/ethyl acetate 1:1 as eluent) to obtain 22 mg (72%) of major component **25** as an oily liquid; IR (film, cm^{-1}) 3418; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (m, 2 H), 6.81 (m, 2 H), 4.68 (d, J = 6.7 Hz, 1 H), 4.61 (d, J = 6.7 Hz, 1 H), 4.40 (m, 2 H), 4.22 (m, 1 H), 3.95 (m, 1 H), 3.74 (s, 3 H), 3.61 (m, 1 H), 3.47 (m, 2 H), 3.32 (s, 3 H), 2.19−1.61 (series of m, 14 H), 1.36 (td, J = 12.6, 6.0 Hz, 1 H), 0.86 (m, 1 H), 0.81 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 159.4, 129.5, 114.0, 99.7, 96.1, 78.0, 77.3, 76.8, 73.0, 72.4, 70.5, 55.4, 55.2, 53.3, 42.0, 41.3, 40.9, 39.2, 38.7, 38.2, 30.1, 29.5, 25.9, 18.1, −4.75, −4.80; MS *m*/*z* (M^+) calcd 534.3377, obsd 534.3389. Anal. Calcd for $C_{30}H_{50}O_6Si$: C, 67.38; H, 9.42. Found: C, 67.42; H, 9.41.

***tert*-Butyl[[(2*R*,3*R*,3a*R*,5*S*,5a*S*,7*S*,8a*S*S,8b*S*)-7-(*tert*-butyldimethylsiloxy)dodecahydro-3-[2-[(*p*-methoxybenzyl)oxy]ethyl]-5-(methoxymethoxy)-*as*-indacen-2-yl]oxy]diphenylsilane (26).** A solution of **25** (0.50 g, 0.94 mmol), imidazole (0.32 g, 4.68 mmol), and DMAP (55 mg, 0.45 mmol) in 15 mL of dry CH_2Cl_2 was stirred for 15 min at 0 °C, treated with *tert*-butyldiphenylsilyl chloride (0.69 g, 2.3 mmol), stirred at 0 °C overnight, quenched with 0.8 mL of absolute ethanol, and after 1 h poured into 10 mL of cold (0 °C) $NaHCO_3$ solution. The separated aqueous phase was extracted with CH_2Cl_2, and the combined organic extracts were washed with water (5 mL) and brine (5 mL). After drying and removal of solvent, the crude product was purified by chromatography on silica gel (elution with hexanes−ethyl acetate 6:1) to yield 0.70 g (96%) of **26** as a colorless oil; IR (film, cm^{-1}) 1472, 1248, 1110; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71−7.64 (m, 4 H), 7.45−7.36 (m, 6 H), 7.26−7.21 (m, 2 H), 6.90−6.85 (m, 2 H), 4.63 (ABq, J = 6.7 Hz, $\Delta\nu$ = 20.4 Hz, 2 H), 4.37 (ABq, J = 11.5 Hz, $\Delta\nu$ = 14.0 Hz, 2 H), 4.25 (m, 1 H), 4.06 (m, 1 H), 3.81 (s, 3 H), 3.49 (m, 1 H), 3.41 (t, J = 6.8 Hz, 2 H), 3.35 (s, 3 H), 2.21−1.42 (series of m, 12 H), 1.29−1.26 (m, 2 H), 1.05 (s, 9 H), 0.87 (s, 9 H), 0.84 (m, 1 H), 0.02 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 159.1, 135.9, 134.4, 130.8, 129.50, 129.46, 129.1, 127.51, 127.47, 113.8, 95.7, 78.8, 78.0, 72.5, 72.3, 69.5, 55.4, 55.3, 50.6, 41.9, 41.7, 41.4, 39.3, 39.0, 38.8, 37.5, 29.0, 28.7, 27.1, 25.9, 18.1, 14.1, −4.7, −4.8; MS *m*/*z* (M^+) calcd 772.4554, obsd 772.4538. Anal. Calcd for $C_{46}H_{68}O_6Si_2$: C, 71.46; H, 8.86. Found: C, 71.64; H, 8.99.

