α-Methyldeoxybenzoin (4) was prepared according to ref 26: NMR δ 1.58 (d, 3 H), 4.60 (q, 1 H).

α-Methylbenzoin (6) was prepared according to ref 27: NMR δ 1.87 (s, 3 H).

Bidesyl (3)[28] was characterized as the only product resulting from reaction of 1 under N_2 (IR, TLC). The NMR spectrum exhibited two singlets at δ 5.40 and 5.78 of nearly equal intensity, which together integrated to 1/10th of the aromatic signal. The two signals are believed to arise from the meso and *d,l* diastereomers, and no attempt was made to elucidate the correct assignment. The mp of the mixture (259–260 °C) corresponds closely to the 256–257 °C value reported in the literature for one of the diastereomers (the other melts at 158–159 °C).[29]

The dimethyl congener of bidesyl (5) was not characterized fully, although it does not appear to have been reported previously. It was obtained as the sole product (TLC) from reaction of 4 under N_2 and exhibited two singlets in the NMR (δ 1.70 and 3.20, together integrating as 3/10ths of the aromatic signal), believed to arise from the two possible diastereomers (meso and *d,l*).

4,4′-Dimethyldeoxybenzoin (see footnote 12) was prepared according to ref 30 and the 4,4′-dimethylbenzil used was that obtained as the neutral product of Cu(II)–O_2 oxidation of the corresponding deoxybenzoin.

All other materials were ACS reagent grade. The methanol used as solvent contained 0.1% water.

Reaction Procedure. Reactions were initiated by the addition of the organic substrate to the remaining ingredients, preequilibrated with and maintained under either N_2 or O_2. For reactions conducted at greater than 1 atm of O_2, a pressure bottle (Parr) was fitted with a one-hole neoprene stopper containing a copper tube insert and connected via a pressure gauge to the O_2 source. All reactions were worked up by addition of aqueous 3 N HCl to pH 1, evaporation of the methanol in vacuo, and extraction with 1:1 $CHCl_3$–CCl_4 (the use of CCl_4 effectively prevented the extraction of both py·HCl and Et_3N·HCl into the organic layer).

Quantitative Product Determination. The benzoic acid was removed from the $CHCl_3$–CCl_4 extract by extracting with aqueous $NaHCO_3$, reacidifying, and extracting into $CHCl_3$. Evaporation of the solvent in a preweighed flask gave the yield of benzoic acid (no contaminants could be detected by TLC, IR, or NMR). The initial organic extract was subsequently evaporated in vacuo in a preweighed flask, giving the combined weight of the remaining product(s): 2 or (2 + 3) in experiments with 1 (no other materials could be detected by TLC or NMR). Individual yields of 2 and 3 were determined from the integration of the aliphatic protons of 3 (two isomers) relative to that of the aromatic protons. For the quantitative determination of benzaldehyde, the removal of MeOH after the initial acidification was conducted in vacuo with a cold finger apparatus cooled with dry ice in 2-propanol. The condensate was treated with 2,4-dinitrophenylhydrazine, and the resulting hydrazone derivative was filtered, washed, dried, and weighed. It ran as a single spot on TLC and had mp 236–238 °C (lit.[31] mp 237 °C). A control study established that this sequence of azeotropic distillation followed by derivatization resulted in a 98% isolated yield.

Registry No. 1, 451-40-1; 2, 134-81-6; *meso*-3, 21072-57-1; (±)-3, 81176-44-5; 4, 2042-85-5; *meso*-5, 91112-28-6; (±)-5, 91112-29-7; 6, 5623-26-7; PhCHO, 100-52-7; $PhCO_2H$, 65-85-0; $PhCOCH_3$, 98-86-2; Cu^{2+}, 15158-11-9; Et_3N, 121-44-8; MeOH, 67-56-1; O_2, 7782-44-7; $Cu(NO_3)_2py_2$, 14842-51-4; *p*-$MeC_6H_4COCOC_6H_4$-*p*-Me, 3457-48-5; *p*-$MeC_6H_4CH_2COC_6H_4$-*p*-Me, 51490-06-3; *p*-MeC_6H_4CHO, 104-87-0; *p*-$MeC_6H_4CO_2H$, 99-94-5; $Cu(NO_3)_2$, 3251-23-8; py, 110-86-1.

(25) Biagetti, R. V.; Battjer, W. G.; Haendler, H. M. *Inorg. Chem.* **1966**, *5*, 379.
(26) Pomerantz, M.; Witherup, T. H. *J. Am. Chem. Soc.* **1973**, *95*, 5977.
(27) Heine, H. G. *Liebigs Ann. Chem.* **1970**, *735*, 56.
(28) Lutz, R. E.; Dickerson, C. L.; Welstead, W. J.; Bass, R. G. *J. Org. Chem.* **1963**, *28*, 711.
(29) Pailer, M.; Muller, U. *Monatsh. Chem.* **1948**, *79*, 615.
(30) Newman, M. S.; George, M. V. *J. Org. Chem.* **1961**, *26*, 4306.
(31) Shriner, R. L.; Fuson, R. C. "Identification of Organic Compounds", 3rd ed.; Wiley: New York, 1948.

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

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The total synthesis of the ionophore antibiotic X-14547A (indanomycin) (1) is described by using a convergent strategy. 2-Ethylvalerolactone was converted into ethyl (*E,E,E*)-11-[[(β-methoxy)ethoxy]methoxy]-6-ethyl-2,7,9-undecatrienoate (8) in eight steps. Intramolecular Diels–Alder reaction of 8 at 110 °C followed by deprotection to give the racemic tricyclic lactone 7 proceeded with very high stereoselectivity (>90%) and in 38% overall yield from 2-ethylvalerolactone. The tricyclic lactone 7 was resolved via the diastereomeric amides 24 and 25 to provide the optically pure lactones 26 and 27. Reaction of 7 with 1-pyrrolylmagnesium bromide gave the pyrrolylcarbonyl derivative 28 whose structure was determined by X-ray crystallography. Alternatively, the optically pure lactone 26 was reacted with 2-lithio-1-[[(β-trimethylsilyl)ethoxy]methyl]pyrrole to give the corresponding *N*-SEM protected pyrrolylcarbonyl 32. Elaboration of 32 afforded the phenylsulfone 34 which constituted an appropriate right-hand fragment suitable for later coupling. Synthesis of the left-hand tetrahydropyranyl α,β-unsaturated aldehyde 3 was achieved by using levoglucosan (1,6-anhydro-β-D-glucopyranose) as the starting material. Coupling of 3 with the lithio anion from 34 followed by trapping with benzoyl chloride gave the benzoyloxy phenyl sulfones 57. Reduction of these with sodium amalgam stereoselectively afforded the *E,E*-diene 58. The synthesis was completed by deprotection and hydrolysis to afford the antibiotic X-14547A (indanomycin).

Naturally occurring ionophore antibiotics, with their wide range of structural and stereochemical features, continue to provide challenging synthetic targets. As a result of the complexity of these molecules structural determinations have been slow, and total syntheses have only recently been achieved.[1] In 1978 a new polyether iono-

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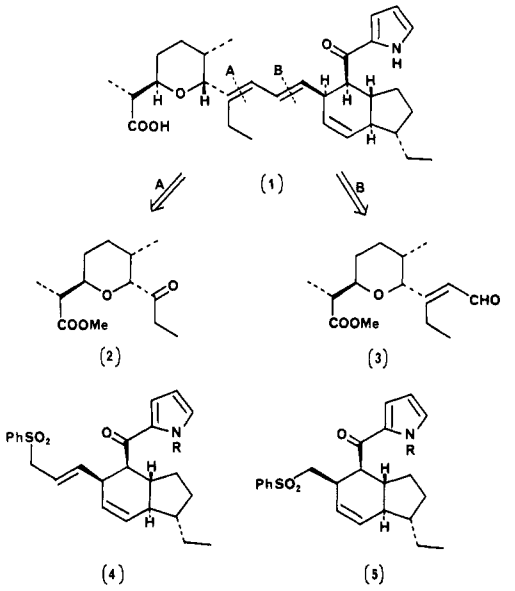
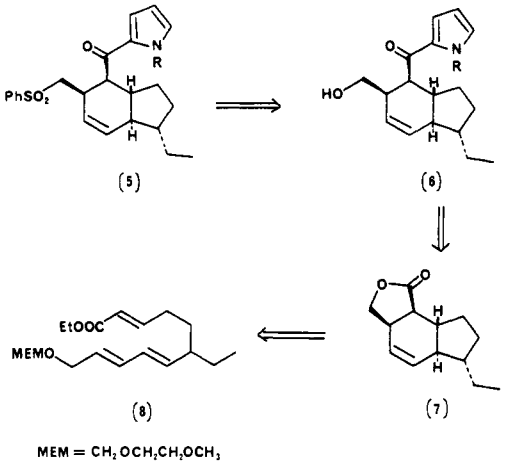
Scheme I



Scheme II



phore antibiotic was isolated by chemists at Hoffmann La-Roche, Nutley, NJ, from a culture of *Streptomyces antibioticus* (NRRL 8167).[2] Designated the number X-14547A and now known as indanomycin[3] the antibiotic is active in vitro primarily against Gram-positive bacteria, possessing a spectrum of activity similar to that of other polyether antibiotics. As an ionophore indanomycin facilitates the extraction of both monovalent and divalent cations from an aqueous solution into a nonmiscible organic solvent. The particular ability of transporting divalent cations, such as Ca^{+2} and Rb^{+2}, is unusual and is shared with only a few other carboxylic acid ionophores (such as lasalocid, calcimycin, ionomycin, lysocellin). Indanomycin also exhibits antitumor and antihypertensive properties, and is effective as a growth promotant for ruminants, increasing the feed utilization of these animals.[4] The acute toxicity in the mouse (LD_{50} 129 mg/kg po) is in the middle of the range of polyether toxicities.[5]

The structure and absolute configuration of indanomycin was determined by Westley et al. by X-ray analysis of a crystal of the derived (*R*)-(+)-1-amino-1-(4-bromophenyl)ethane salt, which is surprisingly formed in a 2:1 antibiotic:amine ratio.[2] Indanomycin (1) is novel in that it is only the second example of a trans-fused tetrahydroindan from natural sources (the other being ircinianin[6]). Although the tetrahydropyran A ring is similar to that of many of the other polyether antibiotics (e.g., salinomycin) the 1(*E*),3(*E*)-butadienyl unit encompassing C-8 to C-11 has not hitherto been observed.[7] The pyrrolylcarbonyl functionality is found in only a few other ionophores of the calcimycin type,[8] molecules which also show particular specificity and transport ability for divalent cations.

The presence of the 1(*E*),3(*E*)-butadienyl unsaturation facilitates a convergent synthesis of indanomycin (1) via coupling of a left-hand fragment (containing the four asymmetric centers of the tetrahydropyranyl-2-acetic acid moiety) and an N-protected right-hand fragment (containing the five asymmetric centers of the tetrahydroindanyl ring system) by a stereospecific olefination reaction and subsequent deprotection of the pyrrole nitrogen. Each of the two possible coupling modes indicated by A and B in Scheme I relies on the coupling of nucleophilic right-hand fragments **4** and **5** with appropriate electrophilic left-hand units **2** and **3**. This route was chosen as we anticipated that these left-hand fragments might also be available by degradation of the natural product.

A most promising coupling route appeared to be the Lythgoe modification of the Julia olefin synthesis.[9] Anions derived from α,β-unsaturated diphenylphosphine oxides had been shown to be effective in the preparation of *E*,*E*-1,3-dienes in reactions with ketones,[10] and although yields of conjugated dienes in reactions with α,β-unsaturated aldehydes were less satisfactory,[11] it was considered that the anion derived from the right-hand sulfone **5** should undergo smooth reaction with the α,β-unsaturated aldehyde **3**[12] and with a high degree of stereoselectivity to give the desired *E*,*E*-1,3-diene unit, after elimination of

(1) Wierenga, W. In "The Total Synthesis of Natural Products"; ApSimon, J., Ed.; Wiley-Interscience: New York, 1981; Vol 4, 263. Dobler, M, "Ionophores and their Structures"; Wiley-Interscience: New York 1981. Hilgenfeld, R.; Saenger, W. "Topics in Current Chemistry Host Guest Complex Chemistry II"; Springer-Verlag: New York, 1982; No. 101. "Polyether Antibiotics", Westley, J. W., Ed.; Marcel Dekker: New York and Basel, 1983; Vol. 1 and 2.

(2) Westley, J. W.; Evans, R. H., Jr.; Liu, C.; Hermann, T.; Blount, J. F. *J. Am. Chem. Soc.* **1978**, *105*, 6784. Westley, J. W.; Evans, R. H., Jr.; Sello, L. H.; Troupe, N.; Liu, C.; Blount, J. F. *J. Antibiot.* **1979**, 100.

(3) Following discussions with Dr. J. W. Westley, Hoffmann La-Roche, we propose the name indanomycin for this structurally unique ionophore.

(4) Liu, C.; Hermann, T. E.; Liu, M.; Bull, D. N.; Palleroni, N. J.; Prosser, B. La T.; Westley, J. W.; Miller, P. A., *J. Antibiot.* **1979**, 95.

(5) Westley, J. W. *Adv. Appl. Microbiol.* **1977**, *22*, 177.

(6) Hofheinz, W.; Schönholzer, P. *Helv. Chim. Acta* **1977**, *60*, 1367.

(7) Indanomycin numbering system is used throughout this discussion for clarity.

(8) Chaney, M. O.; Demarco, P. V.; Jones, N. D.; Occolowitz, J. L. *J. Am. Chem. Soc.* **1974**, *96*, 1932. David, L.; Kergomard, A., *J. Antibiot.* **1982**, 1409.

(9) Kocienski, P. J.; Lythgoe, B. *J. Chem. Soc., Perkin Trans. 1*, **1980**, 1400. Kocienski, P. J.; Lythgoe, B.; Waterhouse, I. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1045. Lythgoe, B.; Waterhouse, I. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2429. Kocienski, P. J.; Lythgoe, B.; Roberts, D. A. *J. Chem. Soc., Perkin Trans. 1* **1978**, 834. Kocienski, P. J.; Lythgoe, B.; Ruston, S. *J. Chem. Soc., Perkin Trans. 1* **1978**, 829.

(10) Lythgoe, B.; Moran, T. A.; Nambudiry, M. E. N.; Rushton, S. *J. Chem. Soc. Perkin Trans. 1* **1976**, 2386. Lythgoe, B.; Moran, T. A.; Nambudiry, M. E. N.; Tideswell, J.; Wright, P. W. *J. Chem. Soc., Perkin Trans. 1* **1978**, 590. Davidson, A. H.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1976**, 639. Schlosser, M.; Tuong, H. B. *Chimia* **1976**, *30*, 197.

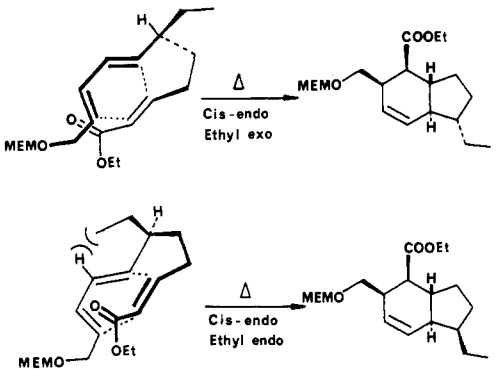
(11) Clough, J. M.; Pattenden, G. *Tetrahedron* **1981**, *37*, 3911.

(12) For previous synthetic studies on X-14547A see: (a) Edwards, M. P.; Ley, S. V.; Lister, S. G. *Tetrahedron Lett.* **1981**, *22*, 361. (b) Nicolaou, K. C.; Magolda, R. L. *J. Org. Chem.* **1981**, *46*, 1506. (c) Roush, W. R.; Myers, A. G. *Ibid.* **1981**, *46*, 1509. (d) Nicolaou, K. C.; Claremon, D. A.; Papahatjis, D. P. *Tetrahedron Lett.* **1981**, *22*, 4647. (e) Nicolaou, K. C.; Papahatjis, D. P.; Claremon, D. A.; Dolle, R. E., III *J. Am. Chem. Soc.* **1981**, *103*, 6967. (f) Nicolaou, K. C.; Claremon, D. A.; Papahatjis, D. P.; Magolda, R. L. *J. Am. Chem. Soc.* **1981**, *103*, 6969. (g) Ho, P-T. *Can. J. Chem.* **1982**, *60*, 90. (h) Roush, W. R.; Peseckis, S. M. *Tetrahedron Lett.* **1982**, *23*, 4879. (i) Edwards, M. P.; Ley, S. V.; Lister, S. G.; Palmer, B. D. *J. Chem. Soc., Chem. Commun.* **1983**, 630.

the intermediate benzoyloxy phenyl sulfones. Herein we report a successful total synthesis of (+)-indanomycin (1) based on this approach.

Synthesis of the Tetrahydroindan Sulfone (5). For synthesis of the sulfone 5 a route was chosen which entailed formation of the pyrrolylcarbonyl unit by reaction of a 2-lithio-N-protected pyrrole with the lactone 7 (Scheme II). It was thought that the lactone 7 could be prepared via an intramolecular Diels–Alder reaction of the *E,E,E*-triene ester 8.[13]

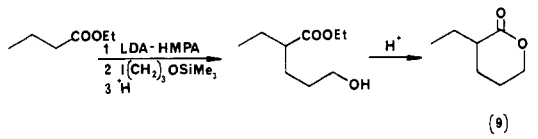
It was hoped that the required five chiral centers of 7 could be created in one step with correct relative stereochemistry via a more favored, least hindered endo cyclo-



addition, rather than the alternative more hindered endo cycloaddition mode.

