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Total Synthesis of Ionophore Antibiotic X-14547A[1]

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A highly stereocontrolled and convergent total synthesis of optically active ionophore antibiotic X-14547A (**1**) was designed and carried out. Degradative reactions led to the key intermediates **3** and **6**, which served as convenient comparison stages. The tetrahydropyran building block **3** was totally synthesized in its natural form from (−)-diethyl D-tartrate by a series of highly efficient steps and an epoxide opening–ring closure reaction accompanied by clean inversion, whereas the requisite tetrahydroindan block **4** was synthesized in its racemic (from δ-valerolactone) and optically active form (from the SAMP hydrazone **25**) employing an Enders-type stereoselective alkylation and an intramolecular Diels–Alder reaction as the key steps. Coupling of the two fragments by a two-carbon link using Grignard and sulfone anion chemistry followed by stereoselective construction of the *trans*-butadienyl system and functional group elaboration afforded the advanced intermediate **42**. Finally attachment of the 2-ketopyrrole system by new technology involving the 2-pyridinethiol ester functionality and a magnesium–pyrrole reagent proceeded smoothly and after base hydrolysis completed the total synthesis of X-14547A.

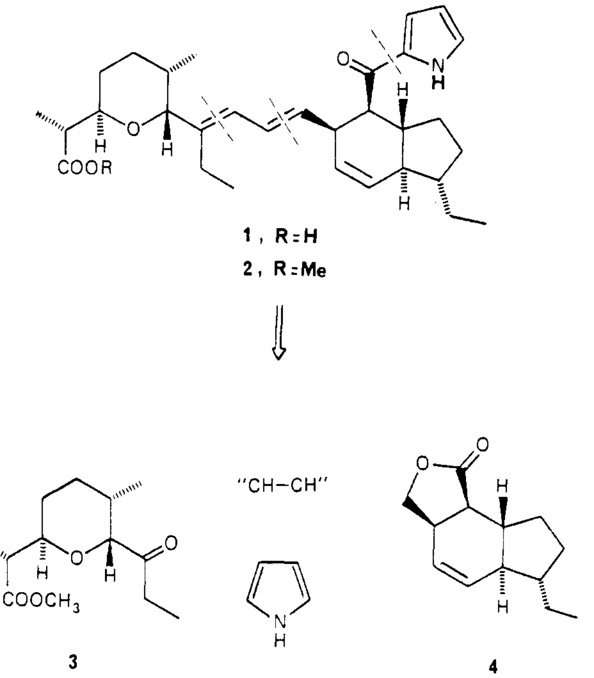
The ionophore group of antibiotics represents a biologically and commercially important class of compounds whose number, utility, and significance continue to increase.[2] The rather intense interest in these compounds arises from their ability to complex cations and exert a variety of biological activities. The fascinating and challenging structural features of these molecules have brought them into focus as synthetic targets. Lasalocid A, monensin, and calcimycin (A23187) are some examples of these molecules, the syntheses of which have recently been reported.[3] Among the naturally occurring ionophores, X-14547A,[4] a Hoffman La-Roche compound isolated from *Streptomyces antibioticus* NRRL 8167, by Westley et al.,[5] represents a structurally unique molecule. Although it contains fewer oxygens than most of the other members of this family, it possesses an array of rather rare and synthetically challenging features, including a *trans*-butadienyl moiety, a trans-fused tetrahydroindan system, a (more commonly found) substituted tetrahydropyran ring, and a ketopyrrole grouping (also found in calcimycin). The complete molecular structure, including absolute stereochemistry, of X-14547A has been determined by X-ray crystallographic analysis carried out on the salt of the antibiotic with (*R*)-(+)-1-amino-1-(4-bromophenyl)ethane. Interestingly, this salt is formed in 2:1 X-14547A/base stoichiometry, despite the fact that both components are monobasic.[5] Other properties of this unusual molecule include transport of monovalent cations such as Na^+ and K^+ and divalent cations such as Ca^{2+} and Rb^{2+}, a feature common to only a few other ionophores such as calcimycin, iononycin, lysocellin, and lasalocid A.[2] Its biological properties include antibiotic activity against Gram-positive bacteria, antihypertensive and antitumor activities, and growth promotion in ruminants by improvement of feed utilization.[5]

Our total synthesis of X-14547A was first outlined in 1980[1a] and reported in preliminary form in 1981.[1b–d] We now disclose the full details of this work.

Results and Discussion

1. Strategy and Retrosynthetic Studies. Retrosynthetic analysis of ionophore antibiotic X-14547A (**1**) revealed the three strategic bonds indicated in Scheme I, disconnection and simple functional group interchange of which led to the tetrahydropyran fragment **3**, a two-carbon unit "CH–CH", the tetrahydroindan fragment **4**, and pyrrole. Our synthetic strategy recognized and required solutions to the following problems: (i) enantioselective

Scheme I



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† Fellow of the A. P. Sloan Foundation, 1979–1983; recipient of a Camille and Henry Dreyfus Teacher–Scholar Award, 1980–1985; J. S. Guggenheim Fellow, 1984.

[1] Preliminary communications: (a) Nicolaou, K. C.; Magolda, R. L., 2nd Chemical Congress of the North American Continent, Las Vegas, Aug, 1980; ORGN 156. (b) Nicolaou, K. C.; Magolda, R. L. *J. Org. Chem.* **1981**, *46*, 1506. (c) Nicolaou, K. C.; Papahatjis, D. P.; Claremon, D. A.; Dolle, R. E. *J. Am. Chem. Soc.* **1981**, *103*, 6967. (d) Nicolaou, K. C.; Claremon, D. A.; Papahatjis, D. P.; Magolda, R. L. *J. Am. Chem. Soc.* **1981**, *103*, 6969.

[2] (a) Pressman, B. C. *Annu. Rev. Biochem.* **1976**, *45*, 501. (b) Westley, J. W. *Adv. Appl. Microbiol.* **1977**, *22*, 177. (c) Doblem, M. "Ionophores and their Structures"; Wiley-Interscience: New York, 1981. (d) Westley, J. W., Ed. "Polyether Antibiotics"; Marcel Dekker: New York, 1983; Vol. I and II.

[3] Lacalocid: (a) Nakata, T.; Schmid, G.; Vranesic, B.; Okigawa, M.; Smith-Palmer, T.; Kishi, Y. *J. Am. Chem. Soc.* **1978**, *100*, 2933. (b) Ireland, R. E.; Thaisrivongs, S.; Wilcox, C. S. *Ibid.* **1980**, *102*, 1155. (ce Ireland, R. E.; McGarvey, G. J.; Anderson, R., C.; Badoud, R.; Fitzimmons, B.; Thaisrivongs, S. *Ibid.* **1980**, *102*, 6178. Monensin: (d) Schmid, G.; Fukuyama, T.; Akasaka, K.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 259. (e) Fukuyama, T.; Wang, C.-L. J.; Kishi, Y. *Ibid.* **1979**, *101*, 260. (f) Fukuyama, T.; Akasaka, K.; Karanewsky, D. S.; Wang, C.-L. J.; Schmid, G.; Kishi, Y. *Ibid.* **1979**, *101*, 262. (g) Collum, D. D.; McDonald, J. H., III; Still, W. C. *Ibid.* **1980**, *102*, 2117, 2118, 2120. Calcimycin: (h) Evans, D. A.; Sacks, C. F.; Kleschick, W. C.; Taber, T. R. *J. Am. Chem. Soc.* **1979**, *101*, 6789. (i) Grieco, P. A.; Williams, E.; Tanaka, H.; Gilman, S. *J. Org. Chem.* **1980**, *45*, 3537. Narasin and salinomycin: (j) Kishi, Y.; Hatakeyama, S.; Lewis, M. D. In "Frontiers of Chemistry";; Laidler, K. J., Ed.; Pergamon Press: New York, 1982; p 287.

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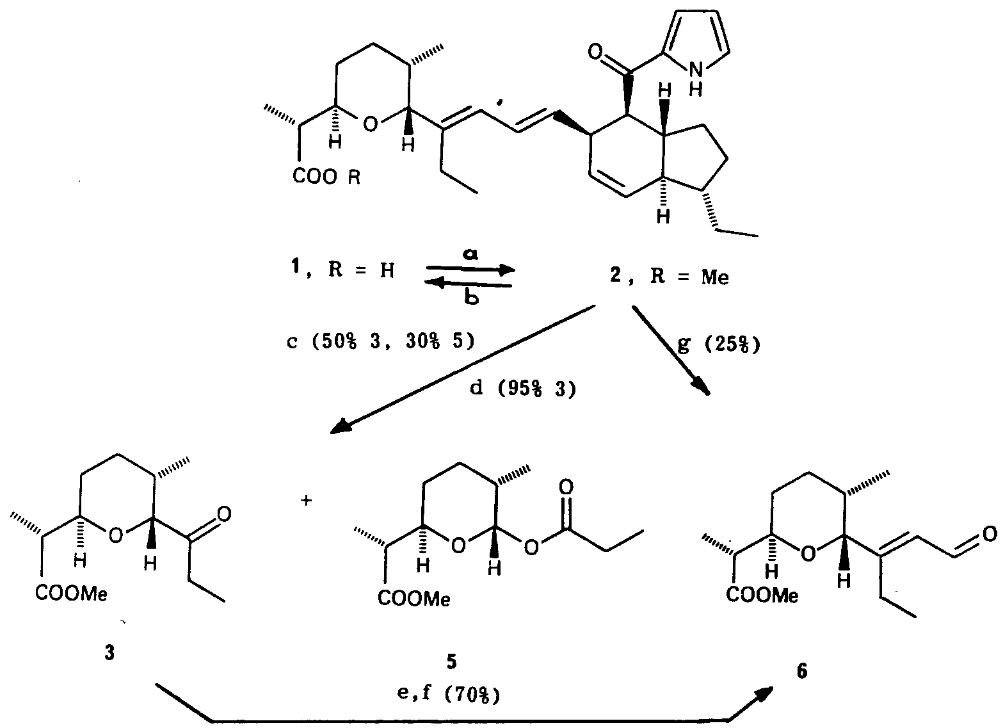
Scheme II[a]



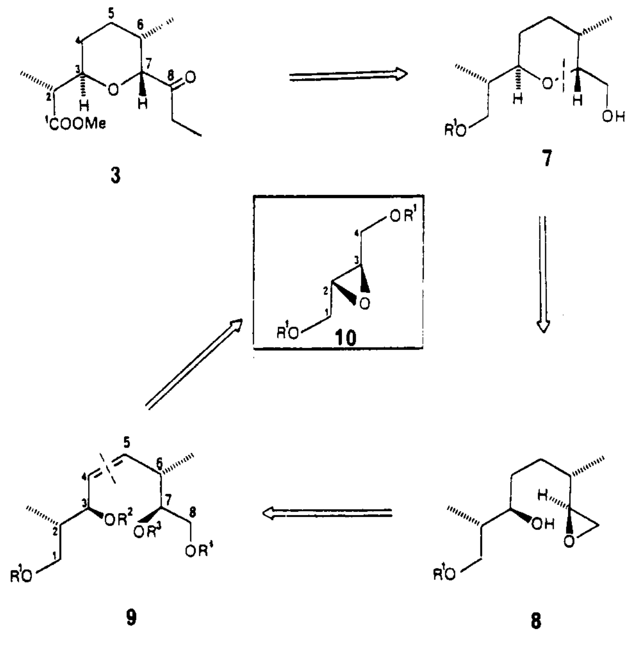
[a] (a) CH_2N_2, ether, 0 °C; (b) 10 equiv of LiOH, THF-H_2O, 1:1, 25 °C, 7 days; (c) O_3-CH_2Cl_2, −78 °C then excess Me_2S; (d) 2.0 equiv of AcOH, O_3, CH_2Cl_2, −78 °C then excess Me_2S; (e) 1.1 equiv of CH_2=CHMgBr, THF, −78 °C; (f) 5.0 equiv of CrO_3·pyr·HCl, CH_2Cl_2, 40 °C; (g) OsO_4 catalytic $NaIO_4$, *t*-BuOH-H_2O, 25 °C.

construction of 3, (ii) enantioselective synthesis of fragment 4, and (iii) coupling of these two segments 3 and 4 and selective generation of the *trans*-butadienyl and 2-keto-pyrrole systems.

In order to prepare the ground for the final stages of the synthesis and establish useful comparison points along the synthetic route, we undertook a brief degradation study of X-14547A (1) (Scheme II). Since a number of asymmetric centers in X-14547A (1) are potentially epimerizable, it was of crucial interest to determine whether hydrolysis of its methyl ester 2 to the natural product 1 could be achieved without altering the stereochemical integrity of the molecule. To provide an answer to this question, the methyl ester of the antibiotic 2 was prepared (excess CH_2N_2, 100%) and subjected to alkaline (excess LiOH) hydrolysis. Although relatively slow, the hydrolysis proceeded smoothly and without epimerization at any of the asymmetric centers leading to the free acid 1 in 100% yield. It was interesting to observe significant changes in ^1H and ^{13}C NMR chemical shifts at different concentrations of X-14547A (1), a rare phenomenon presumably due to strong intermolecular complexation in solution resulting in a "shift reagent effect".

