Total Synthesis of Spinosyn A. 2. Degradation Studies Involving the Pure Factor and Its Complete Reconstitution

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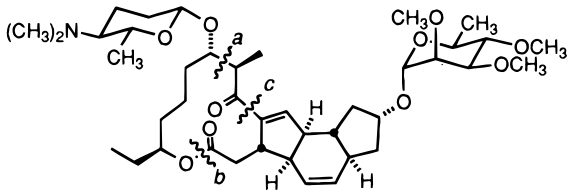
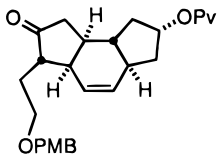
Abstract: A total synthesis of natural levorotatory spinosyn A (**1**) has been achieved. The first objective, to confirm the absolute configurational assignment of tricyclic ketone **2** prepared earlier, was accomplished by oxidative degradation of the macrocyclic lactone ring in **1**. The route began with the implementation of a four-step one-pot process that resulted in the efficient conversion of **6** into **18**. A combination of periodate cleavage and peracid oxidation events then led to **2**. In the reconstruction phase, a Pd-catalyzed coupling of a vinylstannane with an acid chloride reestablished the great majority of the structure in an enantiocontrolled manner. Once macrolactonization had been effected, the 2,3,4-tri-*O*-methylrhamnose unit was introduced first with exceptionally good stereocontrol. The final glycosidation, which involved a 2-mercaptopyrimidine derivative of D-forosamine, was met with an expectedly diminished percentage of the desired β-anomer.

In this two-part full account of a total synthesis of spinosyn A (**1**),[2] we describe our studies on the chemistry of this commercially important insecticidal macrocyclic lactone.[3] Particular emphasis is accorded the degradation of **1** to the levorotatory tricyclic building block **2**, the subsequent elaboration of which into **1** completes our enantioselective construction of this structurally complex macrolide. The conversion of **1** to **2** confirms the previously assigned structure.[2] The scheme developed here for arrival at **1** is divergent from, and complementary to, an asymmetric route to *ent*-spinosyn A[4] reported by Evans and Black.[7]

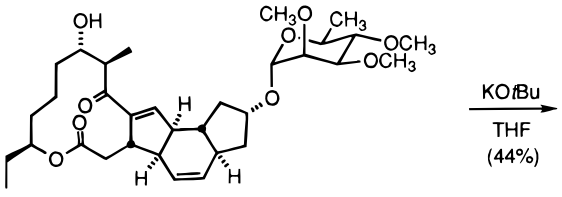


1



2

Retrosynthetically, one can expect to derive **1** from **2** either by way of a late-stage macroaldolization with generation of bond *a* or via a macrolactonization step to set bond *b*. The decision to adopt the latter pathway followed upon cleavage of the pseudoaglycone **3** to aldehyde **4** and a detailed examination of the ease of reinstallation of the twelve-membered ring.[8] When none of the many attempts at the macroaldolization of **4** gave evidence for reclosure to **3**, the unacceptable nature of this



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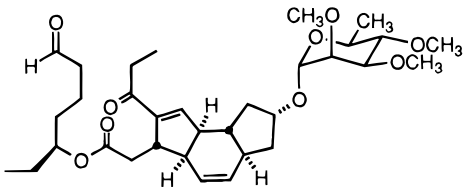

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approach was made abundantly clear. As will be seen, macrolactonization technology does not suffer from comparable complications and is ideally suited to provide access to **1**.

Preliminary Attempts To Cleave the C-14/C-15 Bond. The conversion of spinosyn A to **2** necessitates that bond *c* (the C-14/C-15 bond) be cleaved oxidatively. We began by investigating the possibility that this transformation could be accomplished after saturation of the C-13/C-14 double bond. Martynow and Kirst had previously demonstrated that the silyl-

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(2) Paquette, L. A.; Gao, Z.; Ni, Z.; Smith, G. F. *J. Am. Chem. Soc.* **1998**, *120*, 2543−2552.

(3) Spinosyn A is presently being marketed by DowElanco Inc.

(4) The names initially adopted for **1** (LY232105,[5] A83543A,[6] and lepicidin A[7]) have been recently abandoned in favor of spinosyn A (Kirst, H. A.; communication dated June 7, 1994).

(5) The LY232105 label was assigned following initial discovery of this secondary metabolite in the Eli Lilly laboratories.

(6) 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.

(7) Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1992**, *114*, 2260; **1993**, *115*, 4497.

(8) The authors thank Dr. Graham F. Smith for these studies.

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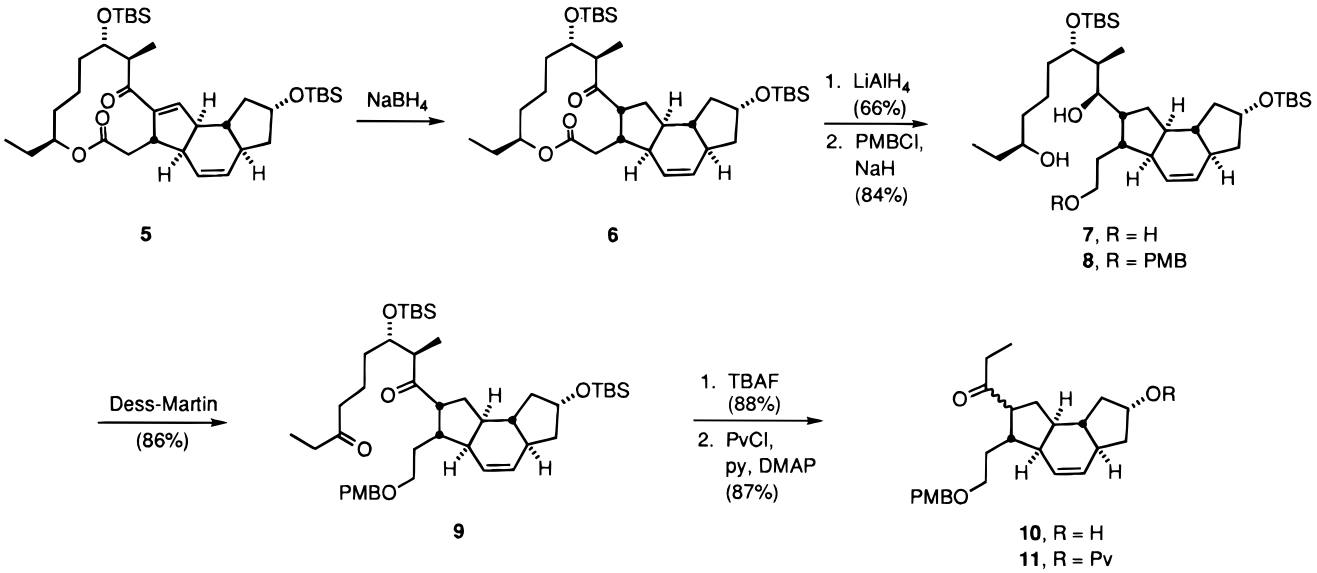
Scheme 1



protected aglycone **5** was exceptionally prone to 1,4-reduction in the presence of sodium borohydride[9] (Scheme 1). A particularly attractive facet of this reaction is exclusive formation of the 13,14β-dihydro derivative **6**. A generous sample of natural spinosyn A (**1**), kindly provided by DowElanco Laboratories (Indianapolis, IN), enabled us to probe a first attempt to degrade the lactone ring suitably via **6**. Formation of triol **7** by way of lithium aluminum hydride reduction made possible the installation of only one *p*-methoxybenzyl protecting group as in **8**. The conversion of **6** to **7** initially proved to be capricious, exhibiting widely variable yields. However, this complication was skirted and good reproducibility achieved through use of an excess of $LiAlH_4$ under concentrated conditions.

Treatment of **8** with the Dess−Martin periodinane[10] led to diketone **9**, exposure of which to a fluoride ion source resulted in retro-aldol cleavage to give **10**. Standard pivaloylation conditions delivered **11**, a tricyclic ketone bearing close structural similarity to **2**. The fact that **11** consisted of a 2.5:1 mixture of C-14 epimers was considered inconsequential in view of the pending need to introduce a carbonyl group at that site. One can consider several protocols for implementing this chemical change. A route involving enolate oxidation by means of MoOPh[11] or an oxaziridine[12] and subsequent chemoselective cleavage of the α-hydroxy ketone with alkaline hydrogen peroxide[13] was evaluated first. When the thermodynamic enolate anion derived from **11** was discovered to be unreactive to these conditions, recourse was made instead to the Rubottom procedure.[14] The singular unreactivity of **11** was now clearly discerned, a feature that persisted in the course of additional experimental studies.[15,16] In view of the substantial steric screening in the vicinity of C-14, these results perhaps need occasion no surprise.

Exploration of a Dehydrative Route for the Activation of C-14. The information gained from the preceding study prompted consideration of a radically different, but equally direct route to **2**. Compound **12**, previously isolated by the Lilly group in 31% yield by exposure of **6** to lithium methoxide in methanol,[9] seemed to be a highly suitable precursor of the functionality-differentiated dehydro C-14/C-15 system **14** (Scheme 2). We came to favor Triton B in tetrahydrofuran as a base better suited to the generation of **12**. This reagent is more tolerant of the elevated base-sensitivity of the enone lactone and is more adaptable to controlled acidification (HOAc) in order to maximize the levels of **6** and **12** returned after a short reaction time (5 min).

The expectation was that phenyllithium would add in 1,2-fashion to **12** with formation of **13**. However, attack at the lactone carbonyl is roughly competitive with formation of the allylic alcohols such that the efficiency with which **13** is formed is relatively low (37%). Other organometallics such as the magnesium, titanium, cerium, and zinc reagents proved less satisfactory. Notwithstanding, the dehydration of **13** was readily accomplished in completely regioselective fashion. Direct hydride reduction of this intermediate furnished **14** in 56% overall yield.

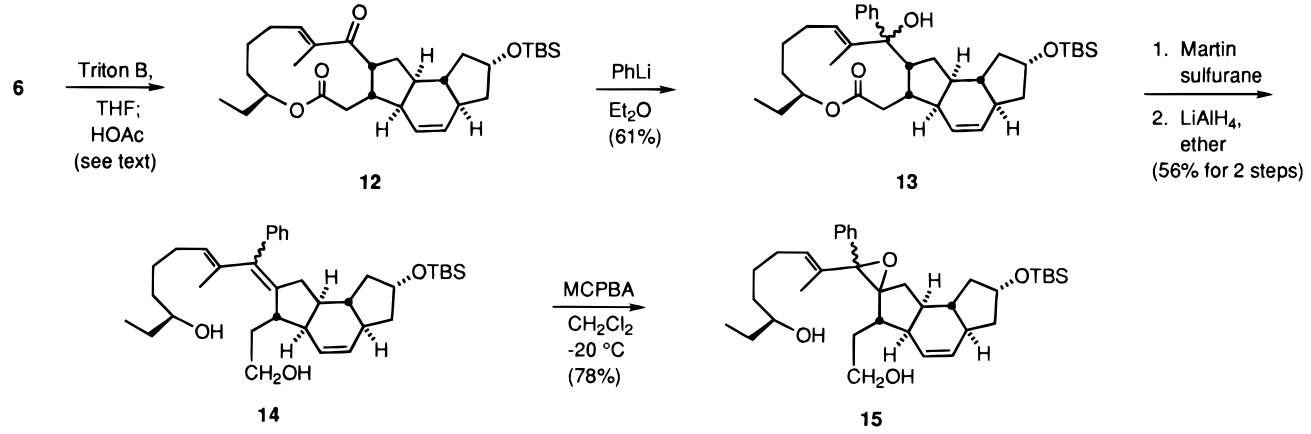
Whereas attempted controlled ozonolysis of **14** (or its diacetate) resulted only in decomposition, epoxide **15** could be produced satisfactorily by reaction with *m*-chloroperbenzoic acid in CH_2Cl_2 at −20 °C. Quite unexpectedly, **15** proved recalcitrant to cleavage with periodic acid or sodium periodate and was not amenable to diol formation via hydrolysis.