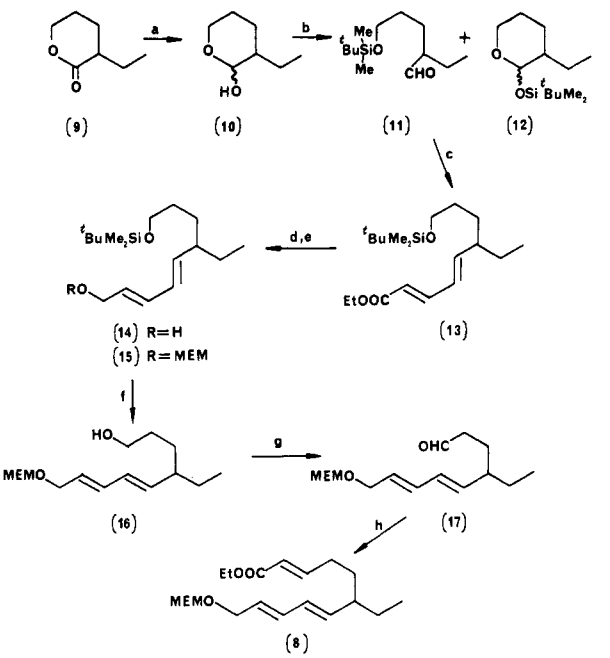
Ample precedent for such a proposal existed in the work of Roush,[14] who has subsequently published a number of detailed studies on these and related Diels–Alder cyclizations. In general, endo products are favored, with the highest ratio of endo to exo products being formed at lower reaction temperatures.

The main requirements for the synthesis of the triene 8 were two stereoselective trans olefination reactions and a suitable choice of alcohol protecting groups such that one could be selectively removed in the presence of the other (Scheme III). The starting material for the synthesis of 8 was 2-ethyl-δ-valerolactone (9). Material of high purity was best obtained by alkylation of ethyl butyrate with 1-[(trimethylsilyl)oxy]-3-iodopropane,[15] followed by acid-catalyzed cyclization of the crude hydroxy ester with *p*-toluenesulfonic acid in toluene. After careful optimization of reaction conditions, yields of up to 76% for 30–40-g batches of 2-ethyl-δ-valerolactone were achieved.[16]



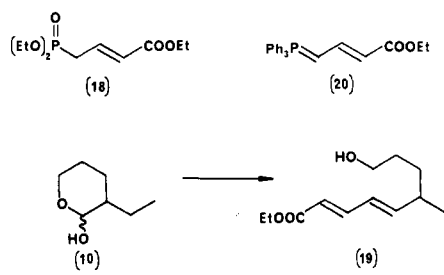
(9)

Scheme III



[a] (a) Dibal, −78 °C, toluene; (b) *tert*-butyldimethylsilyl chloride, imidazole/DMF, 2 h, room temperature; (c) ethyl 4-diethylphosphonocrotonate/LDA, −45 °C, room temperature over 2 h; (d) dibal, 0 °C, toluene; (e) β-methoxyethoxymethyl chloride, diisopropylethylamine, 2 h, room temperature; (f) tetra-*n*-butylammonium fluoride, THF, 20 min; (g) chromium trioxide/pyridine; (h) ((carbethoxy)methylene)triphenylphosphorane, CH_2Cl_2, room temperature 7 h.

Diisobutylaluminium hydride reduction of lactone 9 afforded a quantitative yield of 2-ethyl-δ-valerolactol 10, as a 1.3:1 mixture of anti ($J_{AB} \simeq 7$ Hz) and syn ($J_{AB} \simeq 0$ Hz) diastereomers. The lactols were found to be remarkably unreactive toward the anion of ethyl 4-(diethoxyphosphinyl)crotonate (18).



At temperatures of up to 0 °C only small amounts of the (*E,E*)-hydroxy dienoate 19 were formed, while under forcing conditions (DMF, 60–120 °C) up to 23% yields of 19 could be prepared by reaction of the lactols 10 with the ylid [3-(ethoxycarbonyl)allylidene]triphenylphosphorane (20). In another approach the lactols 10 were quantitatively converted into a mixture of the desired silyl-protected aldehyde 11 and the lactol silyl ether 12 (ratio 2-3:1) by treatment with *tert*-butyldimethylchlorosilane and imidazole in DMF. Flash chromatography gave yields of 67–80% of the aldehyde 11, based on lactols 10 recovered

(13) For recent reviews see: Carlson, R. G. *Annu. Rep. Med. Chem.* **1974**, *9*, 270. Mehta, G. *J. Chem. Ed.* **1976**, *53*, 551. Oppolzer, W., *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10. Brieger, G.; Bennett, J. N. *Chem. Rev.* **1980**, *80*, 63. Kametani, T. *Pure Appl. Chem.* **1979**, *51*, 747. Kametani, T.; Nemoto, H. *Tetrahedron* **1981**, *37*, 3. Oppolzer, W. *Synthesis* **1978**, 793. Oppolzer, W. In "New Synthetic Methods"; Verlag Chemie: Weinheim and New York, 1979; Vol. 6, p 1. Oppolzer, W. *Heterocycles* **1980**, *4*, 1615. Funk, R. L.; Vollhardt, K. P. C. *Chem. Soc. Rev.* **1980**, *9*, 41. Vollhardt, K. P. C. *Ann. N.Y. Acad. Sci.* **1980**, *333*, 241. Ciganiek, E. "Organic Reactions"; J. Wiley: New York, in press.

(14) See, for example (and references therein): Roush, W. R. *J. Am. Chem. Soc.* **1980**, *102*, 1309. Roush, W. R.; Ko, A. I.; Gillis, H. R. *J. Org. Chem.* **1980**, *45*, 4264. Roush, W. R.; Gillis, H. R. *J. Org. Chem.* **1980**, *45*, 4267. Roush, W. R.; Gillis, H. R.; Ko, A. I. *J. Am. Chem. Soc.* **1982**, *104*, 2269. Roush, W. R.; Hall, S. E. *J. Am. Chem. Soc.* **1981**, *103*, 5200.

(15) The iodide was prepared in 82% overall yield from commercially available 3-chloropropan-1-ol by silylation of crude 3-iodopropan-1-ol (prepared by chloride displacement with sodium iodide in refluxing acetone).

(16) In our hands direct alkylation of δ-valerolactone with varying amounts of LDA in THF at temperatures of up to −20 °C followed by quenching with various amounts of ethyl iodide in HMPA, following the procedure of Schlessinger,[17] led to inferior yields of product.

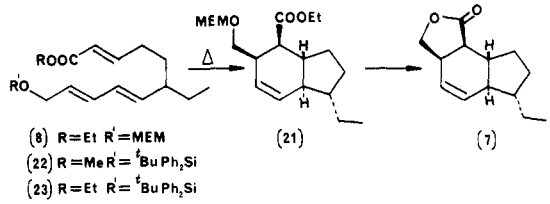
(17) Cregge, R. J.; Hermann, J. L.; Lee, C. S.; Richman, J. E.; Schlessinger, R. H. *Tetrahedron Lett.* **1975**, *16*, 2425.

after quantitative desilylation of the unwanted silylated lactols **12**. Losses occurred due to the volatility of both **11** and **12**.

Reaction of the anion formed from ethyl 4-(diethoxyphosphinyl)crotonate (**18**) with freshly prepared aldehyde **11** gave a 97% yield of the required *E,E*-dienoate **13**, contaminated with 2–3% of the *Z,E*-isomer and a trace (<1%) of the *Z,Z*-isomer. The *E,E*-dienoate **13** was smoothly reduced with 2.2 equiv of diisobutylaluminum hydride to give the unstable allylic alcohol **14**. Immediate protection of crude **14** with MEM–chloride gave the diprotected *E,E*-dienediol **15** in 96% overall yield from the ester **13**. Selective monodeprotection of **15** to give **16** was accomplished in quantitative yield and completed the exchange of protection from one end of the diol to the other. Trans-olefin coupling constants $J_{2,3}$ and $J_{4,5}$ of 15 Hz in the high-field ^{1}H NMR spectrum of **16** clearly established the *E,E*-stereochemistry of the diene.

In situ Collins oxidation cleanly and quantitatively converted the alcohol **16** into the aldehyde **17**.[18] The crude aldehyde was treated with (carbethoxymethylene)triphenylphosphorane to give the required *E,E,E*-trienoate **8** in 95% yield. The ^{1}H NMR coupling constant of 16 Hz for the olefinic protons of the α,β-unsaturated ester confirmed the expected *E* stereochemistry of the newly formed double bond. No *E,E,Z*-isomer was detected from this reaction.

When the *E,E,E*-trienoate was heated in refluxing toluene smooth reaction occurred to give the tetrahydroindan **21**, resulting from the desired endo cyclization. This material was contaminated with less than 10% of other possible cyclization products.



Treatment of **21** with concentrated hydrochloric acid under phase-transfer conditions resulted in removal of the MEM-protecting group and concomitant lactonization to provide the desired lactone **7** in 65% yield.[19] This lactone **7** was identical with that prepared by Nicolaou[12b] and structurally confirmed by X-ray crystallography. Nicolaou[12b] also prepared the lactone **7** by intramolecular Diels–Alder cyclization of the silyl-protected trienoate **22**. In this case the reaction afforded a 70:15 ratio of endo to exo isomers, and this was confirmed in the present work when the analogous silylated ester **23** was prepared and cyclized to give a 7:2 mixture of endo to exo products. Thus there is a notable difference between the intramolecular Diels–Alder reactions of the MEM- and TBDPS-protected trienoates: in the former case there is a significantly greater (at least 9:1) selectivity for the endo trans-fused tetrahydroindan product over the exo cis-fused compound.[21]

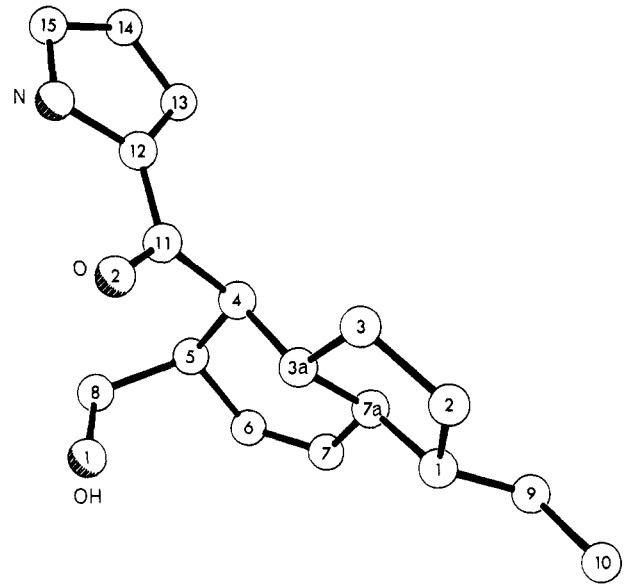
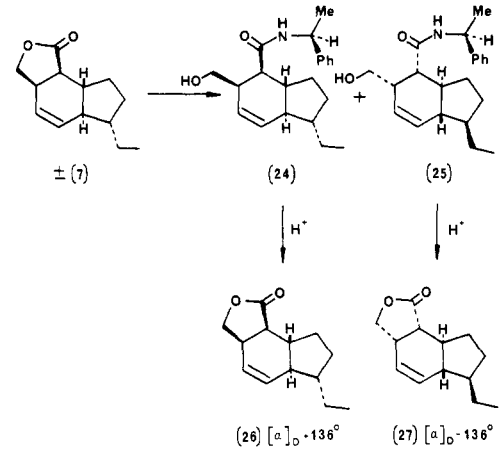


Figure 1. The molecular structure of **28**.

With the racemic tetrahydroindan lactone **7** now readily available, methods for resolving this material and for converting the enantiomer of natural configuration efficiently into the sulfone **5** were investigated.[23] When the procedure of Helmchen and Youssef[25] was followed, the lactone **7** was treated with (–)-1(*S*)-phenylethylamine and 2-hydroxypyridine to give the diastereomeric amides **24** and **25**. This reaction appeared to reach equilibrium at



60–70% conversion—all attempts at improving the yield of the amides were unsuccessful. The amides were isolated in almost quantitative yield (based on recovered lactone **7**) after simple flash chromatography. Effective resolution of the lactone was completed by treatment of the amides

(18) PCC or PDC gave only 74% and 72% yields of aldehyde **17**, respectively.

(19) The MEM-protecting group could also be removed to give the lactone **7** by using $ZnBr_2$ in yields of approximately 60%. This reaction, however, proved to be capricious and often failed to proceed at all. The recommended procedure[20] of treatment with $TiCl_4$ led to complete decomposition of starting material.

(20) Corey, E. J.; Gras, J-L.; Ulrich, P. *Tetrahedron Lett.* **1976**, *17*, 809.

(21) Roush[14] has recently observed dramatic effect in Lewis acid-catalyzed intramolecular Diels–Alder reactions of methyl (*E,E,E*)-deca-2,7,9-trienoates. In the present work $AlCl_3$ proved ineffective as a catalyst and while $EtAlCl_2$ led to cyclization, this was accompanied by considerable decomposition of material. With the milder Lewis acid, Et_2AlCl much cleaner cyclizations were achieved, although a maximum conversion of only 75% could be obtained even after prolonged reaction times. Other workers[14,22] have reported difficulties in catalyzing Diels–Alder reactions of trienes incorporating ether functionality.

(22) Parker, K. A.; Adamchuk, M. R. *Tetrahedron Lett.* **1978**, *19*, 1689.

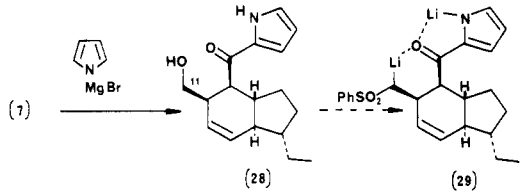
(23) An attempted enantioselective synthesis of lactone **7** starting from optically pure 2-ethyl-δ-valerolactone[24] was unsuccessful due primarily to problems in preparing large quantities of starting material of sufficiently high optical purity.

(24) For example: Meyers, A. I.; Yamamoto, Y.; Mihelich, E. D.; Bell, R. A. *J. Org. Chem.* **1980**, *45*, 2792.

(25) Helmchen, G.; Nill, G.; Flockerzi, D.; Youssef, M. S. K. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 63.

with 1 N sulfuric acid which afforded the optically active lactones **26** and **27** as crystalline solids, mp 83–84 °C, $[\alpha]^{25}_D$ ±136°. Assignment of lactone **26** as the enantiomer with correct natural absolute configuration was based on the results of Nicolaou,[12] who reported a rotation of +113° for material with an enantiomeric excess of 82%. Our samples of the resolved lactones (+)-**26** and (−)-**27** were thus, as expected, of very high optical purity (ca. 99% ee).

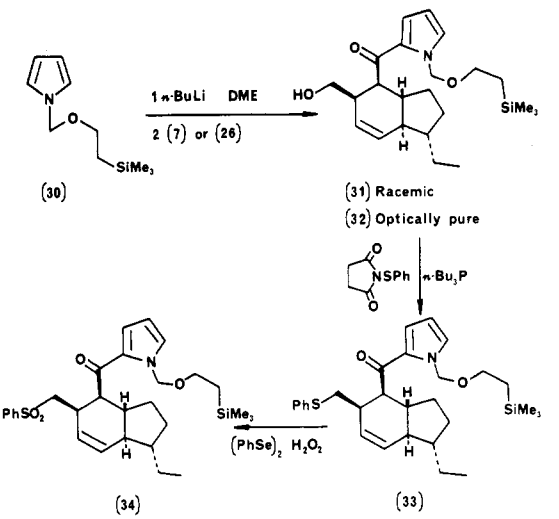
Initial attempts at introducing the pyrrolylcarbonyl functionality were carried out by using racemic lactone **7**. Reaction with pyrrolylmagnesium bromide[26] proceeded smoothly at 100 °C to give the crystalline hydroxy pyrrolylcarbonyl **28** in 94% yield. An X-ray crystallographic



analysis of this material confirmed the stereochemistry at all five chiral centers[27] (Figure 1). An initial plan, involving the use of dianion **29** derived from the sulfone **5** necessitated manipulation of the hydroxyl functionality of **28**. The intention was to create the phenylsulfone functionality in a standard fashion by chemoselective oxidation of a phenylsulfide, to be prepared by displacement of a leaving group at C-11. Surprisingly, however, it was found impossible to prepare a compound with the desired leaving group at C-11 via tosylation of the hydroxyl group in **28**. This result was tentatively attributed to interference in the reaction by the pyrrole nitrogen, and we therefore turned our attention to systems containing an N-protected pyrrole unit.

The first attempts at developing synthetically useful 2-lithio-N-protected pyrroles have appeared only very recently[28] and at the time there seemed to be no suitable reagent available for our purposes. Sundberg and Russell[29] had found that good yields of 2-indolylcarbonyls could be produced by using 2-lithio-*N*-(methoxymethyl)indole. We considered that the structurally similar [(β-trimethylsilyl)ethoxy]methyl (SEM) group, not previously used for N–H protection, could be the ideal protecting group for our purpose. Accordingly, *N*-SEM–pyrrole (**30**) was readily prepared in 60–70% yield by quenching sodiopyrrole with SEM chloride.

