Total Synthesis of Ionophore Antibiotic X-14547A (Indanomycin)

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A convergent, enantioselective total synthesis of ionophore antibiotic X-14547A (indanomycin, 1) is described. The dioxanone-to-dihydropyran variant of the lactonic Ireland–Claisen rearrangement establishes the hydropyran nucleus of the "left wing" fragment 2. Elaboration to the target synthon utilizes a new methodology for the preparation of stereodefined vinylsilanes (24 → 25 → 26) via net S_N2' coupling of [α-(mesyloxy)allyl]silanes with Grignard reagents catalyzed by CuCN. Salient features in the construction of the "right wing" subunit 3 include a modification of the Noyori three-component coupling procedure (32 → 33) and the application of a retro hetero Diels–Alder/intramolecular Diels–Alder ("mock Claisen") process (5 → 39). Palladium-mediated cross coupling of "left wing" and "right wing" synthons using Stille's method tolerates a free carboxylic acid and an unprotected acyl pyrrole, affording indanomycin directly in its natural absolute configuration.

As part of a screen for novel ionophores from soil cultures, the isolation and characterization of antibiotic X-14547A from ethyl acetate extraction of the whole fermentation broth of *Streptomyces antibioticus* NRRL 8167 was reported by Westley and co-workers at Hoffmann-LaRoche in 1978.[1] Now known by the trivial name indanomycin, this water-insoluble fungal metabolite displays *in vitro* activity against Gram-positive bacteria, exhibits both antineoplastic and antihypertensive properties,[2] and functions as an effective ruminant growth promotant by improving feed utilization.[3]

Although containing only a single tetrahydropyranyl residue, indanomycin (1) is capable of binding mono-, di-, and trivalent metal cations, rendering them miscible in organic solvents.[1a] It has been concluded that indanomycin acts primarily as a K^+ carrier in the mitochondrial membrane.[3] Transport of divalent cations such as Ca^{2+} and Rb^{2+} across solvent barriers is a particularly unusual phenomenon and is shared with only a few other carboxylic acid ionophores.[4]

The structure and absolute configuration of indanomycin were determined by single-crystal X-ray analysis of the derived (*R*)-(+)-1-amino-1-(4-bromophenyl)ethane salt, which was formed in a somewhat surprising 2:1 antibiotic/amine ratio.[1c] Examination of crystallographic data reveals a jawlike, head-to-tail dimeric structure wherein the amine salt is encrypted. Extensive NMR data compiled by Lallemand and co-workers[5] has led to the complete assignment of the ^1H and ^{13}C NMR spectra of the natural product.

Although it contains fewer oxygen atoms than most other members of the ionophore family of antibiotics, inspection of the indanomycin framework reveals an array of striking structural features. Five contiguous centers of asymmetry are distributed about the rare *trans*-fused tetrahydroindan[6] nucleus which includes the C_{20} acyl pyrrole moiety, a functional group composite found in only a few other ionophores of the calcimycin type.[7] A trisubstituted tetrahydropyran ring system bearing four stereogenic centers comprises a separate region of the molecule. The (1*E*,3*E*)-butadienyl fragment encompassing C_8–C_{11} constitutes a stereochemical insulator which connects the two dissimilar "left wing" and "right wing" subunits.

The extensive biological profile, unusual structure, and significant physical properties of X-14547A have stimulated a number of synthetic studies. To date, four independent total syntheses of this natural product have been described.[8] Recognizing that the (1*E*,3*E*)-butadienyl unsaturation virtually precludes transmission of stereochemical information from one sector of the molecule to the other, each of these groups devised a convergent plan wherein C_{10}–C_{11} coupling of two chiral subunits was accomplished via a stereoselective olefination protocol. An additional point of conceptual similarity in these synthetic endeavors was the use of a Diels–Alder cycloaddition to secure the hexahydroindene framework of the right wing.

As part of a continuing synthetic program focused upon natural and unnatural hydropyran arrays,[9] we now disclose

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(8) (a) Nicolaou, K. C.; Papahatjis, D. P.; Claremon, D. A.; Magolda, R. L.; Dolle, R. E. *J. Org. Chem.* **1985**, *50*, 1440–1456. (b) Nicolaou, K. C.; Papahatjis, D. P.; Claremon, D. A.; Dolle, R. E. *J. Am. Chem. Soc.* **1981**, *103*, 6967–6969. (c) Nicolaou, K. C.; Claremon, D. A.; Papahatjis, D. P.; Magolda, R. L. *J. Am. Chem. Soc.* **1981**, *103*, 6969–6971. (d) Edwards, M. P.; Ley, S. V.; Lister, S. G.; Palmer, B. D.; Williams, D. J. *J. Org. Chem.* **1984**, *49*, 3503–3516. (e) Edwards, M. P.; Ley, S. V.; Lister, S. G.; Palmer, B. D. *J. Chem. Soc., Chem. Commun.* **1983**, 630–633. (f) Roush, W. R.; Peseckis, S. M.; Walts, A. E. *J. Org. Chem.* **1984**, *49*, 3429–3432. (g) Roush, W. R.; Myers, A. G. *J. Org. Chem.* **1981**, *46*, 1509–1511. (h) Boeckman, R. K., Jr.; Enholm, E. J.; Demko, D. M.; Charette, A. B. *J. Org. Chem.* **1986**, *51*, 4743–4745.

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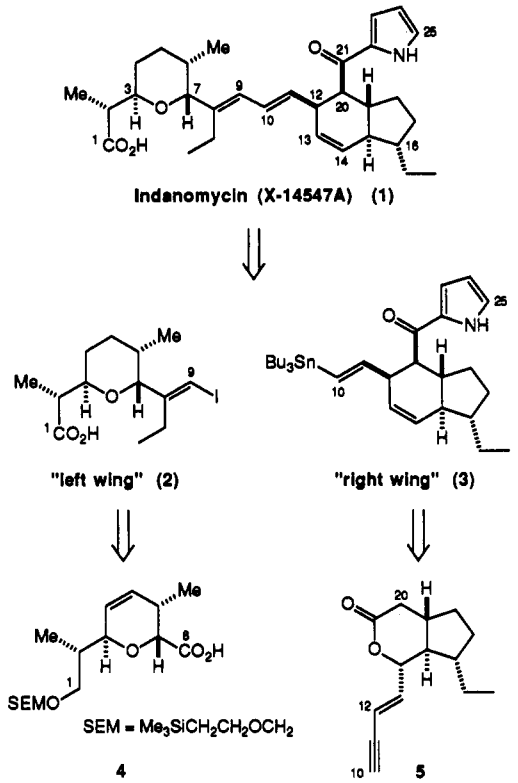
Scheme 1

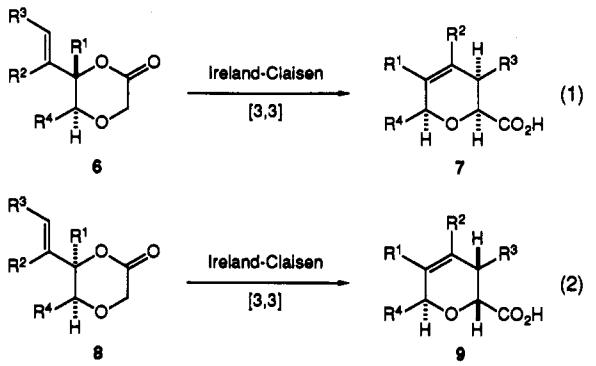


our studies culminating in a convergent, enantioselective total synthesis of indanomycin.

Synthetic Design. Dissection of indanomycin at the C_9–C_{10} σ bond (Scheme 1) forms the basis of a synthetic strategy in which fully functionalized "left wing" and "right wing" subunits would be connected. The emergence of palladium-catalyzed cross couplings of vinyl iodides with vinylstannanes[10] or alkenylboronates[11] as a general method for the preparation of conjugated dienes with retention of olefin stereochemistry made this an especially attractive alternative solution to the indanomycin convergence problem. In a retrosynthetic sense, the task thus reduces to the preparation of subgoals **2** and **3** in enantiomerically pure form. The degree of functional group complexity resident in these intermediates was anticipated to provide an especially challenging test of the tolerance of the Stille methodology.[12] If successful, this coupling would afford the natural product directly, thereby eliminating the need for protecting groups or postcoupling manipulations. Tetrahydropyran **2** was projected to be available from **4**, a structural type for which the dioxanone-to-dihydropyran version[13] of the Claisen rearrangement was designed. Access to the *trans*-fused hydrindene subunit **3** could, in principle, also involve a lactonic Ireland–Claisen rearrangement of **5**; however, an alternative pericyclic process interceded to afford the expected product by an unexpected and unprecedented pathway.[14] Development of these methods and their application to the asymmetric synthesis of indanomycin are described in the following discussion.

Results and Discussion

Preliminary Studies. The prevalence of substituted hydropyran subunits in polyether[4b] and ionophore[4c] antibiotics has inspired the development of numerous methods for their synthesis.[15] The dioxanone-to-dihydropyran transformations generalized in eqs 1 and 2 established an efficient, stereocontrolled entry into the diastereomeric *C*-pyranoside structural types **7** and **9** from appropriately functionalized 6-alkenyl-1,4-dioxan-2-one precursors **6** and **8**.[16] Since structure **9** possesses stereochemical attributes present in the tetrahydropyranyl fragment of indanomycin and in the "left wing" intermediates **2** and **4**, the intended application was pursued.



Establishment of vinyl iodide **2** necessitates both branching and one-carbon homologation of the sterically congested C_8 center in carboxylic acid **4**. Following the lactonic Claisen rearrangement (*vide infra*), **4** was derivatized as its *N*-methoxy-*N*-methylamide **10**,[17] thus providing a versatile handle for carbonyl elaboration. Several unsuccessful attempts at conversion of **10** into precursors of **2** are summarized in eq 3. Although transformation of **10** to ethyl ketone **11** by established methods[18] proved straightforward, halomethylenation protocols[19] (Horner–Wittig, X = Br, I; Takai olefination, X = I) failed

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(11) (a) Miyaura, N.; Satoh, M.; Suzuki, A. *Tetrahedron* **1983**, *39*, 3271–3277. (b) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314–321 and references cited therein.

(12) For general reviews of this topic, see: (a) Mitchell, T. N. *Synthesis* **1992**, 803–815. (b) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508–524.

(13) Burke, S. D.; Armistead, D. M.; Fevig, J. M. *Tetrahedron Lett.* **1985**, *26*, 1163–1166. See supplementary material detailing the preparation of **21**.

(14) Burke, S. D.; Armistead, D. M.; Shankaran, K. *Tetrahedron Lett.* **1986**, *27*, 6295–6298. A formal synthesis of indanomycin is described therein.

(15) For selected recent efforts directed at hydropyran synthesis, see: (a) Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, pp 411–454. (b) Semmelhack, M. F.; Bodurow, C. *J. Am. Chem. Soc.* **1984**, *106*, 1496–1498. (c) Boivin, T. *Tetrahedron* **1987**, *47*, 3309–3362. (d) Danishefsky, S. J.; Selnick, H. G.; Zelle, R. E.; DeNinno, M. P. *J. Am. Chem. Soc.* **1988**, *110*, 4368–4378. (e) Coppi, L.; Ricci, A.; Taddei, M. *J. Org. Chem.* **1988**, *53*, 913–915. (f) Munt, S. P.; Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1989**, 480–482. (g) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5330–5334 and references cited therein. (h) Wagner, A.; Heitz, M.-P.; Mioskowski, C. *Tetrahedron Lett.* **1989**, *30*, 1971–1974. (i) Nicolaou, K. C.; Raja Reddy, K.; Skokotas, G.; Sato, F.; Xiao, X.-Y. *J. Am. Chem. Soc.* **1992**, *114*, 7935–7936.

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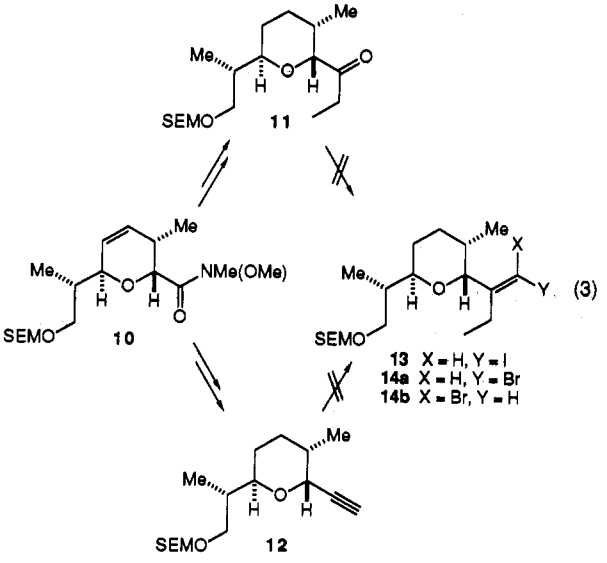
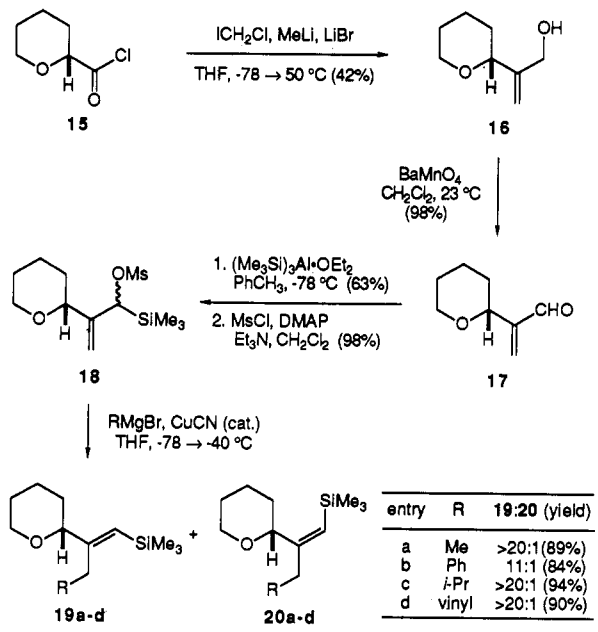
(18) For **10** → **11**: (i) EtMgBr, THF, 0 °C; (ii) H_2, 5% Pd/C, EtOH (90% for two steps).



to produce synthetically useful quantities of **13** or **14**. Similarly, alkyne **12** was generated from **10**[20] as a prelude to a carbometalation/iodination tactic[21] (Et_3Al, Cp_2ZrCl_2; I_2), which also failed.

Vinylsilane Methodology. Recognizing that vinylsilanes are convenient precursors to iodoalkenes via electrophilic substitution,[22] we developed a method for the stereoselective synthesis of (*E*)-vinylsilanes from hydropyrancarboxylic acids (Scheme 2).[23] Acid chloride **15** could be converted to the allylic alcohol **16** in satisfactory yield according to the procedure of Barluenga,[24] which accomplished the required homologation and branching of the carbonyl center. Conversion to the desired α-(mesyloxy)allylsilane **18** required the intermediacy of the sensitive aldehyde **17** which was furnished in virtually quantitative yield by $BaMnO_4$ oxidation[25] of **16**. Exposure of enal **17** to tris(trimethylsilyl)aluminum etherate[26] in toluene at −78 °C resulted in clean 1,2-carbonyl addition of the trimethylsilyl nucleophile. The resulting allylic carbinol was immediately converted (MsCl, DMAP, Et_3N, CH_2Cl_2) to the mesylate **18**. Copper-catalyzed Grignard addition[27] proceeded in excellent yield with high *E*-selectivity, giving **19** and **20** via net S_N2' displacement. The structures of the isomeric vinylsilanes were established by analysis of their ^1H NMR spectra and further corroborated by nuclear Overhauser enhancement (NOE) experiments performed on **19a** and **20a** to discern the spatial relationship between the olefin substituents.[28]

Scheme 2



entry	R	19:20 (yield)
a	Me	>20:1 (89%)
b	Ph	11:1 (84%)
c	*i*-Pr	>20:1 (94%)
d	vinyl	>20:1 (90%)

These results, considered in conjunction with the observations of Ibuka and Yamamoto[29] regarding *E*-stereoselective 1,3-stereogenicity transfer involving γ-(mesyloxy) α,β-enoates with organocyanocopper reagents, seem consistent with the mechanistic paradigm described in Figure 1.[27a,30] Assuming that conditions are *nonequilibrating*, anti-γ-alkylation via rotamer ***i***, wherein steric interactions between the tetrahydropyran and the $SiMe_3$ group are minimized, would give rise to the (*E*)-vinylsilane **19**. Thus, the initial η^2-copper/olefin complex formed in ***i*** undergoes oxidative addition anti to the leaving group (OMs in this case) leading to σ-copper(III) complex ***ii***. Reductive elimination provides the γ-alkylation product **19**.[31]

Assembly of the C_1–C_9 Left Wing. With the conversion of tetrahydropyran carboxylic acid derivative **15** to *E*-β,β-disubstituted alkenylsilane **19** thus demonstrated, the synthesis of the fully elaborated "left wing" subunit

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(20) (a) For **10** → **12**: (i) DIBAL-H, THF, 0 °C; (ii) H_2, 5% Pd/C, EtOH; (iii) Ph_3P, CBr_4, CH_2Cl_2;[20b] (iv) *n*-BuLi (27% for four steps). (b) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769–3773.

(21) The addition of Et_3Al or Et_2AlCl has been achieved thus far only with unbranched, terminal alkynes.[21a,b] (a) Rand, C. L.; VanHorn, D. E.; Negishi, E. *J. Org. Chem.* **1981**, *46*, 4093–4096. (b) Negishi, E. *Acc. Chem. Res.* **1987**, *20*, 65–72 and references cited therein. (c) The zirconium-catalyzed addition of Me_3Al to a similar system also failed.

(22) Fleming, I.; Dunogués, J.; Smithers, R. *Org. React.* **1989**, *37*, 57–575.

(23) (a) Burke, S. D.; Piscopio, A. D.; Kort, M. E. *Tetrahedron Lett.* **1991**, *32*, 855–856. (b) For a related synthesis of 1,2-disubstituted vinylsilanes, see: Chan, T. H.; Mychajlowskij, W. *Tetrahedron Lett.* **1976**, 4439–4442. Stereoselective routes to trisubstituted alkenylsilanes are less common. For example, see: (c) Hayami, H.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1984**, *25*, 4433–4436. (d) Soderquist, J. A.; Colberg, J. C. *Synlett* **1989**, 25–27.

(24) Barluenga, J.; Fernández-Simón, J. L.; Concellón, J. M.; Yus, M. *J. Chem. Soc., Perkin Trans. 1* **1989**, 77–80.

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(28) (a) The preliminary stereochemical assignment was based on the observation that the cis allylic coupling is greater than the trans allylic coupling in the ^1H NMR of similar systems: Snider, B. B.; Karras, M.; Conn, R. S. E. *J. Am. Chem. Soc.* **1978**, *100*, 4624–4626. (b) Irradiation of the olefinic proton (δ 5.48) in **19a** gave a modest NOE enhancement of the allylic, α-pyranyl proton (δ 4.04); no NOE was observed in **20a**.

(29) (a) Ibuka, T.; Tanaka, M.; Nishii, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4864–4872. (b) Ibuka, T.; Tanaka, M.; Nemoto, H.; Yamamoto, Y. *Tetrahedron* **1989**, *45*, 435–442.

(30) For leading references, see: (a) Anderson, R. J.; Henrick, C. A.; Siddall, J. B. *J. Am. Chem. Soc.* **1970**, *92*, 735–737. (b) Goering, H. L.; Singleton, V. D., Jr. *J. Org. Chem.* **1983**, *48*, 1531–1533. (c) Goering, H. L.; Underiner, T. L.; Paisley, S. D.; Schmitter, J.; Lesheski, L. *J. Org. Chem.* **1989**, *54*, 2369–2374 and references cited therein. (d) Valverde, S.; Bernabé, M.; Garcia-Ochoa, S.; Gomez, A. M. *J. Org. Chem.* **1990**, *55*, 2294–2298.

(31) S_N2' reactions involving cuprate reagents and other highly reactive allylic nucleofuges have been described. Phosphates: (a) Yanagisawa, A.; Noritake, Y.; Nomura, N.; Yamamoto, H. *Synlett* **1991**, 251–253. (b) Arai, M.; Nakamura, E.; Lipshutz, B. H. *J. Org. Chem.* **1991**, *56*, 5489–5491. Carbamates and thioethers: *cf.* ref 30d. Carbonates: (c) Boquel, P.; Chapleur, Y. *Tetrahedron Lett.* **1990**, *31*, 1869–1872. (d) Kang, S.-K.; Lee, D.-H.; Sim, H.-S.; Lim, J.-S. *Tetrahedron Lett.* **1993**, *34*, 91–94.

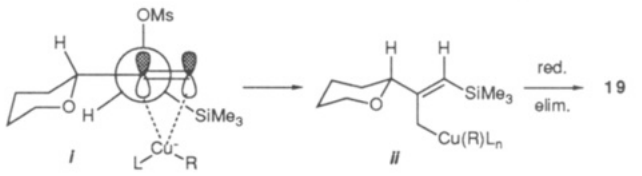


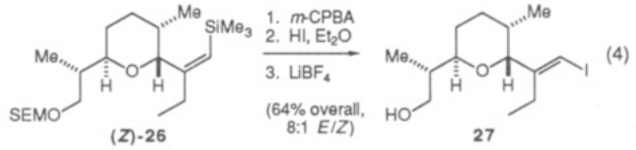
Figure 1.