Extensive ozonolysis of X-14547A methyl ester 2 followed by dimethyl sulfide decomposition of the ozonide afforded ketone 3 (50%) and ketal ester 5 (30%, ^{13}C NMR δ 93.98, ketal). The presence of acetic acid in the ozonolysis mixture suppressed, as expected,[6] almost completely the formation of 5, leading to 3 in 95% yield. In contrast to the ozonolysis rapture, the action of sodium periodate and osmium tetraoxide catalyst in aqueous *tert*-butyl alcohol resulted in the formation and isolation of the α,β-unsaturated aldehyde 6 in 25% yield. Finally, ketone 3 was converted to 6 in a highly stereoselective manner by the action of vinylmagnesium bromide followed by PCC oxidation accompanied by rearrangement[7] (70% overall yield and ca. 6:1 *E*:*Z* ratio by ^1H NMR). With this information at hand we were now ready to turn our attention to the

Scheme III



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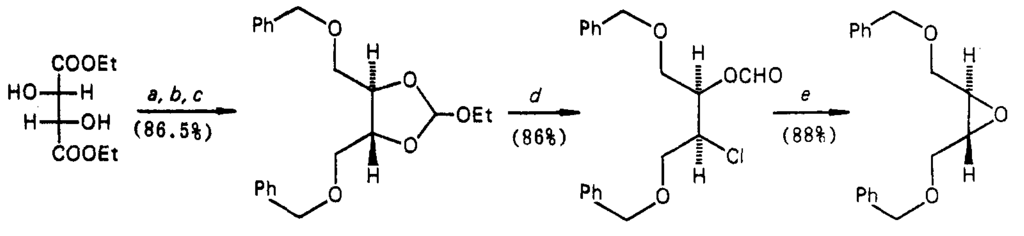
(4) The name indanomycin has recently been proposed for X-14547A: Edwards, M. P.; Ley, S. V.; Lister, S. G.; Palmer, B. D.; Williams, D. J., unpublished results. We thank Professor S. V. Ley for communicating this manuscript to us prior to publication.

(5) (a) Westley, J. W.; Evans, R. H., Jr.; Liu, C.-M.; Hermann, T.; Blount, J. F. *J. Am. Chem. Soc.* **1978**, *100*, 6786. (b) Liu, C.-M.; Hermann, T. E.; Liu, M.; Bull, D. N.; Palleroni, N. J.; Prosser, B. L. T.; Westley, J. W.; Miller, P. A., *J. Antibiot.* **1979**, *32*, 95. (c) Westley, J. W.; Evans, R. H., Jr.; Sello, L. H.; Troupe, N.; Liu, C.-M.; Blount, J. F. *Ibid.* **1979**, *32*, 100. (d) Westley, J. W.; Liu, C.-M.; U.S. Patent 4100171, 1978. (e) Westley, J. W., personal communication.

(6) Story, P. R.; Burgess, J. R. *Tetrahedron Lett.* **1968**, 1287.

(7) Dauben, W. G.; Michmo, D. M. *J. Org. Chem.* **1977**, *42*, 682.

Scheme IV[a]



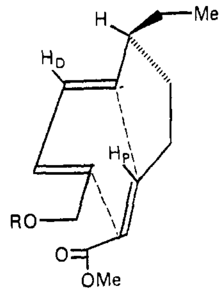
[a] (a) $(EtO)_3CH$-AcOH, $PhCH_3$, reflux; (b) LAH-THF, 0 °C; (c) $PhCH_2Br$-NaH-THF, 0 → 65 °C; (d) 1.2 equiv of PCl_5-CH_2Cl_2, 0 °C; (e) 2.5 equiv of K_2CO_3-MeOH, 25 °C.

total construction of the tetrahydropyran fragment 3.

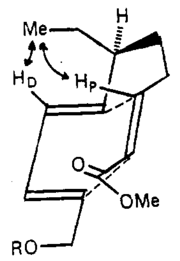
2. **Synthesis of Enantiomerically Pure Tetrahydropyran Building Block 3 (C_1–C_8 Fragment).** By careful inspection of the subtarget 3 and retrosynthetic analysis using functional group interchanges and strategic bond disconnections, one can recognize and take advantage of a rather subtle symmetry arriving at Scheme III (7 → 3, oxidation, organometallic addition; 8 → 7, epoxide opening; 9 → 8, reduction, epoxide formation; 10 → 9, cuprate-induced epoxide opening, Wittig; note inversions of configuration on each epoxide opening). This analysis leads to the identification of the *R*,*R* epoxide 10 as a suitable starting material for a convergent synthesis through two essentially equivalent fragments, C_1–C_4 and C_5–C_8 (structure 9, Scheme III).

The *R*,*R* epoxide 10 is readily available in multigram quantities from (−)-diethyl D-tartrate (11) according to Scheme IV. Thus, starting with 11, orthoformate formation (**11a**) with triethyl orthoformate and glacial acetic acid in refluxing toluene followed by lithium aluminum hydride reduction (**11b**) and protection of the resulting diol as a dibenzyl ether furnished 12 in 86.5% overall yield. Treatment of orthoformate 12 with phosphorus pentachloride led smoothly to the chloroformate 13 (inversion, 86%), which upon basic treatment gave the desired epoxide 10 in high yield (inversion, 88%). Construction of building block 3 in its optically active form involved conversion of the *R*,*R* epoxide 10 to the key intermediate 15 followed by, first, divergence to the two components 17 and 18 and then convergence by coupling these intermediates and elaborating the product to the final target via an epoxide opening–ring closure reaction accompanied by one inversion, a sequence that establishes all four asymmetric centers in their correct stereochemistry. Thus, reaction of epoxide 10 with excess lithium dimethyl cuprate (**10a**) followed by debenzylation–hydrogenolysis furnished the triol 14 in essentially quantitative yield. Selective acetonization of 14 furnished the five-membered ring acetonide 15 (98%), a compound from which both the phosphonium salt 18 and the aldehyde 17 required for the Wittig coupling were formed. Aldehyde 17 was obtained from 15 via 16 by (i) benzylation (**15c**) (90%), (ii) removal of the acetonide to afford 16, (iii) differentiation of the primary and secondary hydroxyls by sequential monopivalate (**16a**) and *tert*-butyldiphenylsilyl ether formation (**16b**) followed by DIBAL-induced removal of the pivalate (**16c**) (85%), and (iv) mild oxidation of the primary hydroxyl to an aldehyde function (85%). Phosphonium salt 18 was obtained from the corresponding iodide **15b** under strictly defined conditions (PPh_3, MeCN-$(EtO)_3CH$, 4:1, 75 °C, 80%), which was obtained from 15 via the tosylate (**15a**) by standard procedures. Coupling of the ylide derived from 18 ($NaCH_2SOCH_3$-Me_2SO) with aldehyde 17 resulted in the formation of olefin 19 (*E*:*Z* ca. 2:1 by ^1H NMR and isolation) in 77% yield. Since this unsaturation is removed later on in the synthesis, this stereoisomerism is of no consequence and, therefore, separation was not required at this stage, although it could be achieved chromatographically for characterization purposes [$R_f(E)$ 0.38, $R_f(Z)$ 0.46, silica, 2.5% ethyl acetate in benzene]. Conversion of 19 to the key intermediate 21 was then smoothly carried out by (i) removing the acetonide under acid conditions (**19a**) (80%), (ii) selective tosylation of the primary hydroxyl (**19b**) (75%), (iii) exposure to freshly prepared sodium methoxide in methanol (**19c**) (100%), (iv) desilylation (**19d**) (100%), and (v) selective hydrogenation of the double bond (H_2–5% Pd-C, EtOAc, 70%). The crucial ring closure of the hydroxy epoxide 20 was found to proceed under acidic conditions (CSA catalyst, CH_2Cl_2, 25 °C, 95%) with complete regio- (tetrahydropyran ring) and stereoselectivity (inversion of epoxide center) affording a hydroxytetrahydropyran derivative, mild oxidation of which (PCC–NaOAc) yielded the aldehyde 21 in high yield (80%). The stereochemistry of 21 was evident from the coupling constant J_{AB} = 6.0 Hz (suggesting a cis relationship for H_A and H_B) and finitely proven by its conversion to the target molecule 3 (Scheme V) by the following sequence: (i) ethylmagnesium bromide addition (**21a**) (80%), (ii) debenzylation by hydrogenolysis (**21b**) (100%), (iii) Jones' oxidation of the primary and secondary hydroxyls (90%), and (iv) methylation of the resulting carboxylic acid (100%). Synthetic 3, $[\alpha]^{25}{}_D$ −21.96° (*c* 0.85, $CHCl_3$), R_f 0.58, silica, 50% ether in petroleum ether) was identical (NMR, IR, MS, [$\alpha^{25}{}_D$, TLC) with the material derived from natural X-14547A (1) as described above.

3. **Synthesis of the Tetrahydroindan Building Block 4 (C_{11}–C_{21} Fragment).** Careful inspection of structure 4 led to a number of strategic disconnections and the generation of the retrosynthetic plan outlined in Scheme VI (22 → 4, Diels–Alder lactonization; 23 → 22, Wittig-type olefinations; 24 → 23, deprotection; 25 → 24, alkylation). Applying the elegant method of Enders for the asymmetric alkylation of aldehydes via optically active SAMP hydrazones this scheme was designed to ensure optically active materials, whereas racemic 4 could be produced more conveniently from δ-valerolactone for preliminary work. The key intramolecular Diels–Alder reaction (22 → 4) was expected to produce predominantly compound 4 with the desired stereochemistry on the basis of the information encoded in the geometry of the double bonds of the precursor and the obvious relative steric comfort enjoyed by transition state TS-1 over TS-2 which is maintained in the final products as indicated by molecular models. The actual synthesis of the tetrahydroindan building block 4 both in its optically active and racemic forms is shown in Scheme VII. For the con-

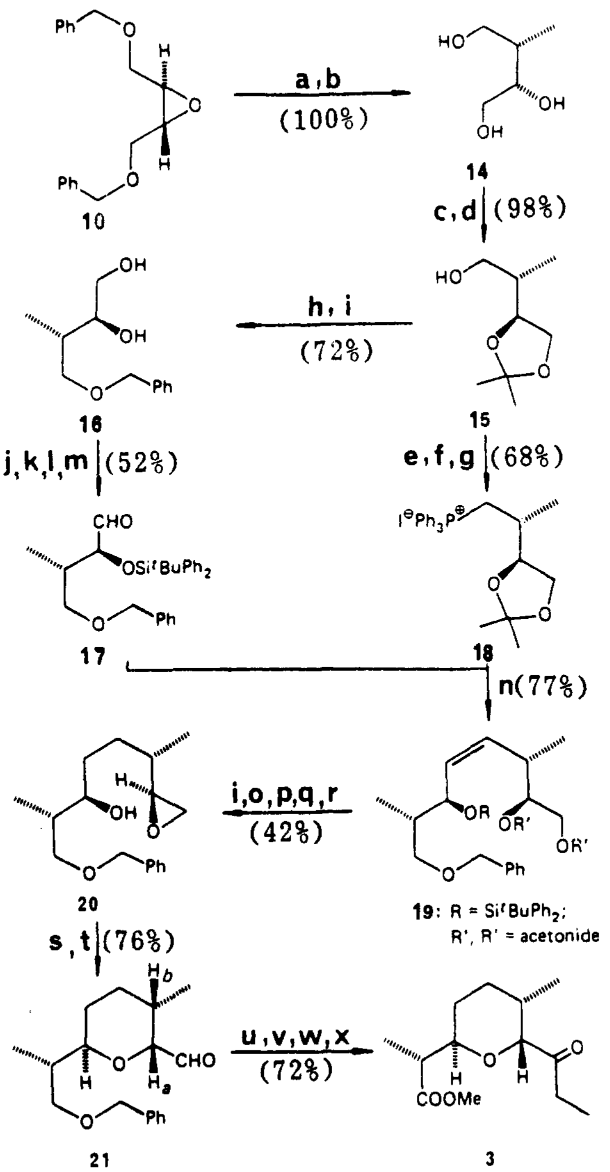


TS-1



TS-2

Scheme V^a



^{a} (a) $LiCuMe_2$-Et_2O, −78 → −40 °C; (b) H_2-10% Pd-C, EtOH, 25 °C; (c) $Me_2C(OMe)_2$-CSA, PhH, 25 °C; (d) MeOH-CSA, 25 °C; (e) TsCl-pyr, 0 °C; (f) NaI-Me_2CO, 25 °C; (g) PPh_3-MeCN-$(EtO)_3CH$, 75 °C; (h) NaH-$PhCH_2Br$, DME, 0–65 °C; (i) amberlite IR-120, $HOCH_2CH_2OH$-DME, 45 °C; (j) 1.2 equiv of Me_3CCOCl-pyr, 0–25 °C; (k) *t*-$BuPh_2SiCl$-imidazole, DMF, 0 → 25 °C; (l) DIBAL, CH_2Cl_2, −78 °C; (m) CrO_3·pyr·HCl, 4 Å MS, CH_2Cl_2, 25 °C; (n) $NaCH_2S(O)Me$-Me_2SO, 25 °C; (o) 1.1 equiv of TsCl-pyr, −20 → 25 °C; (p) NaOMe-MeOH, 25 °C; (q) *n*-Bu_4NF, THF, 25 °C; (r) H_2-5% Pd-C, EtOAc, 25 °C; (s) CSA catalyst, CH_2Cl_2, 25 °C; (t) CrO_3·pyr·HCl-NaOAc, CH_2Cl_2, 25 °C; (u) EtMgBr, PhMe, −78 °C; (v) H_2-10% Pd-C, EtOH, 25 °C; (w) Jones' oxidation, Me_2CO, −40 → −20 °C; (x) CH_3N_2, Et_2O, 0 °C.