The pyrrole **30** was cleanly lithiated at the 2-position by treatment with *n*-butyllithium in DME, and subsequent reaction with the lactone **7** gave the expected product **31** in yields of 50–60% (up to 71% based on recovered lactone **7**).[30,32] The optically pure (*N*-SEM–pyrrolyl)carbonyl (−)-**32** was prepared in 62% yield, as before, by treatment

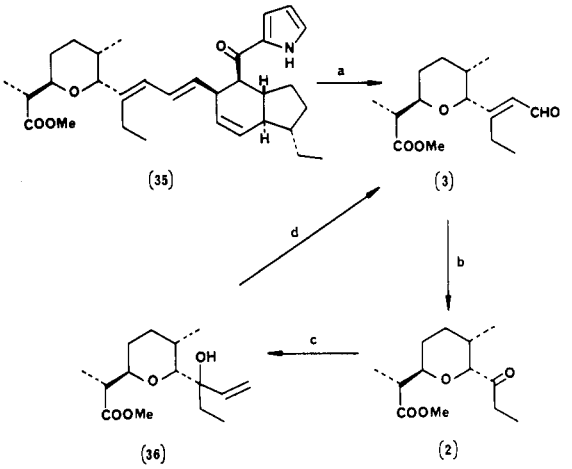


of the resolved lactone **26** with 2-lithio-*N*-SEM–pyrrole. Reaction of alcohol **32** with tri-*n*-butylphosphine and *N*-(phenylsulfenyl)succinimide gave the sulfide **33** in 74% yield.

Finally, chemoselective oxidation of the sulfide **33** was achieved in excellent yield by using hydrogen peroxide and diphenyl diselenide,[34] to give the sulfone **34** via the intermediate diastereomeric sulfoxides (which were not isolated).

Thus the enantiomerically pure right-hand side sulfone (−)-**34** was easily prepared from lactone (+)-**26** in an efficient three-step process, and in up to 47% overall yield (based on converted starting material). The overall yield of the sulfone from 2-ethyl-δ-valerolactone was therefore up to 21%.

Synthesis of the Left-Hand Enal (3). Nicolaou[12b] reported that the unsaturated aldehyde **3** could be obtained from the natural product, albeit in low yield, by osmium-catalyzed periodate cleavage of indanomycin methyl ester (**35**). In our hands high yields of this com-



[a] (a) O_3, −78 °C, trace, HOAc; (b) O_3, −78 °C, trace HOAc; (c) vinylmagnesium bromide, −30 °C; (d) pyridinium chlorochromate, CH_2Cl_2, 40 °C 5 h.

pound, suitable for coupling studies with the right-hand sulfone **5** could best be obtained by careful ozonolysis of **35** at −78 °C. Further ozonolysis at −30 °C afforded the ketone **2**, again in high yield. Although Nicolaou's group failed to isolate **3** during ozonolysis of **35** they showed that

(26) Bean, G. P. *J. Heterocycl. Chem.* **1965**, *2*, 473.
(27) Contrary to the results of Bean[26] on the acylation of pyrryl Grignard reagents, the ester **17** was remarkably unreactive to pyrrylmagnesium bromide even under forcing conditions.
(28) Hasan, I.; Marinelli, E. R.; Chang Lin, L-C.; Fowler, F. W.; Levy, A. *J. Org. Chem.* **1981**, *46*, 157.
(29) Sundberg, R. J.; Russell, H. F. *J. Org. Chem.* **1973**, *38*, 3324.
(30) Significantly lower yields of **31** were obtained by using the lithiation conditions recommended by Chadwick[31] (*n*-BuLi, TMEDA) or *n*-BuLi/HMPA, apparently because of attack of *n*-butyllithium on the SEM group leading to *N*-lithiopyrrole and polymeric products.
(31) Chadwick, D. J.; Cliffe, I. A. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2845.
(32) Subsequent to our work Grieco[33] has developed an alternative reagent, *N*-(*N*,*N*-dimethylamino)pyrrole, for the preparation of 2-pyrrylcarbonyls.
(33) Martinez, G. R.; Grieco, P. A.; Srinivasan, C. V. *J. Org. Chem.* **1981**, *46*, 3760.
(34) Reich, H. J.; Chow, F.; Peake, S. L. *Synthesis* **1978**, 299. Nicolaou, K. C.; Magolda, R. L.; Sipio, W. L.; Barnette, W. E.; Lysenko, Z.; Joullié, M. M. *J. Am. Chem. Soc.* **1980**, *102*, 3784.

the ketone **2** could be converted into the enal **3** by simple addition of a vinyl Grignard reagent followed by oxidation (with concomitant allylic rearrangement) of the resultant vinyl alcohol **36**. These transformations have also been carried out in our laboratory. The synthetic target for the left-hand fragment of indanomycin thus reduces to the ketone **2**.

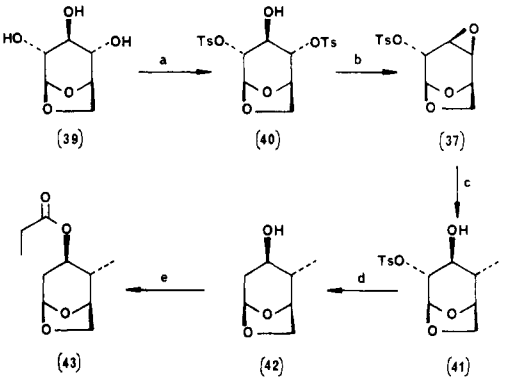
Carbohydrates are finding increasing utilization in the synthesis of complex natural products,[35] and by careful choice of stereospecific reactions involving chirality transfer we evisaged an efficient synthesis of ketone **2**, beginning from a readily available carbohydrate containing the intact pyran ring. The report[36] that sequential treatment of the epoxy tosylate **37** with vinylmagnesium chloride/cuprous iodide and lithium triethylborohydride gave the alcohol **38** in high yield led us to choose **37** as our starting material.

(37) (38)

We visualized an expedient route to the left-hand side ketone **2** from **37** in which the C-6 methyl group could be introduced in a similar fashion. It was anticipated that the Claisen ester–enolate rearrangement recently developed by Ireland[37] could be used to transfer chirality from C-5 to C-3 with stereospecific construction of the chiral propionic acid side chain at C-3.

Levoglucosan (**39**)[38] (1,6-anhydro-β-D-glucopyranose) was transformed, *via* the ditosylate **40**, into the epoxy tosylate **37** following literature procedures.[11] Conversion of the epoxide **37** into the methylated sugar **41** was achieved with some difficulty, and a wide variety of organometallic reagents were attempted before suitable conditions for the transformation were found.

Initial results were obtained by using copper(I)-catalyzed additions of methyl Grignard reagents, under conditions similar to those employed by Kelly and Roberts.[36] It was not until a large excess of stoichiometric cuprate (generated in situ from methylmagnesium chloride (20 equiv) and cuprous bromide–dimethyl sulfide (10 equiv)) was used over extended reaction times that acceptable yields (up

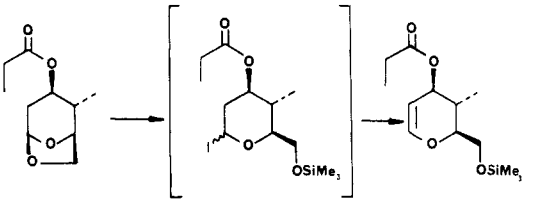


(39) (40) (37) (43) (42) (41)

[a] Ts = p-$MeC_6H_4SO_2$; (a) TsCl (2.0 equiv), pyridine, 20 °C, 48 h; (b) NaOMe, MeOH (5.0 equiv), 20 °C, 36 h; (c) MeMgCl (20.0 equiv), $CuBr \cdot SMe_2$ (10.0 equiv), THF, −10 °C, 4 days; (d) $LiBHEt_3$ (3.4 equiv), THF, 20 °C, 24 h; (e) n-BuLi (1.0 equiv), THF, −78 °C, then $MeCH_2COCl$ (1.05 equiv), 20 °C, 2 h.

to 86%) of **41** were obtained. Numerous results have established that such nucleophilic additions to the epoxy tosylate **37** proceed with the exclusive formation of trans-diaxial products, presumably as a result of the steric influence of the tosyl group.[42]

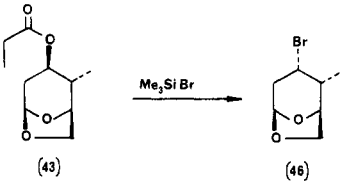
Reductive removal of the tosyl group of **41** was achieved in high yield by using lithium triethylborohydride, affording the alcohol **42** which was cleanly converted into the propanoate **43** by simple acylation. In order to use an



(43) (44) (45)

ester–enolate Claisen rearrangement to construct the tetrahydropyranylacetic acid side chain, it was necessary to cleave the 1,6-anhydrobridge of **43** and to introduce glycal unsaturation. After much experimentation this was achieved in one step by treatment of the anhydro sugar **43** with 3 equiv of in situ prepared iodotrimethylsilane. The presumed intermediate anomeric iodides **44** were not isolated but were treated directly with DBU to give the glycal **45** in yields of 50–75%.[43]

Although the reaction was accompanied by decomposition of both starting material and product, the use of less reagent resulted in significant reductions in the yield of **45**. When the less reactive bromotrimethylsilane was used, cleavage of the anhydro ester group occurred, leading cleanly to the unstable bromide **46**.



(43) (46)

Ireland has defined the conditions required for the stereospecific rearrangement of glycal esters such as **45**.[37]

(35) For reviews see: Hanessian, S.; Dixit, D. M.; Liak, T. *Pure Appl. Chem.* **1981**, *53*, 129. Hanessian, S. *Acc. Chem. Res.* **1979**, *12*, 159. Hanessian, S. *Pure Appl. Chem.* **1977**, *49*, 1201. Fraser-Reid, B.; Anderson, R. C. *Fortschr. Chem. Org. Naturst.* **1980**, *39*, 1. Fraser-Reid, B. *Acc. Chem. Res.* **1974**, *8*, 192. Vasella, A. In "Chiral Building Blocks in Enantiomer Synthesis-Ex Sugars"; Scheffold, R., Ed.; Salle and Sauerländer-Verlag: Frankfurt and Aaron, 1980; Vol. 2, p 173.

(36) Kelly, A. G.; Roberts, J. S. *J. Chem. Soc., Chem. Commun.* **1980**, 228.

(37) Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897. Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868. Ireland, R. E.; Thaisrivongs, S.; Vanier, N.; Wilcox, C. S. *J. Org. Chem.* **1980**, *45*, 48. Ireland, R. E.; Wilcox, C. S.; Thaisrivongs, S.; Vanier, N. R. *Can. J. Chem.* **1979**, *57*, 1743. Ireland, R. E.; Wuts, P. G. M.; Ernst, B. *J. Am. Chem. Soc.* **1981**, *103*, 3205. Ireland, R. E.; Daub, J. P. *J. Org. Chem.* **1981**, *45*, 479. Ireland, R. E.; Vevert, J.-P. *Can. J. Chem.* **1981**, *59*, 572. 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.

(38) Levoglucosan is readily available through controlled pyrolysis of starch.[39] However, we found hydrolysis of phenyl-β-D-glucoside in refluxing KOH[40] a more convenient procedure.

(39) Carlson, L. J. *U.S. Patent* 3 235 541, 1966; *Chem. Abstr.* **1966**, *64*, 16122f. Ward, R. B. In "Methods in Carbohydrate Chemistry"; Whistler, R. L., Wolfrom, M. L., Eds.; Academic Press: New York, 1963; Vol. II, p 394.

(40) Montgomery, E. M.; Richtmeyer, N. K.; Hudson, C. S. *J. Am. Chem. Soc.* **1943**, *65*, 3.

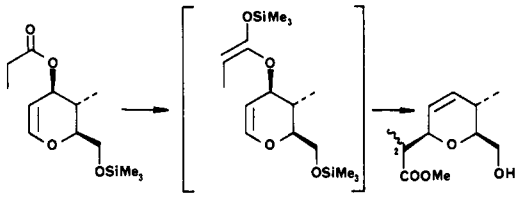
(41) Carlson, L. J. *J. Org. Chem.* **1965**, *30*, 3953. Černý, M.; Gut, V.; Pačak *Collect. Czech. Chem. Commun.* **1961**, *26*, 2542.

(42) Černý, M.; Staněk, J., Jr. *Adv. Carbohydr. Chem. Biochem.* **1977**, *34*, 23.

(43) For other examples of anomeric halide formation using trimethylsilyl halides see: Theim, J.; Meyer, B. *Chem. Ber.* **1980**, *113*, 3058, 3075. Gillard, J. W.; Israel, M. *Tetrahedron Lett.* **1981**, *22*, 513.

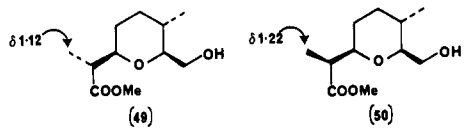
(44) Olah, G. A.; Narang, S. C. *Tetrahedron* **1982**, *38*, 2225. Schmidt, A. H. *Aldrichimica Acta* **1981**, *14*, 31 and references therein.

Assuming the rearrangement proceeds via a boat transition state,[37] formation of a product with the desired 2(*R*)-stereochemistry requires generation of a silyl ketene acetal **47** of *E*-geometry. Such geometries are obtained by en-



(45) (47) (48)

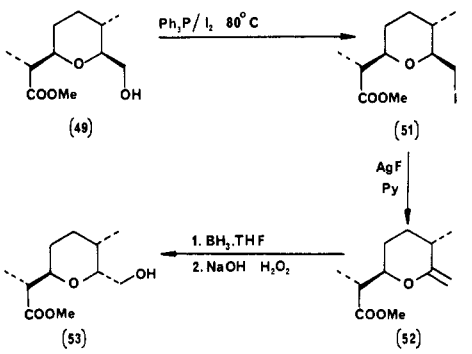
olization of the ester using LDA in the absence of HMPA, followed by trapping of the enolate with a chlorosilane. Treatment of the ester **45** with an excess of LDA followed by quenching with chlorotrimethylsilane gave the silyl ketene acetal **47**. This rearranged smoothly at 50 °C, and the product was worked up by using fluoride and diazomethane to give the unsaturated alcohols **48** in 73% yield, as a 5:1 mixture of C-2 epimers (^{1}H NMR analysis). The mixture **48** could not be separated chromatographically and was hydrogenated directly to afford the saturated alcohols **49** and **50**. The product was now readily separ-



(49) (50)

able by reversed-phase HPLC to give the alcohol **49** in 60% yield from the mixture **48** and the epimer **50** in 11% yield. Assignment of the major isomer as the desired 2(*R*)-alcohol **49** was tentatively made on the basis of the ^{1}H NMR chemical shifts of the C-2 methyl groups of **49** and **50** and the trend observed by Ireland in related examples,[37] and was later verified when the major component of the mixture was successfully converted into a degradation product of the natural antibiotic.

Inversion of the C-7 stereochemistry of the alcohol **49** was achieved via the exocyclic enol ether **52**. Thus



treatment of the iodide **51** with silver fluoride in pyridine[45] gave the desired olefin **52** without isomerization to the endocyclic isomer. It was anticipated that hydroboration of **52** would proceed from the opposite face of the molecule to the methyl group at C-6 to give predominantly the required alcohol **53** after oxidative workup. However, hydroboration using borane–methyl sulfide afforded an 80% yield of alcohols **49** and **53** in which the unwanted epimer **49** predominated (ratio 4:1). Use of the more sterically demanding reagent 9-BBN resulted in almost exclusive formation of the unnatural alcohol **49**. An explanation for this unexpected result could lie in the con-

(45) Helferich, B.; Himmen, H. *Chem. Ber.* **1928**, *61*, 1825.

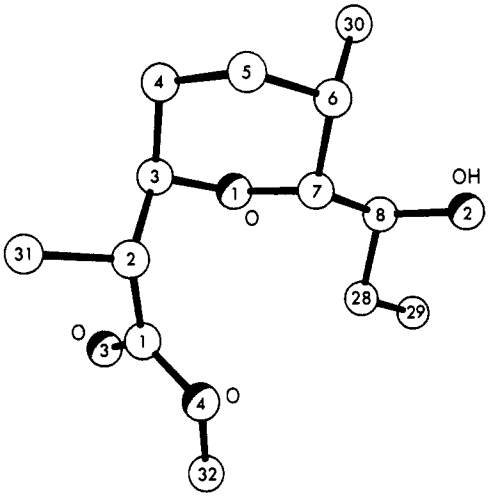
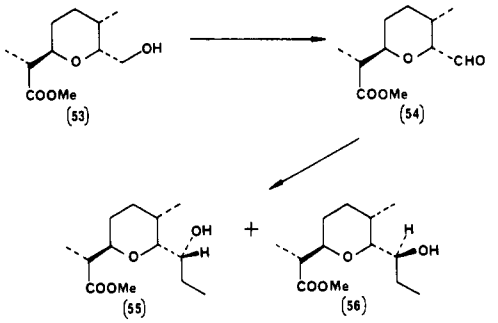


Figure 2. The molecular structure of **56**.

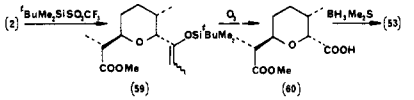
formation of the tetrahydropyran ring in the enol ether **52**. The magnitude of the coupling constants $J_{3,4} \simeq 6$, $J_{3,4} \simeq 4$ Hz observed in the ^{1}H NMR spectra of many of the left-hand synthetic intermediates suggests that in these compounds the propionic acid side chain at C-3, and therefore also the C-6 methyl group, are axial. In the case of the alcohol **55** this has been confirmed by an X-ray crystallographic analysis (see later). In the case of the enol ether **52** this would result in a shielding of the α-face of the double bond to attack by the hydroborating reagent, leading to a predominance of the alcohol **49** in the reaction product. Fortunately when the hydroboration was carried out by using the more reactive borane–THF a 40:60 mixture of the alcohols **49** and **53** was produced, from which the desired isomer **53** was isolated in 55% yield by HPLC. The epimeric alcohol **49** was recycled to provide a further quantity (15%) of the alcohol **53**. The synthetic alcohol **53** was identical in all respects to material obtained by degradation of indanomycin.[46]

Conversion of the alcohol **53** into the ketone **2** was achieved in a straightforward manner. Oxidation of **53** with pyridinium chlorochromate proceeded surprisingly slowly but eventually afforded the aldehyde **54** in 62% yield.