2 was pursued (Scheme 3). Dioxanone **21** was prepared from (*S*)-3-[[2-(trimethylsilyl)ethoxy]methoxy]-2-methylpropionaldehyde as previously described.[13] Formation of the lactone enolate of **21** (LiHMDS, THF, −78 °C), *O*-silylation (Me_3SiCl/Et_3N), and thermolysis of the derived silyl ketene acetal in refluxing toluene effected the Claisen [3,3] sigmatropic rearrangement via the conformation shown in **A**. Interestingly, the projection of the *cis*-oriented C_3 residue (R) into the depicted pericyclic double boat array did not prevent the desired reorganization. The geometric constraints thus imposed on the transition structure account for the stereogenicity transfer leading to the production of carboxylic acid **4** as a single isomer. Conversion of this intermediate to the Weinreb amide[17] under Steglich conditions[32] afforded **10** in 70% overall yield from **21**.

The vinylsilane methodology discussed above was then adapted for the incorporation of the alkenyl iodide moiety in **2**. Addition of [(benzyloxy)methyl]lithium[33] to Weinreb amide **10** generated α-alkoxy ketone **22**. Hydrogenolysis of the (benzyloxy)methyl (BOM) group accompanied C_4–C_5 olefin saturation to give the corresponding hydroxymethyl ketone. Temporary blocking of this primary alcohol as its *tert*-butyldimethylsilyl (TBS) ether afforded ketone **23** in 83% overall yield from **22**. Wittig methylenation[34] (Ph_3PCH_3Br, NaHMDS, THF, −78 → 0 °C) and subsequent silyl ether cleavage provided allylic alcohol **24**. Further embellishment of this crucial intermediate to the requisite [α-(mesyloxy)allyl]silane proceeded in close analogy with the model studies. Thus, barium manganate ($BaMnO_4$) oxidation[25] led to quantitative production of a labile α,β-unsaturated aldehyde which was therefore used immediately without purification. Reaction of the enal with the silyl transfer reagent of Altnau and Trost again resulted in nucleophilic 1,2-addition of the trimethylsilyl group.[26] Treatment of the resulting air and acid sensitive α-silyl carbinol with methanesulfonic anhydride and DMAP cleanly provided the desired [α-(mesyloxy)allyl]-silane **25**, which was used without purification as a mixture of diastereomers, largely one, of undetermined configuration. After screening numerous modified methylcuprate reagents,[29,35] we were delighted to discover that copper-catalyzed addition of MeMgBr gave (*E*)-vinylsilane **26** as the major stereoisomer in good overall yield from alcohol **24**. The level of *E*-selectivity in this case (3.8:1) is *significantly lower* than that observed in the model system (compare Scheme 2). It is likely that in the preferred conformation of **25**, and derived intermediates, the hydropyran C_7 substituent is oriented axially in contrast to **18**, thereby complicating the analysis of those factors controlling the modest stereoselection in the **25** → **26** conversion.

Whereas reaction of vinylsilane **26** with ICl in CCl_4 at −20 °C[36] led to low yields and nonstereoselective incorporation of iodine, accompanied by contamination with byproducts involving electrophilic attack by chlorine, treatment with a 3-fold excess of *N*-iodosuccinimide in THF followed by stirring with silica gel gave vinyl iodide **13** in 79% yield with complete retention of olefin configuration at C_9.[22,37] Cleavage of the SEM ether[38] proceeded without incident, delivering **27** in excellent yield.

The minor *Z*-vinylsilane formed along with **26** could also be processed to *E*-vinyl iodide **27** using a modification of Chou's procedure,[39] wherein vinylsilane-to-vinyl iodide interconversion can be effected with inversion of alkene geometry (eq 4). Although subjection of the α-iodo-β-

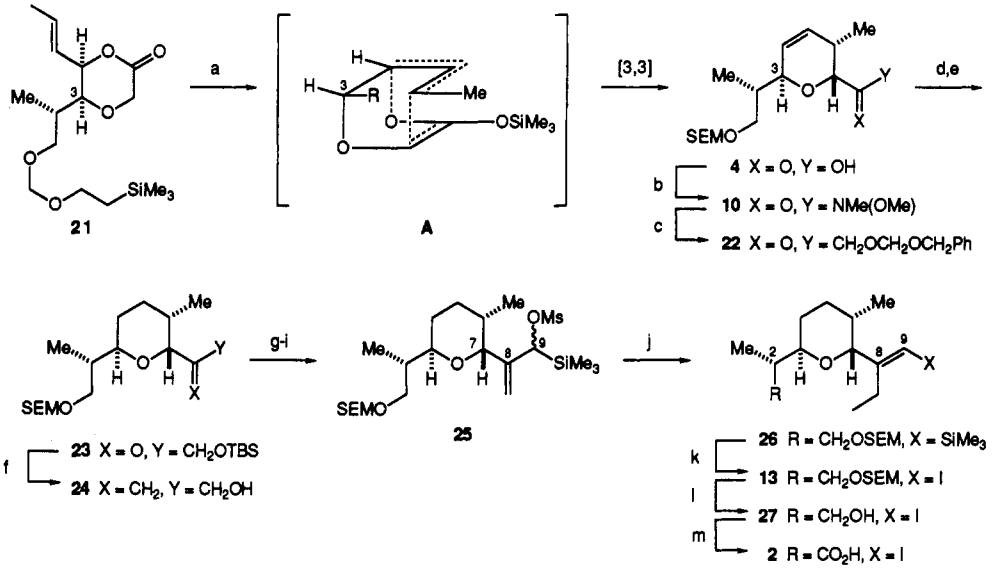


hydroxysilane intermediate to $BF_3{\cdot}OEt_2$ according to the reported protocol gave a complex mixture of products, treatment under the conditions required for SEM ether removal ($LiBF_4$, CH_3CN, 80 °C) also triggered Peterson elimination[40] and furnished **27** as an 8:1 *E*/*Z* mixture. Adjustment of C_1 in **27** to the carboxylic acid oxidation level (Jones' reagent, acetone −20 °C; 92%) proceeded without compromising the stereochemical integrity at C_2, thus completing the synthesis of the fully functionalized left wing synthon **2**.

"Mock Claisen" Rearrangement. Construction of the right wing hydrindene subunit of indanomycin via the intramolecular Diels–Alder reaction had been amply demonstrated,[8] and at the outset of our studies, we consciously sought to avoid that strategy, with an ironic outcome. Imbedded in the *trans*-fused hydrindene framework of indanomycin (**1**) is a γ,δ-unsaturated carbonyl system ($C_{14} \rightarrow C_{13} \rightarrow \rightarrow C_{21}$) suggesting that an ester enolate Claisen rearrangement[41] approach might also be appropriate for the synthesis of the right wing. In addition to creating a unified approach to both left and right wing subtargets, the decisive stereospecificity of this process would avoid production of undesired stereoisomers, as was encountered in the previous intramolecular Diels–Alder approaches. However, further analysis raised serious doubts about the accessibility of the transition state required for the proposed Claisen rearrangement, as illustrated in Scheme 4. Silyl ketene acetal **28**, derived from the lithium enolate of the corresponding δ-lactone

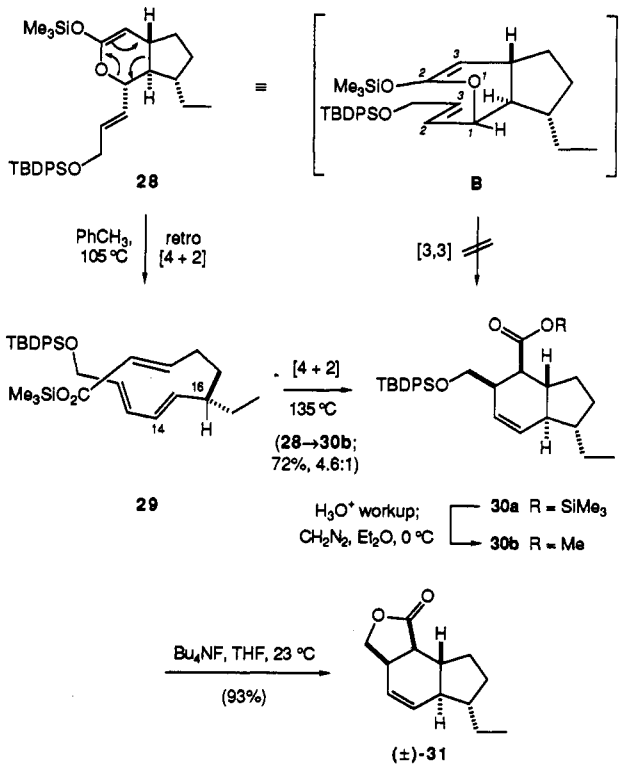
(32) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522–524.
(33) McGarvey, G. J.; Kimura, M. *J. Org. Chem.* **1985**, *50*, 4655–4657.
(34) Plamondon, L.; Weust, J. D. *J. Org. Chem.* **1991**, *56*, 2066–2075.
(35) (a) Attempts to prepare the corresponding allylic phosphate[31a,b] even under forcing conditions [$ClP(O)(OEt)_2$, DMAP, pyridine, 80 °C] resulted in recovery of unreacted starting material. (b) The allylic acetate derivative, when reacted with Me_2CuLi in THF at 0 °C[30b,c] gave a 2:1 mixture of vinylsilanes favoring the undesired *Z*-isomer.
(36) Huynh, C.; Linstrumelle, G. *Tetrahedron Lett.* **1979**, 1073–1076.
(37) (a) Tamao, K.; Akita, M.; Maeda, K.; Kumata, M. *J. Org. Chem.* **1987**, *52*, 1100–1106. (b) Miller, R. B.; McGarvey, G. J. *J. Org. Chem.* **1978**, *43*, 4424–4431.
(38) (a) Lipshutz, B. H.; Harvey, D. F. *Synth. Commun.* **1982**, *12*, 267–277. (b) Ditrich, K.; Bube, T.; Stürmer, R.; Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1986**, *11*, 1028–1030.
(39) Chou, S. P.; Kuo, H.; Wang, C.; Tsai, C.; Sun, C. *J. Org. Chem.* **1989**, *54*, 868–872.
(40) (a) Hudrlik, P. F.; Peterson, D. *Tetrahedron Lett.* **1972**, 1785. (b) Ager, D. *Org. React.* **1990**, *38*, 1–223.
(41) (a) Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897–5898. (b) Ireland, R. E.; Anderson, R. C.; Badoud, R.; Fitzsimmons, B. J.; McGarvey, G. J.; Thaisrivongs, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1983**, *105*, 1988–2006. (c) Danishefsky, S. J.; Funk, R. L.; Kerwin, J. F., Jr. *J. Am. Chem. Soc.* **1980**, *102*, 6889–6891.

Scheme 3[a]



[a] Reagents: (a) LiHMDS, Me_3SiCl/Et_3N, THF, −78 → 23 °C, 40 min; remove THF, add $PhCH_3$, reflux, 4 h; 5% aqueous HCl, Et_2O; (b) NHMe(OMe)·HCl, DCC, DMAP, CH_2Cl_2 (70% from **21**); (c) Bu_3SnCH_2OBOM, *n*-BuLi, THF, −78 °C then amide **10**, THF, −78 → 0 °C (89%); (d) H_2, $Pd(OH)_2$, EtOH, 23 °C, 1.5 h; (e) TBSCl, imidazole, DMAP, CH_2Cl_2, 23 °C (83% from **22**); (f) $Ph_3P{=}CH_2$, THF, −78 → 0 °C; TBAF·$3H_2O$, 0 → 23 °C (95%); (g) $BaMnO_4$, CH_2Cl_2, 23 °C; (h) $(Me_3Si)_3Al{\cdot}OEt_2$, $PhCH_3$, −90 °C; (i) Ms_2O, DMAP, Et_3N, CH_2Cl_2, 0 °C; (j) MeMgBr, CuCN (cat.), THF, −78 → −40 °C (63% from alcohol **24**, 3.8:1 *E*/*Z*); (k) *N*-iodosuccinimide, THF, −15 → 23 °C; SiO_2 (dark) (79%); (l) $LiBF_4$, CH_3CN, 80 °C, 1 h (88%); (m) Jones oxidation (92%).

Scheme 4



using the *in situ* trapping method of Corey,[42] would be expected to lead to the right wing analog **31** via the bracketed conformation **B**. However, because of the geometric constraints enforced by the *trans*-fusion of a five-membered ring on the pericyclic array described therein, the likelihood of adequate overlap for the indicated [3,3] sigmatropic migration appeared questionable.

In the event, thermolysis of **28** at 135 °C followed by acidic workup and treatment with ethereal diazomethane resulted in the production of **30b** in 72% yield as a 4.6:1 mixture of chromatographically separable diastereomers.[14] This lack of stereospecificity was inconsistent with the rigid transition state restrictions of the lactonic enolate Claisen rearrangement and led to the conclusion that an unexpected and unprecedented alternative pathway was in operation which had preempted the desired [3,3] shift. Prohibitive ring strain apparently renders the required transition state energetically inaccessible; instead, fragmentation of **28** by way of the retro hetero Diels–Alder manifold shown (arrows) gave an intermediate trienoate **29** which directly underwent intramolecular Diels–Alder reaction to give **30a**. Cycloaddition via the depicted *endo* transition state, wherein nonbonded C_{14} hydrogen/C_{16} ethyl interactions are minimized, accounts for the production of the major hydrindene component.[43] Thermolysis of **28** at 105 °C and workup as before allowed the isolation and characterization of **29**. The geometry of the intermediate (1*E*,6*E*,8*E*)-nonatriene unit is in turn governed by the relative stereochemistry of the *trans*-fused bicyclic lactone and silyl ketene acetal precursors. Since this pericyclic tandem afforded the product expected of the planned Ireland–Claisen reorganization,[44] it was designated the "mock Claisen" rearrangement. This process has been subsequently generalized and applied repeatedly in our labs.[14,45]

Deprotection of the silyl ether in **30b** with fluoride ion proceeded with concomitant lactonization to give in 93% yield the racemic "right wing" synthon **31**, identical to material reported earlier by Nicolaou[8a] and by Ley.[8d]

(42) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 495–498. Also see ref 8f.

(43) Craig, D. *Chem. Soc. Rev.* **1987**, *16*, 187–238.

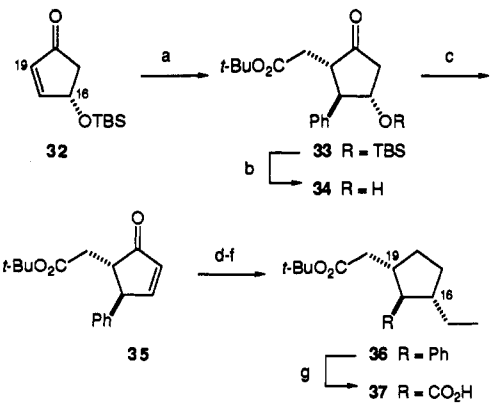
(44) For excellent reviews on the Claisen rearrangement, see: (a) Ziegler, F. *Chem. Rev.* **1988**, *88*, 1423–1452. (b) Wipf, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 5, pp 827–873.

(45) (a) Burke, S. D.; Piscopio, A. D.; Buchanan, J. L. *Tetrahedron Lett.* **1988**, *29*, 2757–2760. (b) In the context of ircinianin synthesis: Parker, M. H. Ph.D. Thesis, University of Wisconsin—Madison, 1991, unpublished results.

Assembly of the C_{10}–C_{25} Right Wing. On the basis of the success of the model transformation described in Scheme 4, we turned our attention to the enantioselective synthesis of the right wing subunit **3**. Application of Noyori's three-component coupling technology[46] provided an efficient route to the *trans,anti*-trisubstituted cyclopentane **37** (Scheme 5). Optically active (*S*)-4-(*tert*-butyldimethylsiloxy)cyclopent-2-en-1-one (**32**), available in >99% enantiomeric excess,[47] was subjected to conjugate addition via phenyl transfer from the mixed higher order cuprate shown. The phenyl group was to serve as a masked carboxyl residue. Enolate trapping at low temperature with triphenyltin chloride and *in situ* alkylation with *tert*-butyl bromoacetate in the presence of HMPA at −25 °C gave a 70% yield of prostaglandin *E*-like[48] cyclopentanoid derivative **33**, along with a small amount of enone **35**.[49] Intentional conversion of **33** to **35** was accomplished in high yield by desilylation (HF, CH_3CN, 23 °C)[50] and elimination (MsCl, pyridine) of the resulting alcohol. Conjugate addition of the ethyl Gilman reagent to the incipient C_{16} center proceeded with clean 1,2-asymmetric induction, completing the introduction of three contiguous asymmetric centers on the five-membered ring with control over their absolute and relative configurations. Reductive removal of the ketone carbonyl via the intermediacy of the enol triflate[51] provided **36**. Oxidative degradation of the phenyl substituent with RuO_4 according to the Sharpless procedure[52] afforded carboxylic acid **37**. The overall yield for the seven step sequence converting **32** → **37** exceeded 45%.

Elaboration of the crucial "mock Claisen" substrate **5** and construction of the right wing coupling partner **3** are delineated in Scheme 6. Palladium-catalyzed acylation[53] of vinylstannane **38**[54] with the acid chloride derived from **37** supplied the product enynone in 76% yield from carboxylic acid **37**. Luche conditions ($CeCl_3$, $NaBH_4$, MeOH, 23 °C)[55] then effected 1,2-reduction of the ketone carbonyl. Ester hydrolysis and lactonization (DIC, DMAP, CH_2Cl_2)[56] afforded **5** along with its chromatographically separable C_{14} epimer, which could be readily recycled by hydrolysis and Mitsunobu lactonization[57] (Ph_3P, DEAD, $PhCH_3$) to the desired stereoisomer **5**.

Scheme 5[a]



[a] Reagents: (a) $Ph_2CuCNLi_2$, THF, −78 °C; Ph_3SnCl, HMPA, $BrCH_2CO_2$-*t*-Bu, −25 °C (70% + 10% enone **35**); (b) HF, CH_3CN, 23 °C (97%); (c) MsCl, pyridine, 0 → 23 °C, 1 h, (93%); (d) $Et_2CuLi{\cdot}P(n\text{-}Bu)_3$, Et_2O, −78 °C, 30 min (95%); (e) LiHMDS, THF, −78 °C; Tf_2NPh, THF, −78 → 23 °C, 2 h (99%); (f) H_2, PtO_2, *t*-BuOH, 35 °C, 2.5 h (88%); (g) $RuCl_3{\cdot}H_2O$, $NaIO_4$, CCl_4, CH_3CN, H_2O, 24 h (77%).

Generation of the silyl ketene acetal **C** as before and heating (refluxing toluene) triggered the fragmentation/cycloaddition tandem shown to give **39** after acidic workup. To reiterate, the net result of this process is to provide the product expected of a lactonic Claisen rearrangement of intermediate **C**. Ironically, the involvement of trienoate **D** and the intramolecular Diels–Alder reaction thereof to afford *trans*-fused hexahydroindene **39** is in direct analogy to the approaches utilized by Nicolaou,[8a] Ley,[8d] Roush,[8f] and Boeckman[8h] for the production of the right wing of the natural product. Carboxylic acid **39** was not isolated but instead converted to thiopyridyl ester **40**[58] which was obtained in 66% overall yield from **5**. At this stage, minor amounts of diastereomeric hydrindenes were removed by silica gel chromatography. Predominance of the indicated *trans*-fused bicyclo[4.3.0] stereoisomer is again rationalized from reaction via preferred *endo* transition state **D**, wherein $A^{1,3}$ strain (C_{14} hydrogen/C_{16} ethyl substituents) and nonbonded interactions associated with the three carbon tether are minimized.[43]

Having secured the carbocyclic core of the right wing, installation of the ketopyrrole moiety was accomplished by addition of **40** to a solution of 2-(bromomagnesio)-pyrrole[8a] which produced **41** in 93% yield. Alkyne desilylation (TBAF·$3H_2O$, THF, 0 °C; 98%) provided **42**, the intended precursor to the Stille coupling partner **3**. Although traditional protocols involving free-radical-initiated hydrostannylation methods (Bu_3SnH, AIBN, benzene, 80 °C)[59] gave unsatisfactory mixtures of regio- and stereoisomers, the palladium-catalyzed hydrostannylation procedure recently introduced by Miyake and Yamamura[60] delivered the desired *E*-vinylstannane right wing synthon **3** in 71% yield along with 16% of the undesired but chromatographically separable regioisomer.

(46) (a) Suzuki, M.; Yanagisawa, A.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 4718–4726. (b) Noyori, R.; Suzuki, M. *Chemtracts: Org. Chem.* **1990**, *3*, 173–197.

(47) Prepared via the electric eel acetylcholinesterase-catalyzed hydrolysis of *cis*-1,4-diacetoxy-2-cyclopentene: (a) Deardorf, D. R.; Mathews, A. J.; McMeekin, D. S.; Craney, C. J. *Tetrahedron Lett.* **1986**, *27*, 1255–1256. (b) Sugai, T.; Mori, K. *Synthesis* **1988**, 19–22. (c) For a comprehensive listing of methods concerning the preparation of optically active **32**, *cf.* ref 46a.

(48) (a) Suzuki, M.; Yanagisawa, A.; Noyori, R. *J. Am. Chem. Soc.* **1985**, *107*, 3348–3349. (b) For a comprehensive list of reviews concerning the chemistry of the prostaglandins, *cf.* ref 46b.

(49) Enone **35**, obtained as a side product, was identical (^1H and ^{13}C NMR, TLC, optical rotation) to material prepared via **33** → **34** → **35**.

(50) Newton, R. F.; Reynolds, D. P.; Finch, M. A.; Kelly, D. R.; Roberts, S. M. *Tetrahedron Lett.* **1979**, 3981–3982.

(51) (a) Scott, W. J.; McMurry, J. E. *Acc. Chem. Res.* **1988**, *21*, 47–54. (b) Jigajinni, V. B.; Wightman, R. H. *Tetrahedron Lett.* **1982**, *23*, 117–120.