(2*S*,3a*S*,4*S*,5a*R*,6*R*,7*R*,8a*S*,8b*S*)-2-(*tert*-Butyldimethylsiloxy)-7-(*tert*-butyldiphenylsiloxy)dodecahydro-6-[2-[(*p*-methoxybenzyl)oxy]-ethyl]-*as*-indacen-4-ol (27). A solution of **26** (39 mg, 0.05 mmol) in 12 mL of dry CH_2Cl_2 was cooled to −78 °C and treated with a solution of *B*-bromocatecholborane in CH_2Cl_2 (0.47 mL of 0.194 M, 0.09 mmol). The reaction mixture was stirred at −78 °C for 15 min, quenched with 2 mL of saturated $NaHCO_3$ solution at −78 °C, allowed to warm to 20 °C, and diluted with 2 mL of 0.2 N sodium hydroxide. The separated aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were washed with 0.1 N aqueous sodium hydroxide, water, and brine prior to drying and concentration. The crude product was purified by chromatography on silica gel (elution with hexanes−ethyl acetate 2:1) to furnish 19 mg (51%) of **27** as a colorless oil; IR (film, cm^{-1}) 3426, 1611, 1513, 1249, 1110; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66−7.44 (m, 4 H), 7.42−7.32 (m, 6 H), 7.25−6.89 (m, 2 H), 6.88−6.86 (m, 2 H), 4.36 (ABq, J = 11.6 Hz, $\Delta\nu$ = 16.4 Hz, 2 H), 4.21 (m, 1 H), 4.05 (m, 1 H), 3.81 (s, 3 H), 3.57 (m, 1 H), 3.41 (t, J = 7.0 Hz, 2 H), 2.16−2.08 (m, 2 H), 1.99−1.68 (series of m, 6 H), 1.64−1.54 (m, 4 H), 1.51−1.36 (m, 3 H), 1.04 (s, 9 H), 0.87 (s, 9 H), 0.74 (m, 1 H), 0.021 (s, 3 H), 0.016 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 159.1, 135.9, 134.8, 134.4, 130.8, 129.51, 129.46, 129.1, 127.51, 127.46, 113.8, 78.8, 72.6, 72.3, 71.7, 69.3, 55.3, 50.6, 43.2, 42.0, 41.6, 39.06, 39.05, 38.8, 37.6, 31.9, 28.6, 27.1, 25.9, 19.2, 18.0, −4.8; MS *m*/*z* (M^+) calcd 728.9429, obsd 728.9464.

(2*S*,3a*S*,5a*R*,6*R*,7*S*,8a*R*,8b*S*)-2-(*tert*-Butyldimethylsiloxy)-7-(*tert*-butyldiphenylsiloxy)decahydro-6-[2-[(*p*-methoxybenzyl)oxy]ethyl]-*as*-indacen-4(1*H*)-one (28). To a solution of **27** (19 mg, 0.026 mmol) in dry CH_2Cl_2 (2.0 mL) was added a 3-fold excess of pyridinium chlorochromate on alumina in small portions with stirring. After 2 h, the brown suspension was passed through a Florisil column (elution with CH_2Cl_2), and the colorless eluate was concentrated to dryness. The residue was purified on silica gel (elution with hexanes−ethyl acetate 5:1) to furnish 16 mg (86%) of pure **28** as a colorless oil; IR (film, cm^{-1}) 1712; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67−7.64 (m, 4 H), 7.43−7.33 (m, 6 H), 7.21 (m, 2 H), 6.87 (m, 2H), 4.33 (ABq, J = 11.6 Hz, $\Delta\nu$ = 12.1 Hz, 2 H), 4.13 (m, 2 H), 3.81 (s, 3 H), 3.26 (t, J = 7.1 Hz, 2 H), 2.61 (m, 1 H), 2.48 (m, 1 H), 2.39 (m, 1 H), 2.23−2.17 (m, 2 H), 2.12−2.06 (m, 2 H), 2.01−1.80 (m, 4 H), 1.68−1.53 (m, 2 H), 1.46 (m, 1 H), 1.31 (m, 1 H), 1.05 (s, 9 H), 0.86 (s, 9 H), 0.03 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 213.2, 159.1, 135.8, 134.4, 134.2, 130.6, 129.61, 129.56, 129.2, 127.6, 127.5, 113.8, 78.2, 72.5, 72.4, 69.0, 55.3, 50.1, 48.1, 43.4, 41.7, 39.6, 39.0, 38.8, 38.5, 35.3, 28.6, 27.0, 25.8, 19.2, 18.0, −4.8, −4.9; MS *m*/*z* (M^+) calcd 711.3921, obsd 711.3925.

(2*S*,3a*R*,5a*R*,6*R*,7*R*,8a*R*,8b*S*)-2-(*tert*-Butyldimethylsiloxy)-7-(*tert*-butyldiphenylsiloxy)decahydro-6-[2-[(*p*-methoxybenzyl)oxy]ethyl]-*as*-indacen-4(1*H*)-one (29). A flame-dried flask was charged with 6.3 mg of NaH (55% dispersion in mineral oil, 0.144 mmol) and a solution of 78 mg (10.7 mmol) of **28** in THF. The suspension was allowed to stir overnight, cooled to −78 °C, and quenched with 0.5 mL of aqueous NH_4Cl solution. The mixture was extracted with ether, and the combined extracts were dried and concentrated. The residue was purified by silica gel chromatography (elution with 3.2% of ethyl acetate in benzene) to afford 24 mg (94%, based on unreacted **28**, 35% conversion) of the epimerized ketone with 53 mg (65% recovery) of the starting material. The recovered **28** can easily be recycled.