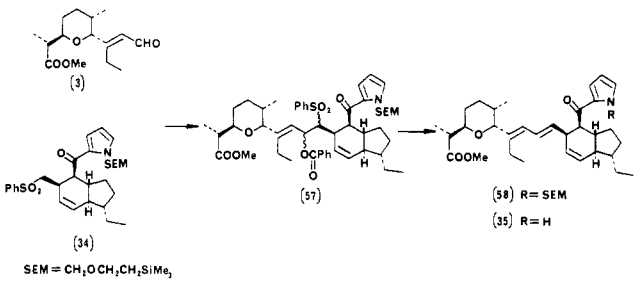
Reaction of the aldehyde **54** with 1 equiv of ethylmagnesium bromide gave the epimeric alcohols **55** and **56** as a 3:2 mixture. The mixture was readily separated by flash chromatography, and the C-8 configuration of the major isomer **55** was determined by an X-ray crystallo-

(46) Quantities of authentic alcohol **53** could be prepared from the naturally derived ketone **2** via intermediates **59** and **60**.



graphic analysis (Figure 2). Surprisingly the C-3 and C-6 ring substituents adopt axial orientations in the crystal, and ^1H NMR coupling constants suggest that this is also the case in solution. Oxidation of the alcohol mixture with Jones' reagent gave the ketone **2** in 96% yield, thereby formally completing the total synthesis of the left-hand fragment **3** of indanomycin.

Coupling of the Fragments 3 and 34. Initial attempts at Julia coupling of the sulfone **5** and the aldehyde **3** using the standard conditions developed by Lythgoe and Kocienski[9] were unsuccessful, due to a failure of the sulfone **34** to undergo metalation. However, the addition of HMPA to the metalation system was sufficient to produce the bright orange sulfone anion rapidly at −78 °C. Reaction of this anion with the aldehyde **3**, followed by quenching with benzoyl chloride afforded a diastereomeric mixture of benzoyloxy phenylsulfones **57**. Treatment of



the crude mixture with sodium amalgam resulted in a smooth conversion into *N*-SEM-protected indanomycin methyl ester **58**, in 53% overall yield. As expected, an examination of the product by high-field ^1H NMR indicated that the Julia reaction was totally stereospecific in producing only the *E,E*-1,3-butadienyl system.

The SEM protecting group was removed cleanly in 72% yield by treatment with a dry, concentrated solution of tetra-*n*-butylammonium fluoride in THF.[47,48] The product was identical to indanomycin methyl ester **35** prepared from the natural product by esterification using diazomethane.

The total synthesis of indanomycin was completed by the smooth hydrolysis of the ester **35** using 1 N aqueous sodium hydroxide to provide the natural product in 90% yield. The coupling of the left- and right-hand fragments and elaboration to the natural product was thus accomplished in only three steps and in 34% overall yield.

Experimental Section

Unless otherwise stated, IR spectra were recorded for solutions in chloroform or liquid films on a Perkin Elmer 298 machine. ^1H NMR spectra were recorded at 60 MHz on a Varian EM 360A, at 250 MHz on a Bruker WM 250, and at 400 MHz on a Bruker WH 400 instrument for solutions in $CDCl_3$ with tetramethylsilane as internal standard. Optical rotations were determined on a Perkin-Elmer 141 polarimeter. Mass spectra were determined with a VG Micromass 7070B instrument. Microanalyses were performed in the Imperial College Chemistry Department microanalytical laboratory. Analytical thin-layer chromatography (TLC) was performed on Merck precoated silica gel F_{254} plates. Preparative chromatography was carried out on columns of Merck Kieselgel H. Flash chromatography was carried out on columns of Merck 9385 Kieselgel 60 or MN-Kieselgel 60 (both 230–400 mesh). All solvents used for chromatography were redistilled. Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification or purified by standard means. Tetrahydrofuran (THF) was redistilled from sodium/benzophenone ketyl onto activated 4A molecular sieves and used within two days; dichloromethane was freshly distilled from phosphorus pentoxide; pyridine, diisopropylamine, chlorotrimethylsilane, triethylamine, tetra-*N*-methylethylenediamine (TMEDA), and 1,2-dimethoxyethane (DME) were distilled from calcium hydride and stored over 4A molecular sieves or sodium hydroxide pellets; dimethyl sulfoxide (Me_2SO) was distilled from calcium hydride and *N,N*-dimethylformamide (DMF) from 4A molecular sieves, both under reduced pressure; acetonitrile was dried with 4A molecular sieves and redistilled; toluene was freshly distilled from sodium wire; diethyl ether and benzene were dried over sodium wire; hexamethylphosphoramide (HMPA) was heated at 200 °C with calcium hydride overnight before distillation onto 4A molecular sieves at reduced pressure; pyrrole was redistilled from calcium hydride at slightly reduced pressure immediately prior to use. All purified and dried solvents and reagents were stored under dry argon. Anhydrous reactions were performed, under dry argon, in glassware dried at 150–200 °C for at least three hours, assembled and cooled under a stream of dry argon. Organic solutions were routinely dried with anhydrous sodium or magnesium sulfate and evaporated with a rotary evaporator using a water aspirator followed by static evaporation with an oil pump. Melting points were determined with a Kofler hot stage apparatus and are uncorrected. The numbering system used in the experimental section is in accord with accepted IUPAC rules.

1-[(Trimethylsilyl)oxy]-3-iodopropane. A solution of 30 g (0.317 mol) of 3-chloropropan-1-ol and 100 g (0.667 mol) of dry sodium iodide in 500 mL of acetone was refluxed in the dark for 24 h. The solution was filtered and concentrated in vacuo, and the residue taken up in 250 mL of ether. After filtration of the remaining solids the ethereal solution was washed with 5% aqueous $NaHSO_3$ and water before drying ($MgSO_4$) and concentration. The resulting oil was dissolved in 300 mL of THF and stirred vigorously at 0 °C while 58.5 g (0.74 mol) of dry pyridine and 60.3 g (0.56 mol) of chlorotrimethylsilane were added dropwise over 80 min. After stirring at room temperature for 1 h the reaction mixture was filtered through a Celite pad and concentrated to an oil which was distilled in vacuo to give 67 g (82%) of 1-[(trimethylsilyl)oxy]-3-iodopropane as a colorless liquid: bp 40–43 °C (0.2 mmHg); IR (neat) 2960, 2900, 2870, 1250, 1100, 840 cm^{-1}; ^1H NMR (CCl_4) δ 0.1 (s, 9 H), 1.9 (m, 2 H), 3.2 (t, 2 H, J = 6 Hz), 3.55 (t, 2 H, J = 6 Hz).

3-Ethyl-2-oxotetrahydropyran (2-Ethyl-δ-valerolactone) (9). To a stirred solution of 63 mL (0.45 mol) of diisopropylamine in 45 mL of THF at 0 °C was added 150 mL (0.45 mol) of a 3 N solution of *n*-butyllithium in hexane over 30 min. After a further 30 min at −10 °C, 600 mL of THF was added before cooling to −78 °C and addition of 156 mL (1.03 mol) of HMPA over 1 h. A solution of 55.8 mL (0.45 mol) of ethyl butyrate in 240 mL of THF was added over 145 min, and after the solution had stirred at −78 °C for a further 80 min, 61 mL (0.35 mol) of 1-[(trimethylsilyl)oxy]-3-iodopropane was added rapidly in one portion. After it was stirred at −78 °C for 1 h and at 0 °C for 45 min, the solution was cooled to −60 °C and poured onto a mixture of 950 mL of 10% aqueous HCl and 200 g of ice. The mixture was extracted with 600 mL of ether and the organic solution was washed successively with 200 mL of 5% aqueous $Na_2S_2O_3$, 200 mL of 5% aqueous $NaHCO_3$, and six 150-mL portions of brine before drying ($MgSO_4$) and concentration. The crude 4-(ethoxycarbonyl)hexan-1-ol was refluxed with 0.5 g of *p*-toluenesulfonic acid in 4 L of toluene with removal of ca. 150 mL of an ethanol–toluene mixture by distillation over 1 h. After washing with two 200-mL portions of brine the solution was dried ($MgSO_4$) and concentrated to give the crude lactone. Flash chromatography on silica with 5:5:1 CH_2Cl_2–petroleum ether–diethyl ether gave 34.0 g (76%) of 2-ethyl-δ-valerolactone (**9**): bp 44–46 °C (0.7 mmHg) [lit.[24] bp 108–112 °C (12 mmHg)]; IR (neat) 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (t, 3 H, J = 7 Hz), 0.8–2.7 (m, 7 H), 4.2

(47) Prepared by azeotropic removal of water from the commercially available trihydrate (5 times) followed by heating at 50 °C under high vacuum (12 h). But see also: Sharma, R. K.; Fry, J. L. *J. Org. Chem.* **1983**, *48*, 2112.

(48) The *N*-SEM pyrrolylcarbonyl compound **55** was recovered unchanged after reaction with commercially available solutions of tetra-*n*-butylammonium fluoride in THF or anhydrous ZnF_2. The recommended procedure using $LiBF_4$[49] also failed to remove the protecting group, but led instead to a novel rearrangement reaction.[50]

(49) Lipshutz, B. H.; Pegram, J. J.; Morey, M. C. *Tetrahedron Lett.* **1981**, *22*, 4603.

(50) Edwards, M. P.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1761.

(m, 2 H); exact mass calcd for $C_7H_{12}O_2$ 128.0837, found 128.0834.

3-Ethyl-2-hydroxytetrahydropyran (10). To a stirred solution of 34.0 g (0.27 mol) of lactone **9** in 690 mL of toluene at −78 °C was added 150.6 mL (0.34 mol) of a 25% solution of diisobutylaluminium hydride in toluene. After a further 45 min at −78 °C the solution was carefully poured onto a mixture of 670 mL of 10% HCl and 100 g of ice. The aqueous phase was extracted with four 150-mL portions of ether and the combined organic solutions were washed with two 150-mL portions of 5% aqueous $NaHCO_3$, 150 mL of water, and 150 mL of brine before drying ($MgSO_4$) and concentration to give 34.6 g (100%) of the lactol **10** as a 1.3:1 mixture of anti and syn diastereoisomers: IR (neat) 3390 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 and 0.92 (2 t, 3 H, J = 7 Hz), 1.1–1.35 (m, 2 H), 1.5–1.8 (m, 4 H), 2.9 (syn) and 3.32 (anti) (2 brs, 1 H, OH), 3.5 (anti) and 4.0 (syn) (2 m, 2 H), 4.45 (d, 0.56 H, J = 7 Hz, anti anomeric H), 5.1 (s, 0.44 H, syn anomeric H). Anal. Calcd for $C_7H_{14}O_2$: C, 64.58; H, 10.83. Found: C, 64.72; H, 11.04.

Ethyl (*E*,*E*)-6-Ethyl-9-hydroxynona-2,4-dienoate (19). A solution of 2.39 g (5.0 mmol) of [3-(ethoxycarbonyl)allylidene]-triphenylphosphonium bromide in 19 mL of chloroform was extracted at 0 °C with 11 mL of ice and water containing 0.2 g (5.5 mmol) of sodium hydroxide. The resulting chloroform solution of the ylide **18** was dried ($CaCl_2$) and concentrated to an oil which was immediately covered with an argon atmosphere. The product was dissolved in 4 mL of DMF by warming to 60 °C, and a solution of 0.42 g (4.0 mmol) of the lactol **10** in 1.5 mL of DMF was added. When the solution was stirred at 60 °C for 2 h, 100 °C for 90 min, and 120 °C for 1 h, it was poured onto 20 mL of 10% HCl and 10 g of ice overlaid with 50 mL of ether. The aqueous phase was extracted with three 50-mL portions of ether and the combined organic solutions were washed with 10% HCl, 5% aqueous $NaHCO_3$, and water before drying ($MgSO_4$) and concentration to give an oil. Flash chromatography with 25% ethyl acetate–petroleum ether gave 0.18 g (34%) of recovered lactol (**10**), followed by 0.21 g (23%) of the dienoic ester (**19**) as a colorless oil: IR (neat) 3410, 1710, 1640, 1618 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80 (t, 3 H, J = 7 Hz), 1.25 (t, 3 H, J = 7 Hz), 1.1–1.8 (m, 7 H), 2.35 (br s, 1 H, OH), 3.55 (m, 2 H), 4.15 (q, 2 H, J = 7 Hz), 5.4–6.5 (m, 3 H), 6.9–7.4 (m, 1 H).

Ethyl (*E*,*E*)-9-[(*tert*-Butyldimethylsilyl)oxy]-6-ethyl-2,4-nonadienoate (13). A solution of 109 mL of 1.4 N *n*-butyllithium in hexane (0.152 mol) was added dropwise at 0 °C to a solution of 20.82 mL (0.152 mol) of diisopropylamine in 174 mL of THF. After 20 min at 0 °C the solution was cooled to −78 °C and a solution of 38.1 g (0.152 mol) of ethyl 4-(diethoxyphosphinyl)crotonate in 30 mL of THF was added dropwise over 100 min. After a further 60 min at −78 °C and 10 min at −50 °C a solution of 30 g (0.123 mol) of the aldehyde **11** in 36 mL of THF was added. The mixture was allowed to warm to room temperature over 1 h before addition of 25 mL of ethanol. After removal of solvents in vacuo the residue was dissolved in 1 L of ether and washed with five 100-mL portions of water, two 50-mL portions of 1% HCl, and 50 mL of water before drying ($MgSO_4$) and concentration to an oil. Flash chromatography on silica with 5% ethyl acetate–light petroleum gave 27.56 g (66%) of the silylated ester **13** as an oil: IR (neat) 1718, 1640, 1615 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.0 (s, 6 H), 0.8 (s, 9 H), 1.2 (t, 3 H, J = 7 Hz), 0.7–1.6 (m, 9 H), 3.45 (m, 2 H), 4.05 (q, 2 H, J = 7 Hz), 5.5–6.0 (m, 3 H), 7.2 (ddd, 1 H, J = 15, 10, 1 Hz). Anal. Calcd for $C_{19}H_{36}O_3Si$: C, 67.01; H, 10.65. Found: C, 67.28; H, 10.76.

5-[(*tert*-Butyldimethylsilyl)oxy]-2-ethylpentanal (11). To a stirred solution of 34.6 g (0.27 mol) of lactol **10** and 27.1 g (0.40 mol) of imidazole in 20 mL of DMF was added a solution of 44.0 g (0.29 mol) of *tert*-butyldimethylchlorosilane in 70 mL of DMF dropwise over 1 h. After the mixture was stirred at room temperature for 2 h, it was diluted with 500 mL of ether and 100 mL of water. The organic layer was washed with two 100-mL portions of 0.1 N HCl, 100 mL of brine, two 100-mL portions of 5% aqueous $NaHCO_3$, and 100 mL of brine before drying ($MgSO_4$) and careful concentration in vacuo to give an oil. Flash chromatography on silica with 9% ether–petroleum ether gave 31.5 g (48%) of the silylated aldehyde **11** as an oil: IR (neat) 2700, 1725, 1470, 1460, 1250, 1100, 840, 775 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (s, 6 H), 0.80 (s, 9 H), 0.7–2.3 (m, 10 H), 3.55 (m, 2 H), 9.50 (d, 1 H, J = 3.2 Hz). Further elution afforded 18.0 g (28%) of 2-[(*tert*-butyldimethylsilyl)oxy]-3-ethyltetrahydropyran (**12**) as an oil: IR (neat) 1460, 1385, 1250, 1160, 1075, 830, 775 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (s, 6 H), 0.80 (s, 9 H), 0.6–2.0 (m, 10 H), 3.30 (m, 1 H), 3.8 (m, 1 H), 4.25 (d, 1 H, J = 5.2 Hz).

Silylation of 0.28 g (1.23 mmol) of the alcohol **19** with 0.22 g (1.48 mmol) of *tert*-butyldimethylchlorosilane and 0.21 g (3.08 mmol) of imidazole in 0.6 mL DMF at room temperature for 8 h afforded 0.41 g (99%) of the silyl ester **13**, identical with the material prepared above.

(*E*,*E*)-9-[(*tert*-Butyldimethylsilyl)oxy]-6-ethyl-2,4-nonadien-1-ol (14). A solution of 18.83 mL (18.83 mmol) of 1.0 N diisobutylaluminium hydride in hexane was added dropwise over 30 min to a solution of 2.91 g (8.56 mmol) of the ester **13** in 8 mL of toluene at −5 °C. After a further 15 min at this temperature the solution was poured onto a mixture of 36 mL of 10% HCl and 50 g of ice. Extraction with 300 mL of ether, followed by washing with three 25-mL portions of 1% HCl, two 25-mL portions of 5% $NaHCO_3$, and 50 mL of water afforded, after drying ($MgSO_4$) and concentration, 2.5 g (98%) of the alcohol **13** as an oil, homogeneous by TLC. Chromatography on silica with 45% ether–petroleum ether afforded an analytical sample: IR (neat) 3360, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.0 (s, 6 H), 0.8 (s, 9 H), 0.7–2.1 (m, 10 H), 2.55 (br s, 1 H, OH), 3.95 (d, 2 H, J = 6 Hz), 5.2–6.1 (m, 4 H). Anal. Calcd for $C_{17}H_{34}O_2Si$: C, 68.39; H, 11.48. Found: C, 68.24; H, 11.64.