struction of the racemic compound, 2-ethyl-δ-valerolactone (**31**), obtained by alkylation of δ-valerolactone with ethyl iodide, was subjected to DIBAL reduction (**31a**) and silylation under standard conditions, to afford (±)-**27** in good overall yield (70%) (together with 28% of the protected lactol **31b**). For the optically active series, highly enriched (+)-**27** was produced from propionaldehyde via the SAMP hydrazone **25**,[8] by alkylation with $ICH_2CH_2CH_2OSi$-*t*-$BuMe_2$[9] to afford **26** and ozonolysis of the hydrazone grouping (85% overall yield). The SAMP hydrazone alkylation proceeded in excess of 95% diastereomeric selectivity as determined by ^1H NMR $Eu(fod)_3$ techniques ($[\alpha]^{25}_D$ − 4.2° (*c* 2.00, $CHCl_3$)) and the mixture was carried through the rest of the sequence until the coupling with the optically pure tetrahydropyran fragment allowed convenient separation of diastereoisomers. Attachment of the diene system onto **27** was efficiently achieved by (i) condensation with the lithio salt of methyl 4-(dimethylphosphono)crotonate (**27a**) (2–3% of the isomeric *E,Z* dienoate formed in this reaction was chromatographically removed), (ii) reduction with excess DIBAL (**27b**) and (iii) protection with *tert*-butyldiphenylsilyl chloride (**27c**). The dienophilic portion of the molecule was cleanly constructed by selective removal of the *tert*-butyldimethylsilyl group (**27d**) followed by oxidation to the aldehyde and condensation with (carbomethoxymethylidene)triphenylphosphorane, affording the requisite intramolecular Diels–Alder precursor **28** (ca. 60% overall from **27**). When triene **28** was heated in degassed toluene in a sealed tube bicycle **29** was obtained as the major cycloadduct in 70% yield. The additionally (cs. 15%) formed mixture of isomers of **29** was easily removed by chromatography. Desilylation of **29** with fluoride ion led directly and quantitatively to the crystalline tricyclic lactone **4**, mp 68–68.5 °C (racemic, from hexane). The ^1H NMR spectroscopic data of **29** [$J_{12,20}$ = 7.2, $J_{19,20}$ = 11.2 Hz] and **4** [$J_{12,20}$ = 6.7, $J_{19,20}$ = 11.0 Hz] strongly suggested the indicated stereochemistry at C-2, C-3, and C-10 in agreement with Roush's results[10] but provided little information about the remaining asymmetric centers. The complete stereochemical characterization of these compounds was, therefore, sought and secured at this stage by X-ray crystallographic analysis carried out on **4**.[1b]

With the tetrahydroindan system constructed efficiently and in both racemic and highly enriched natural form, we then turned our attention to the problem of constructing the 2-ketopyrrole system. Two alternative approaches were considered at this juncture. The first option envisioned building the ketopyrrole function at this stage utilizing the γ-lactone present in **4** as the activating form of the carboxyl group, whereas the second option postponed this construction until the end and envisioned a different method to activate the carboxyl group. Both approaches appeared to be reasonable on the basis of initial experiments. Thus, model studies (Scheme VIII) with γ-butyrolactone (**32**) revealed that the reagent derived from pyrrole and MeMgCl[11] in toluene leads to hydroxy amide

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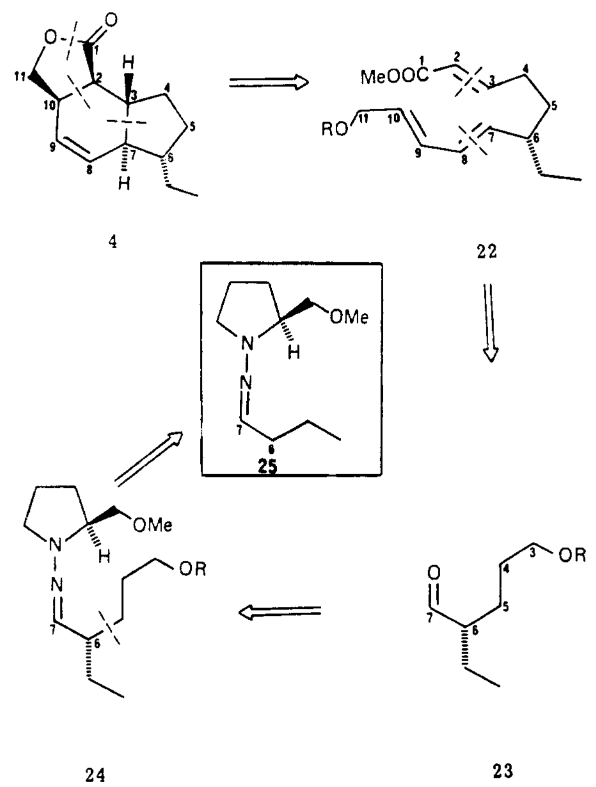
[8] (a) Enders, D.; Eichenauer, H. *Chem. Ber.* **1979**, *112*, 2933; (b) *Tetrahedron Lett.* 1977, 191.

[9] Prepared from 3-chloro-1-propanol by sequential treatment with *t*-$BuMe_2SiCl$-Et_3N-DMAP in CH_2Cl_2 and sodium iodide in acetone [80% overall yield, bp 102–105 °C (15 mmHg)]; see Experimental Section.

[10] (a) Roush, W. R. *J. Am. Chem. Soc.* **1980**, *102*, 1390. (b) Roush, W. R. *J. Org. Chem.* **1979**, *44*, 4008.

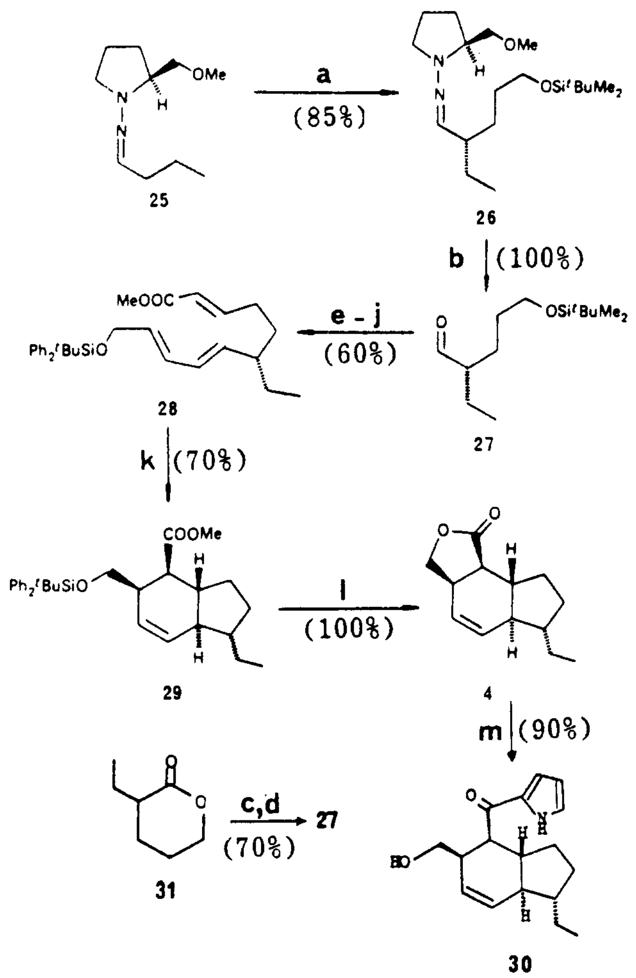
[11] (a) Bean, G. F. *J. Heterocycl. Chem.* **1965**, *2*, 473. (b) Hobbs, C. F.; McMillin, C. K.; Papadopoulos, E. P.; Vander Werf, C. A. *J. Am. Chem. Soc.* **1962**, *84*, 43.

Scheme VI



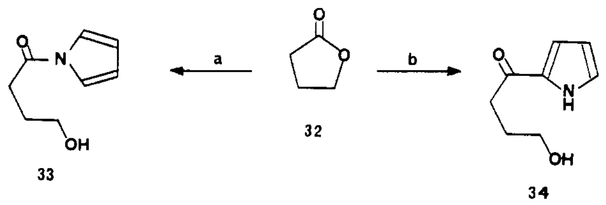
33 by C–N bond formation at 25 °C, whereas the same reagent at 100–110 °C leads to the corresponding hydroxy 2-ketopyrrole compound (34) exclusively by C–C bond formation. When these conditions were applied to the tricyclic intermediate 4 at 100–110 °C the 2-ketopyrole compound 30 was obtained in 90% yield, whereas the corresponding hydroxy amide was detected by TLC at 25 °C but reverted rapidly back to lactone 4 on attempted chromatographic isolation. Although this approach appeared to be promising, initial problems in the follow-up sequence and a deliberate attempt to develop new and more general synthetic methodology for the construction of 2-ketopyrroles prompted us to abandon it in favor of the second scenario in which construction of the 2-ketopyrrole moiety was postponed until the end and after coupling of the two fragments and formation of the *trans*-butadienyl bridge.

Scheme VII



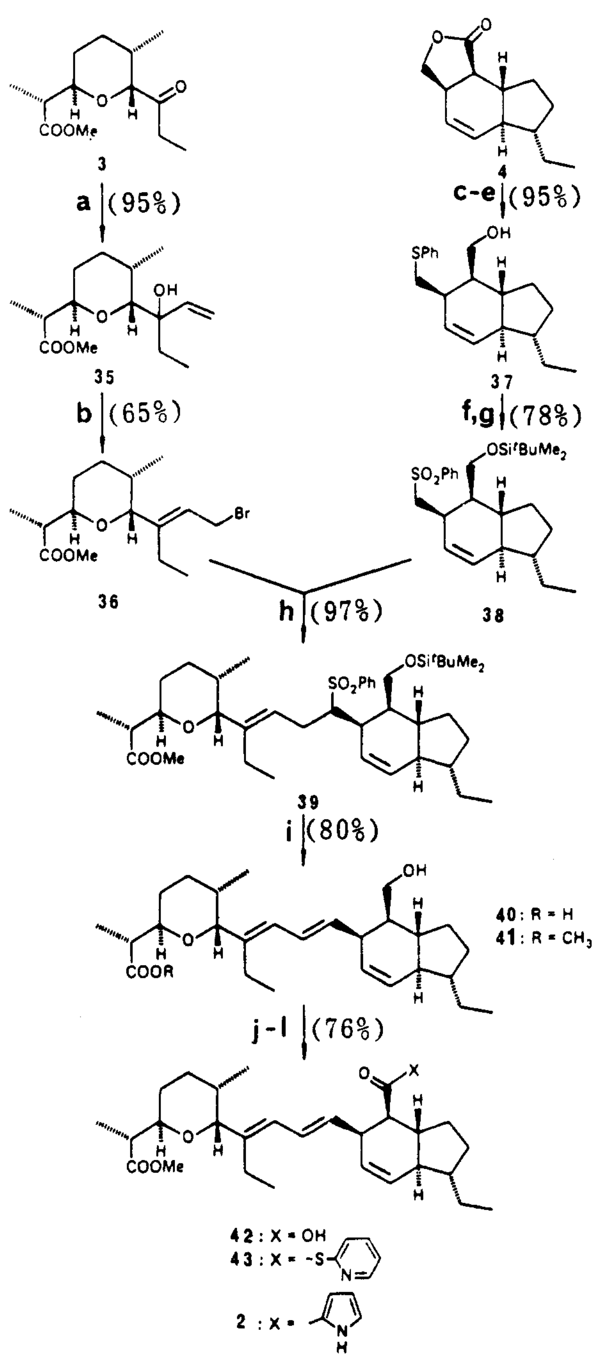
[a] (a) 1.1 equiv of LDA, Et$_2$O, 0 °C then −78 °C and add 1.1 equiv of ICH$_2$CH$_2$CH$_2$OSi-*t*-BuMe$_2$, 0 °C; (b) O$_3$, CH$_2$Cl$_2$, −78 °C; (c) 1.05 equiv of DIBAL, CH$_2$Cl$_2$, −78 °C; (d) 1.5 equiv of BuMe$_2$SiCl-1.5 equiv of imidazole, DMF, 25 °C; (e) 1.2 equiv of LDA-1.2 equiv of (MeO)$_2$P(O)CH$_2$CH=CHCOOMe, THF, −78 °C; (f) 2.1 equiv of DIBAL, CH$_2$Cl$_2$, −78 °C; (g) 1.5 equiv of BuPh$_2$SiCl, 1.5 equiv of imidazole, DMF, 25 °C; (h) AcOH-AcOH-THF-H$_2$O, 25 °C; (i) 1.5 equiv of CrO$_3$·pyr·HCl, CH$_2$Cl$_2$, 25 °C; (j) 1.5 equiv of Ph$_3$P=CHCOOMe, PhMe, 25 °C; (k) PhMe, sealed tube, 130 °C; (l) 1.1 equiv of *n*-BuNF, THF, 25 °C; (m) "MeMgCl-pyrrole", PhMe, 100-110 °C.