(52) (a) Carlsen, P. H.; Katsuki, T.; Martin, V.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936–3938. (b) Teresa Nuñez, T.; Martín, V. S. *J. Org. Chem.* **1990**, *55*, 1928–1932.

(53) (a) Milstein, D.; Stille, J. K. *J. Org. Chem.* **1979**, *44*, 1613–1618. (b) Labadie, J. W.; Stille, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 6129–6137. (c) Stille, J. K. *Pure Appl. Chem.* **1985**, *57*, 1771–1780.

(54) Vinylstannane **38** was prepared from the known (*E*)-3-(tri-*n*-butylstannyl)propenal (Wender, P. A.; Sieberth, S. *Tetrahedron Lett.* **1981**, *22*, 2471–2474) via a three step sequence (see supplementary material for details).

(55) Luche, J.; Gemal, A. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454–5459.

(56) (a) Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394–2395. (b) Hydrolysis of the *tert*-butyl ester proceeded with concomitant removal of the acetylenic trimethylsilyl group which was reinstalled upon formation of the silyl ketene acetal from lactone **5**.

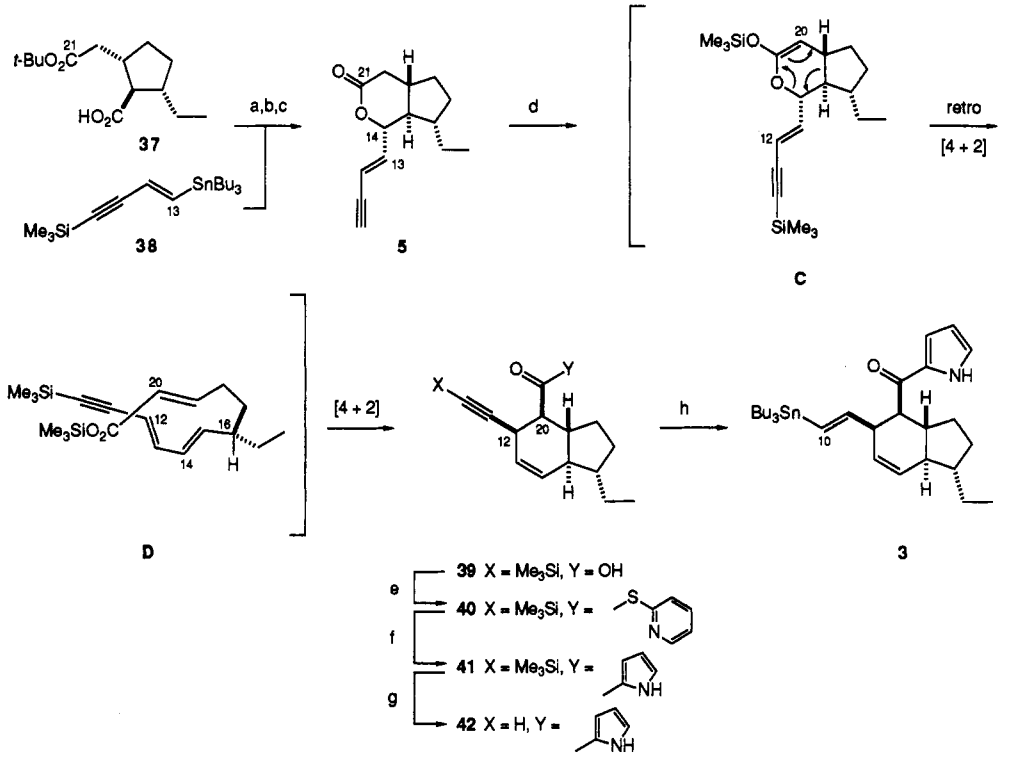
(57) (a) Mitsunobu, O. *Synthesis* **1981**, 1–28. (b) Hughes, D. L. *Org. React.* **1992**, *42*, 335–656.

(58) Nicolaou, K. C.; Claremon, D. A.; Papahatjis, D. P. *Tetrahedron Lett.* **1981**, *22*, 4647–4650.

(59) Jung, M. E.; Light, L. A. *Tetrahedron Lett.* **1982**, *23*, 3851–3854.

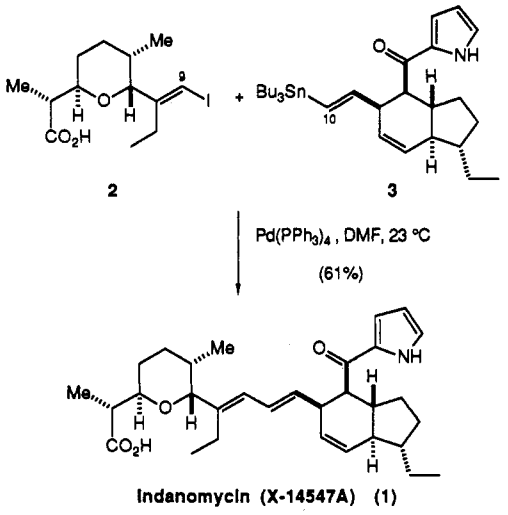
(60) (a) Miyake, H.; Yamamura, K. *Chem. Lett.* **1989**, 989–992. (b) See also: Zhang, H.; Guibé, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857–1867.

Scheme 6[a]



[a] Reagents: (a) $(COCl)_2$, PhH, DMF (cat.); (b) $PhCH_2PdCl(PPh_3)_2$ (5 mol %), vinylstannane **38**, THF, 50 °C (76%); (c) $NaBH_4$, $CeCl_3$, MeOH, 23 °C, 10 min; aqueous NaOH, MeOH, THF, 24 h then aqueous HCl; DIC, DMAP, CH_2Cl_2, 23 °C (71%, 1.2:1 *epi*-**5**/**5**); (d) LiHMDS, Me_3SiCl/Et_3N, −100 → 23 °C, 40 min; remove THF, add $PhCH_3$, reflux, 36 h; 5% aqueous HCl, Et_2O; (e) Aldrithiol-2(2,2′-dipyridyl sulfide), $PhCH_3$, 23 °C (66% from **5**); (f) EtMgBr, pyrrole, $PhCH_3$, THF, 0 °C then thioester **40**, THF, 0 °C (93%); (g) TBAF·$3H_2O$, THF, 0 °C (98%); (h) Bu_3SnH, $Pd(PPh_3)_4$ (3 mol %), PhH, 23 °C (71%).

Scheme 7



Endgame: Stille Coupling. Coupling of the intact left and right wing subunits **2** and **3** via the Stille reaction[12] proceeded as intended (Scheme 7), affording indanomycin (**1**) directly in its natural absolute configuration in 61% yield.[61] Preliminary cross-coupling trials had demonstrated that catalyst choice was crucial, since the use of $(CH_3CN)_2PdCl_2$ led to extensive homocoupling of the right wing vinylstannane. Fortunately, the reductive dimerization process was effectively suppressed by the use of freshly prepared $(Ph_3P)_4Pd$[61a] in DMF. The analytical data (^1H and ^{13}C NMR, IR, MS, TLC) of the synthetic material proved to be identical in all respects to those of natural indanomycin.[62] The methyl ester prepared (CH_2N_2, Et_2O, 0 °C) from synthetic **1** was also identical (^1H and ^{13}C NMR, IR, MS, TLC) to a sample of methyl ester prepared from an authentic specimen of indanomycin.[63]

The success of this coupling in the presence of free carboxylic acid and acyl pyrrole groups underscores the specificity and utility of the Stille procedure for carbon–carbon bond forming reactions involving densely functionalized partners. Of practical importance in this case is the avoidance of any deprotection or oxidation level adjustments at the conclusion of the synthesis.

It should also be noted that the successive Pd(0)-catalyzed reactions by which the conversions **42** → **3** → **1** were effected could be accomplished in one pot. Thus, vinylstannane **3** was formed by treatment of **42** with tributyltin hydride and 10 mol % $(Ph_3P)_4Pd$ in benzene for 5 min at 23 °C. Addition of left wing alkenyl iodide **2** in DMF, stirring 96 h at 23 °C, and diazomethane workup gave indanomycin methyl ester in 38% yield.[64]

Summary and Overview

Pericyclic processes developed in these laboratories (the dioxanone-to-dihydropyran reorganization and the "mock Claisen" cycloreversion/cycloaddition sequence) feature

(61) (a) Coulson, D. R. *Inorg. Synth.* **1972**, *13*, 121–124. (b) For a mechanistic discussion of this reaction, see: Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585–9595.

(62) Optical rotation of synthetic indanomycin: $[\alpha]^{23}_D$ −300.6° (*c* 0.40, $CHCl_3$). Optical rotation of natural indanomycin: $[\alpha]_D$ −328° (*c* 1.0, $CHCl_3$).[2b]

(63) We thank the Hoffman-LaRoche Co., Inc. for generously providing us with a sample of natural indanomycin for comparison.

(64) Yield based on alkyne **42**.

prominently in the stereocontrolled, asymmetric construction of both "left wing" and "right wing" fragments of indanomycin. The ready availability of a wide range of Grignard reagents recommends the stereoselective vinylsilane synthesis described herein as a versatile alternative to traditional olefin-forming reactions and alkyne carbometalation/iodination protocols. Transformation to the corresponding vinyl iodides proceeds with either retention or inversion of olefin stereochemistry, thereby extending the availability of various geometrically defined, trisubstituted olefins. The successful palladium-mediated cross coupling of 2 and 3 via the Stille protocol represents one of the most complex examples of such a reaction yet reported.[65]

Experimental Section

General Methods. Melting points (mp) were obtained using a Laboratory Devices Mel-Temp apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 digital polarimeter. Infrared spectra (IR) were recorded on a Perkin-Elmer 781 or on a Mattson Polaris FT-IR equipped with a DTGS detector and are reported in wavenumbers (cm^{-1}). Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on a Bruker WP-270 (270 MHz) or Bruker AM-500 (500 MHz) spectrometer as indicated. *Indanomycin numbering is used for assignments on all intermediates.* Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker WP-270 spectrometer at 67.93 MHz or Bruker AM-500 spectrometer at 125.76 MHz as indicated. Mass spectra (MS) were obtained using a Kratos MS-80RFA mass spectrometer (DS-55/DS-90 peak matching option) by electron impact (EI) operation at 30 or 70 eV. Elemental analyses were performed by Spang Microanalytical Laboratories (Eagle Harbor, MI).

All moisture-sensitive reactions were performed in flame-dried glassware under a stream of nitrogen unless indicated otherwise. Bath temperatures were used to record the reaction temperature in all cases. All reactions were stirred magnetically unless otherwise indicated. Analytical thin-layer chromatography (TLC) was carried out on E. Merck (Darmstadt) TLC plates precoated with silica gel 60 F_{254} (250-μm layer thickness). Preparative TLC was carried out using 0.5- and 2.0-mm × 10-cm × 10-cm E. Merck precoated silica gel 60 (60 F_{254}) plates. TLC visualization was accomplished using either a UV lamp, iodine adsorbed on silica gel, or a charring solution (*p*-anisaldehyde, phosphomolybdic acid, ceric ammonium molybdate, potassium permanganate). Flash chromatography was performed in analogy to the description by Still[66] on EM Science silica gel 60 (230–400 mesh). High-performance liquid chromatography (HPLC) was conducted using a Waters 501 pump equipped with a Waters Model 481 LC spectrophotometer and Hewlett-Packard 3392A integrator.

Tetrahydrofuran (THF), diethyl ether (Et_2O), benzene (PhH or C_6H_6), and 1,2-dimethoxyethane (DME) were distilled from sodium/benzophenone ketyl. Toluene ($PhCH_3$) was distilled from sodium metal. Triethylamine (Et_3N), diisopropylethylamine (*i*-Pr_2NEt; Hünig's base), pyridine, and 2,6-lutidine were distilled from calcium hydride and stored over potassium hydroxide (KOH) pellets. Dichloromethane (CH_2Cl_2) and acetonitrile (CH_3CN) were distilled from calcium hydride immediately before use. Cyclohexane (C_6H_{12}) was distilled from calcium hydride and stored over 4-Å molecular sieves. Dimethyl sulfoxide (DMSO) and *N*,*N*-dimethylformamide (DMF) were distilled under reduced pressure from calcium hydride and stored over 4-Å molecular sieves. Deuteriochloroform ($CDCl_3$) and deuteriobenzene (C_6D_6) were stored over 4-Å molecular sieves before use. Chlorotrimethylsilane (Me_3SiCl) was distilled from calcium hydride and stored over 4-Å molecular sieves. All other commercially obtained reagents and solvents were used as received without further purification unless indicated otherwise.

(5*S*,6*R*)-5-[(1*S*)-1-Methyl-2-[[2-(trimethylsilyl)ethoxy]methoxy]ethyl]-6-[(1*E*)-propenyl]-1,4-dioxan-2-one (21). This compound was prepared in direct analogy to the sequence described in ref 13 (see supplementary material for details) and exhibited the following physical and spectroscopic characteristics: viscous oil; R_f 0.38 (60% Et_2O/hexanes); $[\alpha]^{22}_D$ +54.3° (*c* 1.75, $CHCl_3$); IR (thin film) 2900, 2700, 1740, 1650, 1440, 1330 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.90 (dq, 1 H, J = 15.2, 6.3 Hz, C_6-*H*), 5.68 (ddq, 1 H, J = 15.2, 8.8, 1 .7 Hz, C_5-*H*), 4.78 (dd, 1 H, J = 8.7, 2.5 Hz, C_4-*H*), 4.61 (s, 2 H, OCH_2O), 4.32 (AB quartet, 2 H, J_{AB} = 17.6 Hz, $\Delta\nu_{AB}$ = 50.9 Hz, OCH_2CO_2R), 3.66 (dd, 1 H, J = 10.2, 2.3 Hz, one of C_1-*H*), 3.64–3.53 (m, 3 H, C_3-*H* and $OCH_2CH_2SiMe_3$), 3.51 (dd, 1 H, J = 10.3, 3.0 Hz, one of C_1-*H*), 1.75 (dd, 3 H, J = 6.2, 1.3 Hz, C_6-CH_3), 1.73–1.67 (m, 1 H, C_2-*H*), 0.92 (d, 3 H, J = 7.0 Hz, C_2-CH_3), 0.91–0.87 (m, 2 H, $OCH_2CH_2SiMe_3$), –0.01 (s, 9 H, $Si(CH_3)_3$); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 166.62, 133.76, 123.47, 94.76, 81.74, 75.06, 68.34, 66.01, 64.59, 34.43, 17.76, 17.70, 12.63, –1.67 (3). Anal. Calcd for $C_{16}H_{30}O_5Si$: C, 58.14; H, 9.15. Found: C, 58.30; H, 9.11.

(2*R*,3*S*,6*R*)-3,6-Dihydro-*N*,3-dimethyl-*N*-methoxy-6-[(1*S*)-1-methyl-2-[[2-(trimethylsilyl)ethoxy]methoxy]ethyl]-2*H*-pyran-2-carboxamide (10). To a solution of LiHMDS (4.70 mL of a 1.0 M in THF, 4.70 mmol) in 3 mL of THF at –78 °C was added dioxanone **21** (775 mg, 2.35 mmol) in THF (2 mL + 0.3 mL rinse). After the mixture had stirred at –78 °C for 30 min, the solution was treated with 3.0 mL of the supernatant from the centrifugation of a 1:1 mixture of Me_3SiCl and Et_3N. The mixture was allowed to stir for an additional 10 min at –78 °C at which time it was warmed to 25 °C and stirred for 30 min. Solvent was removed *in vacuo* and replaced with toluene (10 mL). This solution was heated at reflux (bath temperature 130 °C) for 4 h at which time it was cooled and concentrated. The residue was dissolved in Et_2O (10 mL) and treated with 5% HCl solution (10 mL). After vigorous stirring for 10 min, the layers were partitioned and the aqueous layer extracted with Et_2O (20 mL). Ethereal extracts were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo*.

The crude carboxylic acid **4** was dissolved in 5 mL of CH_2Cl_2 and cooled to 0 °C and the stirred solution treated with *N*-methyl-*N*-methoxyamine hydrochloride (630 mg, 7.05 mmol) followed by DMAP (920 mg, 7.30 mmol) and DCC (1.36 g, 6.60 mmol). The resulting homogeneous mixture was slowly warmed to ambient temperature and allowed to stir for 5 h at which time it was diluted with hexanes (10 mL) and filtered through a pad of Celite. Following concentration of this solution, the residue which remained was purified by flash chromatography (elution with 75% Et_2O/hexanes) affording 617 mg (1.64 mmol, 70%) of amide **10** as a colorless oil: R_f 0.34 (60:35:5 Et_2O–hexanes–acetone); $[\alpha]^{22}_D$ +97.2° (*c* 1.95, $CHCl_3$); IR (thin film) 2900, 1670, 1450, 1370, 1320 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.83 (ddd, 1 H, J = 10.4, 4.6, 1.8 Hz, C_4-*H*), 5.75 (dd, 1 H, J = 10 .4, 1.8 Hz, C_5-*H*), 4.69 (d, 1 H, J = 4.0 Hz, C_7-*H*), 4.61 (AB quartet, 2 H, J_{AB} = 6.9 Hz, $\Delta\nu_{AB}$ = 8.6 Hz, OCH_2O), 4.17 (br d, 1 H, J = 7.6 Hz, C_3-*H*), 3.67 (dd obscured by s, 1 H, J = 9.6, 4.3 Hz, one of C_1-*H*), 3.66 (s, 3 H, OCH_3), 3.59–3.53 (m, 2 H, $OCH_2CH_2SiMe_3$), 3.39 (dd, 1 H, J = 9.6, 7.4 Hz, one of C_1-*H*), 3.19 (s, 3 H, NCH_3), 2.51–2.44 (m, 1 H, C_6-*H*), 2.11–1.96 (m, 1 H, C_2-*H*), 0.96 (d, 3 H, J = 7.2 Hz, C_2-CH_3), 0.95 (d, 3 H, J = 7.1 Hz, C_6-CH_3), 0.95–0.86 (m, 2 H, $OCH_2CH_2SiMe_3$), –0.02 (s, 9 H, $Si(CH_3)_3$); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 170.90, 130.10, 126.03, 94.88, 74.54, 70.12, 69.67, 64.66, 61.07, 37.27, 31.95, 30.24, 17.85, 14.44, 13.80, –1.61 (3). Anal. Calcd for $C_{18}H_{35}O_5NSi$: C, 57.76; H, 9.66. Found: C, 57.87; H, 9.44.

(2*R*,3*S*,6*R*)-2-[2-[(Benzyloxy)methoxy]-1-oxoethyl]-3,6-dihydro-3-methyl-6-[(1*S*)-1-methyl-2-[[2-(trimethylsilyl)ethoxy]methoxy]ethyl]-2*H*-pyran (22). A solution of (tributylstannyl)methanol (benzyloxy)methyl ether (2.70 g, 6.12 mmol) in 13.5 mL of THF at –78 °C was treated with *n*-BuLi (3.85 mL

(65) For other intesting examples of the Stille reaction involving complex coupling partners, see: (a) Férézon, J. P.; Julia, M.; Liu, L. W.; Pancrazi, A. *Synlett* **1991**, 614–617 (avermectin B_{1b}). (b) Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497–4513 (lepicidin A). (c) Nicolaou, K. C.; Chakraborty, T. K.; Piscopio, A. D.; Minowa, N.; Bertinato, P. *J. Am. Chem. Soc.* **1993**, *115*, 4419–4420 (rapamycin). (d) Piscopio, A. D.; Minowa, N.; Chakraborty, T. K.; Koide, K.; Bertinato, P.; Nicolaou, K. C. *J. Chem. Soc., Chem. Commun.* **1993**, 617–618. Nicolaou, K. C.; Bertinato, P.; Piscopio, A. D.; Chakraborty, T. K.; Minowa, N. *J. Chem. Soc., Chem. Commun.* **1993**, 619–622 (rapamycin).

(66) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

of a 1.59 M solution in hexanes, 6.16 mmol). After 25 min at −78 °C, a solution of amide **10** (718 mg, 1.92 mmol) in THF (5 mL + 0.5 mL rinse) was added in a dropwise fashion via cannula. After 15 min at −78 °C, the reaction was quenched by addition of 4 mL of saturated aqueous NH_4Cl solution. The mixture was diluted with 4 mL of H_2O and extracted with Et_2O (2 × 45 mL). The combined organic portions were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (elution with 30% Et_2O/hexanes) to give 795 mg (1.71 mmol, 89%) of the α-alkoxy ketone **22** as a colorless oil: R_f 0.58 (2:1 Et_2O–hexanes); $[\alpha]^{23}_D$ +116.5° (*c* 1.75, $CHCl_3$); IR (thin film) 3000, 2870 (br), 1710, 1475, 1435, 1230 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.39–7.26 (m, 5 H, Ar-*H*), 5.91 (ddd, 1 H, *J* = 10.4, 5.7, 2.2 Hz, C_4-*H*), 5.76 (dd, 1 H, *J* = 10.3, 2.1 Hz, C_5-*H*), 4.81 (s, 2 H, OCH_2OCH_2Ph), 4.63 (overlapping s, 4 H, OCH_2OCH_2Ph and $OCH_2OCH_2CH_2SiMe_3$), 4.61 (AB quartet, 2 H, J_{AB} = 6.7 Hz, $\Delta\nu_{AB}$ = 6.2 Hz, C_9-*H*), 4.25 (br d, 1 H, *J* = 3.3 Hz, C_7-*H*), 4.11 (br dt, 1 H, *J* = 6.8, 0.8 Hz, C_3-*H*), 3.63–3.47 (m, 4 H, C_1-*H* and $OCH_2CH_2SiMe_3$), 2.52–2.44 (m, 1 H, C_6-*H*), 2.04–1.93 (m, 1 H, C_2-*H*), 0.96 (d, 3 H, *J* = 6.8 Hz, C_2-CH_3), 0.90 (d, 3 H, *J* = 6.9 Hz, C_6-CH_3), 0.90–0.82 (m, 2 H, $OCH_2CH_2SiMe_3$), −0.01 (s, 9 H, $Si(CH_3)_3$); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 207.44, 137.50, 130.55, 128.35 (2), 127.87 (2), 127.68, 126.29, 94.94, 94.57, 76.87, 75.10, 71.57, 69.78, 69.72, 64.91, 37.30, 31.08, 18.00, 14.03, 13.71, −1.43 (3). Anal. Calcd for $C_{25}H_{40}O_6Si$: C, 64.62; H, 8.68. Found: C, 64.66; H, 8.73.