(*E*,*E*)-1-[[(β-Methoxy)ethoxy]methoxy]-9-[(*tert*-butyldimethylsilyl)oxy]-6-ethyl-2,4-nonadiene (15). A solution of 2.5 g (8.37 mmol) of the alcohol **14** in a mixture of 2.41 mL (13.7 mmol) of diisopropylethylamine and 24 mL of dichloromethane was stirred with 1.58 mL (13.7 mmol) of (β-methoxy)ethoxychloromethane at room temperature for 2 h. After dilution with 250 mL of dichloromethane and 50 mL of water the aqueous phase was extracted with two 50-mL portions of dichloromethane. The combined organic solutions were washed with 100 mL of 1% HCl and three 50-mL portions of water before drying ($MgSO_4$) and concentration to an oil. Flash chromatography on silica with 15% ethyl acetate–petroleum ether gave 3.17 g (98%) of the MEM ether **15** as an oil: IR (neat) 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.0 (s, 6 H), 0.8 (s, 9 H), 0.6–2.0 (m, 10 H), 3.3 (s, 3 H), 3.6 (m, 6 H), 4.0 (d, 2 H, J = 6 Hz), 4.6 (s, 2 H), 5.2–6.3 (m, 4 H). Anal. Calcd for $C_{21}H_{42}O_4Si$: C, 65.44; H, 10.95. Found: C, 65.23; H, 11.14.

(*E*,*E*)-1-[[(β-Methoxy)ethoxy]methoxy]-6-ethyl-2,4-nonadien-9-ol (16). A solution of 23.9 mL (22.8 mmol) of 0.99 N tetra-*n*-butylammonium fluoride in THF was added dropwise to a solution of 7.35 g (19 mmol) of the silyl ether **15** in 10 mL of THF at room temperature. After a further 15 min the THF was removed in vacuo and the oil was partitioned between 600 mL of ether and 100 mL of water. Two further 50-mL ether extracts of the aqueous phase were combined with the organic phase and washed with 40 mL of 1% HCl and 40 mL of water before drying ($MgSO_4$) and concentration to give 5.12 g (99%) of the alcohol **16** as a pale yellow oil, homogeneous by TLC. Flash chromatography on silica with 20% ethyl acetate–petroleum ether afforded an analytical sample: IR (neat) 3380, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (t, 3 H, J = 7 Hz), 1.2–2.0 (m, 10 H), 1.9 (br s, 1 H, OH), 3.4 (s, 3 H), 3.6 (m, 4 H), 3.7 (m, 2 H), 4.1 (d, 2 H, J = 6.3 Hz), 4.75 (s, 2 H), 5.44 (dd, 1 H, J = 15.2, 8.9 Hz, H-5), 5.65 (dt, 1 H, J = 15.2, 6.3 Hz, H-2), 6.0 (dd, 1 H, J = 15.2, 10.4 Hz, H-4), 6.25 (dd, 1 H, J = 15.2, 10.4 Hz, H-3). Anal. Calcd for $C_{15}H_{28}O_4$: C, 66.14; H, 10.36. Found: C, 66.13; H, 10.67.

(*E*,*E*)-9-[[(β-Methoxy)ethoxy]methoxy]-4-ethyl-5,7-nonadienal (17). Collin's reagent was prepared by the addition of 6.6 g (66 mmol) of chromium trioxide to a mixture of 10.44 g (0.13 mol) of pyridine and 170 mL of dichloromethane with waterbath cooling, followed by stirring for 25 min. To this was added, with vigorous stirring, 3.0 g (11 mmol) of the alcohol **16** in 3 mL of dichloromethane and the mixture was stirred at room temperature for 25 min. After decantation and trituration of the residue with five 10-mL portions of ether the combined organic solutions were washed with six 40-mL portions of 5% NaOH, 40 mL of 5% HCl, 40 mL of 5% $NaHCO_3$, and 40 mL of saturated brine. Concentration of the dried ($MgSO_4$) solution gave an oil which was dissolved in 5 mL of ether and filtered through a pad of Kieselgel, eluting with 100 mL of ether. Concentration of the eluate gave 2.97 g (100%) of the aldehyde **17** as an oil: IR (neat) 2720, 1760, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.8 (t, 3 H, J = 7 Hz), 1.1–2.1 (m,

5 H), 2.3 (m, 2 H), 3.3 (s, 3 H), 3.6 (m, 4 H), 4.0 (d, 2 H, J = 6.3 Hz), 4.65 (s, 2 H), 5.0–6.3 (m, 4 H), 9.15 (t, 1 H, J = 2 Hz). Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.68; H, 9.70. Found: C, 66.69; H, 9.77.

Ethyl (*E*,*E*,*E*)-11-[[(β-Methoxy)ethoxy]methoxy]-6-ethyl-2,7,9-undecatrienoate (8). A solution of 0.20 g (0.73 mmol) of the aldehyde **17** and 0.28 g (0.81 mmol) of (carbethoxymethylene)triphenylphosphorane in 1.12 mL of dichloromethane was stirred at room temperature for 7 h. The dichloromethane was removed in vacuo and the residue triturated with three 5-mL portions of ether. The ethereal solution was filtered through a pad of Kieselgel and concentrated to give 0.24 g (95%) of ethyl ester **8** as an oil, homogeneous by TLC. Flash chromatography with 24% ethyl acetate–petroleum ether afforded an analytical sample: IR (neat) 1725, 1660 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.85 (t, 3 H, J = 7 Hz), 1.3 (t, 3 H, J = 7 Hz), 1.2–1.65 (m, 4 H), 1.92 (m, 1 H), 2.15 (m, 2 H), 3.41 (s, 3 H), 3.58 (m, 2 H), 3.71 (m, 2 H), 4.1 (d, 2 H, J = 6.3 Hz), 4.18 (q, 2 H, J = 7 Hz), 4.75 (s, 2 H), 5.4 (dd, 1 H, J = 15.3, 9.4 Hz, H-5), 5.63 (dt, 1 H, J = 15.3, 6.3 Hz, H-2), 5.8 (d, 1 H, J = 15.6 Hz, H-10), 6.02 (dd, 1 H, J = 15.3, 10.5 Hz, H-4), 6.25 (dd, 1 H, J = 15.3, 10.5 Hz, H-3), 6.95 (dt, 1 H, J = 15.6, 6.8 Hz, H-9). Anal. Calcd for $C_{19}H_{32}O_5$: C, 67.03; H, 9.47. Found: C, 66.72; H, 9.61.

(±)-Ethyl 5β-[[[(2′-methoxy)ethoxy]methoxy]methyl]-1α-ethyl-3aβ,4,5,7aα-tetrahydroindan-4β-carboxylate (21). A solution of 0.5 g (1.47 mmol) of the trienoate **8** in 140 mL of argon-flushed toluene was heated at reflux for 80 h. The toluene was removed in vacuo to give the tetrahydroindan **21** as an oil, contaminated with a trace of starting material and less than 10% of the other possible isomers (100% yield of material). Flash chromatography with 10% ether–dichloromethane provided an analytical sample: IR (neat) 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.91 (t, 3 H, J = 7.2 Hz), 1.28 (t, 3 H, J = 6.7 Hz), 1.1–2.05 (m, 9 H), 2.62 (dd, 1 H, J = 11.2, 6.7 Hz, H-4), 2.88 (m, 1 H, H-5), 3.39 (s, 3 H), 3.47 (m, 2 H), 3.5 (m, 2 H), 3.67 (m, 2 H), 4.1 (dq, 2 H, J = 6.7, 1.5 Hz), 4.59 (d, 1 H, J = 6.7 Hz), 4.63 (d, 1 H, J = 6.7 Hz), 5.55 (ddd, 1 H, J = 10.3, 4.0, 2.6 Hz, H-6), 5.95 (d, 1 H, J = 10.3 Hz, H-7). Anal. Calcd for $C_{19}H_{32}O_5$: C, 67.03; H, 9.47. Found: C, 66.90; H, 9.54.

(±)-1α-Ethyl-5β-(hydroxymethyl)-3aβ,4,5,7aα-tetrahydroindan-4β-carboxylic Acid, γ-Lactone (7). A solution of 0.62 g (1.82 mmol) of the protected hydroxy ester **21** and 0.80 g (1.90 mmol) of tetra-*n*-butylammonium bromide in 36 mL of dichloromethane was vigorously stirred with 5 mL of concentrated HCl at room temperature for 6 h. The reaction mixture was poured into 50 mL of water and 10 g of ice over 100 mL of dichloromethane. The organic layer was washed with two 30-mL portions of saturated aqueous $NaHCO_3$ and 50 mL of water before drying ($MgSO_4$) and concentration to an oil. Flash chromatography on silica with 22% ethyl acetate–petroleum ether gave 0.24 g (65%) of the lactone **7**: mp 67.5–68.5 °C (petroleum ether) (lit.[12b] mp 68–68.5 °C); IR ($CHCl_3$) 1760 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 3 H, J = 7.14 Hz, CH_2CH_3), 1.1–1.8 (m, 7 H), 1.99 (m, 2 H), 2.54 (dd, 1 H, J = 11.5, 7.6 Hz, H-4), 3.2 (m, 1 H, H-5), 3.9 (dd, 1 H, J = 8.8, 11.5 Hz, CH_2O), 4.51 (dd, 1 H, J = 8.8, 8.8 Hz, CH_2O), 5.58 (ddd, 1 H, J = 10.2, 3.8, 2.0 Hz, H-6), 6.07 (d, 1 H, J = 10.2 Hz, H-7). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.41; H, 8.77.

Resolution of the Tetrahydroindan Lactone 7. A solution of 0.20 g (0.97 mmol) of the racemic lactone **7**, 0.25 mL (1.93 mmol) of (−)-1(*S*)-phenylethylamine, and 92.3 mg (0.97 mmol) of 2-hydroxypyridine in 0.5 mL of toluene was heated at 110 °C for 6 h. Dichloromethane was added and the solution was washed with three 10-mL portions of 10% aqueous HCl. The organic solution was combined with three 10-mL dichloromethane back extracts of the acidic aqueous phase and washed with 10 mL of water, 10 mL of aqueous $NaHCO_3$, and 10 mL of brine. Drying ($MgSO_4$) and concentration afforded 0.3 g of solid. Flash chromatography with 40% ethyl acetate–petroleum ether gave 81.4 mg (41%) of unreacted lactone **7**. Further elution afforded 91.5 mg (29%) of the less polar amide **24**: mp 176–177 °C (chloroform–petroleum ether); IR ($CHCl_3$) 3280, 3450, 1630 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.85 (t, 3 H, J = 7 Hz, CH_2CH_3) 1.0–2.0 (m, 9 H), 1.45 (d, 3 H, J = 7.5 Hz, $PhCHCH_3$), 2.33 (dd, 1 H, J = 11, 7.4 Hz, H-4), 2.45 (m, 1 H, H-5), 3.4 (s, 1 H, OH), 3.40 and 3.55 (m, both 1 H, CH_2OH) [with D_2O exchange 3.40 (dd, 1 H, J = 12.4, 2.7 Hz), and 3.55 (dd, 1 H, J = 12.4, 5 Hz)], 5.1 (dq, 1 H, J = 7.5, 7.5 Hz, $PhCHCH_3$), 5.4 (br d, 1 H, J = 10 Hz, H-6), 6.95 (d, 1 H, J = 10 Hz, H-7), 6.15 (br d, 1 H, J = 7.5 Hz, NH), 7.25 (m, 5 H, ArH). Anal. Calcd for $C_{21}H_{29}NO_2$: C, 77.02; H, 8.93; N, 4.28. Found: C, 76.92; H, 9.00; N, 4.28; followed by 89 mg (28%) of the more polar amide **25**: mp 170–173 °C (chloroform–petroleum ether); IR ($CHCl_3$) 3280, 3450, 1630 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.85 (t, 3 H, J = 7 Hz, CH_2CH_3), 0.9–2.0 (m, 9 H), 1.45 (d, 3 H, J = 7.5 Hz, $PhCHCH_3$), 2.3 (dd, 1 H, J = 11, 6.5 Hz, H-4), 2.5 (m, 1 H, H-5), 3.45 (dd, 1 H, J = 16, 6.25 Hz, OH), 3.5–3.7 (m, 2 H, CH_2OH), 5.1 (dq, 1 H, J = 7.5, 7 Hz, $PhCHCH_3$), 5.4 (ddd, 1 H, J = 10, 3.5, 2 Hz, H-6), 5.95 (d, 1 H, J = 10 Hz, H-7), 6.0 (br s, 1 H, NH), 7.25 (m, 5 H, ArH). Anal. Calcd for $C_{21}H_{29}NO_2$: C, 77.02; H, 8.93; N, 4.28. Found: C, 77.11; H, 8.92; N, 4.24.

A solution of 0.16 g (0.49 mmol) of the less polar amide **24** in 4 mL of a 1:1 mixture of 1 N H_2SO_4 and dioxan was stirred at 80 °C for 1 h. The cooled reaction mixture was diluted with 20 mL of water and extracted with 50 mL of dichloromethane. The organic phase, combined with three 20-mL dichloromethane extracts of the aqueous phase, was washed with 20 mL of 5% aqueous $NaHCO_3$ and 20 mL of brine before drying ($MgSO_4$) and concentration to a solid. Chromatography on Kieselgel with 30% dichloromethane–petroleum ether gave 99 mg (98%) of the (+)-lactone **26**: mp 83–84 °C (petroleum ether); $[\alpha]^{25}_D$ +136° (*c* 1.02, $CHCl_3$) (lit.[12e] $[\alpha]_D$ +113° for lactone of 82% ee); other data as for the racemic lactone. Similar treatment of the more polar amide afforded a 99% yield of the (−)-lactone **27**: mp 83–84 °C, $[\alpha]^{25}_D$ −136° (*c* 0.52, $CHCl_3$).

(±)-4β-(2-Pyrrolylcarbonyl)-1α-ethyl-3aβ,4,5,7aα-tetrahydroindan-5β-methanol (28). To 5 mL of a 3 N solution of ethylmagnesium bromide in ether (15 mmol) (prepared from 1.46 g of magnesium turnings and 4.48 mL of ethyl bromide in 20 mL of ether) was added dropwise 1.05 mL (15 mmol) of freshly distilled pyrrole at 0 °C. After the solution had stirred at room temperature for 30 min, the solvent was removed in a stream of argon and 5 mL of a 3:1 toluene–ether mixture was added. An aliquot of 1.09 mL (3.26 mmol) of the resulting 3 N solution of pyrrolylmagnesium bromide was added to a solution of 0.168 g (0.82 mmol) of the lactone **7** in 0.5 mL of toluene at 100 °C. After 10 min at this temperature the solution was cooled to 0 °C before the addition of 1 mL of saturated aqueous NH_4Cl. The mixture was extracted with 50 mL of ether and 10 mL of water, and the aqueous phase re-extracted with three 50-mL portions of ether. The combined organic solutions were washed with two 10-mL portions of 5% aqueous sodium carbonate and 20 mL of water before drying ($MgSO_4$) and concentration to an oil. Flash chromatography on silica with 85% ether–petroleum ether gave 0.21 g (94%) of the pyrrolylcarbonyl alcohol **28**: mp 88–90 °C (petroleum ether); IR ($CHCl_3$) 3440, 3300, 1620, 1535 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.92 (t, 3 H, J = 7.35 Hz, CH_2CH_3), 1.0–2.2 (m, 9 H), 2.74 (dd, 1 H, J = 8.2, 6 Hz, H-4), 2.94 (br s, 1 H, OH), 3.45 (dd, 1 H, J = 12, 7 Hz, H-5), 3.55 and 3.63 (dd, both 1 H, J = 12, 4.4 Hz, CH_2OH), 5.60 (ddd, 1 H, J = 10.1, 3.9, 2.5 Hz, H-6), 6.1 (d, 1 H, J = 10.1 Hz, H-7), 6.3, 6.95, 7.1 (m, each 1 H, pyrrole H), 10.3 (br s, 1 H, NH). Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.58; H, 8.51; N, 5.13.