Scheme VIII



4. Coupling of the Tetrahydropyran and Tetrahydroindan Building Blocks and Total Synthesis of X-14547A (1). With the two main fragments at hand, the task of building the *trans*-butadienyl bridge and the 2-ketopyrrole system was undertaken. The location of the ketopyrrole unit and the double bond in the tetrahydroindan system imposed some complications on the coupling of the two segments and the regioselective formation of the *trans*-butadienyl grouping due to interference from these systems. For example, Wittig-type approaches involving the phosphorane derived from bromide 36 (vide infra, Scheme IX) and the aldehyde derived from the hydroxyketopyrrole 30 (vide supra, Scheme VI) were unsuccessful, despite encouraging results from model studies. Rather than using protection–deprotection techniques, we, therefore, decided to reverse the order of the operations as outlined in the second scenario above and to utilize the phenylsulfonyl moiety as an auxiliary group for both the coupling reaction and the stereo- and regioselective construction of the *trans*-butadienyl system. The actual synthetic sequence for the coupling and elatoration to X-14547A (1) is presented in Scheme IX. Our plan required alkylation of sulfone 38 as its lithium anion with bromide 36 and, therefore, the first task was to prepare these intermediates from 3 and 4, respectively. Reaction of vinylmagnesium bromide with ketone 3 as already described above, proved to be highly efficient and completely stereoselective, producing tertiary alcohol 35 (stereochemistry, however, unassigned). This alcohol was directly brominated by concomitant rearrangement on exposure to phosphorous tribromide affording the *E* allylic bromide

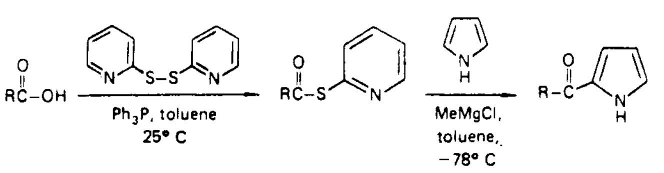
Scheme IX[a]



[a] (a) 1.5 equiv of CH_2=CHMgBr, THF, −78 °C; (b) 1.5 equiv of PBr_3, Et_2O, −10 °C; (c) 5.0 equiv of LiSPh, DMF, 110 °C; (d) CH_2N_2, Et_2O, 0 °C; (e) 1.0 equiv of LAH, Et Et_2O, 0 °C; (f) PhSeSePh-30% aqueous H_2O_2, Et_2O-CH_2Cl_2, 0-25 °C; (g) 1.2 equiv of *t*-$BuMe_2SiCl$, 1.5 equiv of Et_3N, 0.1 equiv of DMAP, CH_2Cl_2, 25 °C; (h) **38**, 1.2 equiv of LDA, THF, −78 °C, then 2.0 equiv of HMPA, then 1.5 equiv of **36**; (i) 40% Triton B in MeOH, 45 °C then CH_2N_2, Et_2O, 0 °C; (j) Jones' oxidation, Me_2CO, −20 → 5 °C; (k) 1.5 equiv of pyrSSpyr, 1.5 equiv of Ph_3P, PhMe, 25 °C; (l) 5.0 equiv of "MeMgCl-pyrrole", PhMe-THF, −78 °C.

36 as the major product (65%) together with smaller amounts of its *Z* isomer (25%) separated chromatographically. A more stereoselective (*E*:*Z* ca. 6:1) but rather longer route to **4** involved transformation of the allylic alcohol **35** to the α,β-unsaturated aldehyde **6** (identical with product derived from degradation of X-14547A (**1**), vide supra) by PCC oxidation–rearrangement as described above followed by reduction with sodium borohydride in the presence of cerium trichloride[12] to the allylic alcohol corresponding to **36** and bromination with triphenylphosphine–carbon tetrabromide (70% overall yield).

Scheme X



Ring opening of lactone **4** with lithium thiophenoxide (**4a**) followed by esterification of the resulting carboxylic acid (**4b**) and reduction with lithium aluminum hydride led smoothly to the hydroxy sulfide **37** (95%). Selective oxidation of the sulfur to the sulfone stage (**37a**) without attack on the double bond was achieved quite cleanly (82%) by the use of hydrogen peroxide in the presence of diphenyl diselenide,[13] whereas protection of the hydroxyl group as a *tert*-butyldimethylsilyl ether proceeded uneventfully (95%) leading smoothly to the requisite key intermediate **38**. The coupling of the anion of sulfone **38** generated at −78 °C with LDA with bromide **36** in the presence of HMPA[14] proved exceptionally efficient (97%) and highly stereoselective. Thus, when racemic **38** was utilized in the coupling reaction, only two diastereoisomers of **39** (and **39′**) were obtained in ca. 1:1 ratio (R_f 0.28 and 0.36, silica, 25% ether in petroleum ether); whereas when the naturally enriched material obtained by the SAMP hydrazone method of Enders[8] was employed, the ratio of these diastereoisomers changed to ca. 10:1[15] after separation by flash column chromatography. The major, more polar isomer, **39** ($[\alpha]^{25}_D$ −49.5° (*c* 2.10, $CHCl_3$), was confirmed as the natural diastereoisomer by eventual conversion to X-14547A (**1**) (vide infra). The less polar isomer of **39**, **39′**, was also carried through the sequence to an isomer of X-14547A methyl ester (vide infra). The stereochemistry of the generated asymmetric center in the coupling reaction (**38** + **36** → **39**) was not determined, but it was interesting to observe that the reaction of the dianion derived from the hydroxy sulfone corresponding to **38** and bromide **36**, under similar conditions, produced a set of different diastereoisomers, after silylation. Proceeding with the synthesis, pure **39** was subjected to elimination in order to generate the desired trans double bond in the requisite direction under carefully defined conditions (40% Triton B[16] in MeOH at 45 °C) furnishing **40** by a number of concomitant reactions: (a) hydrolysis of the methyl ester (which presumably protects the molecule from potential epimerization at C-2 and cleavage of the tetrahydropyran ring), (b) desilylation (which may be partly responsible for the regioselectivity of the elimination), and (c) elimination of phenylsulfonic acid. After esterification of the crude reaction mixture and chromatographic purification, the methyl ester 4 was isolated in 80% overall yield (50% conversion, recovered desilylated form of **39**, compound **39a**) and the primary hydroxyl group was oxidized under Jones' conditions to afford the

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[12] Luche, J.-L.; Gemal, A. L. *J. Am. Chem. Soc.* **1979**, *101*, 5848.

[13] (a) Nicolaou, K. C.; Barnette, W. E.; Gasic, G. P.; Magolda, R. L. *J. Am. Chem. Soc.* **1977**, *99*, 7736. (b) Reich, H. J.; Chow, F.; Peake, S. L. *Synthesis* **1978**, 299. (c) Nicolaou, K. C.; Magolda, R. L.; Sipio, W. J.; Barnette, W. E.; Lysenko, Z.; Joullie, M. M. *J. Am. Chem. Soc.* **1980**, *102*, 3784.

[14] Lavielle, S.; Borg, S.; Moreau, B.; Luche, M. J.; Marquet, A. *J. Am. Chem. Soc.* **1978**, *100*, 1558.

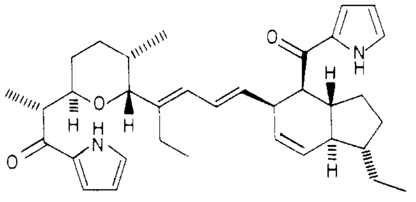
[15] This ratio is somewhat less than expected from the observed enrichment at the SAMP hydrazone alkylation stage. This is probably due to partial racemization of the aldehyde **27** during handling.

[16] Kondo, K.; Tunemoto, D. *Tetrahedron Lett.* **1975**, 1007.

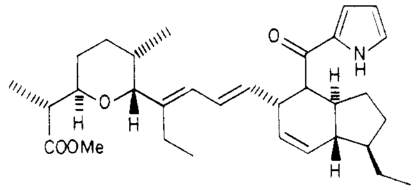
carboxylic acid methyl ester **42** (85%).

The final operation remaining for the completion of the synthesis, namely, the incorporation of the 2-ketopyrrole system, required some rather delicate chemistry in order to avoid interference from the ester functionality present at C-1. For this purpose, it was envisioned that a method involving high activation of the C-21 carboxyl group with a group capable of coordination to the organometallic species carrying the pyrrole moiety might be successful. In this connection a systematic study revealed the 2-pyridinethiol group to be an excellent activator for this task.[17] When this general methodology, depicted in Scheme X, was applied to the case at hand (compound **42**) the desired 2-ketopyrrole moiety was introduced under exceptionally mild conditions and in a selective and efficient way. Thus, the 2-pyridinethiol derivative **43** was first produced from **40** and reacted, without isolation, with excess of the reagent derived from methylmagnesium chloride and pyrrole (toluene–tetrahydrofuran, −20 °C) at −78 °C resulting in 90% yield of X-14547A methyl ester (**2**), exhibiting identical properties (^{1}H NMR, IR, MS, $[\alpha]^{25}_{D}$, TLC) with naturally derived material. Saponification of **2** as described above completed the total synthesis of enantiomerically pure X-14547A (**1**).

Furthermore, the reaction of (pyrrole)magnesium chloride with **43** or **2** at higher temperatures (80 °C) produced cleanly the novel diketopyrrole compound **44** ($[\alpha]^{25}_{D}$ −205.0° (c 0.65, $CHCl_3$)), in excellent yield (95%), whereas a diastereomer of X-14547A methyl ester, compound **45**, was synthesized from the less polar isomer of **39** (compound **39′**) following similar methodology (via **40′**, **41′**, and **42′**) for the preparation of (**2**).



44



45

Conclusion

A highly convergent and stereocontrolled total synthesis of ionophore antibiotic X-14547A (**1**) was developed. For this synthesis, it was demonstrated that D-tartaric acid can serve as chiral precursor to the tetrahydropyran system of this molecule by a series of highly efficient and stereoselective transformations and an intramolecular hydroxy epoxide ring closure as a key step. It was also shown that the rather rare trans-fused tetrahydroindan system of X-14547A could be efficiently constructed in a highly stereoselective manner via SAMP hydrazone methodology and a 4 + 2 cycloaddition reaction as the key steps. Linking of the two ring systems by C–C bond formation employing sulfone anion technology followed by regio- and stereoselective construction of the *trans*-butadienyl bridge and the 2-ketopyrrole moiety completed the synthesis. As demonstrated the described technology is suitable for the production of novel analogues of the natural product for biological investigations. A number of other studies and a total synthesis bearing some similarities to the present work have been carried out.[18]

Experimental Section

General. ^{1}H NMR spectra were recorded in $CDCl_3/Me_4Si$ and are reported in values from Me_4Si. IR spectra are reported as ν_{max} in cm^{-1}. Mass spectral data were provided by the Mass Spectrometry Center of the Chemistry Department, University of Pennsylvania, and are within acceptable limits unless otherwise stated. Optical rotations were recorded at the sodium D line and ambient temperatures.

Thin-layer chromatography (TLC) was carried out on 0.25-mm E. Merck precoated silica gel plates (50F-254) using UV light and/or 7% polyphosphomolybdic acid in ethanol–heat as developing agent. Preparative-layer chromatography (PLC) was performed on 0.25, 0.5, 1, and 2 mm × 20 cm × 20 cm E. Merck precoated silica gel-60 plates (60F-254). For flash column chromatography silica gel-60 (230–400 mesh) was used.

All reactions were carried out under an argon atmosphere using dry, freshly distilled solvents under anhydrous conditions unless otherwise stated. Etherial and hydrocarbon solvents were dried and distilled under argon from sodium benzophenone ketyl. Methylene chloride and acetonitrile were distilled under argon from calcium hydride. Reaction temperatures were measured externally. NMR multiplicities are reported using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; J, coupling constant (Hz). Only the strongest and/or structurally most important peaks are reported for the IR and mass spectra. Low-resolution mass data were obtained from electron impact (EI) spectra and high-resolution mass spectra (HRMS) were obtained by the chemical ionization (CI) technique. Yields refer to chromatographically and spectroscopically pure compounds.