(2*R*,3*S*,6*R*)-2-[2-(*tert*-Butyldimethylsiloxy)-1-oxoethyl]-3-methyl-6-[(1*S*)-1-methyl-2-[[2-(trimethylsilyl)ethoxy]methoxy]ethyl]tetrahydropyran (23). To a solution of **22** (827 mg, 1.78 mmol) in 13 mL of EtOH in a 100-mL recovery flask was added 15% $Pd(OH)_2$ on carbon (125 mg of moist Pearlman's catalyst). A three-way adapter connected to a water aspirator and equipped with a hydrogen balloon was attached; the system was then evacuated by aspiration and filled with hydrogen (repeated three times). The suspension was vigorously stirred at 23 °C until removal of the (benzyloxy)methyl group was complete (generally between 4–5 h as observed by TLC) at which time the solution was opened to an atmosphere of nitrogen, diluted with Et_2O (20 mL), filtered through a pad of Celite, and concentrated *in vacuo*, affording a pale brown oil.

The residue was taken up in 10 mL of CH_2Cl_2 and the solution treated sequentially with *tert*-butyldimethylsilyl chloride (406 mg, 2.69 mmol), imidazole (371 mg, 5.45 mmol), and DMAP (60 mg, 0.49 mmol) at 23 °C. After being stirred for 2 h, the solution was diluted with 5 mL of H_2O and extracted with Et_2O (2 × 40 mL). The combined organic portions were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (elution with 15% Et_2O/hexanes) afforded 682 mg (1.48 mmol, 83% for the two steps) of **23** as a colorless oil: R_f 0.41 (3:1 hexanes–Et_2O); $[\alpha]^{23}_D$ −11.16° (*c* 1.70, $CHCl_3$); IR (thin film) 2910, 2890, 2840, 1710, 1440, 1235 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.61 (collapsed AB quartet, 2 H, OCH_2O), 4.40 (AB quartet, 2 H, J_{AB} = 7.3 Hz, $\Delta\nu_{AB}$ = 8.8 Hz, C_9-*H*), 4.24 (d, 1 H, *J* = 4.3 Hz, C_7-*H*), 3.62–3.52 (AA′ portion of AA′BB′, 2 H, $OCH_2CH_2SiMe_3$), 3.58–3.50 (m, 1 H, one of C_1-*H*), 3.51 (obscured ddd, 1 H, *J* = 7.9, 7.3, 3.5 Hz, C_3-*H*), 3.33 (dd, 1 H, *J* = 8.1, 7.1 Hz, one of C_1-*H*), 2.06–1.90 (m, 1 H, C_6-*H*), 1.80–1.61 (m, 4 H, C_2-*H* and C_4-*H* and C_5-*H*), 1.43–1.32 (m, 1 H, one of C_4-*H*), 0.96–0.86 (BB′ portion of AA′BB′, 2 H, $OCH_2CH_2SiMe_3$), 0.89 (s, 9 H, $SiMe_2C(CH_3)_3$), 0.88 (obscured d, 3 H, *J* = 7.4 Hz, C_6-CH_3), 0.87 (d, 3 H, *J* = 7.4 Hz, C_2-CH_3), 0.12 (s, 3 H, one of $SiMe(CH_3)C(CH_3)_3$), 0.11 (s, 3 H, one of $SiMe(CH_3)C(CH_3)_3$), −0.01 (s, 9 H, $Si(CH_3)_3$); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 208.38, 94.90, 74.60, 69.69, 68.75, 64.82, 35.81, 31.38, 26.21, 25.78 (3), 25.00, 18.40, 18.02, 15.01, 13.78, −0.06, −0.09, −0.25, −1.46 (3); MS (EI) *m/e* (relative intensity) 403 ($M^+ - C_4H_9$, 0.6), 343 (2.9), 237 (6.0), 147 (20), 109 (32), 103 (100); exact mass calcd for $C_{19}H_{39}O_5Si_2$ ($M^+ - C_4H_9$) requires 403.2290, found 403.2295. Anal. Calcd for $C_{23}H_{48}O_5Si_2$: C, 59.95; H, 10.50. Found: C, 60.08; H, 10.72.

(2*R*,3*S*,6*R*)-2-[1-(Hydroxymethyl)vinyl]-3-methyl-6-[(1*S*)-1-methyl-2-[[2-(trimethylsilyl)ethoxy]methoxy]ethyl]tetrahydropyran (24). To a solution of methyltriphenylphosphonium bromide (3.66 g, 10.2 mmol) in 25 mL of THF at −78 °C was added NaHMDS (10.2 mL of a 1.0 M solution in THF, 10.2 mmol) in a dropwise fashion. The resulting bright yellow suspension was immediately warmed to 0 °C and stirred for 10 min at which time it was recooled to −78 °C. A solution of **23** (945 mg, 2.05 mmol) in THF (6 mL + 0.8 mL rinse) was then added via cannula and the solution slowly warmed to ambient temperature over a period of 2.5 h. The solution was diluted with 15 mL of hexanes, and the solids were removed by filtration through Celite. The solution was concentrated to give a yellow oil containing some solids and used without purification in the subsequent reaction.

The residue from the reaction above was dissolved in 15 mL of THF and the solution treated with $Bu_4NF{\cdot}3H_2O$ (590 mg, 1.87 mmol), added in three equal portions over a 5-min period at ambient temperature. The mixture was stirred for 2 h, concentrated, and immediately subjected to purification by flash chromatography (elution with 50% Et_2O/hexanes) to afford 670 mg (1.94 mmol, 95%) of allylic alcohol **24** as a colorless oil: R_f 0.58 (2:1 Et_2O–hexanes); $[\alpha]^{23}_D$ −18.8° (*c* 1.60, $CHCl_3$); IR (thin film) 3400 (br), 2900, 2840, 1645, 1440, 1190 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.19 (br t, 1 H, *J* = 1.1 Hz, C_8=CH_Z), 5.08 (br s, 1 H, C_8=CH_E), 4.63 (app s, 2 H, OCH_2O), 4.31 (br d, 1 H, *J* = 3.3 Hz, C_7-*H*), 4.12–3.98 (m, 2 H, C_9-*H*), 3.62–3.53 (m, 4 H, C_3-*H* and one of C_1-*H* and $OCH_2CH_2SiMe_3$), 3.42 (dd, 1 H, *J* = 9.5, 6.6 Hz, one of C_1-*H*), 2.22–2.11 (m, 1 H, one of C_4-*H*), 2.00–1.88 (m, 1 H, C_6-*H*), 1.88–1.74 (m, 2 H, C_2-*H* and one of C_4-*H*), 1.59–1.49 (m, 1 H, one of C_5-*H*), 1.47–1.37 (m, 1 H, one of C_5-*H*), 0.93 (d, 3 H, *J* = 7.2 Hz, C_6-CH_3), 0.92–0.89 (m, 2 H, $OCH_2CH_2SiMe_3$), 0.90 (d, 3 H, *J* = 6.8 Hz, C_2-CH_3), 0.00 (s, 9 H, $Si(CH_3)_3$), (C_9-O*H* hydroxyl proton was not observed); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 146.60, 112.19, 94.96, 73.84, 73.68, 69.99, 65.51, 64.90, 33.75, 31.76, 26.29, 22.93, 18.04, 14.43, 13.89, −1.45 (3); MS (EI) *m/e* (relative intensity) 326 ($M^+ - H_2O$, 0.2), 271 (0.2), 214 (2.9), 73 (100). Anal. Calcd for $C_{18}H_{36}O_4Si$: C, 62.75; H, 10.53. Found: C, 62.89; H, 10.57.

Preparation of Tris(trimethylsilyl)aluminum Etherate.[26] (*Caution*: This material is moisture sensitive and exceedingly pyrophoric!). In a two-necked 500-mL round-bottom flask equipped with a reflux condenser was placed powdered aluminum (6.67 g, 247 mmol), granular aluminum (1.66 g, 62.0 mmol), 80 mL of Et_2O, and a crystal of iodine. After the magnetically stirred suspension was rigorously purged with argon, mercury (6.67 g, 33.0 mmol) and doubly distilled Me_3SiCl (42.3 mL, 333 mmol) were added and the gray suspension stirred at ambient temperature for 9 h. Lithium wire (2.33 g, 336 mmol; *low sodium content*) was then added under a stream of argon, and the vigorously stirred mixture was heated to a gentle reflux. Heating was maintained until nearly all of the lithium had been consumed (approximately 36 h). Upon cooling to ambient temperature, the thick gray mixture was diluted with 35 mL of Et_2O and the supernatant transferred via cannula (positive argon pressure) to a Schlenk funnel where it was vacuum filtered. Volatiles were removed *in vacuo* and the resulting pale yellow syrup resuspended in 75 mL of Et_2O, yielding an amber brown colored solution. The exact concentration of this nominally 1.4 M solution was determined by addition of an aliquot to a known excess of iodine in toluene followed by back-titration of the brownish red solution to a colorless endpoint using a 1.0 M aqueous sodium thiosulfate solution. The 1.30 M solution of reagent obtained was diluted with an equal volume of Et_2O to give a 0.65 M solution of $(Me_3Si)_3Al{\cdot}OEt_2$ in Et_2O.

Conversion of 24 to 26. (2*R*,3*S*,6*R*)-2-(1-Formylvinyl)-3-methyl-6-[(1*S*)-1-methyl-2-[[2-(trimethylsilyl)ethoxy]methoxy]ethyl]tetrahydropyran (24a). To a solution of **24** (184 mg, 0.534 mmol) in 50 mL CH_2Cl_2 at 23 °C was added $BaMnO_4$ (1.37 g, 5.34 mmol, 10 equiv) in a single portion. The mixture was vigorously stirred for 11 h and then filtered through a pad of Celite. Concentration afforded 181 mg (0.523 mmol, 98%) of the corresponding enal **24a**, as a colorless oil which was homogeneous by inspection of the ^1H NMR spectrum. Because of sensitivity to silica gel and exceptional susceptibility to oxidative decomposition, this compound was used immediately and without further purification: R_f 0.42 (15% EtOAc/hexanes); $[\alpha]^{23}_D$ −18.6° (*c* 1.05, $CHCl_3$); IR (thin film) 2900, 2820, 1670, 1600, 1440, 1360 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 9.45 (s, 1 H, *CHO*), 6.44 (t, 1 H, *J* = 1.4 Hz, C_8=CH_Z), 6.05 (t, 1 H, *J* = 1.2 Hz, C_8=CH_E), 4.57 (app s, 2 H, OCH_2O), 4.57–4.53 (br s, 1 H, C_7-*H*), 3.64 (dt, 1 H, *J* = 10.1, 4.7 Hz, C_3-*H*), 3.58–3.50 (AA′ portion of AA′BB′,

2 H, $OCH_2CH_2SiMe_3$), 3.46 (dd, 1 H, J = 9.5, 3.5 Hz, one of C_1-H), 3.30 (dd, 1 H, J = 9.5, 6.8 Hz, one of C_1-H), 2.36–2.21 (m, 1 H, C_6-H), 2.86–1.97 (m, 1 H, one of C_4-H), 1.93–1.78 (m, 2 H, C_2-H and one of C_4-H), 1.47–1.37 (m, 2 H, C_5-H), 0.87 (d, 3 H, J = 6.8 Hz, C_2-CH_3), 0.86–0.79 (BB′ portion of AA′BB′, 2 H, OCH_2CH_2-$SiMe_3$), 0.72 (d, 3 H, J = 6.8 Hz, C_6-CH_3), –0.04 (s, 9 H, $Si(CH_3)_3$); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 193.52, 149.43, 134.95, 95.05, 75.07, 69.87, 68.55, 64.67, 32.06, 29.17, 25.58, 20.59, 18.00, 14.49, 12.67, –1.46 (3).

(2*R*,3*S*,6*R*)-2-[(1*E*)-1-Ethyl-2-(trimethylsilyl)vinyl]-3-methyl-6-[(1*S*)-1-methyl-2-[[2-(trimethylsilyl)ethoxy]methoxy]ethyl]tetrahydropyran ((*E*)-26) and (2*R*,3*S*,6*R*)-2-[(1*Z*)-1-Ethyl-2-(trimethylsilyl)vinyl]-3-methyl-6-[(1*S*)-1-methyl-2-[[2-(trimethylsilyl)ethoxy]methoxy]ethyl]tetrahydropyran ((*Z*)-26). The crude enal **24a** (181 mg, 0.523 mmol) was dissolved in 9.5 mL of toluene and the solution cooled to –89 °C (Et_2O/CO_2 bath) whereupon $(Me_3Si)_3Al{\cdot}OEt_2$ (3.32 mL of a 0.28 M solution in Et_2O, 0.961 mmol) was added in a dropwise manner. After 5 min, the reaction was warmed to –78 °C and stirred for an additional 10 min; TLC analysis indicated complete consumption of starting material and the presence of a slightly more polar (R_f 0.39, 15% EtOAc/hexanes) substance. The reaction was then quenched with saturated aqueous NH_4Cl solution (4.5 mL) and warmed to ambient temperature. The heterogeneous mixture was diluted with 15 mL of Et_2O, and 7 mL of 15% aqueous Rochelle's salt solution was added. After being stirred for 20 min, the biphasic mixture was transferred to a separatory funnel and partitioned. The aqueous layer was then extracted with Et_2O (2 × 15 mL) and the combined ethereal portions stirred over anhydrous Na_2SO_4 for 15 min, filtered, and concentrated to a 2-mL volume. (Note: The α-silyl carbinol, a colorless oil, is extremely unstable in the absence of solvent, rapidly decomposing to a uncharacterized pink substance. Although this material could be purified by rapid flash chromatography on silica gel, it was generally taken on as a crude oil dissolved in some residual toluene.)

The residue was dissolved in 8 mL of CH_2Cl_2 along with DMAP (72 mg, 0.587 mmol) followed by Et_3N (0.521 mL, 3.74 mmol). Upon cooling to 0 °C, the solution was treated with methanesulfonic anhydride (233 mg, 1.34 mmol), added in a portionwise fashion under a stream of nitrogen. After slowly warming to ambient temperature over a period of 2.5 h, the solution was diluted with 25 mL of Et_2O and washed with 3.5 mL of cold 5% HCl solution followed by 5 mL of saturated aqueous $NaHCO_3$ solution. The solution was dried over Na_2SO_4, filtered through a small plug of Celite, and concentrated to give the allylic mesylate **25** (R_f 0.37, 15% EtOAc/hexanes), a yellow-orange oil. Attempted purification of this material by chromatography on either silica gel or Florisil led to significant decomposition; ^1H NMR analysis of the partially decomposed mesylate indicated a mixture of diastereomers heavily enriched in one diastereomer.

In a 25-mL recovery flask was placed CuCN (4.1 mg, 0.046 mmol, 10 mol %) along with 3.1 mL of THF. The white suspension was then cooled to 0 °C and treated with MeMgBr (0.763 mL of a 3.0 M solution in Et_2O, 2.28 mmol). After 15 min, the yellow slurry was cooled to –78 °C (temperature-regulated cryocool bath), and a solution of the crude mesylate **25** in THF (2.1 mL + 0.4 mL rinse) was added via cannula in a dropwise fashion. The yellow suspension was then stirred at –78 °C for 3 h, warmed to –40 °C over a 4-h period and stirred at that temperature for 7 h. The mixture was then warmed to 0 °C over a 1-h period and the reaction quenched by addition of a 1:1 solution of saturated aqueous NH_4Cl and 3% NH_4OH solution (3.0 mL). The reaction mixture was diluted with Et_2O (6 mL), warmed to ambient temperature, and vigorously stirred for 30 min. The layers were then separated and the aqueous layer extracted with Et_2O (2 × 15 mL). The combined organic portions were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Analysis of this crude material by 270-MHz ^1H NMR indicated a 3.8:1 ratio of olefin isomers, with the *E*-isomer in predominance. Flash chromatography of the resulting yellow oil (elution with 3% Et_2O/hexanes) gave the isomeric vinylsilanes as colorless oils, with 30 mg (0.072 mmol) of the *Z*-isomer (*Z*)-**26** eluting first followed by 112 mg (0.270 mol) of the *E*-isomer (*E*)-**26** (142 mg total, a 3.8:1 mixture olefin isomers, 0.342 mmol, 63% over 4 steps from alcohol **24**).

Data for (*E*)-**26**: R_f 0.31 (5% EtOAc/hexanes); $[\alpha]^{23}_D$ –16.1° (*c* 1.65, $CHCl_3$); IR (thin film) 2940, 1615, 1470, 1380, 1260 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.38 (d, 1 H, J = 3.3 Hz, C_9-H), 4.27 (AB quartet, 2 H, J_{AB} = 6.7 Hz, $\Delta\nu_{AB}$ = 7.8 Hz, OCH_2O), 4.09 (br s, 1 H, C_7-H), 3.65–3.52 (m, 4 H, C_1-H and $OCH_2CH_2SiMe_3$), 3.29 (dd, 1 H, J = 10.0, 9.1 Hz, C_3-H), 2.38–2.25 (m, 1 H, one of C_8-CH_2CH_3), 2.25–2.12 (m, 1 H, one of C_8-CH_2CH_3), 1.98–1.80 (m, 4 H, C_2-H and C_4-H and C_6-H), 1.54–1.38 (m, 2 H, C_5-H), 0.97 (t, 3 H, J = 6.2 Hz, C_8-CH_2CH_3), 0.94–0.87 (m, 2 H, OCH_2CH_2-$SiMe_3$), 0.90 (d, 3 H, J = 7.0 Hz, C_2-CH_3), 0.89 (d, 3 H, J = 7.0 Hz, C_6-CH_3), 0.09 (s, 9 H, vinyl $Si(CH_3)_3$), –0.01 (s, 9 H, $Si(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.13, 121.71, 95.28, 75.10, 72.80, 70.62, 64.75, 32.43, 30.01, 26.65, 26.41, 21.07, 18.09, 14.81, 12.63, 12.75, 0.51 (3), –1.36 (3); MS (EI) *m/e* (relative intensity) 414 (M^+, 32), 341 (4.5), 284 (16), 103 (100); exact mass calcd for $C_{22}H_{46}O_3Si_2$ (M^+) requires 414.2985, found 414.2982.

Data for (*Z*)-**26**: R_f 0.41 (5% EtOAc/hexanes); $[\alpha]^{23}_D$ –21.6° (*c* 1.50, $CHCl_3$); IR (thin film) 2940, 1610, 1465, 1385, 1260 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.21–5.19 (m, 1 H, C_9-H), 4.65 (AB quartet, 2 H, J_{AB} = 5.8 Hz, $\Delta\nu$ = 6.1 Hz, OCH_2O), 4.19 (br s, 1 H, C_7-H), 3.66–3.53 (m, 4 H, C_1-H and $OCH_2CH_2SiMe_3$), 3.26 (app t, 1 H, J = 9.0 Hz, C_3-H), 2.48–2.34 (m, 2 H, C_8-CH_2CH_3), 2.09–1.78 (m, 4 H, C_2-H and C_4-H and C_6-H), 1.47–1.37 (m, 2 H, C_5-H), 0.99 (t, 3 H, J = 6.2 Hz, C_8-CH_2CH_3), 0.95–0.87 (m, 2 H, $OCH_2CH_2SiMe_3$), 0.89 (d, 3 H, J = 6.1 Hz, C_2-CH_3), 0.85 (d, 3 H, J = 7.0 Hz, C_6-CH_3), 0.05 (s, 9 H, vinyl $Si(CH_3)_3$), –0.03 (s, 9 H, $Si(CH_3)_3$); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 155.33, 121.60, 95.16, 74.70, 74.44, 70.50, 64.88, 31.18, 29.98, 28.13, 25.71, 19.82, 18.12, 14.88, 12.98, 12.80, 1.62 (3), –1.38 (3); MS (EI) *m/e* (relative intensity) 414 (M^+, 4.9), 341 (1.1), 253 (2.2), 73 (100); exact mass calcd for $C_{22}H_{46}O_3Si_2$ (M^+) requires 414.2985, found 414.2988.

General Procedure for the Synthesis of Vinylsilanes from Mesylates. A representative experiment is as follows. In a 25-mL recovery flask was placed CuCN (0.050 mmol, 10 mol %) along with 3.0 mL of THF. The resulting white suspension was then cooled to 0 °C and treated with the alkylmagnesium bromide in Et_2O or THF (2.5 mmol, 5 equiv). After 15 min, the mixture was cooled to –78 °C and a solution of the crude allylic mesylate (0.50 mmol) in THF (2.0 mL) was added via cannula in a dropwise fashion. This suspension was then stirred at –78 °C for 1 h and the reaction quenched by addition of a 1:1 solution of saturated aqueous NH_4Cl and 3% NH_4OH solution (2.0 mL). The mixture was then diluted with Et_2O (6 mL), warmed to ambient temperature, and vigorously stirred for 30 min. The layers were then separated and the aqueous layer extracted with Et_2O (15 mL). The combined organic portions were dried over $MgSO_4$, filtered through Celite, and concentrated *in vacuo* to give a clean mixture of isomeric vinylsilanes. Analysis of the product by ^1H NMR and capillary GC allowed for determination of olefin isomer ratios. Reported yields are based on material isolated following flash chromatography on silica gel.