Concurrent with the above developments, the discovery was made that mesylate **16**, available from **3** in two steps and 92% yield, experiences ready elimination in the presence of DBU to generate **17** (81%) (Scheme 3). In this way, a highly efficient pathway was opened to a *Z*-olefinic counterpart of **12**. Consequently, both α,β-unsaturated keto lactones were available for degradation to **2**.

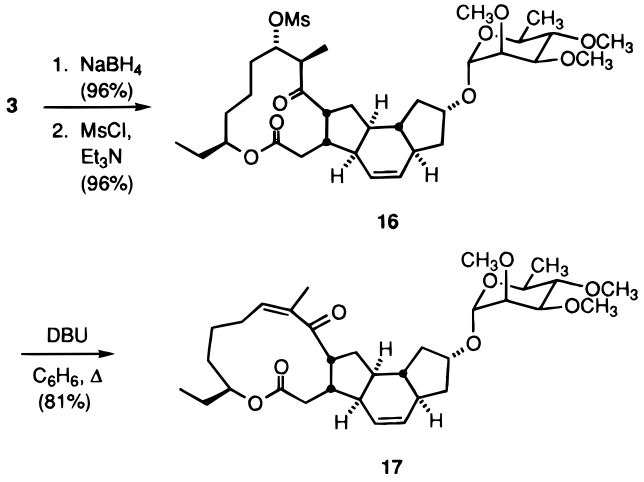
The Successful Strategy for Truncation of the Macrolactone Ring. Central to the scenario that ultimately proved to be successful was oxidation of either **12** or **17** to the α,β-epoxy ketone. In actuality, **12** reacted readily with *tert*-butyl hydroperoxide in the presence of Triton B as catalyst, giving rise to

(9) Martynow, J. G.; Kirst, H. A. *J. Org. Chem.* **1994**, *59*, 1548.
(10) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.
(11) (a) Vedejs, E. *J. Am. Chem. Soc.* **1974**, *96*, 5944. (b) Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188. (c) Vedejs, E.; Larsen, S. *Org. Synth.* **1986**, *64*, 127.
(12) (a) Davis, F. A.; Sheppard, A. C. *Tetrahedron* **1989**, *45*, 5703. (b) Davis, F. A.; Chen, B.-C. *Chem. Rev.* **1992**, *92*, 919.
(13) Ogata, Y.; Sawaki, Y.; Shiroyama, M. *J. Org. Chem.* **1977**, *42*, 4061.
(14) (a) Rubottom, G. M.; Vazquez, M. A.; Pelegrina, D. R. *Tetrahedron Lett.* **1974**, 4319. (b) Rubottom, G. M.; Gruber, J. M.; Juve, H. D., Jr.; Charleson, D. A. *Organic Syntheses*; Wiley: New York, 1990; Coll. Vol. VII, p 282.
(15) Purdie, M. Unpublished work from this laboratory.
(16) Collado, I. Unpublished work from this laboratory.

Scheme 2



Scheme 3



a single diastereomer in 74% yield.[17] In contrast, the geometric isomer **17** gave no indication of reaction after 2 days. Further studies involving **12** revealed not only that this sensitive intermediate need not be isolated (with concomitant diminution in yield), but that **6** could be transformed directly into the ring-cleaved epoxy acid in a one-pot reaction. Direct esterification of this product with diazomethane then provided **18** in 72% overall yield for the four-step conversion (Scheme 4).

The availability of **18** made possible the ensuing hydride reduction to polyol **19** (87%). Although the loss of configurational integrity at C-14 that was earlier experienced was passed along to this point, this factor is not at all problematic in view of the strategy considerations that follow. The next step involved oxidative cleavage of the 1,2-diol substructure present in **19** with sodium periodate. The result involved the excision of 9 carbons to give a hydroxy aldehyde (85% yield), which exists predominantly in its cyclic lactol form **20**. Although crystalline in nature, the material produced in this manner could be clearly discerned by ^{1}H NMR spectroscopy to consist of a mixture of three diastereomers.[18] Noteworthy here is that all three lactols were amenable to concurrent conversion to the isomerically homogeneous silylated enol ether **21** (92%) after deprotonation with excess potassium hexamethyldisilazide and exhaustive silylation with *tert*-butyldimethylsilyl triflate.[19] The high stereoselectivity of this step owes its origin to the steric contributions of the protected β-hydroxyethyl side chain.

With a successful procedure for truncation of the macrolactone ring in place, the remainder of the degradation was designed to reach **2** as expediently as possible. Toward this end, **21** was subjected to the Rubottom oxidation,[14] a step which led after brief exposure to tetra-*n*-butylammonium fluoride to an α-hydroxy lactol. Direct subjection of this polar substance to sodium periodate expectedly gave rise to **22** with 62% overall efficiency.[20] With removal of the final carbon atom in this manner, C-14 is seen to be properly functionalized as a ketone. There remained only the need to effect pivaloylation and transposition of the formate functionality into a *p*-methoxybenzyl ether. Indeed, application of this protocol afforded the oily ketone **2**, whose spectral properties and optical rotation confirmed its identity with the synthetic sample prepared earlier by us.[2]

Reconstruction of the Macrolide Chain. With the preceding results in hand, the time had come to initiate the conversion of **2** to spinosyn A. In light of our plan to elaborate bond *c* in advance of bond *b* (see **1**), attention was now focused on proper elaboration of the nine-carbon chain with its three stereogenic centers. Adaptation of the previously described conversion of δ-valerolactone to aldehydo ester **24**[21] was followed by the chemoselective and enantioselective addition of diethylzinc to this bifunctional compound in the presence of (−)-(1*S*,2*R*)-*N*,*N*-dibutylnorephedrine.[22] The resulting secondary carbinol **25** (Scheme 5), produced with 92% ee, was immediately protected as the silyl ether **26** in order to ward off adventitious lactonization. Subsequent reduction of **26** with DIBAL-H proceeded uneventfully in THF at −78 °C to deliver the aldehyde **27**.

Continued buildup of the fragment involved an asymmetric aldol reaction of the boron enolate derived from *N*-propionyloxazolidinone **28**[23] to **27**. The high diastereoselectivity (>99% de) of this coupling resulted in setting of the proper absolute

(17) NOE experiments designed to reveal the stereochemistry of this α,β-epoxy ketone proved not to be definitive.

(18) In an effort to bypass lactol formation as in **20**, the primary hydroxyl group in **19** was protected as the PMB derivative. This intermediate was not utilized further when it was recognized that oxidative cleavage of its 1,2-diol moiety with sodium periodate provided the aldehyde in only 22% yield for the two steps.

(19) Remarkably, when lithium hexamethyldisilazide was employed as the base, only the corresponding ring-closed silyl acetal was produced (92%) as a mixture of two isomers.

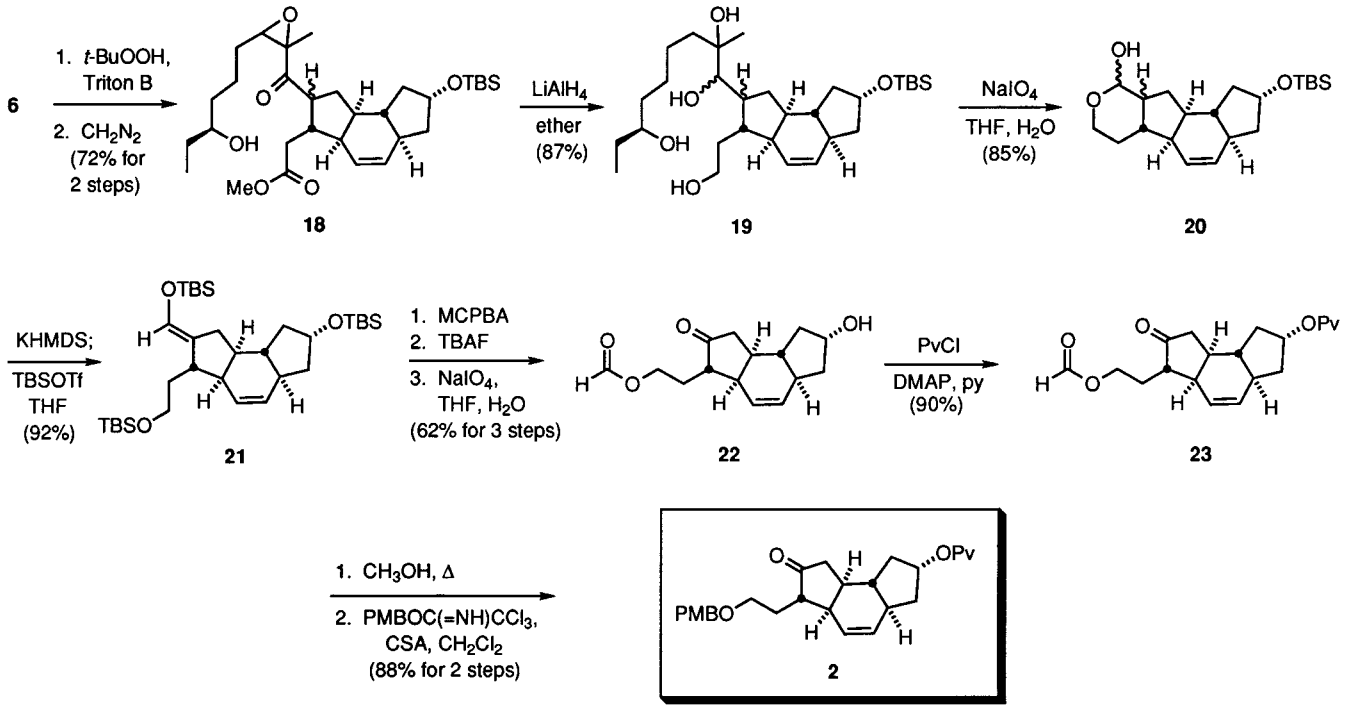
(20) Other methods for the enolate oxidation of **20** were briefly examined. Examples include deprotonation with potassium hexamethyldisilazide and subsequent exposure of the enolate anion to oxygen or the Davis oxaziridine. However, subsequent sodium periodate oxidation in these cases proceeded in only 34% and 15% yield, respectively.

(21) Huckstep, M.; Taylor, R. J. K.; Caton, M. P. L. *Synthesis* **1982**, 881.