X-14547A Methyl Ester (2). To a cold (0 °C) stirring etherial solution (5 mL) of X-14547A (**1**) (50 mg, 0.10 mmol) was introduced in a dropwise fashion excess ethereal diazomethane. The esterification proceeded with the usual liberation of nitrogen. Upon completion (TLC), the solution was degassed (5 min, stream of argon) and the solvent removed in vacuo providing an oil which after purification by flash column chromatography (silica, 30% ether–petroleum ether) supplied the methyl ester of X-14547A (**2**) (53 mg, 100% yield). For physical data see below under synthetic **2**.

Saponification of X-14547A Methyl Ester (2) to X-14547A (1). X-14547A methyl ester (**2**) (20 mg 0.04 mmol) was dissolved in $THF-H_2O$ (3:2, 0.5 mL) and treated, while vigorously stirred under argon, with aqueous LiOH solution (1 M, 394 μL, 0.39 mmol) in a dropwise fashion at 25 °C. The reaction was complete (TLC monitoring) in 7 days (faster on heating to 50 °C). Methylene chloride (30 mL) was added and the mixture adjusted to pH 3.0 with 10% aqueous HCl. Separation of the organic phase, followed by reextraction of the aqueous phase (3 × 30 mL) with methylene chloride, washing of the combined extracts (2 × 20 mL) with water, and filtration afforded a clear solution of the product. Concentration, followed by preparative-layer chromatography (silica, 75% ether in petroleum ether) furnished pure X-14547A (**1**) (19 mg, 100%) identical with an authentic sample, although the ^{1}H NMR spectrum was found to be concentration dependent. Its methyl ester was identical in all respects with the methyl ester derived directly from the natural product. **1**: white amorphous solid; R_f 0.23 (silica, 75% ether in petroleum ether; $[\alpha]^{25}_{D}$ −307° (c 1.5, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3420 (m), 3240 (m), 2950 (s), 2910 (s), 2860 (s), 1710 (s), 1635 (s), 1540 (m), 1450 (m), 1410 (s), 1370 (m), 1200 (s), 1110 (m), 1100 (s), 1040 (s), 960 (m) cm^{-1}; ^{1}H NMR (10 mg/0.5 mL, $CDCl_3$) δ 10 (br s, 1 H, NH), 8.80 (br s, 1 H,

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[17] Nicolaou, K. C.; Claremon, D. A.; Papahatjis, D. P. *Tetrahedron Lett.* **1981**, 4, 647.

[18] (a) Edwards, M. P.; Ley, S. V.; Lister, S. G. *Tetrahedron Lett.* **1981**, 361. (b) Edwards, M. P.; Ley, S. V.; Lister, S. G.; Palmer, B. D. *J. Chem. Soc., Chem. Commun.* **1983**, 630. (ce Edwards, M. P.; Ley, S. V.; Lister, S. G.; Palmer, B. D.; Williams, D. J., unpublished results. We thank Professor Ley for a preprint. (d) Roush, W. R.; Myers, A. G. *J. Org. Chem.* **1981**, *46*, 1509. (e) Roush, W. R.; Peseckis, S. M. *Tetrahedron Lett.* **1982**, 4879; (f) Ho, P.-T. *Can. J. Chem.* **1982**, *60*, 90.

COOH), 7.00 (m, 1 H, HC=), 6.91 (m, 1 H, HC=), 6.25 (m, 1 H, HC=), 5.95 (d, J = 10.0 Hz, 1 H, HC=), 5.91 (d, J = 13.0 Hz, 1 H, HC=), 5.82 (dd, J = 13.0, 15.0 Hz, 1 H, HC=), 5.46 (dt, J = 10.0, 2.5 Hz, 1 H, HC=), 5.38 (dd, J = 10.0, 15.0 Hz, 1 H, HC=), 4.20 (d, J = 2.5 Hz, 1 H, HCO), 3.88 (dt, J = 10, 5.0 Hz, 1 H, HCO), 3.35 (m, 2 H), 3.50–3.25 (m, 2 H), (m, 1 H), 2.10–0.95 (m, 13 H), 1.60 (d, J = 7.0 Hz, 3 H, CH_3), 0.80 (d, J = 7.0 Hz, 3 H, CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 191.48, 179.60, 140.11, 132.47, 132.29, 129.41, 129.26, 127.29, 125.35, 124.68, 116.03, 110.15, 74.78, 74.69, 52.61, 49.99, 45.22, 43.87, 41.73, 40.55, 30.73, 29.73, 27, 41, 27.11, 26.55, 22.35, 22.05, 13.91, 13.70, 13.56, 12.50; mass spectrum, m/e (relative intensity) 493 (M^+, 8), 334 (6), 159 (12), 157 (11), 133 (21), 95 (24), 94 (base peak); HRMS, m/e calcd for $C_{31}H_{43}O_4N$ 493.3191, found 493.3237.

Ozonolysis of X-14547A Methyl Ester (2). X-14547A methyl ester (2) (0.50 g, 0.99 mmol) was dissolved in CH_2Cl_2 (25 mL) and cooled to −78 °C. The solution was successively treated with a stream of oxygen (15 min), ozone (40 min, until blue color persisted), and then oxygen again (15 min). Dimethyl sulfide (233 μL, 3.00 mmol) was added at −78 °C; the solution was allowed to reach ambient temperature and then was stirred for 1 h. The reaction mixture was then diluted with CH_2Cl_2 (100 mL) and washed with water (2 × 50 mL) and a saturated NaCl aqueous solution (brine, 2 × 50 mL). Drying ($MgSO_4$), concentration, and flash column chromatography (silica, ether in petroleum ether mixtures) afforded keto ester **3** (120 mg, 50% yield) and diester **5** (77 mg, 30% yield, in order of elution).

A modified procedure with acetic acid present [3.50 g, 6.90 mmol of **2**; glacial acetic acid, 0.828 g, 13.81 mmol; 175 mL of CH_2Cl_2; 4.86 mL, 20.71 mmol of dimethyl sulfide; workup, 700 mL of CH_2Cl_2, wash with water (4 × 200 mL), 5% $NaHCO_3$(aq) (2 × 100 mL), saturated NaCl (50 mL)] afforded exclusively the keto ester **3** (1.64 g, 98% yield).

3: oil; R_f 0.58 (silica, 50% ether in petroleum ether); $[\alpha]^{25}_D$ −22.20° (c 1.6, $CHCl_3$); IR (CCl_4) ν_{max} 2970 (m), 2945 (s), 2875 (m), 1738 (ester, s), 1715 (ketone, s), 1455 (s), 1440 (m), 1375 (m), 1345 (w), 1200 (m), 1160 (m), 1115 (w), 1075 (m), 1050 (m) cm^{-1}; ^1H NMR δ 4.18 (d, J = 5.0 Hz, 1 H, HCO), 3.72 (m, 1 H, HCO), 3.70 (s, 3 H, OCH_3), 2.80–2.30 (m, 4 H), 2.10–1.65 (m, 3 H), 1.35 (m, 1 H), 1.10 (d, J = 7.2 Hz, 3 H, CH_3), 1.05 (t, J = 7.0 Hz, 3 H, CH_3), 0.98 (d, J = 6.0 Hz, 3 H, CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 211.13 (s), 175, 25 (s), 79.60 (d), 75.39 (d), 51.49 (q), 43.55 (d), 33.64 (t), 31.64 (d), 26.29 (t), 25.46 (t), 15.14 (q), 13.64 (q), 7.23 (q); mass spectrum, m/e (relative intensity), 213 ($M^+ - C_2H_5$, 0.4), 185 (7), 153 (8), 125 (7), 97 (10), 88 (12), 57 (base peak); HRMS, m/e calcd for $C_{10}H_{17}O_3$ 185.1177, found 185.1173. Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.42; H, 9.16. Found: C, 64.56; H, 9.22.

5: oil; R_f 0.47 (silica, 50% ether in petroleum ether); $[\alpha]^{25}_D$ 10.67° (c 0.30, $CHCl_3$); IR (CCl_4) ν_{max} 2985 (m), 2950 (s), 2880 (w), 1740 (esters, br s), 1460 (m), 1435 (m), 1375 (w), 1345 (w), 1255 (m), 1175 (s), 1120 (m), 1070 (s), 980 (m), 950 (w), 920 (m), 910 (m), 880 (m) cm^{-1}; ^1H NMR δ 5.98 (d, J = 5.0 Hz, 1 H, HCO), 3.93 (dt, J = 10, 2.5 Hz, 1 H, HCO), 3.65 (s, 3 H, OCH_3), 2.60–2.35 (m, 3 H), 1.90–1.30 (m, 5 H), 1.18 (t, J = 6.3 Hz, 3 H, CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 175.08 (s), 173.13 (s), 93.98 (d), 71.89 (d), 51.61 (q), 44.99 (d), 33.43 (t), 27.82 (d), 27.38 (t), 26.17 (t), 16.20 (q), 12.70 (q), 9.20 (q); mass spectrum, m/e (relative intensity), 243 ($M^+ - CH_3$, 0.3), 201 ($M^+ - C_3H_5O$, 2), 185 ($M^+ - C_3H_5O_2$, 60), 155 (24), 154 (10), 153 (base peak); HRMS, m/e calcd for $C_{10}H_{17}O_3$ ($M^+ - C_3H_5O_2$) 185.1177, found 185.1182. Anal. Calcd for $C_{13}H_{22}O_5$: C, 60.43; H, 8.59. Found: C, 60.59; H, 8.73.

Methyl (*αR*,2*R*,5*S*,6*R*)-6-[(*E*)-1-Ethyl-2-formylvinyl]-tetrahydro-α,5-dimethyl-2*H*-pyran-2-acetate (6). A mixture of X-14547A methyl ester (2) (256 mg, 0.5 mmol), OsO_4 (1.3 mg) and sodium metaperiodate (258 mg, 1.20 mmol) in t-BuOH–H_2O (1:1, 7 mL) was magnetically stirred under argon at 25 °C for 14 h. Saturated $NaHCO_3$ aqueous solution (50 mL) was added and the mixture extracted with ether (100 mL). The aqueous phase was reextracted with ether (3 × 50 mL) and the combined extract was washed with 5% aqueous Na_2S (4 × 50 mL) and brine (50 mL) and dried ($MgSO_4$). Removal of the solvents followed by flash column chromatography (silica, ether–petroleum ether mixtures) afforded aldehyde **6** (25 mg, 25% yield).

6: low-melting solid; R_f 0.32 (silica, 50% ether in petroleum ether); $[\alpha]^{25}_D$ −32.74° (c 0.70, $CHCl_3$); IR (neat) ν_{max} 2950 (m), 2860 (m), 2780 (w), 1740 (aldehyde, s), 1675 (olefin, s), 1455 (m), 1265 (m), 1160 (m), 1125 (m), 875 (w) cm^{-1}; ^1H NMR δ 10.05 (d, J = 8.2 Hz, 1 H, HCO), 6.03 (dd, J = 8.2, 1.4 Hz, 1 H, HC=), 4.42 (m, 1 H, HCO), 4.00 (m, 1 H, HCO), 3.62 (s, 3 H, OCH_3), 3.12 (m, 1 H, HCCOO), 2.75 (m, 1 H), 2.20 (m, 1 H), 2.10–1.85 (m, 3 H, 1.65–1.40 (m, 2 H), 1.17 (t, J = 8.3 Hz, CH_3), 1.19 (d, J = 6.9 Hz, 3 H, CH_3), 0.85 (d, J = 6.9 Hz, 3 H, CH_3); mass spectrum, m/e (relative intensity), 268 (M^+, 2), 239 (18), 136 (28), 123 (34), 109 (25), 95 (39), 88 (37), 83 (34), 55 (base peak); HRMS, m/e calcd for $C_{15}H_{24}O_4$ 268.1674, found 268.1684.

Diethyl D-Tartrate, Cyclic Ethyl Orthoformate (11a). (−)-Diethyl D-tartrate (**11**, 52.0 g, 252.2 mmol) in toluene (200 mL) was treated with triethyl orthoformate (100.7 g, 0.68 mmol) and glacial acetic acid (0.2 mL) and was magnetically stirred in a single-neck round-bottom flask equipped with a Dean–Stark receiver and condenser. The solution was refluxed while the ethanol was azeotropically removed. Reaction progress was followed by TLC. At completion the toluene solution was allowed to cool and was then neutralized with saturated aqueous NH_4OH followed by removal of toluene and excess triethylorthoformate in vacuo. Purification was effected by flash column chromatography (silica, 40% ether in petroleum ether) affording orthoformate **11a** (62.15 g, 94% yield).

11a: oil; R_f 0.52 (silica, 50% ether in petroleum ether); $[\alpha]^{25}_D$ +22.87° (c 4.97, $CHCl_3$); IR (neat) ν_{max} 2980, 2938, 2900, 1745 (esters), 1440, 1375, 1230, 1080, 1025, 860 cm^{-1}; ^1H NMR δ 6.09 (s, 1 H, C*H*OEt), 5.06 (d, J = 5 Hz, 1 H, CHO), 4.73 (d, J = 5 Hz, 1 H, CHO), 4.29 (dq, J = 8 Hz, 2 H each, OCH_2CH_3), 3.71 (dq, J = 6 Hz, 1 H each, OCH_2CH_3), 1.33 (dt, J = 8 Hz, 3 H each, CH_3), 1.23 (t, J = 6 Hz, 3 H, CH_3); mass spectrum, m/e (relative intensity) 262 (M^+, 0.6), 217 (M^+ − OEt, 44.5), 190 (9.0), 189 (base peak); HRMS, m/e calcd for $C_{11}H_{17}O_7$ (M^+ − H) 261.0973, found: 261.0984.