Data for **19a** (R = Me): R_f 0.44 (3% Et_2O/hexanes); IR (thin film) 2940, 2845, 1245 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.48 (d, 1 H, J = 1.0 Hz, C=$CH$$SiMe_3$), 4.08–4.00 (m, 1 H, O$CH$RC=C), 3.67 (br d, 1 H, J = 7.4 Hz, one of OCH_2CH_2), 3.52–3.40 (m, 1 H, one of OCH_2CH_2), 2.20 (dq, 1 H, J = 8.8, 7.5 Hz, one of CH_2-CH_3), 2.09 (dq, 1 H, J = 8.8, 7.5 Hz, one of CH_2CH_3), 1.89–1.22 (m, 6 H), 1.01 (t, 3 H, J = 7.5 Hz, CH_2CH_3), 0.08 (s, 9 H, $Si(CH_3)_3$); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 160.98, 121.47, 80.49, 68.86, 31.75, 26.50, 26.01, 24.07, 14.55, 0.28 (3).

Data for **19b** (R = Ph): R_f 0.40 (4% Et_2O/hexanes); IR (thin film) 3010, 2925, 2840, 1090, 870, 845 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.24–7.11 (m, 5 H, ArH), 5.73 (d, 1 H, J = 1.2 Hz, C=$CH$$SiMe_3$), 3.96 (ddt, 1 H, J = 11.3, 4.5, 2.4 Hz, OCHRC=C), 3.52 (AB quartet, 2 H, J_{AB} = 15.2 Hz, $\Delta\nu_{AB}$ = 52.4 Hz, C=CCH_2-Ph), 3.42–3.36 (m, 1 H, one of OCH_2CH_2), 3.27 (td, 1 H, J = 11.4, 2.5 Hz, one of OCH_2CH_2), 1.75–1.13 (m, 6 H), 0.08 (s, 9 H, $Si(CH_3)_3$); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 156.61, 139.61, 128.70 (2), 128.29 (2), 125.99, 124.39, 74.49, 68.75, 39.23, 31.25, 25.95, 23.81, 0.31 (3).

Data for **19c** (R = *i*-Pr): R_f 0.45 (4% Et_2O/hexanes); IR (thin film) 2940, 2845, 1245 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.58 (d, 1 H, J = 1.2 Hz, C=$CH$$SiMe_3$), 4.08–4.02 (m, 1 H, O$CH$RC=C), 3.62 (br d, 1 H, J = 10.6 Hz, one of OCH_2CH_2), 3.46 (td, 1 H, J = 10.5, 2.8 Hz, one of OCH_2CH_2), 2.13 (dd, 1 H, J = 13.5, 8.1 Hz, one of C=CCH_2R), 1.97 (dd, 1 H, J = 13.6, 6.8 Hz, one of

C=CCH_2R), 1.91–1.72 (m, 2 H), 1.64–1.24 (m, 5 H), 0.87 (overlapping d, 6 H, J = 6.6 Hz, CH(CH_3)$_2$), 0.09 (s, 9 H, Si(CH_3)$_3$); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 157.98, 122.65, 80.08, 68.97, 42.67, 31.66, 26.90, 26.05, 24.10, 22.81, 22.32, 0.59 (3).

Data for **19d** (R = vinyl): R_f 0.50 (4% Et_2O/hexanes); IR (thin film) 2905, 2820, 1590, 1425, 1240 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.75 (dddd, 1 H, J = 15.4, 10.1, 6.9, 6.0 Hz, RHC=CH$_2$), 5.63 (d, 1 H, J = 1.2 Hz, C=CHSiMe$_3$), 5.04 (app dq, 1 H, J = 15.4, 1.7 Hz, RC=CH$_t$H$_c$), 5.02 (ddt, 1 H, J = 10.1, 1.8, 1.7 Hz, RC=CH$_t$H$_c$), 4.08–4.01 (m, 1 H, OCHRC=C), 3.64 (dt, 1 H, J = 11.1, 1.5 Hz, one of OCH_2CH$_2$), 3.46 (td, 1 H, J = 11.2, 2.8 Hz, one of OCH_2CH$_2$), 3.01 (ddt, 1 H, J = 16.0, 6.0, 1.8 Hz, one of C=CCH_2C=C), 2.84 (ddt, 1 H, J = 16.0, 6.9, 1.8 Hz, one of C=CCH_2C=C), 1.88–1.22 (m, 6 H), 0.10 (s, 9 H, Si(CH_3)$_3$); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 156.39, 136.96, 123.58, 116.00, 80.29, 68.87, 37.72, 31.42, 26.01, 23.98, 0.27 (3).

(2*R*,3*S*,6*R*)-2-[(1*E*)-1-Ethyl-2-iodovinyl]-3-methyl-6-[(1*S*)-1-methyl-2-[[2-(trimethylsilyl)ethoxy]methoxy]ethyl]-tetrahydropyran (13). (Note: This experiment was conducted in the absence of light owing to the photosensitivity of *N*-iodosuccinimide over extended periods of time.) A stirred solution of (*E*)-**26** (72 mg, 0.17 mmol) in 1.4 mL of THF, protected from light with aluminum foil, was cooled to −15 °C (temperature-controlled cryocool bath). In a second flask, freshly recrystallized *N*-iodosuccinimide (484 mg, 1.70 mmol) was dissolved in 1.0 mL of THF. A 0.25-mL aliquot of this solution (2.5 equiv) was added and stirring continued at 0 °C. Two additional 0.10-mL aliquots of the NIS solution were added after 2 and 4 h, respectively. After 6 h, the solution was brought to 23 °C over a 2-h period, silica gel (0.6 g) was added, and vigorous stirring maintained for 25 min. The slurry was then poured onto a 2-g plug of silica gel and, *after 5 min*, rinsed through with Et_2O (20 mL). A solution of 15% aqueous sodium thiosulfate (4 mL) was added to the filtrate, and the layers were separated. The organic layer was washed with brine (2 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the oily residue by flash chromatography (elution with 4% EtOAc/hexanes) gave 62 mg (0.13 mmol, 79%) of the vinyl iodide **13** as a colorless oil: R_f 0.29 (5% EtOAc/hexanes, 2× elution); $[\alpha]^{23}_D$ −9.2° (*c* 1.00, $CHCl_3$); IR (thin film) 2965, 2940, 2885, 1460, 1385 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.10 (d, 1 H, J = 1.3 Hz, C$_8$-*H*), 4.62 (AB quartet, 2 H, J_{AB} = 6.6 Hz, $\Delta\nu_{AB}$ = 11.3 Hz, OCH_2O), 4.16 (br s, 1 H, C$_7$-*H*), 3.59–3.53 (m, 3 H, C$_3$-*H* and OCH_2CH$_2$SiMe$_3$), 3.54 (obscured dd, 1 H, J = 9.5, 3.7 Hz, one of C$_1$-*H*), 3.32 (dd, 1 H, J = 9.5, 7.2 Hz, one of C$_1$-*H*), 2.32–2.20 (m, 2 H, C$_2$-*H* and one of C$_8$-CH_2CH$_3$), 1.97 (qd, 1 H, J = 7.4, 6.8 Hz, one of C$_8$-CH_2CH$_3$), 1.96–1.91 (m, 1 H, C$_6$-*H*), 1.86–1.78 (m, 2 H, one of C$_4$-*H* and one of C$_5$-*H*), 1.50–1.38 (m, 2 H, one of C$_4$-*H* and one of C$_5$-*H*), 0.98 (t, 3 H, J = 7.4 Hz, C$_8$-CH$_2$CH_3), 0.93–0.88 (m, 2 H, OCH$_2$CH_2SiMe$_3$), 0.88 (d, 3 H, J = 6.9 Hz, C$_2$-CH_3), 0.82 (d, 3 H, J = 7.0 Hz, C$_6$-CH_3), 0.00 (s, 9 H, Si(CH_3)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.58, 95.20, 76.94, 74.93, 74.15, 70.26, 64.82, 32.62, 30.23, 29.13, 26.19, 21.23, 18.10, 14.62, 13.18, 12.03, −1.36 (3); MS (EI) *m/e* (relative intensity) 414 (32), 233 (100): exact mass calcd for $C_{19}H_{37}O_3ISi$ (M^+) requires 468.1558, found 468.1562.

(2*R*,3*S*,6*R*)-2-[(1*E*)-1-Ethyl-2-iodovinyl]-6-[(1*S*)-2-hydroxyl-1-methylethyl]-3-methyltetrahydropyran (27). To a solution of **13** (82 mg, 0.20 mmol) in 3.3 mL of wet CH_3CN (2% water content) was added $LiBF_4$ (53 mg, 0.57 mmol) in a single portion at 23 °C. The flask was fitted with a reflux condenser and the mixture heated at 80 °C for 1 h and then cooled to ambient temperature. Ice–water (2.6 mL) was added to the stirred mixture (slight effervescence) and the mixture poured into a separatory funnel containing brine (3 mL) and Et_2O (20 mL) and partitioned. The aqueous portion was extracted with Et_2O (3 × 15 mL), and the combined organic portions were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Flash chromatography (elution with 40% Et_2O/hexanes) provided 58 mg (0.17 mmol, 88%) of vinyl iodide **27** as a colorless oil: R_f 0.29 (40% Et_2O/hexanes); $[\alpha]^{23}_D$ −8.0 (*c* 0.50, $CHCl_3$); IR (thin film) 3400 (br), 2970, 2940, 2880, 1465, 1385, 1245 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.15 (br d, 1 H, J = 1.5 Hz, C$_8$-*H*), 4.28 (br dd, 1 H, J = 3.3, 1.4 Hz, C$_7$-*H*), 3.64 (dt, 1 H, J = 10.0, 4.2 Hz, C$_3$-*H*), 3.54 (app d, 2 H, J = 6.1 Hz, C$_1$-*H*), 2.69 (br s, 1 H, O*H*), 2.26 (qd, 1 H, J = 7.7, 6.0 Hz, one of C$_8$-CH_2CH$_3$), 2.25–2.16 (m, 1 H, C$_2$-*H*), 2.02 (qd, 1 H, J = 7.7, 6.1 Hz, one of C$_8$-CH_2CH$_3$), 2.01–1.95 (m, 1 H, C$_6$-*H*), 1.90–1.79 (m, 2 H, one of C$_4$-*H* and one of C$_5$-*H*), 1.52–1.42 (m, 2 H, one of C$_4$-*H* and one of C$_5$-*H*), 0.99 (t, 3 H, J = 7.7 Hz, C$_8$-CH$_2$CH_3), 0.83 (d, 3 H, J = 7.0 Hz, C$_2$-CH_3), 0.78 (d, 3 H, J = 6.9 Hz, C$_6$-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.46, 78.73, 77.38, 74.90, 68.16, 34.00, 30.32, 29.35, 26.14, 22.33, 14.04, 13.45, 11.90; MS (EI) *m/e* (relative intensity) 339 (M^+, 0.3), 211 (80), 210 (100); exact mass calcd for $C_{13}H_{23}O_2$ (M^+ − I) requires 211.1698, found 211.1704.

Preparation of 27 from (*Z*)-26. To a solution of (*Z*)-**26** (34 mg, 0.082 mmol) in 2 mL of CH_2Cl_2 at 0 °C was added *m*-CPBA (25 mg, 0.090 mmol) in a single portion. After the solution was stirred for 4 h at 0 °C, aqueous sodium thiosulfate solution (1.1 mL) was added followed by Et_2O (14 mL). The biphasic mixture was warmed to ambient temperature, the layers were partitioned, and the organic portion was washed with 1 N aqueous NaOH solution (2.5 mL). The combined aqueous layers were extracted with EtOAc (6 mL) and the organic portions dried over Na_2SO_4, filtered, and concentrated to give a yellow oil. The clean mixture of epoxide diastereomers was then used without subsequent purification: R_f 0.48 (10% Et_2O/hexanes).

The mixture of diastereomeric epoxysilanes was dissolved in 2 mL of Et_2O and the solution cooled to −25 °C and treated with HI (0.025 mL of a 57% aqueous solution, 0.11 mmol). The resulting pale yellow solution was stirred at −25 °C for 5 min at which time saturated aqueous $NaHCO_3$ solution (0.8 mL) was added along with Et_2O (3 mL). The solution was warmed to ambient temperature and poured into 15 mL of Et_2O. The layers were separated, and the organic layer was washed with 15% aqueous sodium thiosulfate solution (2 mL) and brine (2 mL). The aqueous layer was extracted with one portion of Et_2O (7 mL) and dried over Na_2SO_4. Filtration and concentration gave a mixture of β-hydroxy silanes (colorless oils) which was used directly in the next step. Analytically pure samples could be obtained via flash chromatography (elution with 30% Et_2O/hexanes). Data for less polar (minor) component: R_f 0.60 (20% Et_2O/hexanes); IR (thin film) 3540 (br), 2950, 2890, 1395 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.61 (collapsed AB quartet, 2 H, OCH_2O), 3.83–3.76 (m, 1 H, one of C$_1$-*H*), 3.79 (br d, 1 H, J = 3.3 Hz, C$_7$-*H*), 3.70–3.49 (m, 4 H, C$_3$-*H* and one of C$_1$-*H* and OCH_2-CH$_2$SiMe$_3$), 3.38 (s, 1 H, C$_9$-*H*), 2.34–2.26 (m, 1 H, C$_2$-*H*), 2.11–2.05 (m, 1 H, C$_8$-*H*), 1.93–1.63 (m, 2 H, one of C$_4$-*H* and one of C$_5$-*H*), 1.77 (q, 2 H, J = 6.8 Hz, C$_8$-CH_2CH$_3$), 1.57 (br s, disappears upon addition of D_2O, 1 H, O*H*), 1.50–1.35 (m, 2 H, one of C$_4$-*H* and one of C$_5$-*H*), 1.17 (d, 3 H, J = 6.9 Hz, C$_2$-CH_3), 0.97 (t, 3 H, J = 6.9 Hz, C$_8$-CH$_2$CH_3), 0.96–0.88 (m, 2 H, OCH$_2$CH_2SiMe$_3$), 0.89 (obscured d, 3 H, J = 6.8 Hz, C$_6$-CH_3), 0.51 (s, 9 H, C$_9$-Si(CH_3)$_3$), −0.02 (s, 9 H, OCH$_2$CH_2SiMe$_3$). Data for more polar (major) component: R_f 0.42 (20% Et_2O/hexanes); IR (thin film) 3530 (br), 3415 (br), 2950, 2890, 1385, 1265 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.64 (AB quartet, 2 H, J_{AB} = 4.3 Hz, $\Delta\nu_{AB}$ = 6.8 Hz, OCH_2O), 3.74 (app s, 2 H, OCH_2CH$_2$SiMe$_3$), 3.71 (obscured dd, 1 H, J = 5.7, 3.7 Hz, C$_7$-*H*), 3.63–3.54 (m, 2 H, J = 6.9 Hz, C$_1$-*H*), 3.34 (dd, 1 H, J = 7.3, 6.9 Hz, C$_3$-*H*), 2.59 (s, 1 H, C$_9$-*H*), 2.34–2.24 (m, 1 H, C$_2$-*H*), 1.97–1.69 (m, 3 H, C$_6$-*H* and one of C$_4$-*H* and one of C$_5$-*H*), 1.73 (q superimposed on m, 2 H, J = 6.7 Hz, C$_8$-CH_2CH$_3$), 1.67 (br s, disappears upon of D_2O, 1 H, O*H*), 1.51–1.34 (m, 2 H, one of C$_4$-*H* and one of C$_5$-*H*), 1.16 (d, 3 H, J = 6.9 Hz, C$_2$-CH_3), 1.03 (t, 3 H, J = 6.7 Hz, C$_8$-CH$_2$CH_3), 0.96–0.87 (m, 2 H, OCH$_2$CH_2SiMe$_3$), 0.90 (d superimposed on m, 3 H, J = 7.0 Hz, C$_6$-CH_3), 0.23 (s, 9 H, C$_9$-Si(CH_3)$_3$), −0.02 (s, 9 H, OCH$_2$CH_2-SiMe$_3$).

To a solution of the crude β-hydroxy silanes in 1.1 mL of CH_3-CN was added $LiBF_4$ (23 mg, 0.25 mmol). The mixture was heated at 80 °C for 3 h and cooled to ambient temperature. Water (0.6 mL) was added to the stirred mixture (slight effervescence) and the mixture poured into a separatory funnel containing brine (1 mL) and Et_2O (10 mL) and partitioned. The aqueous portion was extracted with Et_2O (2 × 10 mL), and the combined extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Analysis of the crude material by 270-MHz ^{1}H NMR indicated an 8:1 *E*/*Z* mixture of olefin isomers. Flash chromatography (elution with 40% Et_2O/hexanes) provided 2 mg (0.0058 mmol, 7% from vinylsilane (*Z*)-**26**) of the (*Z*)-vinyl iodide, a colorless oil (R_f 0.40, 40% Et_2O/hexanes), along with 16 mg (0.047 mmol, 57% from vinylsilane (*Z*)-**26**) of (*E*)-vinyl iodide **27**, a colorless oil (R_f 0.29, 40% Et_2O/hexanes) which was identical in all respects

to the material prepared from the deprotection of SEM ether (*E*)-**26** as described above.

(αR,2R,5S,6R)-α,5-Dimethyl-6-[(1*E*)-1-ethyl-2-iodovinyl]-tetrahydropyran-2-acetic Acid (2). To a solution of alcohol **27** (41 mg, 0.12 mmol) in 2.3 mL of acetone at −30 °C was added Jones reagent[67] (0.137 mL of a 1.94 M solution, 0.70 mmol) in a single portion. The solution was allowed to warm to −10 °C over a period of 30 min, stirred for 20 min at −10 °C, and then warmed very slowly towards 0 °C, monitoring carefully by TLC. The reaction was treated at −5 °C by addition of 5% HCl solution (2 mL) and diluted with Et_2O (5 mL) whereupon metal salts began to precipitate. Saturated aqueous $NaHSO_3$ (2 mL) was added to destroy the excess oxidant, and the solution was reacidified to pH 2.5 with 2 M HCl added in dropwise fashion. After partitioning of the layers, the aqueous portion was extracted with EtOAc (2 × 15 mL) and $CHCl_3$ (2 × 15 mL), and the combined extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification via flash chromatography (gradient elution: 30% Et_2O/hexanes; 50% Et_2O/hexanes; 100% Et_2O) gave 40 mg (0.11 mmol, 92%) of carboxylic acid **2** as a viscous oil: R_f 0.27 (40% Et_2O/hexanes, 2× elution); $[\alpha]^{23}_D$ −11.3° (*c* 0.95, $CHCl_3$); IR (thin film) 3150 (br), 2960, 2930, 2870, 2490 (br), 1715, 1460, 1300 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.48 (br s, 1 H, CO_2H), 6.09 (d, 1 H, *J* = 1.5 Hz, C_9-*H*), 4.34 (dd, 1 H, *J* = 3.1, 1.4 Hz, C_7-*H*), 3.91 (app dt, 1 H, *J* = 10.2, 4.4 Hz, C_3-*H*), 2.97 (dq, 1 H, *J* = 10.4, 6.9 Hz, one of C_8-CH_2CH$_3$), 2.26 (dq, 1 H, *J* = 10.4, 7.4 Hz, one of C_8-CH_2CH$_3$), 2.00–1.93 (m, 1 H, C_6-*H*), 1.98 (dq, 1 H, *J* = 10.2, 6.9 Hz, C_2-*H*), 1.92–1.86 (m, 1 H, one of C_4-*H*), 1.84–1.77 (m, 1 H, one of C_5-*H*), 1.56–1.49 (m, 1 H, one of C_5-*H*), 1.44–1.37 (m, 1 H, one of C_4-*H*), 1.11 (d, 3 H, *J* = 6.9 Hz, C_2-CH_3), 0.97 (br t, 3 H, *J* = 7.1 Hz, C_8-CH$_2$CH_3), 0.83 (d, 3 H, *J* = 6.9 Hz, C_6-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.31, 150.46, 74.44, 75.19, 74.82, 40.71, 30.21, 29.29, 25.93, 21.29, 14.06, 13.33, 11.82; MS (EI) *m/e* (relative intensity) 351 (M^+ − H, 1.2), 279 (1.3), 225 (37), 57 (100); exact mass calcd for $C_{13}H_{20}IO_3$ (M^+ − H) requires 351.0459, found 351.0434.