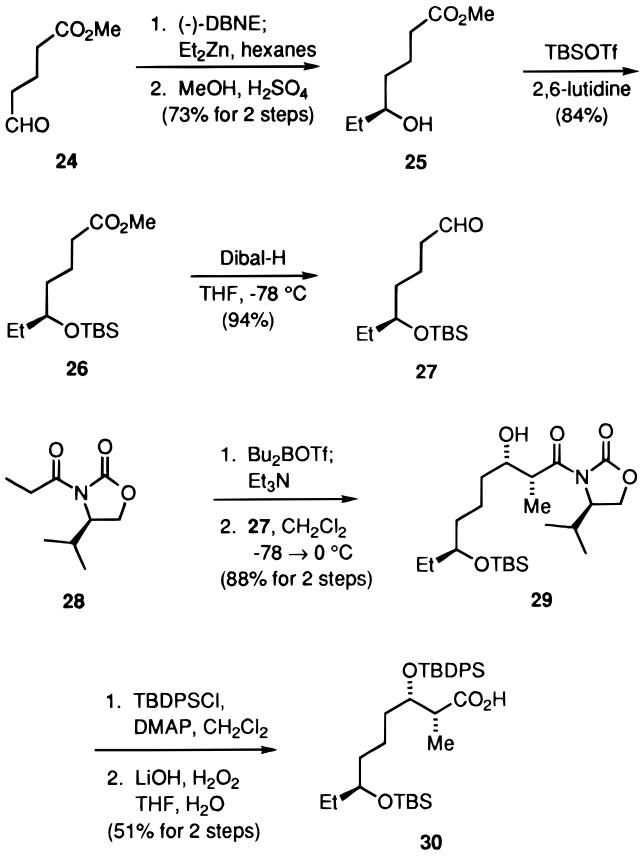
(22) Soai, K.; Yokoyama, S.; Hayasaka, T.; Ebihara, K. *Chem. Lett.* **1988**, 843.

(23) (a) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127. (b) Evans, D. A.; Rieger, D. L.; Jones, T. K.; Kaldor, S. W. *J. Org. Chem.* **1990**, *55*, 6260.

Scheme 4



Scheme 5



configuration of the syn aldol stereocenters as in **29** (88% yield). After initial masking of the hydroxyl group as the *tert*-butyldiphenylsilyl ether, conversion to carboxylic acid **30** was successfully accomplished without detectable epimerization through use of alkaline hydrogen peroxide.

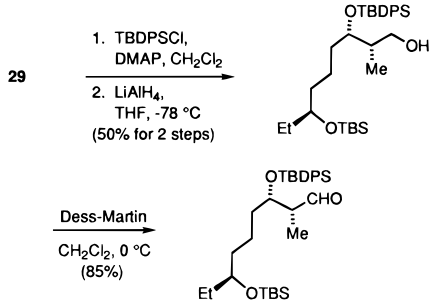
Convergent Arrival at Spinosyn A. The first salient feature of the end game is that tricyclic ketone **2** proved quite amenable to regiospecific conversion to the enol triflate **32** upon treatment with potassium hexamethyldisilazide and *N*-(5-chloro-2-pyridyl)-bis(trifluoromethanesulfonimide) (**31**)[24] (Scheme 6). The possibility of bringing about a Ni(II)/Cr(II)-mediated coupling[25,26] of **32** with the aldehyde related to **30**[27] was examined first. In this setting,[28] the methodology proved ineffective and invariably returned unreacted **32**. In an alternative approach for appending the side chain, **32** was transformed into vinylstannane **33** by reaction with hexamethylditin and lithium chloride in the presence of tetrakis(triphenylphosphine)palladium.[29] At this point, we were able to affect the formation of **35** through the aegis of $Pd_2(dba)_3$·$CHCl_3$ in the presence of Hunig's base[30] without any evidence of epimerization (75% for the two steps).

(24) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299.

(25) Jin, H.; Uenishi, J.-i.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644.

(26) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048.

(27) This aldehyde was prepared by lithium aluminum hydride reduction of TBDPS-protected **29** followed by oxidation with the Dess−Martin periodinane.[16]

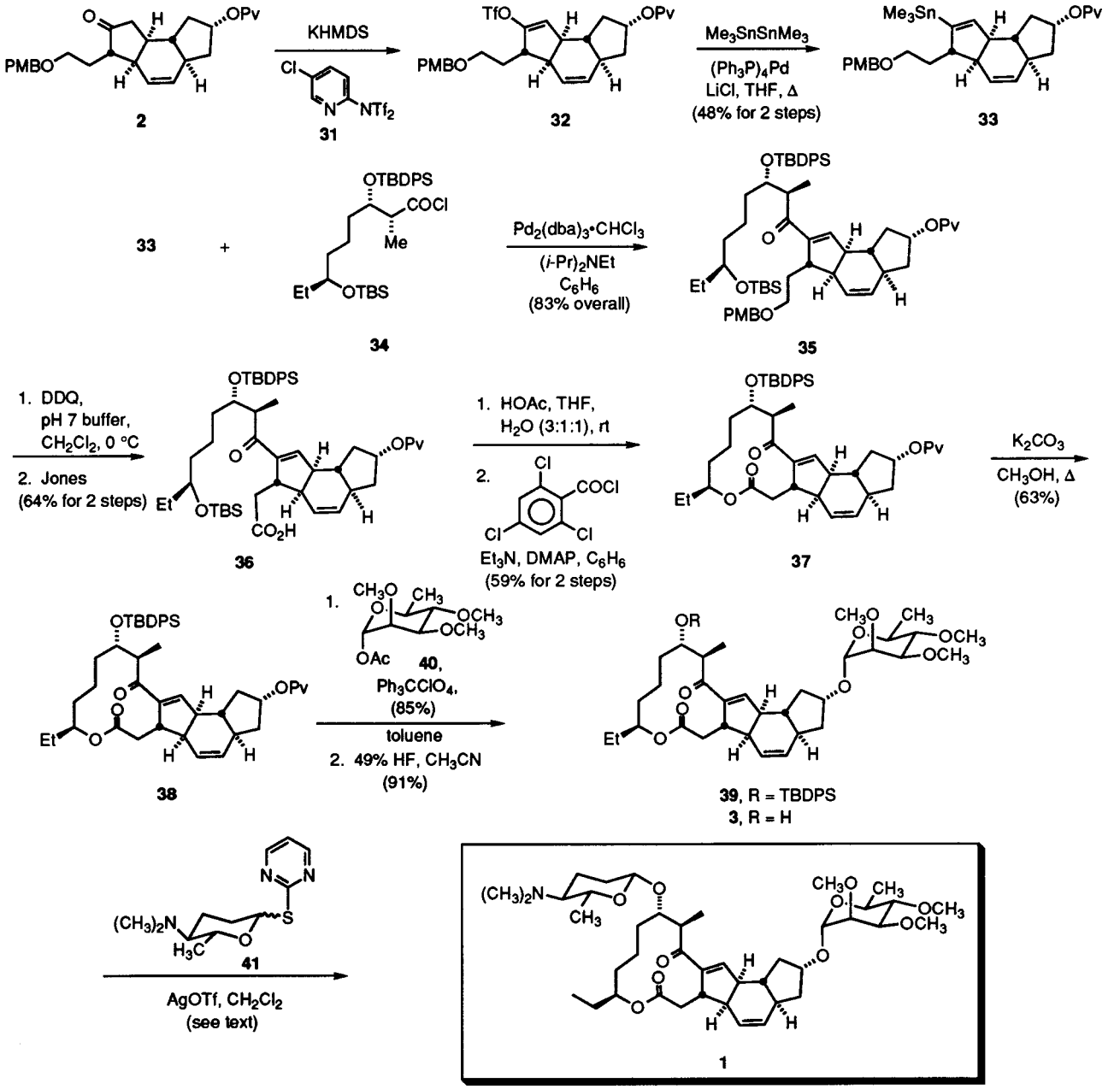


(28) The $CrCl_2$ utilized was generated by $LiAlH_4$ reduction of $CrCl_3$: (a) Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 3179. (b) Hiyama, T.; Okude, Y.; Kimura, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 561.

(29) 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.

(30) Evans, D. A.; Kim, A. S. *J. Am. Chem. Soc.* **1996**, *118*, 11323 and references therein.

Scheme 6



This successful development provided a secure basis for proceeding forward to spinosyn A.

Deprotection of the OPMB group in **35** via DDQ oxidation was followed by Jones oxidation to deliver carboxylic acid **36**. Once again, ^{1}H NMR analysis provided no evidence for loss of stereochemical integrity at the one enolizable center. Further hydrolytic removal of the TBS substituent gave rise uneventfully to the seco acid, cyclization of which under Yonemitsu conditions[31] smoothly afforded lactone **37**.

Our adaptation of the sequence of steps to follow was founded on the well-recognized complexities associated with proper incorporation of amino sugars into higher molecular weight alcohols at their anomeric center.[32] Consequently, this maneuver was deferred until the final stages of the synthesis. Selective removal of the pivalate functionality in **37** by saponification afforded the free alcohol **38** required for glycosidation. With trityl perchlorate as catalyst,[7,33,34] the condensation of **38** with glycosyl acetate **40** in toluene at room temperature provided exclusively the α-anomeric pseudoaglycone in 85% yield. Spectroscopic analysis of the unpurified reaction mixture gave no observable hint that the *β*-anomer had been produced. Desilylation of **39** with 49% hydrogen fluoride in acetonitrile led to **3** (91% yield), the physical and spectral properties of which (mp, $[\alpha]_D$, IR, MS, ^{1}H, ^{13}C NMR) established its identity with the natural material earlier generated from **1**.

No methods have been reported that effectively modulate stereocontrolled *β*-linkage to a 2-deoxy sugar such as D-(+)-forosamine.[35] The availability of this enantiomerically pure building block to us by way of the controlled degradation of **1**

(31) (a) Hikota, M.; Sakurai, Y.; Horita, K.; Yonemitsu, O. *Tetrahedron Lett.* **1990**, *31*, 6367. (b) Hikota, M.; Tone, H.; Horita, K.; Yonemitsu, O. *J. Org. Chem.* **1990**, *55*, 7.

(32) For selected examples, see: (a) ref 7. (b) Masamune, S.; Yamamoto, H.; Kamata, S.; Fukuzawa, A. *J. Am. Chem. Soc.* **1975**, *97*, 3513. (c) Woodward, R. B. et al. *J. Am. Chem. Soc.* **1981**, *103*, 3215.

(33) Mukaiyama, T.; Kobayashi, S.; Shoda, S.-i. *Chem. Lett.* **1984**, 907.

(34) Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001.

was strong motivation to involve its direct activation in the final step. We opted to use the D-furosaminide **41**, which was prepared by a Mitsunobu reaction with 2-mercaptopyrimidine and triphenylphosphine in THF. The inseparable 2:1 mixture of anomeric sulfides was directly reacted with **3** and silver triflate in CH_2Cl_2.[32c] As expected, this glycosidation suffered from rapid competitive decomposition of **41**. Despite the use of 5 equiv of **41**, 69% of **3** could be recovered following chromatography. The balance of the material consisted of a 2:3 mixture of **1** and its anomer. These data translate into a yield based on recovered **3** of 55%.

Summary

A concise degradative route from spinosyn A (**1**) to the tricyclic ketone **2** has been developed. This accomplishment confirmed the absolute configurational assignment made earlier to this pivotal synthetic intermediate. This linkup has made possible the completion of a total synthesis of natural levorotatory **1**. The route proved to be economical (11 steps), convergent, and quite efficient except for the final glycosylation. From the synthetic point of view, a number of potentially useful observations have emanated from this venture. Among this is the demonstration that macrolactonization is a more reliable process than is macroaldolization. Also, the feasibility of a palladium-catalyzed coupling involving a vinylstannane, and an acid chloride, at both the practical and conceptual levels, warrants consideration as a useful transformation within the scope of complex organic synthesis.

Experimental Section

For general methods, consult ref 2.