For **29**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67−7.64 (m, 4 H), 7.52−7.28 (m, 6 H), 7.23 (m, 2 H), 6.87 (m, 2 H), 4.32 (ABq, J = 11.6 Hz, $\Delta\nu$ = 12.0 Hz, 2 H), 3.95 (m, 2 H), 3.81 (s, 3 H), 3.29 (t, J = 7.1 Hz, 2 H), 2.61−1.70 (series of m, 11 H), 1.69−1.10 (series of m, 4 H), 1.06 (s, 9 H), 0.86 (s, 9 H), 0.02 (s, 6 H); MS *m*/*z* ($M^+ - CH_3$) calcd 711.3921, obsd 711.3940.

(2*R*,3a*S*,5a*R*,6*R*,7*R*,8a*S*,8b*R*)-6-(*tert*-Butyldiphenylsiloxy)-1,2,3,-3a,5a,6,7,8,8a,8b-decahydro-6-[2-[(*p*-methoxybenzyl)oxy]ethyl]-*as*-indacen-2-ol (30). To a cold (−78 °C) solution of **29** (65 mg, 0.09 mmol) in 15 mL of dry CH_2Cl_2 was added 0.91 mL (0.9 mmol) of 1.0 M DIBAL-H in hexanes. The resulting solution was stirred at −78 °C for 10 min, quenched with saturated $NaHCO_3$ (2 mL) and saturated sodium potassium tartrate solutions (5 mL), and warmed to 20 °C during 30 min. The separated aqueous layer was extracted with ethyl acetate (4 × 20 mL). The combined organic layers were washed with 5 mL of saturated sodium potassium tartrate solution and brine, passed through a pad of magnesium sulfate, and concentrated in vacuo. The residue was chromatographed on silica gel (elution with 25% ethyl acetate in hexanes) to give 38 mg of the major α-alcohol and 15 mg of the minor β-alcohol (83% total yield).

For the α-alcohol: IR (film, cm^{-1}) 3449; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66−7.63 (m, 4 H), 7.39−7.34 (m, 6 H), 7.23−7.20 (m, 2 H), 6.88−6.85 (m, 2 H), 4.35 (ABq, J = 11.5 Hz, $\Delta\nu$ = 11.5 Hz, 2 H), 4.20 (m, 1 H), 3.96 (m, 2 H), 3.80 (s, 3 H), 3.35 (t, J = 6.7 Hz, 2 H), 2.09 (m, 2H), 1.95 (m, 3 H), 1.74 (m, 4 H), 1.49 (m, 3 H), 1.33−1.16 (m, 3 H), 1.04 (s, 9 H), 0.88 (m, 1 H), 0.86 (s, 9 H), 0.01 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 159.1, 135.9, 134.6, 134.4, 130.6, 129.6, 129.5, 129.2, 128.1, 127.8, 127.52, 127.50, 113.8, 79.0, 74.1, 72.6, 72.3, 69.7, 55.3, 48.8, 48.6, 47.8, 42.8, 42.0, 40.4, 39.6, 38.6, 34.3, 30.5, 27.0, 25.9, 19.1, 18.1, −4.8.

Martin's sulfurane (70 mg) was suspended in 4 mL of dry CH_2Cl_2, and the suspension was treated with 38 mg (0.05 mmol) of the α-alcohol