(1S*,3aR*,4S*,5R*,7aS*)-5-[(*tert*-Butyldiphenylsiloxy)-methyl]-1-ethyl-2,3,3a,4,5,7a-hexahydro-1*H*-indene-4-carboxylic Acid Methyl Ester (30b). To a mixture of lactone **28** (201 mg, 0.434 mmol) and 0.44 mL of the supernatant from the centrifugation of a 1:1 mixture of Me_3SiCl and Et_3N in 5.0 mL of THF at −100 °C was added freshly prepared LDA (1.30 mmol) in 4.0 mL of THF. The mixture was allowed to stir at −100 °C for 10 min and was then warmed to ambient temperature over 30 min. The solvent was removed *in vacuo* and replaced with 10 mL of toluene. The resulting mixture was stirred at 135 °C for 24 h, whereupon the solution was cooled to 23 °C and the solvent removed under reduced pressure. The residue was taken up in 20 mL of Et_2O and treated with 5 mL of 5% aqueous HCl. This biphasic mixture was stirred at 23 °C for 1 h, partitioned, and the aqueous layer extracted with Et_2O (4 × 20 mL). The combined organic portions were concentrated, and the crude carboxylic acid was dissolved in 10 mL of Et_2O, cooled to 0 °C, and treated with excess ethereal diazomethane. After 2 h, the solution was concentrated and purified by flash chromatography (elution with 2% Et_2O/hexanes) to give 112.6 mg (0.256 mmol) of ester **30b** and 26.6 mg (0.056 mmol) of a diastereomer (combined yield of 0.312 mmol, 72% in a ratio of 4.6:1). Data for **30b**: R_f 0.63 (15:1 hexanes–Et_2O); IR ($CHCl_3$) 3080, 3060, 2960, 2865, 1765, 1435 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (m, 4 H, Ar-*H*), 7.39 (m, 6 H, Ar-*H*), 5.95 (br d, 1 H, *J* = 10.0 Hz, C_{14}-*H*), 5.68 (dt, 1 H, *J* = 10.0, 3.4 Hz, C_{13}-*H*), 3.56 (m, 2 H, C_{11}-*H*), 3.50 (s, 3 H, CO_2CH_3), 2.81 (m, 1 H, C_{12}-*H*), 2.66 (dd, 1 H, *J* = 11.7, 6.8 Hz, C_{20}-*H*), 2.08–1.91 (m, 3 H, C_{19}-*H* and one of C_{18}-*H* and one of C_{17}-*H*), 1.88–1.57 (m, 1 H, one of C_{16}-CH_2CH$_3$), 1.56–1.47 (m, 2 H, C_{15}-*H* and C_{16}-*H*), 1.43–1.06 (m, 3 H, one of C_{18}-*H* and one of C_{16}-CH_2CH$_3$ and one of C_{17}-*H*), 1.04 (s, 9 H, SiC(CH_3)$_3$), 0.91 (br t, 3 H, *J* = 7.4 Hz, C_{16}-CH$_2$CH_3); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 174.05, 135.72 (2), 133.77 (4), 130.20 (2), 129.61 (4), 128.29, 127.65, 65.36, 51.11, 50.18, 48.06, 43.77, 41.71, 41.62, 29.54, 27.48, 27.31, 26.87, 19.23 (3), 12.44; MS (EI) *m/e* (relative intensity) 476 (0.9), 419 (100); exact mass calcd for $C_{30}H_{40}O_3Si$ (M^+) requires 476.7345, found 476.7347.

(67) Meinwald, J.; Crandall, J.; Hymans, W. *Org. Synth.* **1965**, *45*, 77–79.

(3aR*,5aS*,6S*,8aR*,8bS*)-6-Ethyl-3,3a,5a,6,7,8,8a,8b-octahydro-1*H*-indeno[4,5-*c*]furan-1-one (31). To a solution of ester **30b** (74.0 mg, 0.160 mmol) in 2.0 mL of THF at 0 °C was added tetrabutylammonium fluoride (0.230 mL of a 1.0 M solution in THF, 0.230 mmol) and the resulting mixture stirred at 0 °C for 2.5 h. The reaction mixture was then concentrated, diluted with Et_2O (15 mL), and washed with H_2O (3 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. Flash chromatography of the resulting residue (elution with 5% Et_2O/hexanes) gave 20.8 mg (0.150 mmol, 93%) of lactone **31** as a colorless solid. Recrystallization from pentane at −20 °C gave an analytically pure sample of **31**: mp 68–69 °C (lit.[8a,d] 67.5–68.5 °C); R_f 0.42 (50% Et_2O/hexanes); IR ($CHCl_3$) 3015, 2970, 2940, 2880, 1770, 1485, 1465 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.05 (br d, 1 H, *J* = 9.9 Hz, C_{14}-*H*), 5.56 (ddd, 1 H, *J* = 9.9, 3.1, 2.6 Hz, C_{13}-*H*), 4.51 (dd, 1 H, *J* = 8.7, 8.5 Hz, one of C_{11}-*H*), 3.89 (dd, 1 H, *J* = 11.4, 8.8 Hz, one of C_{11}-*H*), 3.20 (m, 1 H, C_{20}-*H*), 2.54 (dd, 1 H, *J* = 11.4, 8.5 Hz, C_{12}-*H*), 2.07–1.90 (m, 3 H, C_{19}-*H* and one of C_{18}-*H* and one of C_{17}-*H*), 1.81–1.49 (m, 1 H, one of C_{16}-CH_2CH$_3$), 1.54–1.45 (m, 2 H, C_{15}-*H* and C_{16}-*H*), 1.41–1.06 (m, 3 H, one of C_{18}-*H* and one of C_{16}-CH_2CH$_3$ and one of C_{17}-*H*), 0.94 (br t, 3 H, *J* = 7.4 Hz, C_{16}-CH$_2$CH_3); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 178.29, 132.26, 124.16, 72.08, 48.71, 44.37, 43.50, 41.70, 37.20, 29.36, 27.41, 27.35, 12.40; MS (EI) *m/e* (relative intensity) 206 (1.8), 97 (100); exact mass calcd for $C_{13}H_{18}O_2$ (M^+) requires 206.2840, found 206.2843.

***tert*-Butyl [(1S,4S,5R)-4-(*tert*-Butyldimethylsiloxy)-2-oxo-5-phenylcyclopent-1-yl]acetate (33).** To a slurry of CuCN (2.68 g, 29.9 mmol) in 18 mL of THF at −78 °C was added phenyllithium (29.3 mL of a 1.8 M solution in cyclohexane/Et_2O, 52.7 mmol). The resulting orange suspension was then warmed to 0 °C, stirred vigorously for 10 min, and recooled to −78 °C. A solution of enone **32** (3.73 g, 17.6 mmol) in THF (10 mL + 1.2 mL rinse), precooled to −78 °C, was introduced via a pressure-equalizing addition funnel over a 1.25-h period. After 1 h at −78 °C, HMPA (17 mL) was slowly added to the creamy yellow mixture over a 20-min period. A solution of Ph_3SnCl (14.9 g, 38.7 mmol) in THF (18 mL) was then added dropwise over a period of 2.5 h. After the mixture was stirred for an additional 30 min at −78 °C, a solution of *tert*-butyl bromoacetate (8.53 mL, 52.8 mmol) in THF (15 mL) was added and the reaction mixture warmed to −30 °C and stirred at that temperature for 1.5 h. Analysis by TLC indicated the presence of a major UV active material and a minor, more polar component which was also UV active. Finally, the solution was brought to −25 °C and stirred for 20 min, at which time 100 mL of a 1:1 solution of 3% aqueous NH_4OH and saturated aqueous NH_4Cl was added. The solution was allowed to warm to ambient temperature and was then diluted with 500 mL of Et_2O, causing the precipitation of inorganic salts. After 2 h of vigorous stirring, the mixture was filtered through a pad of Celite, and the layers were partitioned. The Et_2O layer was washed with brine (60 mL), and the combined aqueous phases were extracted with Et_2O (3 × 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to an oily suspension which was eluted through a thick plug of silica gel. Reconcentration afforded an oily residue which was purified by flash chromatography (gradient elution: 10% Et_2O/hexanes; 20% Et_2O/hexanes; 50% Et_2O/hexanes) to afford 4.97 g (12.3 mmol, 70%) of keto ester **33** as a colorless oil followed by 0.94 g (3.5 mmol, 10%) of enone **35**. (Note: enone **35**, generated as a side product in this reaction, was identical to that prepared via the transformation of **34** to **35** detailed below.) Data for **33**: R_f 0.33 (15% Et_2O/hexanes); $[\alpha]^{22}_D$ +62.7° (*c* 1.64, $CHCl_3$); IR (thin film) 3100, 3050, 2975, 2850, 1765, 1725, 1490, 1460, 1375 cm^{-1}; ^{1}H NMR (270 MHz, C_6D_6) δ 7.78–7.63 (m, 5 H, Ar-*H*), 4.28–4.19 (m, 1 H, C_{16}-*H*), 3.33 (dd, 1 H, *J* = 13.1, 8.9 Hz, C_{15}-*H*), 3.00 (dt, 1 H, *J* = 13.1, 5.4 Hz, C_{19}-*H*), 2.88–2.61 (m, 4 H, C_{17}-*H* and C_{20}-*H*), 1.48 (s, 9 H, $CO_2C(CH_3)_3$), 0.99 (s, 9 H, $SiMe_2C(CH_3)_3$), −0.06 (s, 3 H, one of Si(CH_3)$_2$-*t*-Bu), −0.20 (s, 3 H, one of Si(CH_3)$_2$-*t*-Bu); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 213.17, 170.53, 139.22, 128.47 (2), 127.98 (2), 127.18, 80.74, 74.85, 56.41, 51.64, 47.05, 33.14, 27.86 (3), 25.51 (3), 17.81, −5.32, −5.48. Anal. Calcd for $C_{23}H_{38}O_4Si$: C, 68.27; H, 8.97. Found: C, 68.35; H, 8.98.

***tert*-Butyl [(1S,4S,5R)-4-Hydroxy-2-oxo-5-phenylcyclopent-1-yl]acetate (34).** To a solution of **33** (227 mg, 0.56 mmol) in 15 mL of CH_3CN at 0 °C was added HF (0.50 mL of a 48%

aqueous solution, 0.62 mmol) in dropwise fashion over a period of 10 min. (Note: use of a polypropylene reaction vessel is recommended, particularly for small-scale reactions.) The mixture was slowly warmed to ambient temperature, stirred for 15 min, and monitored carefully by TLC. The solution was quenched with saturated aqueous $NaHCO_3$ (5 mL), diluted with Et_2O (30 mL), and stirred for 10 min. The layers were partitioned, and the aqueous phase was extracted with Et_2O (3 × 50 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (elution with 75% Et_2O/hexanes) to afford 159 mg of alcohol **34** (0.540 mmol, 97%) as a white semisolid: R_f 0.51 (75% Et_2O/hexanes); $[\alpha]^{23}_D$ +49.4° (*c* 1.56, $CHCl_3$); IR (KBr) 3460 (br), 3050, 2975, 2925, 1725 (br), 1610, 1360, 1310 cm^{-1}; ^1H NMR (270 MHz, C_6D_6) δ 7.39–7.20 (m, 5 H, Ar-*H*), 4.04–3.94 (m, 1 H, C_{16}-*H*), 3.23 (dd, 1 H, *J* = 12.7, 9.0 Hz, C_{15}-*H*), 2.78–2.43 (m, 5 H, C_{19}-*H* and C_{17}-*H* and C_{20}-*H*), 1.75 (br s, disappears upon addition of D_2O, 1 H, O*H*), 1.49 (s, 9 H, $CO_2C(CH_3)_3$); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 212.54, 170.53, 138.68, 129.02 (2), 127.77 (2), 127.62, 81.06, 73.84, 56.19, 52.60, 45.90, 32.97, 27.90 (3). Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.40; H, 7.74.

***tert*-Butyl [(1*S*,5*R*)-2-Oxo-5-phenylcyclopent-3-en-1-yl]-acetate (35).** To a solution of **34** (560 mg, 1.93 mmol) in 5.0 mL of pyridine at −10 °C was added methanesulfonyl chloride (296 mL, 3.86 mmol). Stirring was continued for 2 h while the reaction slowly warmed to ambient temperature. The mixture was diluted with 50 mL of Et_2O, poured into a separatory funnel containing ice-cold 5% HCl solution (25 mL), and then further diluted with 75 mL of Et_2O. Following partitioning of the two layers, the organic portion was washed successively with 10% aqueous $NaHCO_3$ solution (20 mL) and brine (15 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (elution with 10% Et_2O/hexanes) to afford 488 mg of enone **35** (1.79 mmol, 93%) as a waxy solid: R_f 0.24 (15% Et_2O/hexanes); $[\alpha]^{22}_D$ −228.8° (*c* 0.62, $CHCl_3$); IR (thin film from $CDCl_3$) 3060, 3025, 2980, 2930, 1715, 1390, 1370 cm^{-1}; ^1H NMR (270 MHz, C_6D_6) δ 7.36–7.35 (m, 1 H, C_{16}-*H*), 7.30–7.19 (m, 2 H, Ar-*H*), 7.07–6.98 (m, 3 H, Ar-*H*), 6.22 (dd, 1 H, *J* = 5.8, 2.1 Hz, C_{17}-*H*), 3.87–3.83 (m, 1 H, C_{15}-*H*), 2.78 (AB portion of ABX, 2 H, J_{AB} = 16.1 Hz, J_{AX} = 4.5 Hz, J_{BX} = 7.0 Hz, $\Delta\nu_{AB}$ = 30.1 Hz, C_{20}-*H*), 2.54 (ddd, 1 H, *J* = 7.0, 4.5, 3.4 Hz, C_{19}-*H*), 1.46 (s, 9 H, $CO_2C(CH_3)_3$); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 209.11, 203.08, 170.48, 164.74, 140.72, 132.96, 128.83 (2), 127.24 (2), 80.92, 52.88, 51.74, 34.46, 27.77 (3). Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.93; H, 7.38.

Conversion of 35 to 36. *tert*-Butyl [(1*S*,4*S*,5*R*)-4-Ethyl-2-oxo-5-phenylcyclopent-1-yl]acetate (35a). To a solution of CuI·PBu_3[68] (2.38 g, 6.06 mmol) in 70 mL of Et_2O at −40 °C was added a solution of ethyllithium[69] (18.9 mL of a 0.64 M in Et_2O, 12.1 mmol) in a dropwise fashion. The resulting purple solution was stirred for 30 min at −40 °C and then cooled to −78 °C. Enone **35** (1.50 g, 5.51 mmol) in Et_2O (19 mL + 1.5 mL rinse) was added in a dropwise manner over a period of 30 min. The pale yellow solution so formed was stirred at −78 °C for 30 min at which time it was quenched by the addition of methanol (10 mL) followed by a 1:1 solution of 3% aqueous NH_4OH and saturated NH_4Cl (25 mL). After the solution was warmed to ambient temperature and stirred vigorously for 1 h, 150 mL of Et_2O was added, and the layers were separated. The organic layer was washed with 50 mL of brine, the aqueous portions were extracted with Et_2O (2 × 100 mL), and the combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the yellow residue by flash chromatography (elution with 20% Et_2O/hexanes) gave 1.58 g (5.23 mmol, 95%) of the corresponding ketone **35a** as a colorless oil: R_f 0.36 (25% Et_2O/hexanes); $[\alpha]^{22}_D$ −56.9° (*c* 0.80, $CHCl_3$); IR (thin film) 2920, 2880, 2840, 1740, 1700, 1580, 1390, 1370 cm^{-1}; ^1H NMR (270 MHz, C_6D_6) δ 7.27–7.06 (m, 5 H, Ar-*H*), 2.71–2.41 (m, 5 H, C_{15}-*H* and C_{20}-*H* and C_{17}-*H*), 1.93–1.62 (m, 3 H, C_{19}-*H* and C_{16}-CH_2CH_3), 1.40 (s, 9 H, $CO_2C(CH_3)_3$), 0.99–0.87 (m, 1 H, C_{16}-*H*), 0.65 (br t, 3 H, *J* = 7.3 Hz, C_{16}-CH_2CH_3); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 216.35, 170.75, 140.71, 128.68 (2), 127.78 (2), 127.00, 80.67, 54.53, 54.00, 43.82, 43.40, 33.13, 27.89 (3), 25.98, 12.16; MS (EI) *m/e* (relative intensity) 246 (13), 229 (19), 200 (41), 188 (43), 187 (100); exact mass calcd for $C_{15}H_{17}O_3$ ($M^+ - C_4H_9$) requires 246.1257, found 246.1256.

***tert*-Butyl [(1*S*,4*R*,5*R*)-4-Ethyl-5-phenyl-2-(trifluoromethanesulfoxy)cyclopent-2-en-1-yl]acetate (35b).** To a solution of LiHMDS (3.70 mL of 1.0 M solution, 3.70 mmol) in 4 mL of THF at −78 °C was added a solution of ketone **35a** (1.02 g, 3.36 mmol) in 3 mL of THF in a dropwise fashion. After the yellow solution had been stirred at −78 °C for a 30-min period, a solution of *N*-phenyltrifluoromethanesulfonimide (1.32 g, 3.70 mmol) in 2.5 mL of THF was slowly added and the solution slowly warmed to 23 °C over a period of 2 h. The solution was concentrated and the residue purified by flash chromatography on silica gel (elution with 5% Et_2O/hexanes) affording 1.46 g (3.33 mmol, 99%) of the corresponding enol triflate **35b** as a colorless oil: R_f 0.30 (15% Et_2O/hexanes); $[\alpha]^{22}_D$ −8.2° (*c* 1.50, $CHCl_3$); IR (thin film) 3040, 3000, 2960, 2900, 2840, 1710, 1680, 1660, 1480, 1460, 1410, 1350, 1240, 1200, 1130, 930, 850, 750, 700 cm^{-1}; ^1H NMR (270 MHz, C_6D_6) δ 7.17–7.05 (m, 5 H, Ar-*H*), 5.85 (dd, 1 H, *J* = 4.0, 2.0 Hz, C_{17}-*H*), 3.54–3.44 (m, 1 H, C_{16}-*H*), 2.69 (br t, 1 H, *J* = 7.3 Hz, C_{15}-*H*), 2.48–2.39 (obscured m, 1 H, C_{19}-*H*), 2.37 (AB portion of ABX, 2 H, J_{AB} = 15.3 Hz, J_{AX} = 6.8 Hz, J_{BX} = 5.7 Hz, ν_A = 644.58 Hz, ν_B = 614.83 Hz, $\Delta\nu_{AB}$ = 49.75 Hz, C_{20}-*H*), 1.34 (s, 9 H, $CO_2C(CH_3)_3$), 1.32–1.07 (m, 2 H, C_{16}-CH_2CH_3), 0.65 (br t, 3 H, *J* = 7.3 Hz, C_{16}-CH_2CH_3); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 169.91, 148.49, 143.05, 128.68 (2), 127.81 (2), 126.90, 120.92, 119.08, 116.20, 80.95, 55.04, 51.17, 48.87, 38.28, 27.75 (3), 11.62. Anal. Calcd for $C_{20}H_{25}O_5SF_3$: C, 55.29; H, 5.80. Found: C, 55.31; H, 5.82.

***tert*-Butyl [(1*S*,2*R*,3*S*)-3-Ethyl-2-phenylcyclopent-1-yl]-acetate (36).** To a solution of the enol triflate **35b** (1.64 g, 3.77 mmol) in 25 mL of 2-methyl-2-propanol at 30 °C was added PtO_2 (328 mg, 1.44 mmol). A three-way adapter connected to a water aspirator and equipped with a hydrogen balloon was attached; the system was then evacuated by aspiration and filled with hydrogen (repeated three times). The suspension was carefully monitored by TLC, and after stirring for 30 min, the system was purged with a stream of nitrogen, diluted with 50 mL of Et_2O, filtered through a pad of Celite, and concentrated. The residue was purified by flash chromatography (elution with 5% Et_2O/hexanes) affording 957 mg (3.12 mmol, 88%) of the cyclopentane derivative **36** as a colorless oil: R_f 0.40 (15% Et_2O/hexanes); $[\alpha]^{22}_D$ −4.3° (*c* 0.75, $CHCl_3$); IR (thin film) 3200, 2960, 2920, 1700, 1580, 1355 cm^{-1}; ^1H NMR (270 MHz, C_6D_6) δ 7.24–7.09 (m, 5 H, Ar-*H*), 2.60–2.45 (m, 1 H, one of C_{17}-*H*), 2.40 (app dd, 1 H, *J* = 14.6, 5.5 Hz, one of C_{20}-*H*), 2.31–2.17 (m, 1 H, one of C_{18}-*H*), 2.07 (app dd, 1 H, *J* = 14.5, 7.6 Hz, one of C_{20}-*H*), 2.03 (obscured br t, 1 H, *J* = 7.4 Hz, C_{15}-*H*), 2.02–1.75 (overlapping m, 2 H, one of C_{17}-*H* and one of C_{18}-*H*), 1.54–1.23 (m, 3 H, C_{19}-*H* and C_{16}-CH_2CH_3), 1.39 (s, 9 H, $CO_2C(CH_3)_3$), 1.14–0.99 (m, 1 H, C_{16}-*H*), 0.79 (br t, 3 H, *J* = 7.5 Hz, C_{16}-CH_2CH_3); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 172.33, 143.30, 128.26 (2), 127.98 (2), 126.11, 79.72, 59.15, 49.54, 44.77, 40.12, 30.18, 29.72, 27.93 (3), 27.06, 12.37. Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.61. Found: C, 78.93; H, 9.79.