(3*S*,3a*R*,5a*S*,7*R*,8a*R*,8b*S*)-7-[(6-Deoxy-2,3,4-tri-*O*-methyl-α-L-mannopyranosyl)oxy]-2-[(2*R*,3*S*,7*S*)-3,7-dihydroxy-2-methylnonanoyl]-3,3a,5a,6,7,8,8a,8b-octahydro-*as*-indacene-3-acetic Acid κ-Lactone (3). Spinosyn A (**1**) (1.99 g, 2.72 mmol) was dissolved in 0.1 N H_2SO_4 (60 mL), and the reaction mixture was stirred overnight at 95−110 °C, cooled to room temperature, and filtered. The solid precipitate was washed with water and air-dried to give **3** (1.52 g, 94%). The filtrate was neutralized by the addition of aqueous sodium hydroxide solution. *n*-Butyl alcohol (40 mL) was added, and the solution was stirred at 50 °C for 1 h. The layers were separated, and the organic phase was washed with water (30 mL). The *n*-butyl alcohol was removed by vacuum distillation to leave a residue which was taken up into tetrahydrofuran and left overnight. This solution was filtered and the solvent removed. Kugelrohr distillation gave forosamine as a white solid (0.17 g, 39%), mp 59−60 °C.

For **3**: mp 168.5−169 °C; IR ($CHCl_3$, cm^{-1}) 1714, 1656; ^1H NMR (300 MHz, $CDCl_3$) δ 6.76 (s, 1 H), 5.87 (d, J = 9.7 Hz, 1 H), 5.80 (dd, J = 9.7, 2.7 Hz, 1 H), 4.84 (d, J = 1.2 Hz, 1 H), 4.70 (m, 1 H), 4.29 (m, 1 H), 3.67 (m, 1 H), 3.56 (m, 1 H), 3.54 (s, 3 H), 3.49 (s, 3 H), 3.48 (s, 3 H), 3.47 (m, 3 H), 3.45 (dd, J = 9.9, 3.3 Hz, 1 H), 3.21 (m, 1 H), 3.11 (m, 2 H), 3.00 (m, 1 H), 2.86 (m, 1 H), 2.39 (dd, J = 13.5, 3.1 Hz, 1 H), 2.26 (m, 1 H), 2.16 (m, 1 H), 1.91 (dd, J = 13.2, 7.0 Hz, 1 H), 1.70−1.22 (series of m, 10 H), 1.26 (d, J = 6.2 Hz, 3 H), 1.20 (dz, 3 H), 0.91 (m, 1 H), 0.81 (t, J = 7.5 Hz, 3 H); MS m/z (M^+) calcd 590.3454, obsd 590.3467; $[\alpha]^{22}_D$ −170 (c 0.45, CH_2Cl_2).

(1*S*)-1-Ethyl-4-formylbutyl (3*S*,3a*R*,5a*S*,7*R*,8a*R*,8b*S*)-7-[(6-Deoxy-2,3,4-tri-*O*-methyl-α-L-mannopyranosyl)oxy]-3,3a,5a,6,7,8,8a,8b-octahydro-2-propionyl-*as*-indacene-3-acetate (4). A solution of **3** (51 mg, 86 μmol) and potassium *tert*-butoxide (2.3 mg, 20 μmol) in dry THF (10 mL) was stirred at room temperature for 48 h and then diluted with saturated NH_4Cl solution (2 mL) and petroleum ether (10 mL). The organic phase was dried and concentrated to leave a residue that was purified by MPLC on silica gel. There were isolated 19 mg (37%) of unreacted **3** and 14 mg (44% adjusted) of **4** as a colorless oil; IR ($CHCl_3$, cm^{-1}) 1725, 1670; ^1H NMR (300 MHz, $CDCl_3$) δ 9.75 (t, J = 1.5 Hz, 1 H), 6.65 (br s, 1 H), 5.87 (br d, J = 9.9 Hz, 1 H), 5.77 (dt, J = 9.8, 2.6 Hz, 1 H), 4.84 (d, J = 1.5 Hz, 1 H), 4.80 (m, 1 H), 4.31 (m, 1 H), 3.55 (s, 3 H), 3.48 (s, 6 H), 3.57−3.43 (m, 3 H), 3.11 (t, J = 9.3 Hz, 1 H), 3.07 (m, 1 H), 2.86−2.59 (m, 6 H), 2.44 (m, 1 H), 2.29 (m, 1H), 2.13 (m, 1 H), 1.91 (dd, J = 13.2, 7.0 Hz, 1 H), 1.27 (d, J = 6.1 Hz, 3 H),1.67−1.21 (series of m, 8 H), 1.08 (t, J = 7.3 Hz, 3 H), 1.03−0.93 (m, 1 H), 0.87 (t, J = 4 Hz, 3 H) (OH not observed); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 202.0, 200.3, 172.3, 144.5, 144.2, 129.7, 129.1, 95.6, 92.3, 81.1, 77.2, 76.2, 74.7, 68.0, 60.9, 59.0, 57.7, 49.5, 46.8, 46.0, 45.0, 43.5, 41.1, 37.5, 37.0, 36.4, 32.8, 32.2, 26.9, 17.8, 17.8, 9.6, 8.2; MS m/z (M^+ − H) calcd 589.3376, obsd 589.3384.

Methyl (3*S*,3a*R*,5a*S*,7*R*,8a*R*,8b*S*)-7-(*tert*-Butyldimethylsiloxy)-2-[(7*S*)-2,3-epoxy-7-hydroxy-2-methylnonanoyl]-1,2,3,3a,5a,6,7,8,8a,-8b-decahydro-*as*-indacene-3-acetate (18). To a solution of **6** (24 g, 38 mmol) in THF (750 mL) was added Triton B (40% in MeOH) (77.5 mL, 185 mmol). The resulting solution was stirred for 15 min, and *tert*-butyl hydroperoxide (21 mL of 70% in water, 162 mmol) was introduced. After 5 days at room temperature, the reaction mixture was poured onto a mixture of ether and saturated NH_4Cl solution (1:1, 3000 mL), and the separated organic layer was washed with saturated NH_4Cl solution, dried, and concentrated in vacuo. The residue was dissolved in ether (300 mL) at 0 °C, and a solution of diazomethane in ether at 0 °C was added dropwise until no carboxylic acid remained. The solvent was removed under a N_2 stream, and the residue was purified by chromatography on silica gel (gradient elution with ethyl acetate/hexanes 1:10 to 1:2) to give 14.9 g (72% overall) of **18** as a mixture of C-14 epimers; colorless gum; IR ($CHCl_3$, cm^{-1}) 3380, 1731, 1699; ^1H NMR (300 MHz, $CDCl_3$) δ 5.86−5.80 (m, 1 H), 5.61−5.55 (m, 1 H), 4.36−4.30 (m, 1 H), 3.61 and 3.59 (2s, 3 H), 3.56−3.49 (m, 1 H), 3.28 and 2.96 (2m, 1 H), 3.09 and 2.91 (2m, 1 H), 2.70−2.44 (m, 2 H), 2.31−1.85 (series of m, 6 H), 1.80−1.35 (series of m, 12 H), 1.44 and 1.40 (2s, 3 H); 1.32−0.98 (m, 2 H), 0.93 (t, J = 7.4 Hz, 3 H), 0.85 (s, 9 H), 0.02 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm (isomer A) 212.9, 173.0, 131.4, 127.2, 72.9, 72.3, 63.6, 60.0, 51.5, 48.2, 47.4, 46.7, 46.5, 42.1, 41.3, 40.8, 3.8, 36.4, 35.7, 30.2, 28.2, 25.9 (3 C), 22.5, 18.1, 12.6, 9.9, −4.7, −4.8; (isomer B) 212.2, 173.9, 130.9, 128.6, 72.8, 72.4, 63.1, 60.3, 51.4, 47.2, 45.7, 44.0, 43.1, 41.6, 41.1, 41.0, 40.8, 40.7, 36.8, 36.2, 34.2, 33.8, 30.2, 28.1, 25.9 (3 C), 22.3, 18.1, 13.2, 9.8, −4.7, −4.8; MS m/z (M^+) calcd 548.3533, obsd 548.3538. Anal. Calcd for $C_{31}H_{52}O_6Si$: C, 67.84; H, 9.55. Found: C, 67.65; H, 9.65.

(7*S*)-[(3*S*,3a*R*,5a*S*,7*R*,8s*R*,8b*S*)-7-(*tert*-Butyldimethylsiloxy)-1,2,3,-3a,5a,6,7,8,8a,8b-decahydro-3-(2-hydroxyethyl)-*as*-indacen-2-yl]-2-methyl-1,2,7-nonanetriol (19). Lithium aluminum hydride (6.9 g, 182 mmol) was added in small portions over a period of 20 min to a solution of **18** (14 g, 26 mmol) in anhydrous ether (550 mL). The mixture was stirred at room temperature for 1 h, quenched with a saturated solution of Rochelle's salt, diluted with ethyl acetate (1000 mL), and stirred for 2 h. The separated aqueous layer was extracted with ethyl acetate (2 × 500 mL), and the combined organic layers were dried and concentrated in vacuo. The residue was purified by chromatography on silica gel (gradient elution from ethyl acetate/hexanes 3:1 to pure ethyl acetate) to give **19** (11.7 g, 87%) as a mixture of three isomers. It was possible to separate and characterize the major diastereomer; white solid, mp 68−69 °C; IR ($CHCl_3$, cm^{-1}) 3419; ^1H NMR (300 MHz, $CDCl_3$) δ 5.81 (d, J = 9.8 Hz, 1 H), 5.66 (dt, J = 9.8, 2.7 Hz, 1 H), 4.39−4.31 (m, 1 H), 3.83−3.73 (m, 1 H), 3.72−3.60 (m, 1 H), 3.57−3.45 (m, 1 H), 3.24 (d, J = 8.5 Hz, 1 H), 2.75 (br s, 1 H), 2.22−2.10 (m, 3 H), 2.07−1.65 (series of m, 8 H), 1.62−1.30 (series of m, 11 H), 1.18 (s, 3 H), 1.14−1.00 (m, 2 H), 0.93 (t, J = 7.4 Hz, 3 H), 0.87 (s, 9 H), 0.03 (s, 6 H) (OH's not observed); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 130.4, 129.0, 84.1, 74.9, 73.3, 72.5, 60.9, 47.6, 47.5, 47.4, 45.2, 42.1, 41.4, 40.9 (2 C), 36.8, 36.0, 35.7, 34.6, 30.2, 26.4, 25.9 (3 C), 24.8, 23.2, 18.2, 9.9, −4.7, −4.8; MS m/z (M^+ − H_2O) calcd 506.3791, obsd 506.3823; $[\alpha]^{22}_D$ −50.6 (c 0.6, CH_2Cl_2). Anal. Calcd for $C_{30}H_{56}O_5Si$: C, 68.65; H, 10.75. Found: C, 68.59; H, 10.75.