1-[[(β-Trimethylsilyl)ethoxy]methyl]pyrrole (30). To a suspension of 4.6 g (0.096 mol) of a 50% dispersion of sodium hydride in oil (prewashed with 3 × 5-mL portions of petroleum ether) in 180 mL of DMF and 32 mL of Me_2SO with ice bath cooling was added dropwise 4.21 mL (0.06 mol) of freshly distilled pyrrole. After removal of the cooling bath and stirring at room temperature for 50 min, hydrogen evolution had ceased and the solution was recooled to 0 °C while 15 g (0.09 mol) of [β-(trimethylsilyl)ethoxy]methyl chloride was added dropwise over 5 min. The solution was stirred at room temperature for 30 min before pouring into a mixture of 200 mL of water and 50 g of ice. The organic solution, combined with three 200-mL extracts of the aqueous phase, was washed with 50 mL of water, two 50-mL portions of 10% aqueous HCl, and 50 mL of water before drying ($MgSO_4$) and concentration to an oil. Flash chromatography on silica with 5% ether–petroleum ether gave 8.29 g (70%) of *N*-SEM-pyrrole (**30**) as a colorless liquid: bp 76 °C (1.5 mmHg); IR (neat) 1495, 1270, 1250, 1070, 860, 835, 720 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.0 (s, 9 H), 1.1 (t, 2 H, J = 8 Hz), 3.6 (t, 2 H, J = 8 Hz), 5.3 (s, 2 H), 6.2 (dd, 2 H, J = 2, 2 Hz), 6.9 (dd, 2 H, J = 2,

2 Hz). Anal. Calcd for $C_{10}H_{19}NOSi$: C, 60.86; H, 9.70; N, 7.10. Found: C, 61.07; H, 9.88; N, 6.85.

(-)-4(*S*)-[[*N*-[[(β-Trimethylsilyl)ethoxy]methyl]pyrrol-2-yl]carbonyl]-1(*S*)-ethyl-3a(*R*),4,5,7a(*S*)-tetrahydroindan-5(*R*)-methanol (32). To a solution of 0.162 g (0.78 mmol) of *N*-SEM-pyrrole in 1.1 mL of DME at 0 °C was added 0.52 mL (0.85 mmol) of a 1.63 *N* solution of *n*-butyllithium in hexane. After 10 min at this temperature 80 mg (0.39 mmol) of the (+)-lactone **26** in 0.20 mL of DME was added rapidly in one portion. The reaction mixture was stirred at room temperature for 5 min before pouring into 10 mL of saturated aqueous NH_4Cl overlaid with 20 mL of ether. The organic solution, combined with three 20-mL ether extracts of the aqueous phase, was washed with three 10-mL portions of 5% aqueous HCl, 20 mL of 5% aqueous $NaHCO_3$, and 20 mL of water before drying ($MgSO_4$) and concentration to an oil. Flash chromatography on silica with 25% ethyl acetate–petroleum ether gave 97.1 mg (62%) of the (-)-alcohol **32** as an oil: $[\alpha]^{25}_D$ -9° (*c* 0.69, $CHCl_3$); IR ($CHCl_3$) 3450, 1630, 1520 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.0 (s, 9 H), 0.9 (m, 2 H, CH_2SiMe_3), 0.92 (t, 3 H, *J* = 7 Hz, CH_2CH_3), 0.9–2.1 (m, 9 H), 2.73 (dd, 1 H, *J* = 8, 6.6 Hz, H-4), 2.73 (m, 1 H, H-5), 3.45 (dd, 1 H, *J* = 6.9, 6.9 Hz, OH), 3.48 and 3.52 (d, both 1 H, *J* = 7.8 Hz, $CH_2OCH_2CH_2SiMe_3$), 3.53 (m, 1 H, CH_2OH), 3.65 (ddd, 1 H, *J* = 12, 6.9, 5 Hz, CH_2OH), 5.55 (ddd, 1 H, *J* = 10, 3.7, 2.6 Hz, H-6), 5.59 and 5.89 (d, both 1 H, *J* = 10 Hz, OCH_2N), 6.06 (br d, 1 H, *J* = 10 Hz, H-7), 6.2 (dd, 1 H, *J* = 3.1, 3.1 Hz, pyrrole H-4), 7.09 (d, 2 H, *J* = 3.1 Hz, pyrrole H-3 and H-5). Anal. Calcd for $C_{23}H_{37}NO_3Si$: C, 68.44; H, 9.24; N, 3.47. Found: C, 68.32; H, 9.31; N, 3.18.

(-)-4(*S*)-[2-[*N*-[[(β-Trimethylsilyl)ethoxy]methyl]-pyrrolyl]carbonyl]-5(*R*)-[(phenylsulfenyl)methyl]-1(*S*)-ethyl-3a(*R*),4,5,7a(*S*)-tetrahydroindan (33). A solution of 82.2 mg (0.20 mmol) of the (-)-alcohol **32** in 0.18 mL of dry benzene was added rapidly in one portion at room temperature to the solution resulting from stirring 73 mg (0.32 mmol) of *N*-(phenylsulfenyl)succinimide and 0.088 mL (0.32 mol) of tri-*n*-butylphosphine in 0.82 mL of benzene for 10 min. After stirring for 3 h the reaction mixture was diluted with 40 mL of ether and washed with 20 mL of water. The organic solution was washed with 10 mL of 1% aqueous HCl, 15 mL of 5% aqueous $NaHCO_3$, and 10 mL of brine before drying ($MgSO_4$) and concentration to an oil. Flash chromatography on silica with 5% ethyl acetate–petroleum ether gave 71 mg (70%) of the (-)-sulfide **33**: $[\alpha]^{25}_D$ -69° (*c* 3.8, $CHCl_3$); IR ($CHCl_3$) 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ -0.1 (m, 9 H), 0.85 (m, 2 H, CH_2SiMe_3), 0.9 (t, 3 H, *J* = 7.3 Hz), 0.9–2.1 (m, 9 H), 2.73 (dd, 1 H, *J* = 12.4, 9.4 Hz, CH_2SPh), 2.85 (m, 1 H, H-5), 3.03 (dd, 1 H, *J* = 12.4, 4.4 Hz, CH_2SPh), 3.45 (dd, 1 H, *J* = 11, 6.3 Hz, H-4), 3.55 (m, 2 H, $CH_2OCH_2CH_2SiMe_3$), 5.70 and 5.85 (d, both 1 H, *J* = 10 Hz, NCH_2O), 5.88 (ddd, 1 H, *J* = 10, 3.8, 2.5 Hz, H-6), 5.97 (d, 1 H, *J* = 10 Hz, H-7), 6.20 (dd, 1 H, *J* = 3.8, 2.5 Hz, pyrrole H-4) 6.95–7.15 (m, 5 H), 7.1 (m, 2 H, pyrrole H-3 and H-5). Anal. Calcd for $C_{29}H_{41}NO_2SSi$: C, 70.25; H, 8.34; N, 2.83. Found: C, 70.20; H, 8.37; N, 3.03. Followed by 7.7 mg (7%) of starting alcohol **30**.

(-)-4(*S*)-[2′-[*N*-[[(β-Trimethylsilyl)ethoxy]methyl]-pyrrolyl]carbonyl]-5(*R*)-[(phenylsulfonyl)methyl]-1(*S*)-ethyl-3a(*R*),4,5,7a(*S*)-tetrahydroindan (34). To a solution of 38 mg (0.077 mol) of the (-)-sulfide **33** and 23.6 mg (0.077 mmol) of diphenyl diselenide in 0.4 mL of a 15% dichloromethane–ether solution was added dropwise at 0 °C 0.052 mL of 30% hydrogen peroxide. After 1 h the cooling bath was removed and stirring was continued for 6 h. The reaction mixture was diluted with 50 mL of dichloromethane before washing with two 10-mL portions of saturated aqueous $NaHCO_3$, 10 mL of 5% aqueous $NaHSO_3$, and 10 mL of brine. The dried ($MgSO_4$) organic solution was concentrated to a gum which was chromatographed on silica. Elution with 28% ethyl acetate–petroleum ether gave 32.1 mg (80%) of the (-)-sulfone **34** as a gum: $[\alpha]^{25}_D$ -79° (*c* 1.05, $CHCl_3$); IR ($CHCl_3$) 1635, 1520 cm^{-1}; ^1H NMR ($CDCl_3$) δ -0.2 (s, 9 H), 0.85 (m, 2 H, CH_2SiMe_3), 0.90 (t, 3 H, *J* = 7 Hz, CH_2CH_3), 0.9–2.0 (m, 9 H), 3.10 (m, 1 H, CH_2SO_2Ph), 3.13 (m, 1 H, H-5), 3.43 (m, 1 H, CH_2SO_2Ph), 3.44 (m, 1 H, H-4), 3.52 (m, 2 H, CH_2O), 5.55 and 5.73 (d, both 1 H, *J* = 9.8 Hz, NCH_2O), 5.96 (m, 2 H, H-6, 7), 6.13 (dd, 1 H, *J* = 4.3, 2.4 Hz, pyrrole H-4), 6.88 (dd, 1 H, *J* = 4.3, 1.2 Hz, H-3), 7.08 (dd, 1 H, *J* = 2.4, 1.2 Hz, pyrrole H-5), 7.35–7.55 (m, 5 H). Anal. Calcd for $C_{20}H_{41}NO_4SSi$: C, 66.00; H, 7.83; N, 2.65. Found: C, 66.08; H, 7.73; N, 2.45.

(1*S*,2*S*,3*S*,4*R*,5*R*)-2-Methyl-4-[(*p*-toluenesulfonyl)-oxy]-6,8-dioxabicyclo[3.2.1]octan-3-ol (41). To a suspension of 12.34 g (60 mmol) of copper(I) bromide–dimethyl sulfide and 1.79 g (6.0 mmol) of the epoxy tosylate[41] **37** in 90 mL of THF at -15 °C was added 40 mL (120 mmol) of a 3 M solution of methylmagnesium chloride in THF. After stirring at -15 °C for 48 h the mixture was diluted with 200 mL of ether and treated with saturated aqueous NH_4Cl until all interfacial solids had dissolved. The organic solution was washed with six 50-mL portions of water before drying ($MgSO_4$) and concentration to a solid. Flash chromatography on silica with 50% ether–chloroform gave 1.62 g (86%) of the alcohol **41**: mp 90–91 °C (ether–petroleum ether); $[\alpha]^{24}_D$ -52° (*c* 2.56, $CHCl_3$); IR ($CHCl_3$) 3395, 1595, 1167, 1142, 1123, 1090 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (d, 3 H, *J* = 7.4 Hz, C-2 Me), 1.79 (m, 1 H, H-2), 2.46 (s, 3 H, ArMe), 2.90 (d, 1 H, *J* = 5.3 Hz, OH) 3.61 (m, 1 H, H-3), 3.67 (dd, 1 H, *J* = 7.0, 4.7 Hz, H-7_{exo}), 4.08 (d, 1 H, *J* = 7.0 Hz, H-7_{endo}), 4.20 (brs, 1 H, *J* = 2.2 Hz, H-4), 4.30 (d, 1 H, *J* = 4.7 Hz, H-1), 5.25 (brs, 1 H, H-5), 7.38 (d, 2 H, *J* = 9Hz, ArH), 7.82 (d, 2 H, *J* = 9 Hz, ArH). Anal. Calcd for $C_{14}H_{18}O_6S$: C, 53.49; H, 5.77; S, 10.20. Found: C, 53.48; H, 5.83; S, 10.43.

(1*S*,2*S*,3*R*,5*R*)-2-Methyl-6,8-dioxabicyclo[3.2.1]octan-3-ol (42). A solution of 8.80 g (28.0 mmol) of the tosylate **41** in 210 mL of THF was treated at 0 °C with 84.0 mL (84.0 mmol) of a 1 M solution of lithium triethylborohydride in THF. The solution was allowed to warm to room temperature and stirred for a further 14 h. After the solution was recooled to 0 °C, 13.5 mL of water was added, followed by a mixture of 47.1 mL of 3 M aqueous NaOH and 37.8 mL of 30% hydrogen peroxide. The mixture was stirred at 0–20 °C over 2 h before dilution with 100 mL of dichloromethane and separation of the organic solution. The aqueous portion was saturated with NaCl and reextracted with two 50-mL portions of dichloromethane. After drying ($MgSO_4$) the combined organic solution was concentrated to give a solid which was chromatographed on silica. Elution with 50% chloroform–ether gave 3.91 g (97%) of the alcohol **42**: mp 79–80 °C (ether–light petroleum); $[\alpha]^{24}_D$ -134.5° (*c* 1.87, $CHCl_3$); IR ($CHCl_3$) 3400, 1190, 1110, 1042, 1018 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.14 (d, 3 H, *J* = 7.5 Hz, C-2 Me), 1.81 (d, 1 H, *J* = 15.0 Hz, H-4_{eq}), 1.99 (m, 1 H, H-2), 2.06 (dd, 1 H, *J* = 15.0, 4.1 Hz, H-4_{ax}), 2.92 (br, 1 H, OH), 3.65 (m, 1 H, H-3), 3.75 (dd, 1 H, *J* = 7.2, 5.5 Hz, H-7_{exo}), 4.29 (d, 1 H, *J* = 5.5 Hz, H-1), 4.33 (d, 1 H, *J* = 7.2 Hz, H-7_{endo}), 5.59 (brs, 1 H, H-5). Anal. Calcd for $C_7H_{12}O_3$: C, 58.32; H, 8.39. Found: C, 58.05; H, 8.17.

(1*S*,2*R*,3*R*,5*R*)-2-Methyl-6,8-dioxabicyclo[3.2.1]octan-3-yl Propanoate (43). To a solution of 3.48 g (24.0 mmol) of the alcohol **42** and 0.15 g (0.96 mmol) of 2,2′-bipyridyl in 96 mL of THF at -78 °C was added dropwise a 1.5 M solution of *n*-butyllithium in hexane until a purple color persisted (ca. 16 mL, 1.0 equiv). After stirring for 15 min at this temperature 2.3 mL (26.35 mmol) of propionyl chloride was added and the mixture was allowed to warm to room temperature over 2 h. Water was added, followed by 32 mL of saturated aqueous $NaHCO_3$. After additional stirring for 30 min the mixture was diluted with 150 mL of dichloromethane, and the aqueous layer was extracted with five 16-mL portions of dichloromethane. The combined organic phases were dried ($MgSO_4$) and concentrated to give, after flash chromatography on silica with 30% ether–petroleum ether, 4.37 g (91%) of the propanoate **43** as an oil: $[\alpha]^{24}_D$ -121° (*c* 5.45, $CHCl_3$); IR (neat) 1730, 1183, 1148, 1125, 1052, 1015 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (t, 3 H, *J* = 7.6 Hz, CH_2CH_3), 1.23 (d, 3 H, *J* = 7.6 Hz, C-2 Me), 1.78 (d, 1 H, *J* = 15.1 Hz, H-4_{eq}), 1.84 (m, 1 H, H-2), 2.04 (ddd, 1 H, *J* = 15.1, 5.5, 2.1 Hz, H-4_{ax}), 2.35 (q, 2 H, *J* = 7.6 Hz, CH_2CH_3), 3.79 (dd, 1 H, *J* = 8.2, 5.5 Hz, H-7_{exo}), 4.22 (d, 1 H, *J* = 8.2 Hz, H-7_{endo}), 4.26 (d, 1 H, *J* = 5.5 Hz, H-1), 4.70 (d, 1 H, *J* = 5.5 Hz, H-3), 5.51 (brs, 1 H, H-5). Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.99; H, 8.15. Found: C, 59.75; H, 8.05.

(2*S*,3*S*,4*R*)-[[3-Methyl-4-(propionyloxy)-3,4-dihydro-2*H*-pyran-2-yl]methoxy]trimethylsilane (45). To a stirred solution of 0.20 g (1.02 mmol) of the anhydro sugar **43** in a mixture of 3.0 mL of toluene and 0.5 mL of cyclohexene was added dropwise at -35 °C a solution of 0.44 mL (3.08 mmol) of freshly prepared iodotrimethylsilane in 0.5 mL of toluene. After the solution was stirred at this temperature for a further 1 h, a solution of 0.48 mL (3.19 mmol) of DBU in 2.0 mL of dichloromethane was added

dropwise. The mixture was stirred at −35 °C for a further 10 min and then chromatographed directly on a short column of Kieselgel, eluting rapidly with 50% ether–petroleum ether to give 0.21 g (75%) of the glycal **45** as an unstable, yellow oil, homogeneous by TLC. Rechromatography with 10% ether–petroleum ether afforded a pure sample: IR (film) 1735, 1680, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.14 (s, 9 H, $SiMe_3$), 1.01 (d, 3 H, J = 7.0 Hz, C-3 Me), 1.16 (t, 3 H, J = 7.2 Hz, CH_2CH_3), 2.13 (m, 1 H, H-3), 2.34 (q, 2 H, J = 7.2 Hz, CH_2CH_3), 3.82 (m, 3 H, H-2 and CH_2OSiMe_3), 4.76 (dd, 1 H, J = 6.5, 3.2 Hz, H-5), 4.98 (ddd, 1 H, J = 6.9, 3.2, 1.1 Hz, H-4), 6.44 (dd, 1 H, J = 6.5, 1.1 Hz, H-6); exact mass calcd for $C_{13}H_{24}O_4Si$ 272.1444, found 272.1438.

Methyl α-(*R* and *S*),5(*S*)-Dimethyl-6(*S*)-(hydroxymethyl)-5,6-dihydropyran-2(*R*)-acetate (48). To 0.28 mL (2.00 mmol) of diisopropylamine at −10 °C was added dropwise 1.16 mL of a 1.66 N solution of *n*-butyllithium in hexane. After stirring at −10 °C for 20 min the hexane was removed in a stream of argon and the residue was dissolved in 2.5 mL of THF and cooled to −78 °C. A solution of 74 mg (0.27 mmol) of the ester **45** in 0.5 mL of THF was added dropwise over 5 min and the mixture was stirred at −78 °C for 30 min and then at −50 °C for 30 min. A solution of 0.26 mL (2.05 mmol) of chlorotrimethylsilane in 0.5 mL of triethylamine was added in one portion with vigorous stirring and the mixture was stirred at 20 °C for 15 min and then at 50 °C for 4 h. The mixture was poured into water, acidified with 3 N aqueous HCl, and extracted with ether. After saturation with sodium chloride the aqueous phase was re-extracted with ether and the combined organic solutions were dried ($MgSO_4$) and concentrated to give an oil. This was taken up in 10 mL of ether and treated directly with an excess of ethereal diazomethane. The solution was concentrated and the residue was dissolved in 2 mL of THF and stirred at room temperature with 0.20 mL (0.20 mmol) of a 1 N solution of tetra-*n*-butylammonium fluoride in THF. After 15 min the solution was diluted with ether, washed with water, dried ($MgSO_4$), and concentrated to give an oil. Flash chromatography on silica with 20% ethyl acetate–petroleum ether gave 42 mg (73%) of the alcohol mixture **48** as an oil, in a ratio of 5:1: IR ($CHCl_3$) 3500, 1735 cm^{-1}; major isomer ^1H NMR ($CDCl_3$) δ 0.93 (d, 3 H, J = 6.6 Hz, C-5 Me), 1.16 (d, 3 H, J = 6.6 Hz, C-α Me), 1.70 (br 1 H, OH), 2.23 (br, 1 H, H-5), 2.68 (dq, 1 H, J = 6.6, 6.6 Hz, H-α), 3.27 (ddd, 1 H, J = 9.5, 6.7, 2.6 Hz, H-6), 3.56 (dd, 1 H, J = 11.6, 6.7 Hz, CH_2OH), 3.71 (s, 3 H, OCH_3), 3.77 (dd, 1 H, J = 11.6, 2.6 Hz, CH_2OH), 4.37 (ddd, 1 H, J = 6.6, 4.0, 0.8 Hz, H-2), 5.67 (br s, 2 H, H-3,4); minor isomer δ 1.17 (d, C-α Me), 2.60 (dq, H-α), 4.46 (br, H-2). Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.32; H, 8.21.