(1*R*,2*S*,5*S*)-2-[2-(*tert*-Butyloxy)-2-oxoethyl]-5-ethylcyclopentane-1-carboxylic Acid (37). In a 100-mL recovery flask, a stirred biphasic solution **36** (127 mg, 0.450 mmol) in 2 mL of CCl_4, 2 mL of CH_3CN, and 9 mL of H_2O was treated with $NaIO_4$ (1.92 g, 8.96 mmol) followed by $RuCl_3·H_2O$ (5 mg, 0.024 mmol).[52] The mixture was vigorously stirred for 24 h under nitrogen. (*Caution*: A slight buildup of internal pressure due to the generation of CO_2 was observed.) Careful, dropwise addition of 2-propanol (3 mL) resulted in a mildly exothermic reaction accompanied by a rapid blackening of the mixture. The heterogeneous suspension was diluted with Et_2O (20 mL) and H_2O (20 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 50 mL) and $CHCl_3$ (2 × 50 mL). The combined organic portions were dried over $MgSO_4$ and treated with decolorizing charcoal (*ca.* 2 g). The mixture was filtered through a pad of Celite and concentrated and the residue purified by flash chromatography (elution with 30% Et_2O/hexanes + 1% HOAc). Azeotropic removal of residual acetic acid with toluene afforded 89 mg (0.35 mmol, 77%) of the pure carboxylic acid **37** as a colorless oil: R_f 0.32 (30% Et_2O/hexanes + 1% HOAc); $[\alpha]^{22}_D$ −6.4° (*c* 1.40, $CHCl_3$); IR (thin film) 3100 (br), 2920, 2820 (br), 1710, 1680, 1440, 1380 cm^{-1}; ^1H NMR (500

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MHz, C_6D_6) δ 12.76 (br s, disappears upon addition of D_2O, 1 H, CO_2H), 2.59–2.51 (m, 1 H, C_{19}-H), 2.45 (app dd, 1 H, J = 15. 3, 6.6 Hz, one of C_{20}-H), 2.23 (app dd, 1 H, J = 15.3, 8.2 Hz, one of C_{20}-H), 2.18–2.10 (m, 1 H, C_{16}-H), 2.03 (br t, 1 H, J = 6.9 Hz, C_{15}-H), 1.99–1.85 (m, 2 H, one of C_{18}-H and one of C_{17}-H), 1.60–1.53 (m, 1 H, one of C_{17}-H), 1.41 (s, 9 H, $CO_2C(CH_3)_3$), 1.40–1.22 (m, 3 H, C_{16}-CH_2CH_3 and one of C_{18}-H), 0.88 (br t, 3 H, J = 7.4 Hz, C_{16}-CH_2CH_3); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 181.83, 171.89, 80.44, 56.37, 46.11, 40.80, 40.76, 30.93, 30.27, 27.97 (3), 25.70, 12.22. Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.69; H, 9.50.

(*E*)-1-(Tri-*n*-butylstannyl)-4-(trimethylsilyl)-1-buten-3-yne (38). This compound was prepared in three steps from *trans*-3-(tributylstannyl)propenal[54] (see supplementary material for details) and exhibited the following physical and spectroscopic characteristics: pale yellow oil; R_f 0.80 (hexanes); IR (thin film) 3280, 2920, 2840, 2820 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.93 (d, 1 H, J = 19.8 Hz, C*H*=CHSnR$_3$), 5.98 (d, 1 H, J = 19.8 Hz, CH=C*H*SnR$_3$), 1.48 (quintet, 6 H, J = 7.4 Hz, ($CH_3CH_2CH_2$-$CH_2)_3Sn$), 1.29 (sextet, 6 H, J = 7.1 Hz, $(CH_3CH_2CH_2CH_2)_3Sn$), 0.89 (t, 9 H, J = 7.2 Hz, $(CH_3CH_2CH_2CH_2)_3Sn$), 0.87 (t, 6 H, J = 7.2 Hz, $(CH_3CH_2CH_2CH_2)_3Sn$), 0.17 (s, 9 H, $Si(CH_3)_3$); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 148.58, 125.66, 105.32, 92.32, 28.98 (3), 27.26 (3), 13.65 (3), 9.59 (3), –0.07 (3); MS (EI) *m/e* (relative intensity) 246 (13), 229 (19), 200 (41), 188 (43), 187 (100); exact mass calcd for $C_{15}H_{29}Si^{120}Sn$ ($M^+ - C_4H_9$) requires 357.1060, found 357.1071; exact mass calcd for $C_{15}H_{29}Si^{118}Sn$ ($M^+ - C_4H_9$) requires 355.1054, found 355.1060. Anal. Calcd for $C_{19}H_{38}SiSn$: C, 55.20; H, 9.27. Found: C, 55.40; H, 9.17.

Conversion of 37 to 5. *tert*-Butyl [(1*S*,2*R*,3*S*)-3-Ethyl-2-[(*E*)-5-(trimethylsilyl)-2-penten-4-ynoyl]cyclopent-1-yl]acetate (37a). To a solution of **37** (91 mg, 0.36 mmol) in 3 mL of benzene at 25 °C was added DMF (*ca.* 3 drops) followed by oxalyl chloride (0.062 mL, 0.71 mmol). The solution was stirred for 1 h and then concentrated *in vacuo*. The residue was taken up in hexanes (7 mL + 1 mL rinse) and the insoluble material removed by filtration through glass wool. The filtrate was concentrated and the residue dissolved in 4.5 mL of THF. A solution of vinylstannane **38** (148 mg, 0.355 mmol) in 3.5 mL of THF was added, followed by *trans*-benzyl(chloro)bis(triphenylphosphine)-palladium(II) (13 mg, 0.0018 mmol, 5 mol %). The flask was fitted with a reflux condenser and the mixture heated at 50 °C under a blanket of nitrogen for 2 h, during which time the amber-colored solution darkened. The resulting black solution was then diluted with 20 mL of Et_2O, washed with 3% NH_4OH solution (4 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by chromatography (elution with 10% Et_2O/hexanes) to give 98 mg (0.27 mmol, 76%) of the corresponding enynone **37a** as a pale yellow oil: R_f 0.38 (10% Et_2O/hexanes); $[\alpha]^{22}_D$ –16.4° (*c* 1.20, $CHCl_3$); IR (thin film) 2920, 2840, 2120, 1870, 1710, 1660 cm^{-1}; ^1H NMR (270 MHz, C_6D_6) δ 6.88 (AB quartet, 2 H, J_{AB} = 15.9 Hz, $\Delta\nu_{AB}$ = 42.8 Hz, C_{12}-H and C_{13}-H), 2.74 (br sextet, 1 H, J = 8.7 Hz, C_{19}-H), 2.32 (t, 1 H, J = 8.5 Hz, C_{15}-H), 2.18 (AB portion of ABX, 2 H, J_{AB} = 14.6 Hz, J_{AX} = 9.0 Hz, J_{BX} = 8.4 Hz, $\Delta\nu_A$ = 606.9 Hz, $\Delta\nu_B$ = 577.9 Hz, $\Delta\nu_{AB}$ = 29.0 Hz, C_{20}-H), 2.09–1.97 (m, 1 H, C_{16}-H), 1.94–1.81 (m, 1 H, one of C_{18}-H), 1.74–1.62 (m, 1 H, one of C_{17}-H), 1.52–0.98 (m, 4 H, C_{16}-CH_2CH_3 and one of C_{17}-H and one of C_{18}-H), 1.35 (s, 9 H, $CO_2C(CH_3)_3$), 0.73 (t, 3 H, J = 7.4 Hz, C_{16}-CH_2CH_3), 0.21 (s, 9 H, $Si(CH_3)_3$); (500 MHz, $CHCl_3$) δ 6.88 (AB quartet, 2 H, J_{AB} = 34.6 Hz, $\Delta\nu_{AB}$ = 17.9 Hz, C_{12}-H and C_{13}-H), 2.52 (br sextet, 1 H, J = 8.7 Hz, C_{19}-H), 2.62 (t, 1 H, J = 8.5 Hz, C_{15}-H), 2.23 (dd, 1 H, J = 14.4 Hz, 8.0 Hz, one of C_{20}-H), 2.16 (dd, 1 H, J = 14.5 Hz, 8.8 Hz, one of C_{20}-H), 2.08–2.01 (m, 1 H, C_{16}-H), 1.97–1.87 (m, 1 H, one of C_{18}-H), 1.92–1.82 (m, 1 H, one of C_{17}-H), 1.41–1.32 (m, 2 H, one of C_{16}-CH_2CH_3 and one of C_{17}-H), 1.38 (s, 9 H, $CO_2C(CH_3)_3$), 1.36–1.19 (m, 2 H, one of C_{16}-CH_2CH_3 and one of C_{18}-H), 0.81 (t, 3 H, J = 7.4 Hz, C_{16}-CH_2CH_3), 0.19 (s, 9 H, $Si(CH_3)_3$); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 201.19, 171.57, 137.50, 122.90, 105.56, 102.29, 80.44, 62.60, 46.50, 40.85, 40.66, 31.16, 30.65, 28.29, 28.03 (3), 12.61, –0.42 (3); MS (EI) *m/e* (relative intensity) 305 (70), 289 (45), 151 (100); exact mass calcd for $C_{17}H_{25}O_3Si$ ($M^+ - C_4H_9$) requires 305.1573, found 305.1583.

***tert*-Butyl [(1*S*,2*R*,2(1*R* and 1*S*),3*S*)-3-Ethyl-2-[(*E*)-1-hydroxy-5-(trimethylsilyl)-2-penten-4-ynyl]cyclopent-1-yl]acetate (37b).** To a solution of the enone **37a** (65 mg, 0.18 mmol) in 6.5 mL of MeOH at 23 °C was added $CeCl_3 \cdot 7H_2O$ (77 mg, 0.21 mmol) followed by $NaBH_4$ (8 mg, 0.21 mmol). The solution was stirred for 10 min at which time H_2O (1.2 mL) was added in a dropwise fashion (slight effervescence). The mixture was extracted with Et_2O (2 × 20 mL), and the combined organic portions were dried over $MgSO_4$, filtered, and concentrated to afford 64 mg of the crude allylic alcohol **37b** as an inseparable 1.2:1 mixture of diastereomers as determined by ^1H NMR analysis: R_f 0.38 (30% Et_2O/hexanes); IR (thin film) 3390 (br), 2925, 2900, 2840, 2135, 1710, 1685 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.24 and 6.18 (overlapping sets of dd, 2 H, J = 15.8, 5.3 Hz and J = 15.8, 6.1 Hz, C_{12}-H and C_{13}-H), 4.20–4.13 and 4.01–3.86 (m, 1 H, C_{16}-H), 3.11 and 2.89 (br d, 1 H, J = 5.3 Hz and J = 4.0 Hz, OH), 2.40–2.12 (m, 3 H), 1.82–1.13 (m, 8 H), 1.41 (s, 9 H, $CO_2C(CH_3)$, 1.92–1.81 (m, 3 H, C_{16}-CH_2CH_3), 0.17 (s, 9 H, $Si(CH_3)_3$).

The residue was taken up in 3 mL of MeOH, 3 mL of THF, and 3 mL of H_2O to effect hydrolysis of the *tert*-butyl ester. Solid NaOH (40 mg, 1.0 mmol) was added and the solution stirred at 23 °C for 24 h at which time it was acidified with 5% HCl. The mixture was diluted with Et_2O (15 mL), and the layers were partitioned. The aqueous portion was extracted with EtOAc (2 × 15 mL) and $CHCl_3$ (2 × 15 mL), dried over $MgSO_4$, filtered, and concentrated to give a yellow oil containing some solid material.

This material was taken up in 3 mL of CH_2Cl_2 and the stirred solution at ambient temperature treated with DIC (0.041 mL, 0.26 mmol) followed by DMAP (4.4 mg, 0.036 mmol). The solution became increasingly turbid and was accompanied by the gradual formation of a crystalline precipitate. After 1 h, the solution was concentrated to give an oil containing some solid material. Purification by flash chromatography (elution with 50% Et_2O/hexanes) yielded 15 mg (0.070 mmol, 39%) of the C_{14} epimeric lactone *epi*-**5**, a colorless oil, followed by 13 mg (0.058 mmol, 32%) of the more polar, desired lactone **5**, a colorless oil.

Data for **(1*S*,4a*S*,7*S*,7a*R*)-1-[(*E*)-1-Buten-3-ynyl]-7-ethylhexahydrocyclopenta[*c*]pyran-3(1*H*)-one (*epi*-5)**: R_f 0.28 (40% Et_2O/hexanes); $[\alpha]^{22}_D$ +154.3° (*c* 1.10, $CHCl_3$); IR (thin film) 3240, 2980, 2840, 2080, 1710, 1610 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.24 (dd, 1 H, J = 15.9, 5.8 Hz, C_{13}-H), 5.73 (ddd, 1 H, J = 15.9, 2.3, 1.8 Hz, C_{12}-H), 5.17 (br dt, 1 H, J = 5.8, 1.8 Hz, C_{14}-H), 2.96 (d, 1 H, J = 2.3 Hz, C_{10}-H), 2.84 (dd, 1 H, J = 17.7, 4.9 Hz, one of C_{20}-H), 2.23 (dd, 1 H, J = 17.7, 11.9 Hz, one of C_{20}-H), 2.07–1.84 (m, 3 H, C_{15}-H and C_{19}-H and one of C_{17}-H), 1.66–1.46 (m, 3 H, C_{18}-H and one of C_{16}-H), 1.45–1.12 (m, 3 H, C_{16}-CH_2CH_3 and one of C_{17}-H), 0.92 (t, 3 H, J = 7.4 Hz, C_{16}-CH_2CH_3); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 170.13, 138.95, 113.13, 81.04, 80.77, 79.31, 49.90, 41.55, 38.36, 35.51, 29.86, 29.51, 27.10, 12.41; MS (EI) *m/e* (relative intensity) 217 (0.2), 163 (1.3), 113 (1.4), 78 (100); exact mass calcd for $C_{14}H_{17}O_2$ (M^+ – H) requires 217.1228, found 217.1220.

Data for **(1*R*,4a*S*,7*S*,7a*R*)-1-[(*E*)-1-Buten-3-ynyl]-7-ethylhexahydrocyclopenta[*c*]pyran-3(1*H*)-one (5)**: R_f 0.23 (40% Et_2O/hexanes); $[\alpha]^{22}_D$ +7.3° (*c* 1.10, $CHCl_3$); IR (thin film) 3220, 2920, 2820, 2080, 1710 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.15 (dd, 1 H, J = 15.8, 8.3 Hz, C_{13}-H), 5.77 (ddd, 1 H, J = 15.7, 2.3, 1.0 Hz, C_{12}-H), 4.59 (br dd, 1 H, J = 10.2, 8.4 Hz, C_{14}-H), 2.94 (d, 1 H, J = 2.3 Hz, C_{10}-H), 2.85 (dd, 1 H, J = 17.7, 4.7 Hz, one of C_{20}-H), 2.43 (dd, 1 H, J = 17.7, 12.4 Hz, one of C_{20}-H), 2.06–1.82 (m, 2 H, C_{15}-H and C_{19}-H), 1.71–1.41 (m, 3 H, C_{16}-H and one of C_{17}-H and one of C_{18}-H), 1.29–1.06 (m, 4 H, C_{16}-CH_2CH_3 and one of C_{17}-H and one of C_{18}-H), 0.87 (t, 3 H, J = 7.3 Hz, C_{16}-CH_2CH_3); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 170.02, 141.40, 112.32, 86.03, 80.79, 79.37, 51.43, 42.17, 41.66, 37.56, 30.08, 29.91, 27.78, 12.15; MS (EI) *m/e* (relative intensity) 218 (1.3), 162 (7.6), 147 (6.3), 128 (15), 95 (100); exact mass calcd for $C_{14}H_{18}O_2$ (M^+) requires 218.1307, found 218.1323.

Conversion of *epi*-5 to 5. To a solution of *epi*-**5** (15 mg, 0.069 mmol) in 0.9 mL of THF, 0.9 mL of MeOH, and 0.9 mL H_2O at 23 °C was added solid NaOH (20 mg, 0.50 mmol) in a single portion. The solution was stirred for 24 h and acidified with 5% HCl. The mixture was diluted with Et_2O (10 mL), and the layers were partitioned. The aqueous portion was extracted with EtOAc (2 × 8 mL) and $CHCl_3$ (2 × 8 mL), dried over $MgSO_4$, filtered, and concentrated to give a yellow oil containing some solid material.

The crude hydroxy acid was dissolved in 2 mL of toluene and the solution cooled to −25 °C. To this stirred solution was added triphenylphosphine (27 mg, 0.11 mmol) followed by diethyl azodicarboxylate (0.17 mL, 0.11 mmol). After 4 h at −25 °C, the solution was warmed to 23 °C and then concentrated to give an orange residue. Purification of this material by flash chromatography (elution with 50% Et_2O/hexanes) provided 9 mg (0.042 mmol, 61%) of lactone **5** which was identical in all respects to the material previously produced.

(1*S*,3a*R*,4*S*,5*R*,7a*S*)-1-Ethyl-5-[2-(trimethylsilyl)ethynyl]-2,3,3a,4,5,7a-hexahydro-1*H*-indene-4-carboxylic Acid (39) and *S*-(2-Pyridyl) (1*S*,3a*R*,4*S*,5*R*,7a*S*)-1-Ethyl-5-[2-(trimethylsilyl)ethynyl]-2,3,3a,4,5,7a-hexahydro-1*H*-indene-4-carboxythiolate (40). A 25-mL recovery flask equipped with a reflux condenser was charged with 1.3 mL of THF and LiHMDS (2.02 mL of a 1.0 M solution in THF, 2.02 mmol) and the solution cooled to −93 °C (Et_2O/CO_2 bath) and treated with the supernatant from the centrifugation of 1.0 mL of a 1:1 mixture of Me_3SiCl and Et_3N (*ca.* 4 equiv). The solution was stirred for 10 min whereupon a solution of lactone **5** (147 mg, 0.673 mmol) in THF (4 mL + 0.5 mL rinse) was slowly added via cannula. Stirring was maintained at that temperature for 15 min, and then the solution was gradually brought to ambient temperature over a period of 1 h. Analysis by TLC indicated consumption of starting material and the presence of a slightly less polar, highly UV active material. Toluene (8 mL) was added, the reflux condenser was fitted with a distillation apparatus, and THF was removed by distillation. The resulting mixture was heated to reflux and stirred for 36 h at which time the solution was cooled to ambient temperature and the solvent removed under reduced pressure. The residue was taken up in 5 mL of Et_2O and acidified with 5% HCl. The solution was stirred vigorously at 23 °C for 30 min. The layers were partitioned and the aqueous phase was extracted repeatedly with 15 mL portions of Et_2O. The combined extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give the crude carboxylic acid **39**.

The crude carboxylic acid was taken up in 4 mL of toluene at 23 °C and the stirred solution treated with 2,2′-dipyridyl disulfide (Aldrithiol-2) (252 mg, 1.14 mmol) followed by triphenylphosphine (299 mg, 1.14 mmol). The mixture was allowed to stir for 2 h and then concentrated to an oil. Purification of the residue by flash chromatography (gradient elution: hexanes; 30% Et_2O/hexanes) provided 168 mg (0.438 mmol, 66%) of the thiopyridyl ester derivative **40** as an amorphous white solid: mp 72–73 °C; R_f 0.34 (35% Et_2O/hexanes); $[\alpha]^{23}_D$ −227.4° (*c* 0.95, $CHCl_3$); IR (thin film from $CHCl_3$) 2980, 2920, 2880, 2850, 2140, 1720, 1430 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 8.57 (dd, 1 H, *J* = 2.6, 0.5 Hz, Ar-$H_{pyr,6}$), 7.74–7.60 (m, 2 H, Ar-$H_{pyr,3}$ and Ar-$H_{pyr,4}$), 7.24 (ddd, 1 H, *J* = 2.6, 1.4, 0.7 Hz, Ar-$H_{pyr,5}$), 5.95 (br d, 1 H, *J* = 9.7 Hz, C_{14}-*H*), 5.81 (ddd, 1 H, *J* = 9.7, 4.2, 2.4 Hz, C_{13}-*H*), 3.77 (ddd, 1 H, *J* = 6.6, 4.3, 1.9 Hz, C_{12}-*H*), 2.98 (dd, 1 H, *J* = 11.0, 6.5 Hz, C_{20}-*H*), 2.08–1.91 (m, 3 H, C_{19}-*H* and one of C_{18}-*H* and one of C_{17}-*H*), 1.88–1.57 (m, 1 H, one of C_{16}-CH_2CH_3), 1.56–1.47 (m, 2 H, C_{15}-*H* and C_{16}-*H*), 1.43–1.06 (m, 3 H, one of C_{18}-*H* and one of C_{16}-CH_2CH_3 and one of C_{17}-*H*), 0.95 (br t, 3 H, *J* = 7.2 Hz, C_{16}-CH_2CH_3), 0.16 (s, 9 H, $Si(CH_3)_3$); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 194.62, 152.20, 150.20. 136.70, 130.05, 129.74, 125.84, 123.18, 104.18, 88.59, 58.18, 49.92, 43.29, 41.19, 34.40, 29.44, 27.13, 27.01, 12.40, −0.03 (3); MS (EI) *m/e* (relative intensity) 383 (0.6), 368 (2.2), 310 (4.1), 272 (20), 112 (65), 73 (100); exact mass calcd for $C_{22}H_{29}NOSSi$ (M^+) requires 383.1739, found 383.1736.