dissolved in 5 mL of dry CH_2Cl_2. The resulting mixture was stirred for 1 h before being quenched with saturated $NaHCO_3$ solution (1.5 mL), diluted with ether (25 mL), and washed with saturated $NaHCO_3$ solution (2 × 5 mL). The organic phase was dried and concentrated to provide a residue which was chromatographed on silica gel (elution with 14% of ethyl acetate in hexanes) to give the dehydration product, which was dissolved in 0.4 mL of THF and treated with 0.4 mL of water, followed by 1.2 mL of acetic acid. The cloudy solution was stirred overnight, cooled in an ice bath, basified with powdered sodium bicarbonate, and extracted with ethyl acetate (6 × 15 mL). The combined organic extracts were washed with brine, dried, and evaporated. The residue was purified by flash chromatography (silica gel, elution with 33% ethyl acetate in hexanes) to give 16 mg (54% over two steps) of **30** as a colorless oil; IR (film, cm^{-1}) 3380; ^1H NMR (300 MHz, $CDCl_3$) δ 7.74−7.63 (m, 4 H), 7.55−7.28 (m, 6 H), 7.24−6.80 (m, 4 H), 5.88 (m, 1 H), 5.63 (m, 1 H), 4.35 (m, 1 H), 4.22 (br s, 2 H), 4.11 (m, 1 H), 3.79 (s, 3 H), 3.22 (m, 1 H), 2.99 (t, J = 9.3 Hz, 2 H), 2.96−2.08 (m, 4 H), 2.05−1.89 (m, 3 H), 1.79 (m, 1 H), 1.71−1.37 (m, 4 H), 1.26 (br s, 1 H), 1.05 (s, 9 H); MS m/z (M^+) calcd 596.8822, obsd 596.8814.

(2*R*,3a*S*,5a*R*,6*R*,7*R*,8a*S*,8a*R*)-7-(*tert*-Butyldiphenylsiloxy)-1,2,3,-3a,5a,6,7,8,8a,8b-decahydro-6-[2-[(*p*-methoxybenzyl)oxy]ethyl]-*as*-indacen-2-yl Pivalate (31). To a cold (0 °C) solution of **30** (16 mg, 0.03 mmol) and 2 mg of DMAP in 0.8 mL of pyridine was added neat pivaloyl chloride (20 mg). The resulting mixture was stirred overnight at 0 °C, quenched with absolute ethanol (0.05 mL), poured into saturated $NaHCO_3$ solution, and extracted with ether (4 × 15 mL). The combined organic layers were dried and evaporated to leave a residue, which was purified by flash chromatography on silica gel to furnish 18 mg (97%) of **31** as a colorless oil; IR (film, cm^{-1}) 1723; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67−7.62 (m, 4 H), 7.43−7.28 (m, 6 H), 7.24−6.80 (m, 4 H), 5.98 (d, J = 15 Hz, 1 H), 5.64 (dt, J = 15, 4.2 Hz, 1 H), 5.09 (m, 1 H), 4.22 (s, 2 H), 4.07 (m, 1 H), 3.80 (s, 3 H), 3.28 (m, 1 H), 3.00 (t, J = 11.0 Hz, 2 H), 2.33−2.23 (m, 2 H), 1.99−1.82 (m, 6 H), 1.58−1.34 (m, 4 H), 1.17 (s, 9 H), 1.05 (s, 9 H); MS m/z (M^+) calcd 681.0001, obsd 681.0026.

(2*R*,3a*S*,5a*R*,6*R*,7*R*,8a*S*,8b*R*)-1,2,3,3a,5a,6,7,8,8a,8b)-Decahydro-7-hydroxy-6-[2-(*p*-methoxybenzyl)oxy]ethyl]-*as*-indacen-2-yl Pivalate (32). A solution of **31** (18 mg, 0.026 mmol) in 2.0 mL of dry THF was treated with tetrabutylammonium fluoride (0.15 mL of 1 M solution in THF, 0.15 mmol). The reaction mixture was stirred at 40 °C for 4 h, cooled in an ice bath, diluted with water (5 mL), and extracted with ethyl acetate (5 × 15 mL). The combined organic layers were dried and evaporated to leave a residue, which was purified by flash chromatography (silica gel, elution with 50% of ethyl acetate in hexanes) to give 11 mg (97%) of **32** as a colorless oil; IR (film, cm^{-1}) 3429, 1723; ^1H NMR (200 MHz, $CDCl_3$) δ 7.24−7.22 (m, 2 H), 6.90−6.85 (m, 2 H), 5.87 (d, J = 9.8 Hz, 1 H), 5.61 (dt, J = 9.8, 2.9 Hz, 1 H), 5.13 (m, 1 H), 4.44 (s, 2 H), 3.97 (m, 1 H), 3.80 (s, 3 H), 3.57 (t, J = 5.6 Hz, 2 H), 3.53 (m, 1 H), 3.02 (m, 1 H), 2.40−2.34 (m, 2 H), 2.17 (m, 1 H), 2.04−1.73 (series of m, 6 H), 1.54 (m, 1 H), 1.41 (m, 1 H), 1.16 (s, 9 H), 0.99 (m, 1 H); MS m/z (M^+) calcd 442.5957, obsd 442.5983.