Methyl α(*R*),5(*S*)-Dimethyl-6(*S*)-(hydroxymethyl)tetrahydropyran-2(*R*)-acetate (49). A solution of 42 mg (0.20 mmol) of the alcohol mixture **48** in 3 mL of ethyl acetate containing 10 mg of PtO_2 was stirred under an atmosphere of hydrogen for 2 h. The catalyst was filtered off and the filtrate concentrated to give an oil. Separation by reversed-phase HPLC gave 4.8 mg (10%) of the minor isomer **50** and 25.2 mg (60%) of the major product **49**. **50** was obtained as an oil and was distilled at 80 °C (0.004 mmHg): $[\alpha]^{21}_D$ +23° (*c* 0.33, $CHCl_3$); IR ($CHCl_3$) 3560, 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82 (d, 3 H, J = 6.4 Hz, C-5 Me), 1.22 (d, 3 H, J = 7 Hz, C-α Me), 1.20–1.70 (m, 4 H, H-4,5, OH), 1.81 (m, 2 H, H-3), 2.54 (dq, 1 H, J = 7.0, 7.0 Hz, H-α), 3.10 (ddd, 1 H, J = 9.6, 7.2, 2.9 Hz, H-6), 3.52 (m, 2 H, H-2, CH_2OH), 3.68 (s, 3 H, OCH_3), 3.72 (m, 1 H, CH_2OH). Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 61.13; H, 9.40. **49** as an oil was distilled at 80 °C (0.004 mm Hg): $[\alpha]^{21}_D$ −6° (*c* 0.25, $CHCl_3$); IR ($CHCl_3$) 3570, 3480, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82 (d, 3 H, J = 6.6 Hz, C-5 Me), 1.12 (d, 3 H, J = 7.1 Hz, C-α Me), 1.20–1.33 (m, 2 H, H-4), 1.61 (br, 1 H, H-5), 1.67–1.86 (m, 2 H, H-3), 2.10 (br, 1 H, OH), 2.54 (dq, 1 H, J = 7.1, 8.2 Hz, H-α), 3.09 (ddd, 1 H, J = 9.8, 7.2, 2.6 Hz, H-6), 3.49 (m, 2 H, H-2, CH_2OH), 3.68 (m, 1 H, CH_2OH), 3.69 (s, 3 H, OCH_3). Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 61.39; H, 9.44.

Methyl α(*R*),5(*S*)-Dimethyl-6(*S*)-(iodomethyl)tetrahydropyran-2(*R*)-acetate (51). To a solution of 19.3 mg (0.089 mmol) of the alcohol **49** in 3 mL of benzene was added, in order, 51.5 mg (0.196 mmol) of triphenylphosphine, 27.3 mg (0.401 mmol) of imidazole, and 47.5 mg (0.187 mmol) of iodine. The mixture was refluxed with stirring for 1.5 h before dilution with 50 mL of ether and washing with three 20-mL portions of water. After drying ($MgSO_4$) and concentration, the product was triturated with petroleum ether. Flash chromatography of the triturate on silica with petroleum ether gave 25.0 mg (86%) of the iodide **51** as an oil: evaporative distillation at 75 °C (0.005 mmHg); $[\alpha]^{21}_D$ +7° (*c* 0.33, $CHCl_3$); IR ($CHCl_3$) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (d, 3 H, J = 6.4 Hz, C-5 Me), 1.12 (d, 3 H, J = 7.1 Hz, C-α Me), 1.22–1.32 (m, 2 H, H-4), 1.59 (br, 1 H, H-5), 1.67–1.86 (m, 2 H, H-3), 2.56 (dq, 1 H, J = 8.7, 7.1 Hz, H-α), 2.88 (ddd, 1 H, J = 10.8, 8.3, 2.4 Hz, H-6), 3.12 (dd, 1 H, J = 10.5, 8.3 Hz, CH_2I), 3.43 (dd, 1 H, J = 10.5, 2.4 Hz, CH_2I), 3.51 (ddd, 1 H, J = 10.8, 8.7, 2.2 Hz, H-2), 3.75 (s, 3 H, OCH_3). Anal. Calcd for $C_{11}H_{19}O_3I$: C, 40.51; H, 5.87. Found: C, 40.35; H, 5.94.

Methyl α(*R*),5(*S*)-Dimethyl-6(*R*)-(hydroxymethyl)tetrahydropyran-2(*R*)-acetate (53). To a solution of 40 mg (0.122 mmol) of the iodide **51** in 2 mL of pyridine was added 30 mg (0.246 mmol) of silver(I) fluoride and the mixture was stirred at room temperature in the dark for 24 h. After dilution with 50 mL of ether the organic solution was washed with eight 20-mL portions of saturated aqueous $CuSO_4$, followed by three 10-mL portions of water. Drying ($MgSO_4$) and concentration gave the crude enol ether **52** as an oil, which was immediately dissolved in 1.0 mL of THF and treated at room temperature with 0.12 mL (0.122 mmol) of a 1 N solution of borane in THF. After stirring at room temperature for 30 min, 1:0 mL of water was added and the mixture was cooled to 0 °C and treated dropwise with 0.080 mL (0.24 mmol) of 3 N aqueous NaOH and 0.024 mL (0.24 mmol) of 30% hydrogen peroxide. After 90 min at 0 °C the solution was diluted with 30 mL of ether and washed with three 10-mL portions of water. Drying ($MgSO_4$) and concentration afforded a 60:40 mixture of the epimeric alcohols **53** and **49**. Separation by reversed-phase HPLC gave 14.9 mg (55%) of the alcohol **53** as an oil: evaporative distillation at 90 °C (1.0 mmHg); $[\alpha]^{22}_D$ −73° (*c* 0.38, $CHCl_3$); IR ($CHCl_3$) 3490, 1727, 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82 (d, 3 H, J = 7.3 Hz, C-5 Me), 1.13 (d, 3 H, J = 7.3 Hz, C-α Me), 1.20–2.10 (m, 5 H, H-3,4,5), 2.51 (dq, 1 H, J = 10.3, 7.3 Hz, H-α), 2.84 (br, 1 H, OH), 3.45 (dd, 1 H, J = 11.2, 3.7 Hz, CH_2OH), 3.71 (m, 1 H, H-2), 3.72 (s, 3 H, OCH_3), 3.88 (m, 1 H, H-6), 4.04 (dd, 1 H, J = 11.2, 11.2 Hz, CH_2OH). Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 61.07; H, 9.57. Also isolated was 10.1 mg (40%) of the epimeric alcohol **49** which upon recycling afforded a further 4.0 mg (15%) of the alcohol **53**.

Methyl α(*R*),5(*S*)-Dimethyl-6(*R*)-formyltetrahydropyran-2(*R*)-acetate (54). A solution of 26 mg (0.12 mmol) of the alcohol **53** in 1 mL of dichloromethane was added in one portion to a vigorously stirred suspension of 52 mg (0.24 mmol) of pyridinium chlorochromate in 2 mL of dichloromethane. After the mixture stirred at 20 °C for 48 h, it was filtered through a short column of silica, eluting with further quantities of dichloromethane. Concentration of the eluate afforded an oil which was rechromatographed on silica with 30% ether–petroleum ether to give 16.0 mg (62%) of the aldehyde **54** as an oil: IR ($CHCl_3$) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12 (d, 3 H, J = 7.3 Hz, C-5 Me), 1.14 (d, 3 H, J = 6.7 Hz, C-α Me), 1.20–2.10 (m, 5 H, H-3,4,5), 2.64 (dq, 1 H, J = 8.3, 6.7 Hz, H-α), 3.72 (s, 3 H, OCH_3), 3.95 (m, 1 H, H-2), 4.13 (d, 1 H, J = 6.0 Hz, H-6), 9.84 (d, 1 H, J = 1.2 Hz, CHO); exact mass calcd for $C_{11}H_{18}O_4$ 214.1205, found 214.1209.

Methyl α(*R*),5(*S*)-Dimethyl-6(*R*)-[1(*R*) and 1(*S*)-hydroxypropyl]tetrahydropyran-2(*R*)-acetate (55 and 56). A solution of 12.4 mg (0.058 mmol) of the aldehyde **54** in 0.5 mL of THF was treated dropwise at −30 °C with 0.27 mL (0.066 mmol) of a 0.27 N solution of ethylmagnesium bromide in THF. After the mixture was stirred for 15 min at this temperature, 10 mL of saturated aqueous NH_4Cl was added and the mixture was extracted with three 20-mL portions of ether. The combined organic solutions were washed with 10 mL of water, then dried ($MgSO_4$), and concentrated to give the epimeric alcohols **55** and **56** as a 3:2 mixture (^1H NMR analysis). Flash chromatography on silica afforded 3.0 mg of the alcohol **55**, followed by 4.8 mg of the alcohol **56** (overall yield 7.8 mg, 55%). Alcohol **55** (high R_f): oil; evaporative distillation at 95 °C (0.080 mmHg); $[\alpha]^{21}_D$ −56° (*c* 0.30, $CHCl_3$); IR ($CHCl_3$) 3540, 1730, 1269, 1162, 1052, 969 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (d, 3 H, J = 7.3 Hz, C-5 Me), 1.00 (t, 3 H, J = 7.3 Hz, CH_2CH_3), 1.10 (d, 3 H, J = 7.3 Hz, C-α Me), 1.20–1.95 (m, 7 H, H-3,4,5, CH_2CH_3), 2.68 (br s, 1 H, OH), 2.91 (dq, 1 H, J = 10.6, 7.3 Hz, H-α), 3.52 (m, 2 H, H-6, CHOH), 3.71 (s, 3 H, OCH_3), 3.93 (ddd, 1 H, J = 10.6, 5.2, 5.0 Hz, H-2).

Anal. Calcd for $C_{13}H_{24}O_4$: C, 63.91; H 9.90. Found: C, 64.00; H, 10.20. Alcohol **56** (low R_f): mp 76–77 °C (petroleum ether); $[\alpha]^{21}_D$ −79.5° (*c* 0.3, $CHCl_3$); IR ($CHCl_3$) 3590, 3500, 1730, 1272, 1162, 1044, 968, 907 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (t, 3 H, *J* = 7.6 Hz, CH_2CH_3), 1.03 (d, 3 H, *J* = 7.3 Hz, C-5 Me), 1.08 (d, 3 H, *J* = 7.3 Hz, C-α Me), 1.20–2.10 (m, 7 H, H-3,4,5, CH_2CH_3), 3.01 (dq, 1 H, *J* = 10.6, 7.3 Hz, H-α), 3.49 (m, 2 H, H-6, CHOH), 3.68 (s, 3 H, OCH_3), 3.89 (ddd, 1 H, *J* = 10.6, 5.2, 3.9 Hz, H-2). Anal. Calcd for $C_{13}H_{24}O_4$: C, 63.91; H, 9.90. Found: C, 63.84; H, 9.84.

Methyl α(*R*),5(*S*)-Dimethyl-6(*R*)-(1-oxopropyl)tetrahydropyran-2(*R*)-acetate (2). Jones' reagent was added dropwise at room temperature to a stirred solution of 60 mg (0.24 mmol) of the alcohol mixture **55** and **56** in 5 mL of acetone until the orange color persisted. After a further 15 min the mixture was diluted with 20 mL of water and the acetone was removed in vacuo. The residue was extracted with three 20-mL portions of ether and the extract was washed with 10 mL of water, dried ($MgSO_4$), and concentrated to an oil. Chromatography on silica with 30% ether–petroleum ether gave 57.6 mg (96%) of the ketone **2** as an oil: evaporative distillation 110 °C (0.05 mmHg); $[\alpha]^{22}_D$ −20° (*c* 0.70, $CHCl_3$) (lit.[12f] $[\alpha]^{25}_D$ −21.96°); IR ($CHCl_3$) 1732, 1720, 1163 cm^{-1}; ^1H NMR ($CDCl_3$) δ (400 MHz) 0.97 (d, 3 H, *J* = 7.1 Hz, C-5 Me), 1.02 (t, 3 H, *J* = 7.3 Hz, CH_2CH_3), 1.09 (d, 3 H, *J* = 7.0 Hz, C-α Me), 1.33 (m, 1 H, H-5), 1.69 (m, 2 H, H-4), 1.84, 2.02 (2 m, 2 H, H-3), 2.40, 2.56 (2 dq, 2 H, *J* = 12.0, 7.3 Hz, $COCH_2CH_3$), 2.72 (dq, 1 H, *J* = 9.6, 7.0 Hz, H-α), 3.68 (s, 3 H, OCH_3), 3.72 (m, 1 H, H-2), 4.16 (d, 1 H, *J* = 4.3 Hz, H-6). Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.32; H, 9.14.

(−)-Methyl α(*R*),5(*S*)-Dimethyl-6(*R*)-[1-ethyl-4-[4(*S*)-[2-[*N*-[[(β-trimethylsilyl)ethoxy]methyl]pyrrolyl]-carbonyl]-1(*S*)-ethyl-3a(*R*),4,5(*S*),7a(*S*)-tetrahydroindan-5-yl]-1(*E*),3(*E*)-butadienyl]tetrahydropyran-2(*R*)-acetate (58). To a solution of 71 mg (0.13 mmol) of the (−)-sulfone **34** in 0.43 mL of THF containing 0.11 mL of HMPA at −78 °C was added 0.10 mL of a 1.6 N solution of *n*-butyllithium in hexane. After 10 min at −78 °C a solution of 43.3 mg (0.16 mmol) of the (+)-aldehyde **3** in 0.2 mL of THF was added over 4 min. After a further 45 min, 0.032 mL (0.27 mmol) of benzoyl chloride was added in one portion. The reaction mixture was allowed to warm to room temperature over 2 h before the addition of 0.035 mL (0.27 mmol) of 3-(*N*,*N*-dimethylamino)propyl-1-amine in one portion. The reaction mixture was diluted with 50 mL of ether and 20 mL of water. The organic solution, combined with three 10-mL extracts of the aqueous phase, was washed with 10 mL of 10% aqueous HCl, 10 mL of 5% aqueous $NaHCO_3$, and 20 mL of brine before drying ($MgSO_4$) and concentration to give 0.12 g of the benzoyloxy sulfones **57** as a gum. The crude benzoyloxy sulfones were stirred with 0.33 g (0.68 mmol) of a 4% sample of sodium amalgam in 1.10 mL of THF and 0.36 mL of methanol at −20 °C for 2 h. A further 0.2 g of sodium amalgam was added and after 1 h at −20 °C the reaction mixture was poured into 100 mL of petroleum ether and 10 mL of water. The organic solution, combined with a 10-mL ether extract of the aqueous phase, was washed with 15 mL of brine before drying ($MgSO_4$) and concentration. Flash chromatography on silica with 22% ether–petroleum ether gave 46 mg (53%) of *N*-SEM–indanomycin methyl ester **58** as an oil: $[\alpha]^{25}_D$ −255° (*c* 0.84, $CHCl_3$); IR ($CHCl_3$) 1725, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.0 (s, 9 H), 0.85 (t, 3 H, *J* = 7 Hz, $CHCH_2CH_3$), 0.88 (d, 3 H, *J* = 7 Hz, C-5 Me), 0.90 (m, 2 H, CH_2SiMe_3), 0.98 (t, 3 H, *J* = 7 Hz, $=CCH_2CH_3$), 1.0–2.1 (m, 16 H), 1.10 (d, 3 H, *J* = 7 Hz, C-α Me), 2.95 (m, 1 H, H-α), 3.35 (m, 1 H, H-5″), 3.45 (dd, 1 H, *J* = 10.5, 6.4 Hz, H-4″), 3.60 (m, 2 H, CH_2CH_2O), 3.65 (s, 3 H, OCH_3), 3.80 (m, 1 H, H-2), 4.20 (d, 1 H, *J* = 3.3 Hz, H-6), 5.38 (d, 1 H, *J* = 10.5 Hz, CH_2N), 5.45 (dd, 1 H, *J* = 13.7, 9.3 Hz, H-4′), 5.52 (ddd, 1 H, *J* = 10, 4.4, 2.5 Hz, H-6″), 5.90 (d, 1 H, *J* = 10.5 Hz, CH_2N), 5.91 (m, 1 H, H-3′), 5.95 (d, 1 H, *J* = 10.6 Hz, H-2′), 6.00 (d, 1 H, *J* = 10 Hz, H-7″), 6.25 (dd, 1 H, *J* = 4.4, 2.5 Hz, pyrrole H-4‴), 7.02 (dd, 1 H, *J* = 4.4, 1.5 Hz, pyrrole H-5‴), 7.1 (dd, 1 H, *J* = 2.5, 1.5 Hz, pyrrole H-3‴); exact mass calcd for $C_{38}H_{59}NO_5Si$ 637.4159, found 637.4145.