(2*R*,3a*S*,5a*R*,5b*S*,10a*S*,10b*R*)-2-(*tert*-Butyldimethylsiloxy)-1,2,3a,-5a,5b,6,7,9,9a,10,10a,10b-decahydro-1*H*-*as*-indaceno[2,3-*c*]pyran-9-ol (20). A solution of **19** (11.7 g, 22.3 mmol) in THF (200 mL) was treated with a solution of sodium periodate (23.8 g. 111 mmol) in

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H_2O (400 mL), stirred overnight at room temperature, and diluted with ethyl acetate (800 mL). The separated aqueous layer was extracted with ethyl acetate (2 × 400 mL), and the combined organic layers were dried and concentrated in vacuo. The residue was purified by chromatography on silica gel (ethyl acetate/hexanes 1:3 as eluant) to give **20** (6.9 g, 85%) as a white solid, mp 76−78 °C, consisting of a mixture of three isomers; IR ($CHCl_3$, cm^{-1}) 3593, 3386; ^1H NMR (300 MHz, $CDCl_3$) δ 5.85−5.80 (m, 1 H), 5.70−5.61 (m, 1 H), 5.29 (t, J = 2.7 Hz, 0.3 H), 4.64−4.59 (m, 0.2 H), 4.43−4.30 (m, 1.6 H), 4.10−4.05 (m, 0.6 H), 3.90−3.77 (m, 0.9 H), 3.69−3.61 (m, 0.5 H), 3.46−3.37 (m, 0.6 H), 3.28 (d, J = 3.2 Hz, 0.3 H), 2.25−1.72 (series of m, 8 H), 1.65−1.27 (m, 3 H), 1.25−0.87 (series of m, 3 H), 0.87 and 0.86 (2s, total 9 H), 0.03 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 131.0, 130.9, 130.7, 129.3, 128.0, 101.0, 96.2, 93.6, 72.5, 72.4, 66.3, 61.1, 59.1, 50.7, 48.9, 48.6, 48.2, 47.9, 47.1, 46.6, 46.4, 44.8, 42.2, 41.8, 41.3, 41.2, 40.9, 40.8, 40.7, 40.5, 40.1, 39.7 (4 C), 32.0, 31.3, 31.2, 30.0, 25.9 (3 C), 18.2, −4.6, −4.7; MS m/z (M^+) calcd 364.2434, obsd 364.3442. Anal. Calcd for $C_{21}H_{36}O_3Si$: C, 69.18; H, 9.95. Found: C, 69.25; H, 10.02.

(3*S*,3a*R*,5a*S*,7*R*,8a*R*,8b*S*)-7-(*tert*-Butyldimethylsiloxy)-3-[2-(*tert*-butyldimethylsiloxy)ethyl]-2-[(*E*)-(*tert*-butyldimethylsiloxy)methylene]-1,2,3,3a,5a,6,7,8,8a,8b-decahydro-*as*-indacene (21). A solution of **20** (1.15 g, 3.15 mmol) in anhydrous THF (70 mL) at −78 °C under N_2 was treated with a 0.5 M solution of KHMDS in toluene (26.8 mL, 13.4 mmol), stirred at this temperature for 15 min and at room temperature for 1.5 h, and cooled to 0 °C prior to the introduction of *tert*-butyldimethylsilyl triflate (3.3 mL, 14.2 mmol). After 1.5 h at 0 °C and 30 min at 20 °C, the reaction mixture was quenched with H_2O (20 mL) and diluted with ether (100 mL). The organic phase was washed with H_2O, dried, and freed of solvent. The residue was purified by chromatography on silica gel (elution with ethyl acetate/hexanes 1:30) to give **21** (1.72 g, 92%) as a single isomer; colorless oil; IR ($CHCl_3$, cm^{-1}) 1761; ^1H NMR (300 MHz, $CDCl_3$) δ 6.12 (t, J = 3.9 Hz, 1 H), 5.72 (s, 2 H), 4.34−4.28 (m, 1H), 3.71−3.66 (m, 2H), 2.45−2.30 (m, 3 H), 2.21−2.09 (m, 2 H), 2.06−1.87 (m, 2H), 1.79−1.73 (m, 1 H), 1.69−1.57 (m, 1 H), 1.39 (dt, J = 12.7, 7.6 Hz, 1 H), 1.13−0.80 (m, 3 H), 0.90 (s, 9 H), 0.89 (s, 9 H), 0.88 (s, 9 H), 0.090 (s, 3 H), 0.088 (s, 3 H), 0.04 (s, 6 H), 0.034 (s, 3 H), 0.032 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 131.6, 131.3, 128.5, 125.1, 72.6, 61.9, 47.6, 43.5, 43.3, 42.4, 41.5, 40.7, 40.5, 38.1, 33.8, 26.0 (3 C), 25.9 (3 C), 25.7 (3 C), 18.3, 18.2 (2 C), −4.6, −4.7, −5.2 (2 C), −5.3, −5.4; MS m/z (M^+) calcd 592.4163, obsd 592.4175; $[\alpha]^{22}_D$ −73.0 (c 0.92, $CHCl_3$). Anal. Calcd for $C_{33}H_{64}O_3Si_3$: C, 66.83; H, 10.88. Found: C, 66.65; H, 10.80.

(3*S*,3a*R*,5a*S*,7*R*,8a*R*,8b*S*)-3,3a,5a,6,7,8,8a,8b-Octahydro-7-hydroxy-3-(2-hydroxyethyl)-*as*-indacen-2(1*H*)-one 3^2-Formate (22). A mixture of **21** (1.60 g, 2.7 mmol) and sodium bicarbonate (0.68 g, 8.1 mmol) in anhydrous CH_2Cl_2 (75 mL) at −20 °C under N_2 was treated with a solution of MCPBA (0.56 g, 3.2 mmol) in anhydrous CH_2Cl_2 (20 mL). After 30 min, the reaction mixture was quenched with 10% sodium sulfite solution, and the organic layer was washed with saturated $NaHCO_3$ solution, dried, and evaporated. The residue was taken up in THF (150 mL), and 27.0 mL (27.0 mmol) of a 1 M solution of TBAF in THF was added. The mixture was stirred at room temperature for 5 h, poured into a mixture of ethyl acetate and water (1:1), and extracted with ethyl acetate. The combined organic layers were dried, filtered, and concentrated to leave a residue, which was taken up in THF (40 mL) and treated with a solution of sodium periodate (5.8 g, 27 mmol) in H_2O (60 mL). The mixture was stirred for 5 h and diluted with ethyl acetate (150 mL). The aqueous layer was extracted with ethyl acetate (2 × 50 mL), and the combined organic layers were dried and concentrated. The residue was purified by chromatography on silica gel (with ethyl acetate/hexanes 1:1 as eluant) to give pure **22** (440 mg, 62%) as a colorless oil; IR ($CHCl_3$, cm^{-1}) 3609, 1726, 1181, 1004; ^1H NMR (300 MHz, $CDCl_3$) δ 8.02 (s, 1 H), 5.93 (d, J = 9.8 Hz, 1 H), 5.76 (dt, J = 9.8, 3.3 Hz, 1 H), 4.98−4.43 (m, 1 H), 4.36−4.28 (m, 2 H), 2.61−2.54 (m, 1 H), 2.50−2.26 (m, 5 H), 2.07−1.83 (m, 4 H), 1.53 (td, J = 13.1, 7.3 Hz, 1 H), 1.30−1.07 (m, 2 H) (OH not observed); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 218.8, 160.9, 130.6, 128.4, 71.7, 61.7, 50.0, 44.9, 43.4, 42.2, 41.3, 40.9, 39.6, 38.2, 28.2; MS m/z (M^+) calcd 264.1362, obsd 264.1357; $[\alpha]^{22}_D$ −35.8 (c 0.52, CH_2Cl_2). Anal. Calcd for $C_{15}H_{20}O_4 \cdot 0.25H_2O$: C, 67.02; H, 7.69. Found: C, 67.03; H, 7.56.

(3*S*,3a*R*,5a*S*,7*R*,8a*R*,8b*S*)-3,3a,5a,6,7,8,8a,8b-Octahydro-7-hydroxy-3-(2-hydroxyethyl)-*as*-indacen-2(1*H*)-one 3^2-Formate 7-Pivalate (23). A solution of **22** (0.16 g, 0.61 mmol) and DMAP (37 mg, 0.30 mmol) in pyridine (18 mL) was treated with pivaloyl chloride (0.37 mL, 3.0 mmol), stirred overnight, and poured into a mixture of ether and saturated NH_4Cl solution (1:1, 50 mL). The separated organic layer was washed with saturated NH_4Cl solution (10 mL), dried, and concentrated in vacuo. The residue was purified by chromatography on silica gel (ethyl acetate/hexanes 1:4 as eluant) to give **23** (0.19 g, 90%) as a white solid, mp 62−64 °C; IR ($CHCl_3$, cm^{-1}) 1720; ^1H NMR (300 MHz, $CDCl_3$) δ 8.01 (s, 1 H), 5.92 (d, J = 9.8 Hz, 1 H), 5.77 (dt, J = 9.8, 3.2 Hz, 1 H), 5.18−5.12 (m, 1 H), 4.36−4.28 (m, 2 H); 2.61−2.54 (m, 1 H), 2.49−2.18 (series of m, 5 H), 2.09−1.83 (series of m, 4 H), 1.57 (td, J = 13.4, 7.6 Hz, 1 H), 1.30−1.14 (m, 2 H), 1.16 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 218.4, 178.1, 160.8, 130.0, 128.7, 74.1, 61.6, 49.9, 44.5, 43.3. 42.0, 41.7, 38.4, 38.1, 37.7, 36.7, 28.1, 27.0 (3 C); MS m/z (M^+) calcd 348.1937, obsd 348.1944; $[\alpha]^{22}_D$ −34.0 (c 0.42, CH_2Cl_2). Anal. Calcd for $C_{20}H_{28}O_5$: C, 68.94; H, 8.10. Found: C, 68.95; H, 8.06.

(2*R*,3a*S*,5a*R*,6*S*,8a*S*,8b*R*)-1,2,3,3a,5a,6,7,8,8a,8b-Decahydro-6-[2-(*p*-methoxybenzyl)oxy]ethyl]-7-oxo-*as*-indacen-2-yl Pivalate (2). A solution of **23** (0.17 g, 0.49 mmol) in MeOH (20 mL) was heated at reflux for one week, cooled, and freed of solvent. The residue was dissolved in CH_2Cl_2 (15 mL), treated with camphorsulfonic acid (12 mg, 0.05 mmol) and *p*-methoxybenzyl trichloroacetamidate (0.52 mL, 2.5 mmol), and stirred for 24 h prior to quenching with saturated $NaHCO_3$ solution. The organic layer was separated, dried, and evaporated. The residue was purified by chromatography on silica gel (ethyl acetate/hexanes 1:5 as eluant) to give **2** (0.19 g, 88%), which was identical in all respects to the material prepared earlier.[2]

Methyl (*S*)-5-Hydroxyheptanoate (25). A flame-dried flask was charged with (−)-(1*S*,2*R*)-*N*,*N*-dibutylnorephedrine (0.36 mL, 1.3 mmol), **24**[17] (2.64 g, 20.3 mmol), and dry hexanes (60 mL). The mixture was stirred at room temperature under N_2 for 30 min and cooled to 0 °C, treated with a 1.1 M solution of diethylzinc in toluene (46.1 mL, 50.7 mmol) via syringe, and stirred at 0 °C for 72 h before being quenched with saturated NH_4Cl solution. The separated aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL), and the combined organic layers were washed with saturated $NaHCO_3$ solution, dried, and concentrated. The residue was purified by chromatography on silica gel (ethyl acetate/hexanes 1:2 as eluant) to give an inseparable mixture of **25** and the derived lactone. This mixture was refluxed in methanol (50 mL) in the presence of 30 μL of 98% H_2SO_4 for 5.5 h, cooled to room temperature, and neutralized with solid $NaHCO_3$ (2.5 g). After filtration and evaporation of the solvent, **25** (2.4 g, 73%) was obtained and used immediately in the next step.