(2*R*,3a*S*,5a*R*,6*S*,8a*S*,9b*S*)-1,2,3,3a,5a,6,7,8,8a,8b-Decahydro-6-[2-[(*p*-methoxybenzyl)oxy]ethyl]-7-oxo-*as*-indacen-2-yl Pivalate (34). To a solution of 11 mg (0.025 mmol) of **32** in 2.5 mL of dry CH_2Cl_2 was added 5 equiv of pyridinium chlorochromate on alumina. The resulting suspension was stirred at 0 °C overnight, passed through a short silica gel column (elution with ethyl acetate), and evaporated in vacuo. The residue was purified by chromatography on silica gel (elution with 25% ethyl acetate in hexanes) to give 9 mg of ketone **33** as a colorless oil; IR (film, cm^{-1}) 1723; ^1H NMR (300 MHz, C_6D_6) δ 7.28−7.21 (m, 2 H), 6.82−6.79 (m, 2 H), 5.73 (d, J = 10.0 Hz, 1 H), 5.42 (dt, J = 10.0, 3.3 Hz, 1 H), 5.07 (m, 1 H), 4.39 (ABq, J = 11.6 Hz, $\Delta\nu$ = 8.4 Hz, 2 H), 3.61 (td, J = 6.5, 1.3 Hz, 1 H), 3.57 (m, 1 H), 3.30 (s, 3 H), 2.65 (m, 1 H), 2.26 (m, 2 H), 2.01−1.92 (m, 4 H), 1.80−1.70 (m, 3 H), 1.21 (m, 1 H), 1.15 (s, 9 H), 0.88 (td, J = 12.4, 4.8 Hz, 1 H), 0.71 (m, 1 H); MS m/z (M^+) calcd 440.2563, obsd 440.2552.

The above ketone was dissolved in 2.5 mL of dry methanol, treated with a crystal of K_2CO_3, heated to reflux for 1 h, and cooled to 20 °C. The solution was diluted with 5 mL of ethyl acetate, passed through a silica gel plug to remove potassium carbonate, and evaporated. The residue was purified by chromatography on silica gel (elution with 25% ethyl acetate in hexanes) to return 6 mg of **33** and give 2 mg of **34** (70% combined recovery) as a colorless oil; IR (CH_2Cl_2, cm^{-1}) 1732, 1716; ^1H NMR (300 MHz, C_6D_6) δ 7.29−7.25 (m, 2 H), 6.87−6.82 (m, 2 H), 5.72 (s, 2 H), 5.19−5.12 (m, 1 H), 4.37 (s, 2 H), 3.67−3.54 (m, 2 H), 3.34 (s, 3 H), 2.34−2.28 (m, 1 H), 2.12−1.94 (m, 6 H), 1.91−1.76 (m, 3 H), 1.32 (td, J = 7.6, 13.3 Hz, 1 H), 1.21 (s, 9 H), 0.96 (td, J = 4.8, 12.3 Hz, 1 H), 0.74 (qd, J = 11.8, 6.4 Hz, 1 H); ^1H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, J = 8.7 Hz, 2 H), 6.87 (d, J = 8.7 Hz, 2 H), 5.90 (d, J = 9.8 Hz, 1 H), 5.80 (dt, J = 9.8, 3.1 Hz, 1 H), 5.21−5.14 (m, 1 H), 4.41 (s, 2 H), 3.81 (s, 3 H), 3.60 (t, J = 6.4 Hz, 2 H), 2.69−2.62 (m, 1 H), 2.47−2.31 (m, 3 H), 2.28−2.17 (m, 2 H), 2.09−1.99 (m, 1 H), 1.96−1.85 (m, 3 H), 1.63−1.52 (m, 1 H), 1.28−1.15 (m, 2 H), 1.19 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 219.3, 178.2, 159.1, 130.4, 129.6, 129.3, 129.2 (2 C), 113.7 (2 C), 74.2, 72.5, 67.3, 55.3, 50.4, 44.6, 43.1, 42.3, 41.7, 38.5, 38.3, 37.8, 36.8, 29.1, 27.1 (3 C); MS m/z (M^+) calcd 440.2563, obsd 440.2557; $[\alpha]_D^{22}$ −30.8 (c 0.60, CH_2Cl_2). Anal. Calcd for $C_{27}H_{36}O_5 \cdot 0.5H_2O$: C, 72.12; H, 8.29. Found: C, 72.35; H, 8.12.

Acknowledgment is made to the National Institutes of Health and Eli Lilly and Company for financial support, Prof. Robin Rogers for the X-ray analysis, Dr. Martyn Earle for early experiments, and Dr. Kurt Loening for assistance with nomenclature.

Supporting Information Available: Crystal data collection for **6** including tables of bond distances and angles, least-squares planes, final fractional coordinates, and thermal parameters (8 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

JA974009L