1,4-Bis-*O*-(benzyloxy)-D-threitol Cyclic Ethyl Orthoformate (12). The diester **11a** obtained above (20 g, 76.3 mmol) was dissolved in dry THF (280 mL) and cooled to 0 °C under an argon atmosphere. To this solution LAH (3.2 g, 84.2 mmol) was added over a period of 15 min. The mixture was stirred for 1 h at 0 °C, followed by addition of wet THF and anhydrous $MgSO_4$. After 30 min, the mixture was filtered, and the filtercake was washed with THF (4 × 100 mL) and ethanol (200 mL). The combined filtrate and washings were concentrated in vacuo affording 13 g (quantitative) of the corresponding diol **11b** sufficiently pure for the next step. This diol (**11b**) (27 g, 152 mmol) was dissolved in dry THF (300 mL), cooled to 0 °C under an argon atmosphere, and treated with NaH (9.1 g, 380 mmol). The mixture was allowed to stir at room temperature for 0.5 h and then cooled to 0 °C and treated with benzyl bromide (41.2 mL, 380 mmol). The reaction was allowed to proceed at room temperature for 1 h and then at 65 °C for 12 h. The cooled reaction mixture was treated with saturated NH_4Cl (50 mL) and the aqueous phase was extracted with ether (4 × 70 mL). The combined organic solution was washed with saturated NaCl (2 × 50 mL) and was dried over $MgSO_4$. Evaporation and purification by flash column chromatography (silica, ether–petroleum ether mixtures) gave **12** (49.9 g, 92%).

12: oil; R_f 0.27 (silica, 30% ether in petroleum ether); $[\alpha]^{25}_D$ −10.13° (c 0.62, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3020, 2980, 2930, 2870, 1495, 1452, 1365, 1207, 1070, 907, 694, 660 cm^{-1}; ^1H NMR δ 7.32 (br s, 10 H, Ar), 5.88 (s, 1 H, C*H*OEt), 4.57 and 4.56 (s, 2 H each, CH_2Ph), 4.27–4.09 (m, 2 H, CHO), 2.79–3.40 (m, 6 H, CH_2O), 1.18 (t, J = 7.5 Hz, 3 H, CH_3); mass spectrum, m/e (relative intensity) 357 (M^+ − H), 313 (2.8), 237 (3.5), 193 (10.1), 175 (4.7), 101 (25.8), 91 (base peak); HRMS, m/e calcd for $C_{21}H_{26}O_5$ (M^+) 358.1780, found 358.1759.

1,4-Bis-*O*-(benzyloxy)-2-chloro-2-deoxy-D-erythritol Formate (13). The dibenzyl ether **12** (10.0 g, 27.93 mmol) in dry CH_2Cl_2 (29 mL) was added to a cool (0 °C) solution of PCl_5 (7.0 g, 33.7 mmol) in dry CH_2Cl_2 (70 mL) under argon. The reaction mixture was allowed to warm up to room temperature and stirring was continued for 3 h. The cooled reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (50 mL) and extracted with ether (4 × 100 mL). Washing of the combined organic layer with saturated aqueous $NaHCO_3$ (3 × 50 mL), H_2O (50 mL), and saturated aqueous NaCl (50 mL) followed by drying ($MgSO_4$) and evaporation afforded an oily residue which was purified by flash column chromatography (silica, 30% ether in petroleum ether) to afford **13** (8.35 g, 86% yield).

13: oil; R_f 0.40 (silica, 30% ether in petroleum ether); $[\alpha]^{25}{}_D$ −6.84° (*c* 5.32, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3019, 2935, 2864, 1730 (formate), 1495, 1454, 1364, 1208, 1170, 1105, 908, 662 cm^{-1}; ^1H NMR δ 8.06 (s, 1 H, CHO), 7.33 (br s, 10 H, Ar), 5.46 (br q, *J* = 6 Hz, 1 H, CHO), 4.66–4.48 (m, 4 H, CH_2Ph), 4.39 (q, *J* = 6 Hz, 1 H, CHCl), 3.90–3.66 (m, 4 H, CH_2O); mass spectrum, *m/e* (relative intensity) 271 (M^+ − Ph), 269 (24.9), 181 (12.3), 151 (13.0), 107 (13.2), 91 (base peak); HRMS, *m/e* calcd for $C_{19}H_{22}O_4Cl$ (M^+ + 1) 349.1207, found 349.1200.

(*R*,*R*)-1,4-Bis(benzyloxy)-2,3-epoxybutane (10). The chloroformate **13** (10.2 g, 29.3 mmol) was dissolved in dry MeOH (58 mL) and stirred with anhydrous K_2CO_3 (10.1 g, 73.0 mmol) under argon, at room temperature for 18 h. The reaction mixture was diluted with ethyl acetate (400 mL) and washed successively with saturated aqueous NaCl (50 mL), aqueous NH_4Cl (2 × 30 mL), and aqueous NaCl (50 mL). The organic phase was dried over $MgSO_4$, concentrated, and purified by flash silica column chromatography using 40% ether in petroleum ether to give **10** (7.33 g, 88% yield).

10: low-melting solid; R_f 0.47 (silica, 50% ether in petroleum ether) $[\alpha]^{25}{}_D$ +7.33° (*c* 3.67, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3085, 3060, 3025, 3000, 2860, 1600, 1585, 1493, 1452, 1365, 1310, 1235, 1110, 1026, 906, 970, 690 cm^{-1}; ^1H NMR δ 7.35 (br s, 10 H, Ar), 4.58 and 4.56 (s, 2 H each, CH_2Ph), 3.78 (dd, *J* = 12, 3 Hz, 2 H, CH_2O), 3.50 (dd, *J* = 11, 6 Hz, 2 H, CH_2O), 3.13 (m, 2 H, CHO); mass spectrum, *m/e* (relative intensity) 193 (M^+ − CH_2Ph), 175 (3.0), 133 (8.1), 107 (21.0), 105 (60.5), 91 (base peak); HRMS, *m/e* calcd for $C_{18}H_{20}O_3$ (M^+) 284.1412, found 284.1423. Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.08. Found: C, 75.81; H, 6.97.

(*S*,*S*)-1,4-Bis(benzyloxy)-3-methyl-2-butanol (10a). Dry CuI (22.8 g, 120.0 mmol) was dissolved in anhydrous diethyl ether (30 mL) and the suspension was cooled to −40 °C under an argon atmosphere. Methyllithium (171 mL of 1.4 M solution in ether, 239.4 mmol) was added and the solution was allowed to warm up to 0 °C and stirred for 30 min. After that period a solution of epoxide **10** (17.0 g, 59.85 mmol) in dry ether (30 mL) was added with stirring and cooling at −78 °C. The mixture was kept at −78 °C for 30 min; then the reaction temperature was gradually raised to 0 °C, and stirring was continued for 3 h while followed by TLC. The reaction mixture was poured into saturated aqueous NH_4Cl solution and ice (200 mL). The ether layer was separated and the aqueous phase extracted with ether (3 × 150 mL). The combined organic solution was washed with saturated aqueous NH_4Cl solution (50 mL), saturated aqueous NaCl (50 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by flash column chromatography (30% ether in petroleum ether) gave **10a** (18.0 g, 100%).

10a: oil; R_f 0.41 (silica, 50% ether in petroleum ether); $[\alpha]^{25}{}_D$ +3.93° (*c* 4.1, $CHCl_3$); IR (neat) ν_{max} 3470, 3085, 3060, 3030, 2960, 2900, 2860, 1950, 1870, 1810, 1605, 1585, 1495, 1450, 1360, 1205, 1090, 1027, 907, 730, 690 cm^{-1}; ^1H NMR δ 7.33 and 7.31 (s, 5 H each, Ar), 4.56 and 4.50 (s, 2 H each, CH_2Ph), 3.74 (m, 1 H, CHO), 3.60–3.44 (m, 4 H, CH_2O), 3.18 (d, *J* = 4 Hz, 1 H, OH), 2.02 (m, 1 H, $CHCH_3$), 0.96 (d, *J* = 7.5 Hz, 3 H, CH_3); mass spectrum, *m/e* (relative intensity) 209 (M^+ − CH_2Ph, 4.3), 179 (4.0), 108 (4.0), 107 (27.3), 92 (17.6), 91 (base peak); HRMS, *m/e* calcd for $C_{19}H_{25}O_3$ (M^+ + 1) 301.1804, found 301.1801.

(β*S*,4*S*)-β,2,2,-Trimethyl-1,3-dioxolane-4-ethanol (15) via 14. The bis(benzyl ether) **10a** obtained above (17 g, 56.7 mmol) was dissolved in EtOH (150 mL), the flask was flushed with argon, and 10% Pb/C (1.7 g) was introduced. Argon was again flushed through the flask, which was then sealed with a rubber septum. Hydrogen was then bubbled through the stirred solution via a syringe needle for 30 min. A hydrogen atmosphere was maintained over the magnetically stirred mixture for 48 h. The reaction was then flushed with argon and filtered. Evaporation of the EtOH gave **14** sufficiently pure for the next step (5.44 g, 100%). *p*-TsOH (40 mg) was added to a solution of triol **14** (9.4 g, 78.33 mmol) in acetone (200 mL) and the reaction mixture was stirred overnight at room temperature. Upon completion (TLC) the solution was neutralized with solid $NaHCO_3$, filtered, and concentrated in vacuo to afford an oily residue which was distilled under vacuum (83 °C, 3.5 mmHg) affording **15** (8.95 g, 98% yield).

15: oil, R_f 0.20 (silica, 50% ether in petroleum ether); $[\alpha]^{25}{}_D$ +18.10° (*c* 0.90, $CHCl_3$); IR (neat) ν_{max} 3460, 2980, 2935, 2875, 1460, 1380, 1370, 1240, 1210, 1155, 1060, 850, 790 cm^{-1}; ^1H NMR δ 4.10 (dd, *J* = 9, 7.5 Hz, 1 H, CH_2O), 3.96 (q, *J* = 7.5 Hz, 1 H, CHO), 3.80–3.54 (m, 3 H, CH_2O), 2.84 (br s, 1 H, OH), 1.86 (m, 1 H, $CHCH_3$), 1.42 and 1.37 (s, 3 H each, acetonide), 0.83 (d, *J* = 7.0 Hz, 3 H, CH_3); mass spectrum, *m/e* (relative intensity) 145 (M^+ − CH_3, 53.2), 129 (6.0), 101 (46.6), 85 (89.7), 73 (17.5), 72 (71.9), 59 (base peak); HRMS, *m/e* calcd for $C_8H_{17}O_3$ (M^+ + 1) 161.1177, found 161.1187.

(β*S*,4*S*)-β,2,2-Trimethyl-1,3-dioxolane-4-ethanol *p*-Toluenesulfonate (15a). To a solution of acetonide alcohol **15** (10.5 g, 65.63 mmol) in pyridine (25 mL), cooled to 0 °C was added tosyl chloride (25.0 g, 131.25 mmol) and an argon atmosphere was secured. Stirring was continued at 0 °C for 2 h and then at room temperature for 3 h. Cold water (50 mL) was added and the solution was extracted with ether (4 × 100 mL). The ether layers were combined, washed with 50% aqueous $NaHCO_3$ (3 × 50 mL) and saturated aqueous NaCl (50 mL), and dried over $MgSO_4$. Evaporation of the ether gave the tosylate **15a** (20 g, 97% yield) sufficiently pure for the next step.

15a: oil; R_f 0.45 (silica, 50% ether in petroleum ether); $[\alpha]^{25}{}_D$ −10.83° (*c* 6.0, $CHCl_3$); IR (neat) ν_{max} 3060, 2980, 2930, 2880, 1600, 1490, 1455, 1355, 1210, 1185, 1160, 1090, 1060, 965, 810, 700, 660 cm^{-1}; ^1H NMR δ 7.82, 7.78, 7.36, 7.34 (s, 1 H each, Ar), 4.16 (dd, *J* = 9, 4 Hz, 1 H, CH_2O), 4.0 (m, 2 H, CH_2O), 2.86 (q, *J* = 7.5 Hz, 1 H, CHO), 3.60 (t, *J* = 7.5 Hz, 1 H, CH_2O), 2.44 (s, 3 H, CH_3), 1.92 (m, 1 H, $CHCH_3$), 1.32 and 1.28 (s, 3 H each, acetonide), 0.92 (d, *J* = 7.5 Hz, 3 H, CH_3); mass spectrum, *m/e* (relative intensity) 299 (M^+ − CH_3, 91.8), 176 (8.9), 127 (22.1), 91 (base peak); HRMS, *m/e* calcd for $C_{15}H_{23}O_5S$ (M^+ + 1) 315.1267, found 315.1272.