(−)-Methyl α(*R*),5(*S*)-Dimethyl-6(*R*)-[1-ethyl-4-[4(*S*)-(2-pyrrolylcarbonyl)-1(*S*)-ethyl-3a(*R*),4,5(*S*),7a(*S*)-tetrahydroindan-5-yl]-1(*E*),3(*E*)-butadienyl]tetrahydropyran-2(*R*)-acetate (35). A solution of 0.10 mL (0.31 mmol) of 3 N anhydrous tetra-*n*-butylammonium fluoride[47] in THF was added dropwise over 5 min to 20 mg (0.031 mmol) of *N*-SEM–indanomycin methyl ester **58** in 0.03 mL of THF at 0 °C. After 10 min at this temperature the mixture was warmed to room temperature and stirred for a further 30 min. The reaction mixture was poured into 50 mL of ether and washed with 5 mL of water. After drying ($MgSO_4$) and concentration, the resulting oil was chromatographed on silica with a gradient elution of 10–50% ether–petroleum ether, to give 11.4 mg (72%) of indanomycin methyl ester **35**: $[\alpha]^{25}_D$ −238° (*c* 0.81, $CHCl_3$); IR ($CHCl_3$) 3460, 1735, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.78 (t, 3 H, *J* = 7.5 Hz, $CHCH_2CH_3$), 0.84 (d, 3 H, *J* = 7 Hz, C-5 Me), 0.95 (t, 3 H, *J* = 7.5 Hz, $=CCH_2CH_3$), 1.1 (d, 3 H, *J* = 7 Hz, C-α Me), 1.0–2.1 (m, 16 H), 2.8 (m, 1 H, H-α), 3.35 (m, 1 H, H-5″), 3.4 (m, 1 H, H-4″), 3.65 (s, 3 H, OCH_3), 3.74 (m, 1 H, H-2), 4.12 (d, 1 H, *J* = 4.2 Hz, H-6), 5.42 (dd, 1 H, *J* = 14, 8.7 Hz, H-4′), 5.52 (ddd, 1 H, *J* = 10, 4, 2.5 Hz, H-6″), 5.77 (dd, 1 H, *J* = 14, 11 Hz, H-3′), 5.85 (d, 1 H, *J* = 11 Hz, H-2′), 5.97 (d, 1 H, *J* = 10 Hz, H-7″), 6.27 (m, 1 H, H-4‴), 6.9 (m, 1 H, H-5‴), 7.02 (m, 1 H, H-3‴), 9.65 (br s, 1 H, NH); exact mass calcd for $C_{32}H_{45}NO_4$ 507.3346, found 507.3336, and was identical to material prepared from the natural product.

(−)-α(*R*),5(*S*)-Dimethyl-6(*R*)-[1-ethyl-4-[4(*S*)-(2-pyrrolylcarbonyl)-1(*S*)-ethyl-3a(*R*),4,5(*S*),7a(*S*)-tetrahydroindan-5-yl]-1(*E*),3(*E*)-butadienyl]tetrahydropyran-2(*R*)-acetic Acid (1) (Indanomycin). A solution of 22 mg (0.043 mmol) of indanomycin methyl ester **35** in 2.2 mL of methanol was stirred with 0.43 mL of 1 N aqueous NaOH at 60 °C for 2.5 h. A further 0.43 mL of sodium hydroxide solution was added and after 45 min the reaction mixture was diluted with 25 mL of ether and 25 mL of 5% aqueous HCl. The organic solution, combined with three 20-mL extracts of the aqueous phase, was washed with 10 mL of 5% aqueous HCl and 20 mL of water before drying ($MgSO_4$) and concentration to afford a semisolid. Chromatography on silica with a gradient of 50–100% ether–petroleum ether gave 19.3 mg (90%) of indanomycin (1), identical with the natural product: $[\alpha]^{25}_D$ −324° (*c* 0.94, $CHCl_3$) (lit.[12f] $[\alpha]_D$ −328°); IR ($CHCl_3$) 3460, 3200, 1720, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ (400 MHz) 0.76 (t, 3 H, *J* = 7.5 Hz, $CHCH_2CH_3$), 0.82 (d, 3 H, *J* = 7 Hz, C-6 Me), 0.95 (t, 3 H, *J* = 7.5 Hz, $=CCH_2CH_3$), 1.13 (d, 3 H, *J* = 7 Hz, C-α Me), 0.85–2.0 (m, 16 H), 2.95 (m, 1 H, H-α), 3.3 (m, 1 H, H-5″), 3.4 (dd, 1 H, *J* = 12, 7 Hz, H-4″), 3.89 (m, 1 H, H-2), 4.2 (d, 1 H, *J* = 4 Hz, H-6), 5.41 (dd, 1 H, *J* = 15, 10 Hz, H-4′), 5.5 (ddd, 1 H, *J* = 10, 4, 2.5 Hz, H-6″), 5.78 (dd, 1 H, *J* = 15, 11Hz, H-3′), 5.92 (d, 1 H, *J* = 11 Hz, H-2′), 5.96 (d, 1 H, *J* = 10 Hz, H-7″), 6.25 (m, 1 H, H-4‴), 6.9 (m, 1 H, H-5‴), 6.99 (m, 1 H, H-3‴), 10.2 (br s, 1 H, NH) (CO_2H not observable); exact mass calcd for $C_{31}H_{43}NO$ 493.3189, found 493.3188.

Indanomycin Methyl Ester (35) (Natural). A solution of 0.40 g (0.81 mmol) of indanomycin in 5 mL of ether was treated with an excess of ethereal diazomethane. Concentration afforded an oil which was chromatographed on silica with 30% ether–petroleum ether to give 0.39 g (95%) of indanomycin methyl ester **35** as a glassy solid: $[\alpha]^{21}_D$ −236° (*c* 2.55, $CHCl_3$) (lit.[12f] $[\alpha]^{25}_D$ −170.6°) ($[\alpha]^{21}_D$ −238° for synthetic material prepared earlier).

Ozonolysis of Indanomycin Methyl Ester 35. A solution of 2.00 g (3.94 mmol) of indanomycin methyl ester in 80 mL of dichloromethane containing 0.47 g (7.82 mmol) of acetic acid was treated with ozone at −78 °C until TLC showed complete absence of starting material. The excess of ozone was removed in a stream of nitrogen and 2.00 mL (27.5 mmol) of dimethyl sulfide was added. After stirring at −78 °C for 30 min and at 20 °C for 1 h the solution was washed with three 20-mL portions of saturated aqueous $NaHCO_3$, followed by two 20-mL portions of water. After drying ($MgSO_4$) and concentration the residue was triturated with petroleum ether. The triturate was concentrated and chromatographed on silica with 20% ether–petroleum ether to give 1.01 g (95%) of methyl α(*R*),5(*S*)-dimethyl-6(*R*)-(1-ethyl-1(*E*)-propenalyl)tetrahydropyran-2(*R*)-acetate (**3**) as a solid: mp 75–78.5 °C; $[\alpha]^{22}_D$ −44° (*c* 0.85); IR ($CHCl_3$) 1732, 1665, 1630, 1119, 985 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.84 (d, 3 H, *J* = 7.1 Hz, C-5 Me), 1.08 (d, 3 H, *J* = 6.6 Hz, C-α Me), 1.18 (t, 3 H, *J* = 7.4 Hz, CH_2CH_3), 1.50–2.10 (m, 5 H, H-3,4,5), 2.22, 2.77 (2 dq, 2 H, *J* = 13.3, 7.4 Hz, CH_2CH_3), 3.12 (dq, 1 H, *J* = 10.9, 6.6 Hz, H-α), 3.60 (s, 3 H, OCH_3), 3.91 (ddd, 1 H, *J* = 10.9, 5.6, 3.6 Hz, H-2), 4.42 (br s, 1 H, $W_{1/2}$ = 5.6 Hz, H-6), 6.02 (dd, 1 H, *J* = 8.1, 1.7 Hz, CHCHO), 10.04 (d, 1 H, *J* = 8.1 Hz, CHO). Anal. Calcd for $C_{15}H_{24}O_4$: C,

67.14; H, 9.01. Found: C, 66.96; H, 9.15.

Ozonolysis of the Unsaturated Aldehyde 3. A solution of 0.15 g (0.55 mmol) of the enal **3** in 25 mL of dichloromethane containing 65 mg (1.09 mmol) of acetic acid was saturated with a stream of ozone at −30 °C. When no starting material remained (TLC) 0.093 mL (1.27 mmol) of dimethyl sulfide was added and the solution was stirred at −30 °C for 15 min and at 20 °C for 1 h. After washing with three 20-mL portions of saturated aqueous $NaHCO_3$ the solution was washed with two 20-mL portions of water, dried ($MgSO_4$), and concentrated to give an oil. Chromatgraphy on silica with 20% ether–petroleum ether gave 0.125 g (93%) of the ketone **2** as an oil, identical in all respects with the synthetic material.

Methyl α(*R*),5(*S*)-Dimethyl-6(*R*)-carboxytetrahydropyran-2(*R*)-acetate (60). To a solution of 70 mg (0.29 mmol) of the ketone **2** and 0.055 mL (0.39 mmol) of triethylamine in 2 mL of 1,2-dichloroethane at 0 °C was added 0.068 mL (0.30 mmol) of *tert*-butyldimethylsilyl trifluoromethanesulfonate. After the reaction had stirred at 20 °C for 2 h, TLC analysis indicated complete conversion to the *tert*-butyldimethylsilyl enol ether **59**. The solution was diluted with 5 mL of dichloromethane, cooled to −78 °C, and saturated with a stream of ozone. After the addition of 0.10 mL of dimethyl sulfide the solution was stirred at −78 °C for 15 min and then at 20 °C for 1.5 h. The solution was washed with three 20-mL portions of 10% aqueous KF, followed by 20 mL of water. After drying ($MgSO_4$) and concentration the resulting oil was chromatographed on a short column of silica with 50% ethyl acetate–petroleum ether to give 58.9 mg (88%) of the carboxylic acid **60** as an oil: evaporative distillation at 140 °C (0.10 mmHg); $[\alpha]^{20}_D$ −22° (*c* 0.20, $CHCl_3$); IR ($CHCl_3$) 3600–2400, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.14 (d, 3 H, *J* = 7.5 Hz, C-α Me), 1.16 (d, 3 H, *J* = 7.0 Hz, C-5 Me), 1.20–2.20 (m, 5 H, H-3,4,5), 2.57 (dq, 1 H, *J* = 8.9, 7.5 Hz, H-α), 3.74 (s, 3 H, OCH_3), 3.83 (ddd, 1 H, *J* = 10.2, 8.9, 2.4 Hz, H-2), 4.33 (d, 1 H, J = 5.4 Hz, H-6) (COOH not observable); exact mass calcd for $C_{11}H_{19}O_5$ 231.1232, found 231.1237. Esterification of the acid **60** using an excess of ethereal diazomethane afforded, after chromatography on silica with 40% ether–petroleum ether, the corresponding methyl ester in 95% yield as an oil: evaporative distillation at 125 °C (1.5 mmHg), $[\alpha]^{20}_D$ −53° (*c* 0.3, $CHCl_3$); IR ($CHCl_3$) 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (d, 3 H, *J* = 6.9 Hz, C-5 Me), 1.11 (d, 3 H, *J* = 6.9 Hz, C-α Me), 1.20–2.10 (m, 5 H, H-3,4,5), 2.57 (dq, 1 H, *J* = 8.5, 6.9 Hz, H-α), 3.68, 3.70 (2 s, 6 H, OCH_3), 4.28 (ddd, 1 H, *J* = 10.9, 8.5, 3.0 Hz, H-2), 4.34 (d, 1 H, *J* = 5.8 Hz, H-6). Anal. Cacld for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 59.18; H, 8.20.

Naturally Derived Alcohol (53). To a solution of 24 mg (0.10 mmol) of naturally derived acid **60** in 2 mL of THF was added 0.12 mL (0.12 mmol) of borane–dimethyl sulfide complex at 0 °C. After stirring at this temperature for 4 h, 10 mL of methanol was added, followed by 10 mL of 3 N aqueous HCl. The mixture was extracted with three 10-mL portions of ether, and the combined ether extract was washed with 10 mL of water, dried ($MgSO_4$), and concentrated to an oil. Chromatography on silica with 20% ethyl acetate–petroleum ether gave 16.1 mg (74%) of the alcohol **5**: $[\alpha]^{22}_D$ −77° (*c* 0.21, $CHCl_3$) ($[\alpha]_D$ −73° for synthetic material prepared earlier) (spectra identical with those of the synthetic material).

Crystallographic Analysis of 28. Crystals of **28**, $C_{17}H_{23}NO_2$, are monoclinic with *a* = 14.546 (2) Å, *b* = 5.734 (1) Å, *c* = 19.187 (2) Å, β = 105.60 (1)°, *U* = 1543 Å^3, space group $P2/n$, *Z* = 4, *M* = 273.4, D_c = 1.18 g cm^{-3}. Refined unit cell parameters were obtained by centering 23 reflections on a Nicolet R3m diffractometer. 1602 independent reflections were measured (Θ < 50°) with Cu K_α radiation (graphite monochromator) and using the ω − 2Θ scan technique. Of these 1513 had $|F_o| > 3\sigma(|F_o|)$ and were considered to be observed. The data were corrected for Lorentz and polarization factors. No absorption correction was applied.

The structure was solved by direct methods and the non-hydrogen atoms refined anisotropically. The hydroxy hydrogen atom was clearly located in a Δ*F* map and refined isotropically. The positions of the other hydrogen atoms were idealized (C–H = 0.96 Å), assigned isotropic thermal parameters, $U(H) = 1.2\ U_{eq}(C)$, and allowed to ride on their parent atoms. The methyl group was refined as a rigid body. Refinement was by block-cascade full-matrix least-squares to $R = 0.043$, $R_w = 0.055$, $[w^{-1} = \sigma^2(F) + 0.00046\ F^2]$. Computations were carried out on an Eclipse S140 computer using the SHELXTL program system.[51] Fractional atomic coordinates for the non-hydrogen atoms are given in Table I. Tables II and III give the bond lengths and valence angles, respectively. (See Supplementary Material.) Figure 1 shows a perspective drawing of the molecule and the numbering scheme adopted. The C(11) carbonyl and the pyrrole ring are nearly coplanar with an N–C(12)–C(11)–O(2) torsion angle of 9.6(2)°. There is an intramolecular hydrogen bond (2.88 Å, O–H···O angle 150°) between the hydroxy and carbonyl groups. There is also an intermolecular hydrogen bond (2.89 Å N–H···O angle 144°) between the pyrrole nitrogen and the hydroxy oxygen across one of the crystallographic centers of symmetry.

Crystallographic Analysis of 56. Crystals of **56**, $C_{13}H_{24}O_4$, are orthorhombic with *a* = 5.006 (1) Å, *b* = 15.894 (4) Å, *c* = 17.448 (6) Å, *U* = 1388 Å^3, space group $P2_12_12_1$, *Z* = 4. *M* = 244.3, D_c = 1.17 g cm^{-3}. Refined unit cell parameters were obtained by centering 16 reflections on a Nicolet R3m diffractometer. 1092 independently observed reflections $[|F_o| > 3\sigma(|F_o|), \Theta < 58°]$ were measured with Cu K_α radiation (graphite monochromator) and using ω-scans. Structure solution and refinement were the same as for **28** above. The hydroxy hydrogen was again clearly resolved in a Δ*F* map and refined isotropically. The C(32) methyl group was found to be disordered with two principal positions for the carbon atom. These were refined isotropically with 50% occupancy assigned to each position. Refinement converged to give $R = 0.042$, $R_w = 0.051$, $[w^{-1} = \sigma^2(F) + 0.00057\ F^2]$. Fractional coordinates, bond lengths and valence angles for the non-hydrogen atoms are given in Tables IV, V, and VI, respectively. (See supplementary material.) Figure 2 shows a perspective view of the molecule and the numbering scheme adopted. The structure shows the substituents on C(3) and C(6) to be axial and that on C(7) to be equatorial. There is an intermolecular hydrogen bond (2.83 Å, O–H···O angle 155°) between the hydroxy oxygen O(2) and the ester carbonyl oxygen O(3).

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Registry No. **1**, 66513-28-8; **2**, 76566-84-2; **3**, 76566-87-5; (±)-**7**, 88244-69-3; (±)-**8**, 91053-81-5; (±)-**9**, 65618-03-3; (±)-*cis*-**10**, 91053-82-6; (±)-*trans*-**10**, 91054-00-1; (±)-**11**, 91109-67-0; **12**, 91053-83-7; (±)-**13**, 91053-84-8; (±)-**14**, 91053-85-9; (±)-**15**, 91053-86-0; (±)-**16**, 91053-87-1; (±)-**17**, 91053-88-2; **18**, 42516-28-9; (±)-**19**, 91053-89-3; (±)-**21**, 91053-90-6; (±)-**23**, 91053-91-7; **24**, 88204-61-9; **25**, 88204-62-0; **26**, 76566-89-7; **27**, 91109-68-1; (±)-**28**, 91109-69-2; **30**, 87954-20-9; (±)-**31**, 91109-70-5; **32**, 88204-64-2; **33**, 91053-92-8; **34**, 88204-59-5; **35**, 76567-01-6; **37**, 6167-32-4; **41**, 85433-11-0; **42**, 85433-13-2; **43**, 91053-93-9; **45**, 88204-52-8; **47**, 91053-94-0; **48** (major isomer), 88204-53-9; **48** (minor isomer), 88204-60-8; **49**, 88204-54-0; **50**, 91053-95-1; **51**, 91053-96-2; **52**, 88204-55-1; **53**, 88204-56-2; **54**, 88204-57-3; **55**, 88211-00-1; **56**, 88204-58-4; **57**, 88204-65-3; **58**, 91083-02-2; **59**, 91053-97-3; **60**, 91053-98-4; **60** (methyl ester), 91053-99-5; $Cl(CH_2)_3OH$, 627-30-5; $I(CH_2)_3OH$, 627-32-7; $I(CH_2)_3OSiMe_3$, 78173-39-4; $CH_3(CH_2)_2COOEt$, 105-54-4; pyrrolylmagnesium bromide, 6123-07-5.

Supplementary Material Available: Tables I–IV and listings of anisotropic thermal parameters, hydrogen coordinates, and temperature factors, and tables of observed and calculated structure factors for the X-ray analysis of compounds **28** and **56** (7 pages). Ordering information is given on any current masthead page.

(51) Sheldrick, G. M. SHELXTL, "An Integrated System for Solving, Refining Displaying Crystal Structures from Diffraction Data", University of Göttingen, Federal Republic of Germany, revised version 1983.