(1*S*,3a*R*,4*S*,5*R*,7a*S*)-1-Ethyl-5-[2-(trimethylsilyl)ethynyl]-4-(2-pyrrolylcarbonyl)-2,3,3a,4,5,7a-hexahydro-1*H*-indene (41). A solution of pyrrolmagnesium bromide was prepared by addition of freshly distilled pyrrole (0.058 mL, 0.083 mmol) to a solution of MeMgBr (0.230 mL of a 3.0 M solution in Et_2O, 0.690 mmol) in 1.5 mL of toluene and 0.3 mL of THF at −10 °C. After being stirred at that temperature for 10 min, the solution was warmed at 0 °C, stirred for an additional 10 min, and then transferred via cannula to a solution of thioester **40** (53 mg, 0.14 mmol) in 1.5 mL of toluene and 0.3 mL of THF at 0 °C. Stirring was continued at 0 °C for 20 min before the reaction was quenched by addition of saturated aqueous NH_4Cl solution (2 mL) and diluted with Et_2O (10 mL). The layers were separated and the organic portion washed with H_2O (4 mL). The aqueous layers were combined and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (elution with 40% Et_2O/hexanes), affording 44 mg (0.13 mmol, 93%) of acylpyrrole 41 as a colorless oil: R_f 0.49 (35% Et_2O/hexanes); $[\alpha]^{22}_D$ −180.8° (*c* 0.60, $CHCl_3$); IR (thin film) 3230, 2920, 2880, 2140, 1700 (br), 1640, 1520 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 9.59 (br s, 1 H, N*H*), 7.00 (ddd, 1 H, *J* = 2.8, 2.6, 1.3 Hz, C_{25}-*H*), 6.82 (ddd, 1 H, *J* = 3.9, 2.4, 1.3 Hz, C_{23}-*H*), 6.25 (dt, 1 H, *J* = 3.8, 2.6 Hz, C_{24}-*H*), 5.95 (br dt, 1 H, *J* = 9.7, 0.8 Hz, C_{14}-*H*), 5.62 (ddd, 1 H, *J* = 9.7, 4.2, 2.5 Hz, C_{13}-*H*), 3.68–3.63 (m, 1 H, C_{12}-*H*), 3.27 (dd, 1 H, *J* = 10.9, 6.8 Hz, C_{20}-*H*), 2.13–1.91 (m, 3 H, C_{19}-*H* and one of C_{18}-*H* and one of C_{17}-*H*), 1.75–1.62 (m, 1 H, one of C_{16}-CH_2CH_3), 1.58–1.48 (m, 2 H, C_{15}-*H* and C_{16}-*H*), 1.34–0.99 (m, 3 H, one of C_{18}-*H* and one of C_{17}-*H* and one of C_{16}-CH_2CH_3), 0.90 (br t, 3 H, *J* = 7.3 Hz, C_{16}-CH_2CH_3), 0.03 (s, 9 H, $Si(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.89, 131.91, 129.88, 126.41, 123.80, 114.88, 110.42, 105.00, 88.33, 51.78, 49.74, 43.40, 40.81, 34.84, 29.58, 27.25, 26.59, 12.51, 0.04 (3); MS (EI) *m/e* (relative intensity) 339 (59), 324 (33), 73 (100); exact mass calcd for $C_{21}H_{29}NOSi$ (M^+) requires 339.2018, found 339.2016.

(1*S*,3a*R*,4*S*,5*R*,7a*S*)-1-Ethyl-5-ethynyl-4-(2-pyrrolylcarbonyl)-2,3,3a,4,5,7a-hexahydro-1*H*-indene (42). To a solution of 41 (27 mg, 0.079 mmol) in 2 mL of THF at 0 °C was added TBAF·$3H_2O$ (75 mg, 0.24 mmol) in two approximately equal portions over a 2-min period. After 30 min, the peach solution was concentrated and purified immediately by flash chromatography (elution with 30% Et_2O/hexanes) providing 21 mg (0.077 mmol, 98%) of the terminal alkyne **42** as a viscous oil: R_f 0.21 (50% Et_2O/hexanes); $[\alpha]^{22}_D$ −120.6° (*c* 0.50, $CHCl_3$); IR (thin film) 3240, 2980, 2880, 2820, 2120, 1700 (br), 1640, 1540 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 9.55 (br s, 1 H, N*H*), 7.01 (ddd, 1 H, *J* = 2.8, 2.6, 1.3 Hz, C_{25}-*H*), 6.83 (ddd, 1 H, *J* = 3.9, 2.4, 1.3 Hz, C_{23}-*H*), 6.25 (dt, 1 H, *J* = 3.8, 2.6 Hz, C_{24}-*H*), 5.99 (br dt, 1 H, *J* = 10.6, 1.4 Hz, C_{14}-*H*), 5.66 (ddd, 1 H, *J* = 9.7, 4.3, 2.6 Hz, C_{13}-*H*), 3.65–3.58 (m, 1 H, C_{12}-*H*), 3.33 (dd, 1 H, *J* = 10.8, 6.3 Hz, C_{20}-*H*), 2.16 (d, 1 H, *J* = 2.4 Hz), 2.15–1.87 (m, 3 H, C_{19}-*H* and one of C_{18}-*H* and one of C_{17}-*H*), 1.75–1.44 (m, 3 H, C_{15}-*H* and C_{16}-*H* and one of C_{16}-CH_2CH_3), 1.33–1.04 (m, 3 H, one of C_{18}-*H* and one of C_{17}-*H* and one of C_{16}-CH_2CH_3), 0.91 (br t, 3 H, *J* = 7.3 Hz, C_{16}-CH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.14, 131.69, 130.23, 126.24, 124.38, 115.30, 110.57, 82.79, 72.37, 51.18, 50.00, 43.39, 40.91, 33.91, 29.53, 27.27, 26.91, 12.48; MS (EI) *m/e* (relative intensity) 266 (31), 251 (17), 73 (100); exact mass calcd for $C_{18}H_{20}NO$ (M^+ − H) requires 266.1545, found 266.1542.

(1*S*,3a*R*,4*S*,5*R*,7a*S*)-1-Ethyl-5-[(*E*)-2-(tri-*n*-butylstannyl)vinyl]-4-(2-pyrrolylcarbonyl)-2,3,3a,4,5,7a-hexahydro-1*H*-indene (3). To a solution of $(Ph_3P)_4Pd$[61a] (18 mg, 0.016 mmol, 10 mol %) in 2.0 mL of benzene at 23 °C was added a solution of **42** (42 mg, 0.16 mmol) in benzene (1 mL) via cannula. Bu_3SnH (0.055 mL, 0.020 mmol) was added as a solution in 0.400 mL of benzene in dropwise fashion over a period of 2 min; complete consumption of starting material after addition of approximately 1 equiv of the tin reagent was accompanied by an immediate darkening of the reaction mixture and evolution of hydrogen gas. Concentration *in vacuo* gave a black oil; analysis of this crude material by 270-MHz ^1H NMR indicated a 4.4:1 ratio of regioisomers, with the desired isomer in predominance. Flash chromatography (gradient elution: hexanes; 10% Et_2O/hexanes) provided 77 mg (0.14 mmol, 87%) of **3**, accompanied by its C_{11} regioisomer. The mixture was further purified by HPLC (10 mm × 250 mm semipreparative normal phase silica gel column; eluant: 2.5% EtOAc/hexanes; flow rate: 4.0 mL/min; retention time: 7.85 min and 8.51 min, respectively) which gave 62 mg (0.11 mmol, 71%) of the desired vinylstannane **3** and 15 mg (0.03 mmol, 16%) of the C_{11} regioisomer.

Data for **3**: R_f 0.38 (15:1 hexanes/EtOAc, 2× elution); $[\alpha]^{22}_D$ −102.6° (*c* 0.40, $CHCl_3$); IR (thin film) 3220, 2990, 2920, 2890, 1700 (br), 1620 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.11 (br s, 1 H, N*H*), 6.94 (ddd, 1 H, *J* = 2.8, 2.6, 1.2 Hz, C_{25}-*H*), 6.86 (ddd, 1 H, *J* = 3.9, 2.4, 1.3 Hz, C_{23}-*H*), 6.25 (dt, 1 H, *J* = 3.8, 2.6 Hz, C_{24}-*H*), 5.94 (br d, 1 H, *J* = 9.9 Hz, C_{14}-*H*), 5.69 (dd, 1 H, *J* = 18.4, 7.6 Hz, $^3J_{Sn-H}$ = 34.5 Hz, C_{11}-*H*), 5.58 (d, 1 H, *J* = 18.5 Hz, $^2J_{Sn-H}$ = 59.4 Hz, C_{10}-*H*), 5.46 (dt, 1 H, *J* = 9.8, 2.9 Hz, C_{13}-*H*), 3.36–3.29 (m, 2 H, C_{12}-*H* and C_{20}-*H*), 2.00–1.90 (m, 3 H, C_{19}-*H* and one of C_{18}-*H* and one of C_{17}-*H*), 1.75–1.67 (m, 1 H, one of C_{16}-CH_2CH_3),

1.59–1.53 (br t, 1 H, J = 7.5 Hz, C_{15}-H), 1.49–1.30 (m, 2 H, C_{16}-H and one of C_{16}-CH_2CH_3), 1.37 (quintet, 6 H, J = 7.4 Hz, $(CH_3CH_2CH_2CH_2)_3Sn$), 1.24 (sextet, 6 H, J = 7.1 Hz, $(CH_3CH_2CH_2CH_2)_3Sn$), 1.18–1.11 (m, 1 H, one of C_{17}-H), 1.05–0.96 (m, 1 H, one of C_{18}-H), 0.92 (t, 3 H, J = 7.3 Hz, C_{16}-CH_2CH_3), 0.85 (t, 9 H, J = 7.2 Hz, $(CH_3CH_2CH_2CH_2)_3Sn$), 0.77 (t, 6 H, J = 7.2 Hz, $(CH_3CH_2CH_2CH_2)_3Sn$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.72, 147.31, 132.55, 129.64, 129.19 , 123.50, 123.44, 114.77, 110.38, 52.25, 49.94, 43.76, 40.62, 29.72, 29.64, 29.00 (3), 28.92, 27.36, 27.21 (3), 13.74 (3), 12.55, 9.43 (3); MS (EI) m/e (relative intensity) 502 (49), 500 (72), 498 (100); exact mass calcd for $C_{26}H_{40}NO^{120}Sn$ ($M^+ - C_4H_9$) requires 502.2131, found 502.2119; exact mass calcd for $C_{26}H_{40}NO^{118}Sn$ ($M^+ - C_4H_9$) requires 500.2126, found 500.2134; exact mass calcd for $C_{26}H_{40}NO^{116}Sn$ ($M^+ - C_4H_9$) requires 498.2127, found: 498.2147.

Data for the regioisomeric vinylstannane **(1*S*,3a*R*,4*S*,5*R*,7a*S*)-1-Ethyl-5-[1-(tri-*n*-butylstannyl)vinyl]-4-(2-pyrrolylcarbonyl)-2,3,3a,4,5,7a-hexahydro-1*H*-indene**: R_f 0.37 (15:1 hexanes/EtOAc, 2× elution); ^1H NMR (500 MHz, $CDCl_3$) δ 9.11 (br s, 1 H, NH), 6.95 (ddd, 1 H, J = 2.8, 2.6, 1.2 Hz, C_{25}-H), 6.86 (ddd, 1 H, J = 3.9, 2.4, 1.3 Hz, C_{23}-H), 6.25 (dt, 1 H, J = 3.8, 2.6 Hz, C_{24}-H), 5.96 (br d, 1 H, J = 9.7 Hz, C_{14}-H), 5.40 (obscured dt, 1 H, J = 9.7, 2.8 Hz, C_{13}-H), 5.38 (t superimposed on dt, 1 H, J = 2.5 Hz, $^3J_{Sn\text{-}H}$ = 57.5 Hz, C_{10}-H_E), 5.05 (d, 1 H, J = 2.5 Hz, $^3J_{SnH}$ = 35.1 Hz, C_{10}-H_Z), 3.59–3.56 (m, 1 H, $^3J_{SnH}$ = 33.8 Hz, C_{12}-H), 3.39 (dd, 1 H, J = 11.6, 7.0 Hz, C_{20}-H), 2.01–1.83 (m, 3 H, C_{19}-H and one of C_{18}-H and one of C_{17}-H), 1.74–1.66 (m, 1 H, one of C_{16}-CH_2CH_3), 1.58–1.28 (m, 3 H, C_{15}-H and C_{16}-H and one of C_{16}-CH_2CH_3), 1.36 (quintet, 6 H, J = 7.4 Hz, $(CH_3CH_2CH_2CH_2)_3Sn$), 1.26 (sextet, 6 H, J = 7.1 Hz, $(CH_3CH_2CH_2CH_2)_3Sn$), 1.24–1.12 (m, 1 H, one of C_{17}-H), 1.03–0.97 (m, 1 H, one of C_{18}-H), 0.92 (t, 3 H, J = 7.3 Hz, C_{16}-CH_2CH_3), 0.85 (t, 9 H, J = 7.2 Hz, $(CH_3CH_2CH_2CH_2)_3Sn$), 0.77 (t, 6 H, J = 7.2 Hz, $(CH_3CH_2CH_2CH_2)_3Sn$).

X-14547A (Indanomycin) (1). Vinyl iodide **2** (20 mg, 0.057 mmol) and vinylstannane **3** (35 mg, 0.063 mmol, 1.1 equiv) were placed in a 2-mL vial equipped with a spin vane and the vessel charged with 0.400 mL of DMF. To this magnetically stirred solution was added freshly prepared $(Ph_3P)_4Pd$[61a] (7.2 mg, 0.0062 mmol, 10 mol %) under a stream of argon; the system was sealed under a stream of argon and stirred at ambient temperature in the absence of light. The amber solution gradually darkened and after 72 h, analysis by TLC indicated complete consumption of the vinyl iodide. The mixture was diluted with EtOAc (5 mL) and filtered through glass wool into a separatory funnel containing EtOAc (10 mL) and H_2O (2 mL). After partitioning, the aqueous layer was extracted with $CHCl_3$ (3 × 6 mL) and the combined organic portions concentrated. The resulting brown residue was azeotroped with benzene (2 × 5 mL) to ensure removal of H_2O then concentrated *in vacuo*. Purification by preparative TLC (elution with 30% EtOAc/pentane then 70% EtOAc/pentane containing 5% ethanol) afforded 17 mg (0.034 mmol, 61%) of the title compound, a colorless glass which solidified on standing to give an amorphous white solid: R_f 0.49 (50% EtOAc/CH_2Cl_2), 0.34 (40% pentane/THF), 0.28 (15% hexanes/Et_2O); $[\alpha]^{23}_D$ −300.6° (*c* 0.40, $CHCl_3$) (lit.[1b] $[\alpha]_D$ −328° (*c* 1.0, $CHCl_3$)); IR (thin film from $CHCl_3$) 3420, 3240, 2910, 2875, 1710, 1640, 1460, 1380, 1120, 1040, 970 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.88 (br s, 1 H, NH), 6.98 (ddd, 1 H, J = 2.8, 2.5, 1.2 Hz, C_{25}-H), 6.88 (ddd, 1 H, J = 3.3, 2.4, 1.3 Hz, C_{23}-H), 6.23 (dt, 1 H, J = 3.3, 2.6 Hz, C_{24}-H), 5.95 (d, 1 H, J = 10.1 Hz, C_{14}-H), 5.91 (d, 1 H, J = 11.0 Hz, C_9-H), 5.78 (dd, 1 H, J = 14.6, 10.9 Hz, C_{10}-H), 5.47 (dt, 1 H, J = 9.9, 2.4 Hz, C_{13}-H), 5.40 (dd, 1 H, J = 14.7, 8.9 Hz, C_{11}-H), 4.16 (br d, 1 H, J = 3.9 Hz, C_7-H), 3.83 (dd, 1 H, J = 9.6, 4.6 Hz, C_3-H), 3.38 (dd, 1 H, J = 9.9, 6.2 Hz, C_{20}-H), 3.31–3.27 (m, 1 H, C_{12}-H), 2.85 (qd, 1 H, J = 6.9, 4.5 Hz, C_2-H), 1.97–1.85 (m, 5 H, C_8-CH_2CH_3 and C_8-H and one of C_{17}-H and one of C_{18}-H and C_{19}-H), 1.78–1.66 (m, 4 H, one of C_{16}-CH_2CH_3 and one of C_5-H and one of C_4-H and one of C_8-CH_2CH_3), 1.62–1.55 (m, 2 H, one of C_5-H and C_{15}-H), 1.47–1.36 (m, 2 H, C_{16}-H and C_4-H), 1.30–1.20 (m, 1 H, one of C_{17}-H), 1.18–1.11 (m, 1 H, one of C_{16}-CH_2CH_3), 1.15 (d, 3 H, J = 7.0 Hz, C_2-CH_3), 1.06–0.99 (m, 1 H, one of C_{18}-H), 0.91 (t, 3 H, J = 7.2 Hz, C_{16}-CH_2CH_3), 0.82 (d, 3 H, J = 6.9 Hz, C_6-CH_3), 0.76 (t, 3 H, J = 7.4 Hz, C_{16}-CH_2CH_3), (CO_2H not observed); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.54, 179.41, 140.18, 132.42, 132.33, 129.41, 129.17, 126.86, 125.39, 124.88, 116.05, 110.18, 75.13, 74.42, 52.53, 49.80, 45.32, 43.78, 41.29, 40.58, 30.13, 29.64, 27.35, 27.14, 26.42, 22.71, 22.20, 14.15, 13.86, 13.48, 12.56; MS (EI) m/e (relative intensity) 493 (M^+, 5.0), 475 ($M^+ - H_2O$, 0.3), 464 ($M^+ - C_2H_5$, 2.0), 446 ($M^+ - H_2O - C_2H_5$, 0.3), 251 (2.0), 94 (100); exact mass calcd for $C_{31}H_{43}NO_4$ (M^+) requires 493.3192, found 493.3211.

Indanomycin Methyl Ester (Synthetic). Ethereal diazomethane (generated at 0 °C from 50% aqueous KOH and a solution of 1-methyl-3-nitro-1-nitrosoguanidine in Et_2O at 0 °C) was added to a solution of synthetic indanomycin (7.4 mg, 0.015 mmol) in 1.3 mL of Et_2O at 0 °C until analysis by TLC indicated that the acid was completely consumed. The reaction was warmed to ambient temperature and stirred for 30 min until the yellow color of the reaction mixture had dissipated. One drop of dilute acetic acid was added to ensure destruction of excess diazomethane and the mixture was concentrated *in vacuo*. Purification by flash chromatography (elution with 20% Et_2O/pentane) gave 6.9 mg (0.014 mmol, 91%) of indanomycin methyl ester as a colorless oil: R_f 0.37 (2:1 pentane–THF), 0.23 (25% Et_2O/hexanes), 0.48 (20% EtOAc/hexanes); $[\alpha]^{23}_D$ −160.3° (*c* 0.35, $CHCl_3$), for material prepared from natural X-14547A: $[\alpha]^{23}_D$ −166.8° (*c* 0.28, $CHCl_3$) (lit.[8a] $[\alpha]^{25}_D$ −174.6° (*c* 0.11, $CHCl_3$)); IR (thin film) 3550, 3020, 2960, 2930, 2875, 1730, 1645, 1540, 1460, 1435, 1410 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.54 (br s, 1 H, NH), 6.99 (ddd, 1 H, J = 2.8, 2.5, 1.2 Hz, C_{25}-H), 6.86 (ddd, 1 H, J = 3.3, 2.4, 1.3 Hz, C_{23}-H), 6.25 (dt, 1 H, J = 3.3, 2.6 Hz, C_{24}-H), 5.95 (d, 1 H, J = 9.9 Hz, C_{14}-H), 5.83 (d, 1 H, J = 10.9 Hz, C_9-H), 5.74 (dd, 1 H, J = 14.4, 11.0 Hz, C_{10}-H), 5.49 (dt, 1 H, J = 10.0, 3.0 Hz, C_{13}-H), 5.39 (dd, 1 H, J = 14.8, 8.9 Hz, C_{11}-H), 4.09 (br d, 1 H, J = 4.2 Hz, C_7-H), 3.71 (dd, 1 H, J = 9.5, 4.7 Hz, C_3-H), 3.64 (s, 3 H, CO_2CH_3), 3.37 (dd, 1 H, J = 10.9, 6.7 Hz, C_{20}-H), 3.35–3.31 (m, 1 H, C_{12}-H), 2.76 (qd, 1 H, J = 6.9, 4.7 Hz, C_2-H), 2.03–1.90 (m, 4 H, C_8-CH_2CH_3 and one of C_5-H and C_{19}-H), 1.92–1.80 (m, 3 H, one of C_{17}-H and C_6-H and C_4-H), 1.74–1.65 (m, 3 H, one of C_{16}-CH_2CH_3 and C_{18}-H and one of C_8-CH_2CH_3), 1.61–1.54 (m, 2 H, one of C_5-H and C_{15}-H), 1.48–1.42 (m, 1 H, one of C_4-H), 1.31–1.02 (m, 4 H, one of C_{17}-H and one of C_{16}-CH_2CH_3 and one of C_{18}-H and C_{16}-H), 1.08 (d, 3 H, J = 6.9 Hz, C_2-CH_3), 0.92 (t, 3 H, J = 7.4 Hz, C_{16}-CH_2CH_3), 0.81 (d, 3 H, J = 7.2 Hz, C_6-CH_3), 0.76 (t, 3 H, J = 7.4 Hz, C_{16}-CH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.92, 176.16, 140.04, 132.61, 132.50, 129.37, 129.35, 127.21, 125.20, 124.23, 114.90, 110.11, 75.79, 73.78, 52.56, 51.67, 49.86, 45.38, 43.80, 42.58, 40.64, 31.57, 29.74, 27.36, 27.29, 26.94, 24.30, 22.37, 14.90, 13.99, 13.51, 12.56; MS (EI) m/e (relative intensity) 507 (M^+, 13), 478 ($M^+ - C_2H_5$, 7.9), 254 (7.2), 94 (100); exact mass calcd for $C_{32}H_{45}NO_4$ (M^+) requires 507.3348, found 507.3345.

Indanomycin Methyl Ester (Authentic). A solution of an authentic sample of indanomycin (5.2 mg, 0.011 mmol) in 1.3 mL of Et_2O at 0 °C was treated with an excess of ethereal diazomethane as described above. Purification by flash chromatography (elution with 20% Et_2O/pentane) gave 4.7 mg (0.010 mmol, 93%) of indanomycin methyl ester as a colorless oil which was identical (^1H and ^{13}C NMR, IR, MS, R_f) to the synthetic material previously prepared: $[\alpha]^{23}_D$ −160.3° (*c* 0.35, $CHCl_3$); compare $[\alpha]^{23}_D$ −166.8° (*c* 0.28, $CHCl_3$) for synthetic material above.

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Supplementary Material Available: Experimental procedures and physical data for intermediates leading to the preparation of dioxanone **21** and vinylstannane **38** and ^1H NMR spectra of **1-3, 5, *epi*-5, 13, 19a-d, 24a, 26, 27, 30b, 31, 35a, 37a, 38, 40-42**, and X-14547A methyl ester (42 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.