(4*S*)-4-[(1*R*)-2-Iodo-1-methylethyl]-2,2-dimethyl-1,3-dioxolane (15b). The tosylate **15a** obtained above (20 g, 63.66 mmol) in distilled acetone (298 mL) and NaI (26 g, 173.4 mmol) were stirred under argon for 18 h at room temperature. The resulting precipitate was filtered off and additional NaI (16 g, 106.7 mmol) was added. The mixture was stirred for 30 more h after which time the precipitate was filtered off, the filtrate poured into H_2O (50 mL), and the mixture extracted with ether (4 × 200 mL). The combined ether phase was washed with 10% aqueous Na_2SO_3 (2 × 60 mL) and saturated aqueous NaCl (60 mL) and dried ($MgSO_4$). Purification of the pale yellow oil obtained after concentration by flash column chromatography (silica, 30% ether in petroleum ether) afforded the iodoacetonide **15b** (15 g, 85% yield).

15b: oil; R_f 0.72 (silica, 30% ether in petroleum ether); $[\alpha]^{25}{}_D$ −6.8° (*c* 0.97, $CHCl_3$); IR (neat) λ_{max} 2980, 2930, 2870, 1455, 1380, 1370, 1250, 1215, 1165, 1065, 960, 910, 855, 790 cm^{-1}; ^1H NMR δ 3.99 (dd, *J* = 8, 6 Hz, 1 H, CH_2O), 3.76 (dt, *J* = 8 Hz, 1 H, CHO), 3.59 (t, *J* = 8 Hz, 1 H, CH_2O), 3.36 (dd, *J* = 10, 4 Hz, 1 H, CH_2I), 3.21 (dd, *J* = 10, 7 Hz, 1 H, CH_2I), 1.47 (m, 1 H, $CHCH_3$), 1.32 and 1.27 (s, 3 H each, acetonide), 0.87 (d, *J* = 7.0 Hz, 3 H, CH_3); mass spectrum, *m/e* (relative intensity) 255 (M^+ − CH_3) 225 (2.2), 167 (39.4), 149 (87.6), 91 (37.4), 69 (44.1), 57 (base peak); HRMS, *m/e* calcd for $C_8H_{16}O_2I$ (M^+ + 1) 271.0196, found 271.0200.

[(2*R*)-2-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]propyl]triphenylphosphonium Iodide (18). The iodide **15b** obtained above (3.15 g, 11.67 mmol) was dissolved in dry CH_3CN–$(EtO)_3CH$ (4:1, 12.5 mL). Triphenylphosphine (4.8 g, 18.4 mmol) was added under argon and the reaction mixture was stirred at 75 °C for 48 h. At completion the solvents were removed under vacuum and pure phosphonium salt **18** was obtained by recrystallization from CH_2Cl_2–ether (5.08 g, 83% yield).

18: Colorless solid; $[\alpha]^{25}{}_D$ +27.96° (*c* 1.08, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3060, 2935, 1590, 1480, 1440, 1380, 1370, 1230, 1210, 1150, 1110, 1070, 1040, 995, 850, 800, 680, 655 cm^{-1}; ^1H NMR δ 8.03–7.67 (m, 15 H, Ar), 4.32 (br q, *J* = 7 Hz, 1 H, CHO), 4.10 (dd, *J* = 8, 7 Hz, 1 H, CH_2O), 3.94 (m, 2 H, CH_2P), 3.52 (t, *J* = 8 Hz, 1 H, CH_2O), 2.10 (m, 1 H, $CHCH_3$), 1.34 and 1.29 (s, 3 H, each acetonide), 0.84 (d, *J* = 7 Hz, CH_3); mass spectrum, *m/e* (relative intensity) 517 (M^+ − CH_3, 0.3), 4.05 (4.5), 303 (4.2), 277 (7.8), 262 (base peak); Anal. Calcd for $C_{26}H_{30}O_2PI$: C, 58.66; H, 5.68, I, 23.84. Found: C, 58.72; H, 5.8; I, 24.08.

(4*S*)-4-[(1*S*)-2-(Benzyloxy)-1-methylethyl]-2,2-dimethyl-1,3-dioxolane (15c). Acetonide alcohol **15** (7.44 g, 46.5 mmol) was dissolved in dry DME (93 mL) and the solution was cooled to 0 °C, under an argon atmosphere. To this solution NaH (2.46 g as 50% oil dispersion, 51 mmol) was added followed by benzyl bromide (5.6 mL, 51.10 mmol). The resulting mixture was allowed to reach 65 °C and was stirred at that temperature for 18 h. Workup under standard conditions followed by flash column chromatography (silica, 30% ether in petroleum ether) provided benzyl ether **15c** (10.7 g, 92%).

15c: oil; R_f 0.41 (silica, 20% ether in petroleum ether); $[\alpha]^{25}{}_D$ −2.25° (c 3.51, $CHCl_3$); IR (neat) ν_{max} 3060, 3030, 2980, 2930, 2860, 1495, 1460, 1455, 1380, 1370, 1245, 1210, 1150, 1100, 1065, 855, 735, 695 cm^{-1}; ^1H NMR δ 7.34 (s, 5 H, Ar), 4.52 (s, 2 H, CH_2Ph), 4.02 (m, 2 H, CH_2O), 3.68 (m, 1 H, CHO), 3.59 (dd, J = 10, 5 Hz, 1 H, CH_2O), 3.42 (dd, J = 10, 7 Hz, 1 H, CH_2O), 1.99 (m, 1 H, $CHCH_3$), 1.39 and 1.35 (s, 3 H each, acetonide), 0.96 (d, J = 7 Hz, 3 H, CH_3); mass spectrum, m/e (relative intensity) 250 (M^+, 0.2), 235 ($M^+ - CH_3$, 5.9), 174 (10.5), 105 (12.1), 101 (15.1), 91 (base peak); HRMS, m/e calcd for $C_{15}H_{22}O_3$ (M^+) 250.1569, found 250.1525.

(2*S*,3*S*)-4-(Benzyloxy)-3-methyl-1,2-butanediol (16). The benzyl ether **15c** (6.0 g, 24.0 mmol) was dissolved in dry ethylene glycol–DME (2:1, 210 mL). Amberlite IR-120HCP (7.0 g) was added, and the reaction mixture was allowed to stir at 45 °C for 48 h. The reaction mixture was filtered and extracted with ethyl acetate (4 × 200 mL) and the organic phase washed successively with 5% aqueous $NaHCO_3$ (3 × 70 mL), H_2O (2 × 30 mL), and saturated aqueous NaCl (2 × 20 mL), and dried over $MgSO_4$. Concentration followed by flash column chromatography (silica, 75% ether in petroleum ether) afforded pure benzyl ether diol **16** (4.0 g, 80% yield).

16: oil; R_f 0.27 (silica, ether); $[\alpha]^{25}{}_D$ +15.67° (c 4.6, $CHCl_3$); IR (neat) ν_{max} 3400, 3060, 3020, 2940, 2920, 2870, 1490, 1450, 1360, 1200, 1065, 1020, 875, 730, 690 cm^{-1}; ^1H NMR 7.30 (s, 5 H, Ar), 4.50 (s, 2 H, CH_2Ph), 3.78 (m, 1 H, CHO), 3.76–3.40 (m, 4 H, CH_2O), 2.73 (br s, 1 H, OH), 2.00 (m, 2 H, OH, $CHCH_3$), 0.88 (d, J = 7 Hz, 3 H, CH_3); mass spectrum, m/e (relative intensity) 210 (M^+, 0.5), 179 (1.6), 120 (4.3), 107 (38.7), 91 (base peak); HRMS, m/e calcd for $O_{12}H_{19}O_3$ ($M^+ + 1$) 211.1335, found 211.1342.

(2*S*,3*S*)-4-(Benzyloxy)-2-hydroxy-3-methylbutyl Pivalate (16a). The diol **16** (5.43 g, 25.85 mmol) was azeotropically dried with benzene (3 × 50 mL) and dissolved in dry pyridine (10 mL) under argon. Trimethylacetyl chloride (3.4 mL, 27.52 mmol) was added at 0 °C and the reaction was allowed to stir at room temperature for 2 h. The reaction mixture was then diluted with cold water (20 mL) and extracted with ether (4 × 100 mL) and the ethereal solution was washed successively with saturated $CuSO_4$ (3 × 40 mL), H_2O (40 mL), saturated aqueous $NaHCO_3$ (2 × 40 mL), water (30 mL), and saturated NaCl aqueous solution (50 mL). The organic phase was dried ($MgSO_4$) filtered and evaporated to afford an oil which was purified by flash column chromatography (silica, 40% ether in petroleum ether) furnishing pivalate ester **16a** (6.4 g, 84% yield).

16a: oil; R_f 0.19 (silica, 30% ether in petroleum ether); $[\alpha]^{25}{}_D$ +10.33° (c 3.32, $CHCl_3$); IR (neat) ν_{max} 3450, 3060, 3020, 2960, 2965, 2900, 1865, 1725 (pivalate), 1470, 1450, 1390, 1360, 1280, 1160, 1090, 1025, 980, 730, 690 cm^{-1}; ^1H NMR δ 7.34 (s, 5 H, Ar), 4.53 (s, 2 H, CH_2Ph), 4.22 (dd, J = 12, 4 Hz, 1 H, CH_2O), 4.12 (dd, J = 12, 7 Hz, 1 H, CH_2O), 3.78 (m, 1 H, CHO), 3.62 (dd, J = 10, 4 Hz, 1 H, CH_2O), 3.53 (dd, J = 10, 7 Hz, 1 H, CH_2O), 3.37 (br s, 1 H, OH), 2.00 (m, 1 H, $CHCH_3$), 7.21 (s, 9 H, $(CH_3)_3$), 0.97 (d, J = 7 Hz, 3 H, CH_3); mass spectrum, m/e (relative intensity) 188 ($M^+ - CH_2Ph, - CH_3$, 1.4), 123 (5.8), 107 (14.0), 105 (41.0), 91 (75.8), 85 (21.5), 77 (18.4), 57 (base peak); HRMS, m/e calcd for $C_{17}H_{25}O_3$ ($M^+ - OH$) 277.1780, found 277.1792.

(2*S*,3*S*)-4-(Benzyloxy)-2-(*tert*-butyldiphenylsiloxy)-3-methylbutyl Pivalate (16b). Pivalate ester **16a** (5.2 g, 17.69 mmol) was dissolved in dry DMF (11.8 mL) under argon cooled to 0 °C and successively treated with imidazole (2.53 g, 3720 mmol) and *tert*-butylchlorodiphenylsilane (9.17 mL, 35.37 mmol) with stirring. The reaction mixture was allowed to stir at room temperature for 48 h and then it was diluted with ether (400 mL). The mixture was washed successively with water (3 × 50 mL) and saturated aqueous NaCl (2 × 50 mL) and dried over $MgSO_4$. Purification by flash column chromatography after evaporation (10% ether in petroleum ether) gave silyl ether **16b** (9.2 g, 98% yield).

16b: oil; R_f 0.65 (silica, 20% ether in petroleum ether); $[\alpha]^{25}{}_D$ −8.04° (c 0.98, $CHCl_3$); IR (neat) ν_{max} 3080, 3060, 3020, 2970, 2940, 2860, 1725 (pivalate), 1590, 1475, 1460, 1430, 1390, 1365, 1285, 1215, 1160, 1110, 980, 820, 755, 700 cm^{-1}; ^1H NMR δ 7.77–7.20 (m, 15 H, Ar), 4.38 (s, 2 H, CH_2Ph), 4.08–3.93 (m, 3 H, CHO, CH_2O), 3.50 (dd, J = 10, 6 Hz, 1 H, CH_2O), 3.37 (dd, J = 10, 7 Hz, 1 H, CH_2O), 2.24 (m, 1 H, $CHCH_3$), 1.09 (s, 9 H, $(CH_3)_3$), 1.03 (s, 9 H, $(CH_3)_3$), 0.94 (d, J = 7 Hz, 3 H, CH_3); mass spectrum, m/e (relative intensity), 373 (2.0), 283 (13.0), 223 (21.7), 199 (43.5), 91 (base peak); HRMS, m/e calcd for $C_{29}H_{35}O_4Si$ (M^+ − t-Bu) 475.2311, found 475.2308.

(2*S*,3*S*)-4-(Benzyloxy)-2-(*tert*-butyldiphenylsiloxy)-3-methyl-2-butanol (16c). Compound **16b** obtained above (5.96 g, 11.2 mmol) was dissolved in dry methylene chloride (11 mL) and protected under argon. The reaction flask was cooled to −78 °C, DIBAL (20.17 mL of a 1 M solution in hexane) was added while stirring, and stirring was continued for 0.5 h, before quenching with methanol (1.0 mL). The reaction mixture was diluted with ethyl acetate (400 mL) and shaken with a saturated solution of sodium potassium tartrate (50 mL) until the emulsion cleared. The organic layer was then washed with brine (2 × 50 mL) and dried over $MgSO_4$. Evaporation and purification by flash column chromatography (silica, 30% ether in petroleum ether) gave alcohol **16c** (4.92 g, 98% yield).