Methyl (*S*)-5-(*tert*-Butyldimethylsiloxy)heptanoate (26). *tert*-Butyldimethylsilyl triflate (3.1 mL, 13.5 mmol) was added to a solution of **25** (1.80 g, 11.2 mmol) and 2,6-lutidine (6.6 mL, 56 mmol) in CH_2Cl_2 (100 mL) at 0 °C, stirred at room temperature for 2 h, and quenched with a 10% aqueous citric acid solution (150 mL). The separated aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL), and the combined organic layers were dried and freed of solvent. The residue was purified by chromatography on silica gel (ethyl acetate/hexanes 1:15 as eluant) to give **26** (2.60 g, 84%) as a colorless oil; IR (film, cm^{-1}) 1744, 1463, 1254, 1168, 1057; ^1H NMR (300 MHz, $CDCl_3$) δ 3.66 (s, 3 H), 3.59 (m, 1 H), 2.31 (t, J = 7.4 Hz, 2 H), 1.70−1.43 (m, 6 H), 0.88 (s, 9 H), 0.85 (t, J = 7.4 Hz, 3 H), 0.04 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 174.1, 73.0, 51.4, 35.8, 34.3, 29.6, 25.9 (3 C), 20.8, 18.1, 9.5, −4.45, −4.52; MS m/z (M^+) calcd 274.1964, obsd 274.1924; $[\alpha]^{22}_D$ +1.2 (c 0.55, CH_2Cl_2). Anal. Calcd for $C_{14}H_{30}O_3Si$: C, 61.26; H, 11.02. Found: C, 61.54; H, 11.00.

(*S*)-5-(*tert*-Butyldimethylsiloxy)heptanal (27). To a solution of **26** (2.20 g, 8.0 mmol) in CH_2Cl_2 (30 mL) at −78 °C under N_2 was added dropwise a 1.0 M solution of DIBAL-H in toluene (10.0 mL, 10.0 mmol). The reaction mixture was stirred at this temperature for 30 min, quenched with MeOH (2 mL) and saturated Rochelle's salt solution (30 mL), diluted with ethyl acetate (300 mL) and stirred for an additional hour. The separated aqueous layer was extracted with ethyl

acetate (2 × 50 mL), and the combined organic layers were dried and evaporated. The resulting residue was purified by chromatography on silica gel (ethyl acetate/hexanes 1:15 as eluant) to give **27** (1.85 g, 94%) as a colorless oil; IR (film, cm^{-1}) 1729; ^1H NMR (300 MHz, $CDCl_3$) δ 9.76 (t, J = 2.6 Hz, 1 H), 3.60 (q, J = 8.5 Hz, 1 H), 2.42 (td, J = 10.8, 2.7 Hz, 2 H), 1.72−1.42 (series of m, 9 H), 0.88 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 202.6, 73.0, 44.0, 35.8, 29.6, 25.9 (3 C), 18.1, 18.0, 9.5, −4.4, −4.5; MS m/z (M^+) calcd 244.1859, obsd 244.1819; $[\alpha]^{22}_D$ +3.6 (c 0.75, CH_2Cl_2). Anal. Calcd for $C_{13}H_{28}O_2Si$: C, 63.88; H, 11.55. Found: C, 63.92; H, 11.40.

(4*R*)-3-[(2*R*,3*S*,7*S*)-7-(*tert*-Butyldimethylsiloxy)-3-hydroxy-2-methylnonanoyl]-4-isopropyl-2-oxazolidinone (29). To a solution of **28** (0.78 g, 4.2 mmol) in CH_2Cl_2 (10 mL) at 0 °C under N_2 was added dropwise (at such a rate to maintain the internal temperature below +5 °C) a 1.0 M solution of dibutylboron triflate in CH_2Cl_2 (4.6 mL, 4.6 mmol). The mixture was stirred for 10 min prior to the dropwise addition of triethylamine (0.7 mL, 5.0 mmol) at such a rate to maintain the internal temperature below +5 °C. After 20 min, the yellow solution was cooled to −78 °C, and a solution of **27** (0.98 g, 4.0 mmol) in CH_2Cl_2 (4 mL) was added dropwise under N_2 (at such a rate to maintain the internal temperature below −70 °C). After 2 h at −78 °C, the reaction medium was slowly warmed to 0 °C, stirred for 1 h at 0 °C, and quenched by the dropwise addition of pH 7.0 phosphate buffer (16 mL) followed by MeOH (12 mL). After an additional 10 min, a premixed solution of hydrogen peroxide (30%) (4 mL) in methanol (8 mL) was added dropwise at 0 °C. After 2 h at this temperature, the layers were separated and the aqueous phase was extracted with ether (3×). The combined organic layers were washed with a saturated $NaHCO_3$ solution, dried, and concentrated. Chromatography of the residue on silica gel (gradient elution with 1:10 → 1:4 ethyl acetate in hexanes) furnished 1.51 g (88%) of **29** as a colorless oil; IR (film, cm^{-1}) 3528, 1783, 1700; ^1H NMR (300 MHz, $CDCl_3$) δ 4.44 (m, 1 H), 4.25 (m, 2 H), 3.92 (m, 1 H), 3.77 (dq, J = 7.1, 2.6 Hz, 1 H), 3.57 (m, 1 H), 2.44 (br s, 1 H), 2.37 (m, 1 H), 1.57−1.38 (series of m, 8 H), 1.23 (d, J = 7.0 Hz, 3 H), 0.91 (d, J = 7.0 Hz, 3 H), 0.88 (d, J = 6.7 Hz, 3 H), 0.88 (s, 9 H), 0.86 (t, J = 7.6 Hz, 3 H), 0.034 (s, 3 H), 0.032 (s, 3 H) (OH not observed); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 177.9, 153.5, 73.4, 71.2, 63.3, 58.2, 42.1, 36.5, 34.0, 29.7, 28.4, 25.9 (3 C), 22.0, 17.9, 14.7, 10.7, 9.5, 8.4, −4.5 (2 C) (OH not observed); MS m/z (M^+ + H) calcd 430.2989, obsd 430.2979; $[\alpha]^{22}_D$ +49.3 (c 0.51, CH_2Cl_2). Anal. Calcd for $C_{22}H_{43}NO_5Si$: C, 61.50; H, 10.09. Found: C, 61.25; H, 9.92.

(2*R*,3*S*,7*S*)-7-(*tert*-Butyldimethylsiloxy)-3-(*tert*-butyldiphenylsiloxy)-2-methylnonanoic Acid (30). A solution of **29** (1.16 g, 2.7 mmol) in CH_2Cl_2 (50 mL) at room temperature was treated sequentially with imidazole (0.92 g, 13.5 mmol), DMAP (160 mg, 1.3 mmol), and *tert*-butyldiphenylchlorosilane (1.75 mL, 6.7 mmol). The reaction mixture was stirred at room temperature for 6 days, quenched with ethanol (5 mL), and later washed with saturated $NaHCO_3$ solution (25 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL), and the combined organic extracts were dried and concentrated. The residue was purified by flash chromatography (silica gel, elution with ethyl acetate/hexanes 1:10) to give 1.41 g of silylated product as a colorless oil which was used without further purification.

A solution of the sample obtained above (0.84 g, 1.2 mmol) in a mixture of THF (12 mL), DMF (12 mL) and H_2O (4 mL) at 0 °C was treated sequentially with hydrogen peroxide (1.7 mL of 30%, 15.1 mmol) and lithium hydroxide monohydrate (0.16 g, 3.8 mmol). The reaction mixture was stirred overnight at 0 °C and quenched with 1.5 N Na_2SO_3 solution (20 mL). After 15 min at 0 °C, HCl (1 N, 10 mL) was introduced (pH 3), and the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were dried, filtered, and evaporated in vacuo. The residue was purified by column chromatography on silica gel (gradient elution with 1:10 → 1:5 ethyl acetate/hexanes) to give **30** (0.46 g, 51% for the two steps) as a colorless oil; IR (CH_2Cl_2, cm^{-1}) 1709; ^1H NMR (300 MHz, C_6D_6) δ 7.87−7.79 (m, 4 H), 7.28−7.17 (m, 6 H), 4.41−4.36 (m, 1 H), 3.33−3.27 (m, 1 H), 2.60−2.55 (m, 1 H), 1.52−1.48 (m, 2 H), 1.31−0.88 (m, 6 H), 1.28 (d, J = 7.0 Hz, 3 H), 1.18 (s, 9 H), 0.96 (s, 9 H), 0.79 (t, J = 7.5 Hz, 3 H), 0.02 (s, 3 H), −0.01 (s, 3 H) (OH not observed); ^{13}C NMR (75 MHz, C_6D_6) ppm 180.5, 136.4 (2 C), 136.3 (2 C), 134.8, 133.9, 129.9, 129.8, 127.8 (2 C), 127.7 (2 C), 74.6, 73.2, 43.9, 36.3, 34.9, 29.7, 27.2 (3 C), 26.1 (3 C), 21.2, 19.8, 18.3, 10.0, 9.7, −4.3 (2 C) (OH not observed); MS m/z ($M^+ - C(CH_3)_3$) calcd 499.2700, obsd 400.2725; $[\alpha]^{22}_D$ −2.0 (c 0.3, CH_2Cl_2). Anal. Calcd for $C_{32}H_{52}O_4Si_2$: C, 69.01; H, 9.41. Found: C, 68.76; H, 9.40.

(2*R*,3a*S*,5a*R*,6*S*,8a*S*,8b*R*)-1,2,3,3a,5a,6,8a,8b-Octahydro-6-[2-[(*p*-methoxybenzyl)oxy]ethyl]-7-(trimethylstannyl)-*as*-indacen-2-yl Pivalate (33). A 0.5 M solution of potassium hexamethyldisilazide in toluene (5.0 mL, 2.5 mmol) was placed under N_2, diluted with 20 mL of anhydrous THF, cooled to −78 °C, and treated with a solution of **2** (0.73 g, 1.66 mmol) in anhydrous THF (40 mL) dropwise via cannula. The mixture was stirred at this temperature for 30 min, treated with a solution of *N*-(5-chloro-2-pyridyl)bis(trifluoromethanesulfonate) (1.17 g, 3.0 mmol) in anhydrous THF (60 mL), stirred for 1 h at −78 °C, and slowly warmed to room temperature during 3 h. After solvent evaporation, the residue was immediately chromatographed on silica gel (elution with ethyl acetate/hexanes 1:12) to give 620 mg of enol triflate **32**, which was used directly.

A solution of **32** (0.62 g, 1.1 mmol) in anhydrous THF (10 mL) at room temperature under N_2 was treated sequentially with hexamethylditin (0.39 g, 1.2 mmol), lithium chloride (0.28 g, 6.5 mmol), and tetrakis(triphenylphosphine)palladium (23 mg, 0.02 mmol). The mixture was stirred at 60 °C for 2 days, poured into a mixture of ether (50 mL) and pH 7.0 phosphate buffer (25 mL), and extracted with ether (2 × 25 mL). The combined organic layers were dried and freed of solvent. The residue was purified by chromatography on silica gel (ethyl acetate/hexanes 1:12 containing 1% triethylamine as eluant) to give **33** (0.46 g, 48% overall); white solid, mp 68−70 °C; IR ($CHCl_3$, cm^{-1}) 1714; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, J = 8.6 Hz, 2 H), 6.88 (d, J = 8.6 Hz, 2 H), 5.86 (s, 1 H), 5.82 (d, J = 9.9 Hz, 1 H), 5.74 (dt, J = 9.9, 2.4 Hz, 1 H), 5.17−5.11 (m, 1 H), 4.44 (AB system, J_{AB} = 11.6 Hz, 2 H), 3.80 (s, 3 H), 3.56−3.51 (m, 2 H), 2.67−2.59 (m, 2 H), 2.48−2.39 (m, 2 H), 2.11−1.99 (m, 2 H), 1.89 (dd, J = 13.6, 6.8 Hz, 1 H), 1.65−1.45 (m, 2 H), 1.28−1.19 (m, 1 H), 1.18 (s, 9 H), 1.05−0.90 (m, 1 H), 0.12 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 178.3, 147.8, 143.1, 131.1, 130.5, 129.3 (2 C), 128.8, 113.8 (2 C), 77.2, 75.1, 72.7, 68.5, 55.3, 54.3, 52.4, 47.6, 46.4, 41.3, 38.5, 37.4, 37.3, 36.0, 27.1 (3 C), −9.3 (3 C); MS m/z (M^+) calcd 573.2027, obsd 573.2005; $[\alpha]^{22}_D$ −72.8 (c 1.0, CH_2Cl_2). Anal. Calcd for $C_{30}H_{44}O_4Sn$: C, 61.35; H, 7.55. Found: C, 61.59; H, 7.62.

(2*R*,3a*S*,5a*R*,6*S*,8a*S*,8b*R*)-7-[(2*R*,3*S*,7*S*)-7-(*tert*-Butyldimethylsiloxy)-3-(*tert*-butyldiphenylsiloxy)-2-methylnonanoyl)-1,2,3,3a,5a,6,8a,8b-octahydro-6-[2-[(*p*-methoxybenzyl)oxy]ethyl]-*as*-incaden-2-yl Pivalate (35). To a solution of **30** (0.39 g, 0.70 mmol) and anhydrous DMF (54 μL, 0.70 mmol) in anhydrous hexanes (30 mL) at room temperature under N_2 was added oxalyl chloride (0.31 mL, 3.5 mmol). The mixture was stirred at this temperature for 45 min, filtered under N_2, and evaporated to afford the correspondent acyl chloride which was used without further purification.

A solution of the acyl chloride and vinylstannane **33** (370 mg, 0.63 mmol) in anhydrous benzene (30 mL) at room temperature under N_2 was treated with $Pd_2(dba)_3 \cdot CHCl_3$ (75 mg, 0.07 mmol). After 10 min, diisopropylethylamine (31 μL, 0.18 mmol) was introduced, and the reaction mixture was stirred for 6 h and poured into a mixture of ether (100 mL) and water (25 mL). The aqueous layer was extracted with ether (2 × 25 mL), and the combined organic layers were dried, filtered, and concentrated. The residue was purified by chromatography on silica gel (gradient elution with ethyl acetate/hexanes 1:15 → 1:12) to give **35** (0.51 g, 83% overall) as a colorless oil; IR ($CHCl_3$, cm^{-1}) 1715, 1658; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67−7.53 (m, 4 H), 7.43−7.32 (m, 6 H), 7.24 (d, J = 8.7 Hz, 2 H), 6.86 (d, J = 8.7 Hz, 2 H), 6.51 (s, 1 H), 5.82 (d, J = 9.8 Hz, 1 H), 5.74 (dt, J = 9.8 Hz, 1 H), 5.16−5.10 (m, 1 H), 4.40 (AB system, J_{AB} = 11.5 Hz, 2 H), 4.06−4.01 (m, 1 H), 3.79 (s, 3 H), 3.55−3.49 (m, 2 H), 3.39−3.23 (m, 2 H), 2.85−2.57 (m, 3 H), 2.42−2.20 (m, 2 H), 2.18−2.04 (m, 1 H), 1.91 (dd, J = 13.7, 6.8 Hz, 1 H), 1.56−0.87 (m, 12 H), 1.18 (s, 9 H), 1.10 (d, J = 6.8 Hz, 3 H), 1.04 (s, 9 H), 0.85 (s, 9 H), 0.76 (t, J = 7.3 Hz, 3 H), −0.01 (s, 3 H), −0.03 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 202.4, 178.1, 159.0, 146.1, 144.4, 136.0 (2 C), 135.9 (2 C), 134.6, 134.0, 130.8, 130.7, 129.6, 129.5, 129.2 (2 C), 128.7, 127.5 (2 C), 127.4 (2

C), 113.7 (2 C), 75.4, 74.8, 73.2, 72.2, 68.4, 55.2, 49.9, 47.7, 46.8, 46.6, 45.6, 41.2, 38.4, 37.3, 37.2, 36.4, 35.1, 34.0, 29.6, 27.1 (3 C), 27.0 (3 C), 25.9 (3 C), 20.7, 19.5, 18.1, 13.5, 9.5, −4.4, −4.5; FAB MS *m*/*z* ($M^+ + H$) calcd 963.60, obsd 963.66; $[\alpha]^{22}_D$ −35.3 (*c* 1.3, CH_2Cl_2). Anal. Calcd for $C_{59}H_{86}O_7Si_2$: C, 73.55; H, 9.00. Found: C, 73.44; H, 9.09.

(3*S*,3a*R*,5a*S*,7*R*,8a*R*,8b*S*)-2-[(2*R*,3*S*,7*S*)-7-(*tert*-Butyldimethylsiloxy)-3-(*tert*-butyldiphenylsiloxy)-2-methylnonanoyl]-3,3a,5a,6,7,8,8a,8b-octahydro-7-hydroxy-*as*-indacene-3-acetic Acid Pivalate (36). A solution of **35** (0.28 g, 0.29 mmol) in cold (0 °C) CH_2Cl_2 (45 mL) was treated sequentially with pH 7.0 phosphate buffer solution (4.5 mL of 0.05 M) and DDQ (220 mg, 0.97 mmol). The mixture was stirred for 2 h and poured into a mixture of ethyl acetate (400 mL) and the same phosphate buffer (20 mL). The separated organic phase was washed with phosphate buffer (5 × 20 mL), dried, and concentrated. Flash chromatography of the residue on silica gel (elution with 1:4 ethyl acetate/hexanes) provided an inseparable mixture of the primary alcohol and *p*-anisaldehyde (280 mg) which was taken up in acetone (6 mL), cooled to 0 °C, and treated dropwise with precooled (0 °C) Jones reagent (0.51 mL). The reaction mixture was stirred for 1.5 h and poured into ethyl acetate (150 mL) and the phosphate buffer (20 mL). The organic layer was washed with phosphate buffer until the washings were at pH 7, dried, and concentrated. Purification of the product by chromatography on silica gel (gradient elution with 1:4 → 1:2 ethyl acetate/hexanes) gave **36** (0.16 g, 64% for two steps) as a colorless oil; IR (film, cm^{-1}) 3244, 1728, 1713, 1665, 1613; ^{1}H NMR (300 MHz, C_6D_6) δ 7.84−7.74 (m, 4 H), 7.30−7.19 (m, 6 H), 6.37 (s, 1 H), 5.85 (dt, *J* = 9.7, 2.5 Hz, 1 H), 5.69 (d, *J* = 9.7 Hz, 1 H), 5.14−5.07 (m, 1 H), 4.40−4.35 (m, 1 H), 3.47−3.34 (m, 2 H), 3.29−3.24 (m, 1 H), 3.16−3.05 (m, 1 H), 2.56−2.39 (m, 3 H), 2.21−2.12 (m, 1 H), 2.01−1.91 (m, 1 H), 1.80 (dd, *J* = 13.7, 6.7 Hz, 1 H), 1.67−1.50 (m, 2 H), 1.42−1.03 (m, 7 H), 1.33 (d, *J* = 6.9 Hz, 3 H), 1.21 (s, 9 H), 1.18 (s, 9 H), 0.99 (s, 9 H), 0.89−0.78 (m, 1 H), 0.83 (t, *J* = 7.4 Hz, 3 H), 0.62−0.55 (m, 1 H), 0.07 (s, 6 H) (OH not observed); ^{13}C NMR (75 MHz, C_6D_6) ppm 201.4, 177.5, 177.3, 144.9, 144.6, 136.4 (2 C), 136.3 (2 C), 135.1, 134.2, 130.1, 130.0, 129.8, 129.3, 128.2 (2 C), 127.9 (2 C), 75.8, 75.0, 73.7, 50.0, 47.0, 46.9, 46.1, 46.0, 41.6, 38.5, 38.3, 37.8, 37.2, 36.6, 35.7, 30.1, 27.4 (3 C), 27.2 (3 C), 26.2 (3 C), 21.0, 19.8, 18.4, 14.2, 9.7, −4.1, −4.3; FAB MS *m*/*z* (M^+) calcd 856.51, obsd 856.59; $[\alpha]^{22}_D$ −24.6 (*c* 2.1, ethyl acetate).

(3*S*,3a*R*,5a*S*,7*R*,8a*R*,8b*S*)-2-[(2*R*,3*S*,7*S*)-3-(*tert*-Butyldiphenylsiloxy)-7-hydroxy-2-methylnonanoyl]-3,3a,5,a6,7,8,8a,8b-octahydro-7-hydroxy-*as*-indacene-3-acetic Acid κ-Lactone Pivalate (37). A solution of **36** (22 mg, 0.03 mmol) in a mixture of THF:H_2O:AcOH (1:1:3, 4.0 mL) was stirred for 15 min at 0 °C and 24 h at room temperature, diluted with ethyl acetate (25 mL), dried, concentrated, and azeotropically dried with benzene (2 × 10 mL) to give the corresponding seco acid, which was dissolved in dry benzene (50 mL), treated with triethylamine (273 μL, 1.9 mmol), 2,4,6-trichlorobenzoyl chloride (160 μL, 1.0 mmol), and DMAP (31 mg, 0.26 mmol), and stirred vigorously under N_2. After 1.5 h, an additional 31 mg of DMAP was introduced, and the cloudy white solution was stirred overnight. On the following day, 31 mg more of DMAP was added and after 3 h the reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed with 0.1 M $KHSO_4$ solution. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic layers were washed with saturated $NaHCO_3$ solution (30 mL), dried, and concentrated in vacuo. The residue was purified by chromatography on silica gel (elution with 1:12 ethyl acetate/hexanes) to furnish **37** as a white solid, mp 162−164 °C (11.0 mg, 59% for two steps); IR (film, cm^{-1}) 1714, 1658; ^{1}H NMR (300 MHz, $CHCl_3$) δ 7.70−7.65 (m 4 H), 7.44−7.34 (m 6 H), 6.85 (s, 1 H), 5.88 (d, *J* = 9.8 Hz, 1 H), 5.78 (dt, *J* = 9.8, 2.5 Hz, 1 H), 5.19−5.12 (m, 1 H), 4.61−4.53 (m, 1 H), 4.00−3.96 (m, 1 H), 3.53−3.47 (m, 1 H), 3.35−3.25 (m, 1 H), 3.06−2.96 (m, 2 H), 2.92−2.85 (m, 1 H), 2.48−2.35 (m, 2 H), 2.23−2.13 (m, 1 H), 1.93 (dd, *J* = 13.7, 6.7 Hz, 1 H), 1.57−1.20 (m, 9 H), 1.19 (s, 9 H), 1.14 (d, *J* = 6.9 Hz, 3 H), 1.07 (s, 9 H), 1.05−0.84 (m, 2 H), 0.76 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CHCl_3$) ppm 203.0, 178.2, 172.5, 147.1, 143.7, 136.0 (2 C), 135.9 (2 C), 134.4, 133.9, 129.6, 129.5, 129.3, 129.0, 127.5 (2 C), 127.4 (2 C), 75.6 (2 C), 74.8, 49.5, 48.7, 47.6, 46.6, 41.7, 41.4, 38.4, 37.2, 37.1, 35.8, 34.5, 30.8, 27.8, 27.1 (3 C), 27.0 (3 C), 19.7, 19.6, 18.2, 9.4; FAB MS *m*/*z* (M^+) calcd 724.42, obsd 724.47; $[\alpha]^{22}_D$ −59.0 (*c* 0.80, CH_2Cl_2). Anal. Calcd for $C_{45}H_{60}O_6Si$: C, 74.55; H, 8.34. Found: C, 74.37; H, 8.41.

(2*R*,3*S*,3a*R*,5a*S*,7*R*,8a*R*,8b*S*)-2-[(2*R*,3*S*,7*S*)-3-(*tert*-Butyldiphenylsiloxy)-7-hydroxy-2-methylnonanoyl]-1,2,3,3a,5a,6,7,8,8a, 8b-decahydro-7-hydroxy-*as*-indacene-3-acetic Acid κ-Lactone (38). A mixture of **37** (27 mg, 0.04 mmol) and potassium carbonate (6 mg, 0.04 mmol) in methanol (4.0 mL) was refluxed for 2 days, freed of solvent, and triturated with ether (5 mL). The concentrated extract was purified by chromatography on silica gel (elution with 3:1 hexanes/ethyl acetate) to give **38** (15 mg, 63%) as a colorless oil; IR (film, cm^{-1}) 3410, 1721, 1659, 1610; ^{1}H NMR (300 MHz, $CHCl_3$) δ 7.71−7.66 (m, 4 H), 7.44−7.34 (m, 6 H), 6.87 (s, 1 H), 5.87 (d, *J* = 9.8 Hz, 1 H), 5.77 (dt, *J* = 9.8, 2.6 Hz, 1 H), 4.61−4.53 (m, 1 H), 4.47−4.41 (m, 1 H), 4.00−3.96 (m, 1 H), 3.52−3.45 (m, 1 H), 3.37−3.27 (m, 1 H), 3.06−2.86 (m, 3 H), 2.41−2.20 (m, 3 H), 1.86 (dd, *J* = 13.3, 6.8 Hz, 1 H), 1.56 (br s, 1 H), 1.54−1.18 (m, 9 H), 1.15 (d, *J* = 6.9 Hz, 3 H), 1.07 (s, 9 H), 1.02−0.84 (m, 2 H), 0.75 (t, *J* = 7.5 Hz, 3 H) (OH not observed); ^{13}C NMR (75 MHz, $CHCl_3$) ppm 203.0, 172.5, 147.5, 143.6, 136.0 (2 C), 135.9 (2 C), 134.5, 133.9, 129.6, 129.5, 129.4, 129.0, 127.5 (2 C), 127.4 (2 C), 75.6, 75.5, 72.4, 49.5, 48.7, 47.6, 47.0, 41.6, 41.0, 40.7, 40.0, 35.8, 34.4, 30.8, 27.9, 27.1 (3 C), 19.7, 19.6, 18.3, 9.4; MS *m*/*z* (M^+) calcd 640.3584, obsd 640.3632; $[\alpha]^{22}_D$ −50.6 (*c* 0.33, CH_2Cl_2). Anal. Calcd for $C_{40}H_{52}O_5Si\cdot 0.5\ H_2O$: C, 73.92; H, 8.22. Found: C, 73.89; H, 8.26.

(3*S*,3a*R*,5a*S*,7*S*,8a*R*,8b*S*)-2-[(2*R*,3*S*,7*S*)-3-(*tert*-Butyldiphenylsiloxy)-7-hydroxy-2-methylnonanoyl]-7-[(6-deoxy-2,3,4-tri-*O*-methyl-α-L-mannopyranosyl)oxy]-3,3a,5a,6,7,8,8a,8b-octahydro-*as*-indacene-3-acetic Acid κ-Lactone (39). To a solution of **38** (40 mg, 0.06 mmol) and acetylated α-glycoside (23 mg, 0.9 mmol) in anhydrous toluene (4 mL) at 0 °C under N_2 was added trityl perchlorate[36] (2 mg, 0.006 mmol). The reaction mixture was stirred at 0 °C for 10 min and at room temperature for 3 h and poured onto a mixture of ether (25 mL) and saturated $NaHCO_3$ solution (10 mL). The separated organic layer was dried and concentrated to leave a residue that was purified by chromatography on silica gel (elution with ethyl acetate/hexanes 1:3) to give **39** (44 mg, 85%) as a white solid followed by unreacted **38** (4 mg, 9%). The β-isomer was not detected.

For **39**: mp 82−85 °C; IR (film, cm^{-1}) 1720, 1660; ^{1}H NMR (300 MHz, $CHCl_3$) δ 7.71−7.66 (m, 4 H), 7.44−7.33 (m, 6 H), 6.84 (s, 1 H), 5.85 (d, *J* = 9.7 Hz, 1 H), 5.75 (dt, *J* = 9.7, 2.6 Hz, 1 H), 4.84 (d, *J* = 1.4 Hz, 1 H), 4.60−4.52 (m, 1 H), 4.34−4.27 (m, 1 H), 4.00−3.95 (m, 1 H), 3.60−3.44 (m, 4 H), 3.56 (s, 3 H), 3.50 (s, 3 H), 3.49 (s, 3 H), 3.36−3.25 (m, 1 H), 3.12 (t, *J* = 9.2 Hz, 1 H), 3.05−2.90 (m, 2 H), 2.89−2.83 (m, 1 H), 2.40−2.35 (m, 1 H), 2.33−2.22 (m, 1 H), 2.21−2.10 (m, 1 H), 1.91 (dd, *J* = 13.3, 7.0 Hz, 1 H), 1.50−1.26 (m, 9 H), 1.28 (d, *J* = 6.2 Hz, 3 H), 1.14 (d, *J* = 6.8 Hz, 3 H), 1.07 (s, 9 H), 0.97−0.79 (m, 2 H), 0.75 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CHCl_3$) ppm 203.0, 172.5, 147.2, 143.6, 136.0 (2 C), 135.9 (2 C), 134.4, 133.9, 129.6, 129.5, 129.2, 129.0, 127.5 (2 C), 127.4 (2 C), 95.5, 82.3, 81.0, 77.7, 76.2, 75.5 (2 C), 67.9, 60.9, 59.0, 57.6, 49.4, 48.6, 47.6, 46.3, 41.6, 41.1, 37.5, 36.4, 35.8, 34.4, 30.8, 27.8, 27.1 (3 C), 19.7, 19.6, 18.3, 17.8, 9.3; FAB MS *m*/*z* (M^+) calcd 829.46, obsd 829.47; $[\alpha]^{22}_D$ −107 (*c* 0.9, CH_2Cl_2). Anal. Calcd for $C_{49}H_{68}O_9Si$: C, 70.98; H, 8.27. Found: C, 70.75; H, 8.21.

(3*S*,3a*R*,5a*S*,7*R*,8a*R*,8b*S*)-7-[(6-Deoxy-2,3,4-tri-*O*-methyl-α-L-mannopyranosyl)oxy]-2-[(2*R*,3*S*,7*S*)-3,7-dihydroxy-2-methylnonanoyl]-3,3a,5a,6,7,8,8a,8b-octahydro-*as*-indacene-3-acetic Acid κ-Lactone (3). To a solution of **39** (44 mg, 0.05 mmol) in acetonitrile (3.0 mL) was added 49% aqueous hydrofluoric acid (0.53 mL). The reaction mixture was stirred for 24 h and diluted with ethyl acetate (25 mL). The organic phase was washed with saturated $NaHCO_3$ solution (2 × 10 mL), dried, and concentrated. The residue was purified by chromatography on silica gel (elution with ethyl acetate/hexanes 1:1) to give **3** (29 mg, 91%) as a white solid, mp 168−169 °C; $[\alpha]^{22}_D$ −163 (*c* 0.43, CH_2Cl_2). This material was identical in all respects to authentic **3** described earlier, mp 168.5−170 °C; $[\alpha]^{22}_D$ −170 (*c* 0.45, CH_2Cl_2).

Spinosyn A (1). A cold (−50 °C), magnetically stirred solution of triphenylphosphine (2.03 g, 7.7 mmol) in anhydrous THF (10 mL) was

(36) Dauben, H. J., Jr.; Honnen, L. R.; Harmon, K. M. *J. Org. Chem.* **1960**, *25*, 1442.

blanketed with N_2, treated with diethyl azodicarboxylate (1.21 mL, 7.7 mmol), and stirred for 10 min. A solution of D-forosamine (0.88 g, 5.5 mmol) in THF (6 mL) was introduced, followed 10 min later by 2-mercaptopyrimidine (0.87 g, 7.8 mmol). The temperature of the reaction mixture was slowly increased to 20 °C during 3 h, at which point the solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (elution with CH_2Cl_2/methanol 20:1). There was isolated a 2:1 mixture of the α- and β-thioglycosides as a yellow oil (0.96 g, 68%) which was used without further purification.

A stirred solution of **3** (35 mg, 0.06 mmol) and silver triflate (90 mg, 0.35 mmol) in anhydrous CH_2Cl_2 (1.0 mL) under N_2 and protected from light was treated with the thioforosamine obtained above (75 mg, 0.3 mmol) dissolved in CH_2Cl_2 (2.0 mL) at a dropwise rate over 1 h. The mixture was stirred for 3 h, quenched with saturated $NaHCO_3$ solution (5 mL), and diluted with CH_2Cl_2 (35 mL). The separated aqueous phase was extracted with CH_2Cl_2 (15 mL), and the combined organic layers were dried, filtered, and concentrated. Chromatography of the residue on silica gel (elution with CH_2Cl_2/methanol 24:1) returned 24 mg (69%) of **3** followed by a 2:3 mixture of **1** and the α-anomer (7.5 mg combined, 55% adjusted). Chromatography of this mixture on silica gel in the manner reported by Evans and Black[7] returned pure spinosyn A exhibiting spectra identical to those reported previously and independently recorded for natural **1**. The unnatural epimer, which was not obtained completely free of **1**, exhibited the following characteristic downfield ^{1}H NMR signals: (300 MHz, $CDCl_3$) δ 6.80 (s, 1 H), 5.88 (d, J = 10.9 Hz, 1 H), 5.80−5.76 (m, 1 H), 4.85 (br s, 1 H), 4.67−4.64 (m, 1 H), 4.33−4.32 (m, 1 H), 4.30 (m, 1 H), 3.87 (m, 1 H), 3.56 (s, 3 H), 3.54−3.52 (m, 1 H), 3.50 (s, 3 H), 3.49 (s, 3 H), 3.48−3.47 (s, 3H), 3.45−3.44 (m, 1 H), 3.34−3.32 (m, 1 H), 3.15−3.14 (m, 2 H), 3.07−3.04 (m, 1 H), 2.90−2.89 (m, 1 H).

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Supporting Information Available: Experimental details for the preparation of **7**−**17** (degradative component of the work not utilized for the core synthesis) (8 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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