16c: oil; R_f 0.27 (silica, 30% ether in petroleum ether); $[\alpha]^{25}{}_D$ +2.11° (c 4.83, $CHCl_3$); IR (neat) ν_{max} 3440, 3075, 3055, 3040, 2960, 2940, 2890, 2860, 1960, 1890, 1820, 1590, 1455, 1430, 1390, 1360, 1310, 1255, 1205, 1105, 1070, 1050, 1000, 935, 910, 817, 730, 690 cm^{-1}; ^1H NMR δ 7.73–7.22 (m, 15 H, Ar), 4.43 (s, 2 H, CH_2Ph), 3.82 (q, J = 7 Hz, 1 H, CHO), 3.63–3.46 (m, 3 H, CH_2O), 3.30 (dd, J = 9, 5 Hz, 1 H, CH_2O), 2.48 (t, J = 6 Hz, 1 H, OH), 2.07 (m, 1 H, $CHCH_3$), 1.06 (s, 9 H, $(CH_3)_3$), 0.95 (d, J = 7 Hz, 3 H, CH_3); mass spectrum, m/e (relative intensity) 417 ($M^+ - CH_2OH$, 0.3), 199 (11.8), 181 (24.5), 91 (base peak); HRMS, m/e calcd for $C_{24}H_{27}O_3Si$ (M^+ − Bu) 391.1713, found 391.1721. Anal. Calcd for $C_{28}H_{36}O_3Si$: C, 74.96; H, 8.09. Found: C, 75.18; H, 8.11.

(2*S*,3*S*)-4-(Benzyloxy)-2-(*tert*-butyldiphenylsiloxy)-3-methylbutyraldehyde (17). Alcohol **16c** obtained above (4.9 g, 10.70 mmol) in methylene chloride (20 mL) was added to a suspension of recrystallized PCC (4.7 g, 21.86 mmol) and 4A molecular sieves (1.4 g) in dry methylene chloride (90 mL) under argon and with stirring. Stirring was continued for 3 h; the reaction mixture was poured into ether (500 mL), the ethereal solution was filtered through florisil, and then the filtrate was concentrated in vacuo to give aldehyde **17** sufficiently pure for the next step (4.4 g, 90% yield).

17: oil; R_f 0.56 (silica, 30% ether in petroleum ether); $[\alpha]^{25}{}_D$ −2.68° (c 1.12, $CHCl_3$); IR (neat) ν_{max} 3080, 3050, 3030, 2960, 2935, 2860, 1960, 1890, 1820, 1730 (aldehyde), 1590, 1470, 1460, 1455, 1427, 1390, 1375, 1360, 1305, 1260, 1130, 1105, 1155, 1025, 1005, 995, 900, 830, 825, 735, 695 cm^{-1}; ^1H NMR δ 9.57 (d, J = 1 Hz, 1 H, CHO), 7.65 (m, 5 H, Ar), 7.36 (m, 10 H, Ar), 4.46 (s, 2 H, CH_2Ph), 4.03 (m, 1 H, CHO), 3.65 (t, J = 9 Hz, 1 H, CH_2O), 3.32 (dd, J = 9, 5 Hz, 1 H, CH_2O), 2.36 (m, 1 H, $CHCH_3$), 1.11 (s, 9 H, $(CH_3)_3$), 0.88 (d, J = 7 Hz, 3 H, CH_3); mass spectrum, m/e (relative intensity), 389 (M^+ − t-Bu, 0.2), 283 (3.8), 221 (32.0), 91 (base peak); HRMS, m/e calcd for $C_{24}H_{25}O_3Si$ (M^+ − t-Bu) 389.1573, found 389.1617.

[[(1*R*,2*Z*/2*E*,4*S*)-1-[(1*S*)-2-(Benzyloxy)-1-methylethyl]-4-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-pentenyl]oxy]-*tert*-butyldiphenylsilane (19). Dry, recrystallized phosphonium salt 18 (3.43 g, 6.46 mmol) was dissolved in dry Me_2SO (6.4 mL) and an argon atmosphere was secured. Dimsylsodium (2.69 mL of a 2 M solution in Me_2SO) was added with stirring at 25 °C and stirring was continued for 10 min to ensure complete formation of the ylide. Azeotropically dried aldehyde **17** (2.1 g, 4.51 mmol) dissolved in dry Me_2SO–benzene (1:1, 26 mL) was added via a syringe to the freshly prepared ylide at 15 °C and stirring was continued for 45 min at 15–20 °C. The reaction mixture was quenched with saturated aqueous NH_4Cl (25 mL) and extracted with ether (100 mL). The water layer was acidified to pH 6 with 0.5 M aqueous $KHSO_4$ solution and reextracted with ether (2 × 150 mL). The combined organic extract was washed successively with water (3 × 50 mL) and brine (2 × 50 mL) and dried over $MgSO_4$. Filtration, evaporation, and purification by flash column chromatography (silica, 15% ether in petroleum ether) gave olefin **19** (2.03 g, 77%) as Z/E mixture ca. 2:1.

19: *E*/*Z* mixture; oil; R_f 0.42 (silica, 2.5% ethyl acetate in benzene); IR (neat) ν_{max} 3060, 3030, 2950, 2925, 2850, 1950, 1200, 1100, 1050, 835, 810, 690, 665 cm^{-1}; ^{1}H NMR δ 7.71 (m, 5 H, Ar), 7.34 (m, 10 H, Ar), 5.56 (t, *J* = 10 Hz, 0.62 H, =CH), 5.42 (dd, *J* = 15, 7.5 Hz, 0.38 H, =CH), 5.22 (dd, *J* = 15, 6.5 Hz, 0.38 H, =CH), 5.12 (t, *J* = 10 Hz, 0.62 H, =CH), 4.55 (dd, *J* = 9, 6 Hz, 0.62 H, CHO), 4.40 (s, 1.24 H, CH_2Ph), 4.38 and 4.36 (s, 0.38 H each, CH_2Ph), 4.27 (t, *J* = 10 Hz, 0.38 H, CH), 3.84–3.24 (m, 5 H, CHO, CH_2O), 2.20 (m, 0.38 H, $CHCH_3$), 2.06 (m, 1.62 H, $CHCH_3$), 1.33, 1.30, 1.26, and 1.24 (s, 6 H, acetonide), 1.05 and 1.03 (s, 9 H, $C(CH_3)_3$), 0.99 (d, *J* = 7 Hz, 1.86 H, CH_3), 0.37 (d, *J* = 8 Hz, 1.14 H, CH_3), 0.82 (d, *J* = 7 Hz, 1.14, CH_3), 0.37 (d, *J* = 7 H, 1.86, CH_3); mass spectrum, *m*/*e* (relative intensity), 557 ($M^+ - CH_3$, 0.2), 289 (12.5), 199 (98.6), 101 (39.5), 91 (base peak); HRMS, *m*/*e* calcd for $C_{35}H_{45}O_4Si$ ($M^+ - CH_3$) 557.3087, found 557.3103. Anal. Calcd for $C_{36}H_{48}O_4Si$: C, 75.55; H, 8.45. Found: C, 75.43; H, 8.41.

Preparation of Diol 19a. The *Z*/*E* olefin mixture **19** (500 mg, 0.87 mmol) was dissolved in dry ethylene glycol–DME (2:1, 30 mL). Amberlite IR-120HCP (0.6 g) was added, and the reaction mixture was allowed to stir at 45 °C for 8 h . Workup under standard conditions followed by flash column chromatography (silica, 50% ethyl acetate in petroleum ether) gave the diol **19a** (372 mg, 80% yield).

19a: *E*/*Z* mixture; oil; R_f 0.54 (silica, ether); IR (neat) ν_{max} 3400, 3060, 3040, 3020, 2950, 2920, 2850, 1585, 1450, 1420, 1355, 1200, 1100, 1050, 810, 830, 690 cm^{-1}; ^{1}H NMR δ 7.70 (m, 5 H, Ar), 7.35 (m, 10 H, Ar), 5.60 (t, *J* = 10 Hz, 0.4 H, =CH), 5.47 (dd, *J* = 15.8 Hz, 0.6 H, =CH), 5.24 (t, *J* = 10 Hz, 0.4 H, =CH), 5.06 (dd, *J* = 15, 9 Hz, 0.6 H, =CH), 4.62 (dd, *J* = 10, 5 Hz, 0.4 H, CHO), 4.38 (1.2 H, AB, CH_2Ph), 4.28 (dd, *J* = 8, 6 Hz, 0.6 H, CHO), 4.18 (0.8 H, AB, CH_2Ph), 3.53–3.14 (m, 4 H, CH_2O), 3.06 (m, 0.4 H, CHO), 2.76 (m, 0.6 H, CHO), 2.07 (m, 1 H, $CHCH_3$), 1.90–1.70 (m, 3 H, $CHCH_3$, 20 H), 1.04–1.02 (s, 9 H, $C(CH_3)_3$), 0.96 (d, *J* = 6.5 Hz, 1.2 H, CH_3), 0.82 (d, *J* = 6 Hz, 1.8 H, CH_3), 0.42 (d, *J* = 7 Hz, 1.2 H, CH_3); mass spectrum, *m*/*e* (relative intensity), 475 (M^+ - *t*-Bu), 385 (0.4), 367 (1.2), 337 (1.3), 277 (23.8), 199 (34.2), 181 (19.7), 109 (76.2), 91 (base peak); HRMS, *m*/*e* calcd for $C_{33}H_{45}O_4Si$ ($M^+ + 1$) 533.3088, found 533.3068.

Preparation of Tosylate 19b. To a solution of the dry diol **19a** (419 mg, 0.79 mmol) in dry pyridine (1.3 mL), cooled to −10 °C, was added recrystallized tosyl chloride (160 mg, 0.83 mmol) under an argon atmosphere and with stirring. Stirring was continued at 0 °C for 4 h and then at room temperature for 24 h. Cold water (2 mL) was added and the solution was extracted with ether (4 × 30 mL). The combined organic phase was washed with 20% aqueous $CuSO_4$ (2 × 10 mL), water (10 mL), saturated aqueous $NaHCO_3$ (2 × 10 mL), and brine (10 mL) and dried over $MgSO_4$. Filtration, evaporation, and purification by flash column chromatography (silica, 40% ether in petroluem ether) gave the primary tosylate **19b** (410 mg, 75%).

19b: *E*/*Z* mixture; oil; R_f 0.28 (silica, 30% ether in petroleum ether); IR (neat) ν_{max} 3400, 3070, 3050, 3030, 2960, 2930, 2860, 1590, 1450, 1420, 1355, 1170, 1100, 970, 810, 730, 695 cm^{-1}; ^{1}H NMR δ 7.80–7.10 (m, 19 H, Ar), 5.57 (t, *J* = 11 Hz, 0.55 H, =CH), 5.45 (dd, *J* = 15, 7.5 Hz, 0.45 H, =CH), 5.20 (dd, *J* = 11 Hz, =CH), 5.09 (dd, *J* = 15, 9 Hz, 0.45 H, =CH), 4.60 (dd, *J* = 9, 5 Hz, 0.55 H, CHO), 4.40–3.98 (2.45 H, CHO, CH_2Ph), 3.90–3.64 (m, 2 H, CH_2OTs), 3.50–3.10 (m, 3 H, CHO, CH_2O), 2.44 and 2.38 (s, 3 H, Ar CH_3), 2.13 (m, 2 H, $CHCH_3$), 1.73 (d, *J* = 5 Hz, OH), 1.05 and 1.02 (s, 9 H, $C(CH_3)_3$), 0.89 (d, *J* = 7.5 Hz, 1.65 H, CH_3), 0.85 (d, *J* = 7 Hz, 1.35 H, CH_3), 0.82 (d, *J* = 8 Hz, 1.35 H, CH_3), 0.43 (d, *J* = 7 Hz, 1.65 H, CH_3); mass spectrum, *m*/*e* (relative intensity) 531 ($M^- -$ Tos, 0.2), 491 (0.1), 377 (0.9), 353 (9.4), 199 (base peak).

Preparation of Epoxide 19c. The dry hydroxy tosylate **19b** (380 mg, 0.55 mmol) was dissolved in dry methanol (0.55 mL) under an argon atmosphere and cooled to 0 °C. Freshly prepared sodium methoxide (1.2 mL of a 0.5 M solution in dry methanol) was added and stirring was continued at room temperature for 2 h. The mixture was diluted with ether (200 mL) and washed with saturated aqueous NH_4Cl (30 mL), water (10 mL), and brine (30 mL). Filtration and evaporation yielded the epoxide **19c** (270 mg, 97%) sufficiently pure for the next step.

19c: *E*/*Z* mixture; oil; R_f 0.59 (silica, 30% ether in petroleum ether); IR (neat) ν_{max} 3050, 2960, 2935, 1590, 1470, 1455, 1430, 1360, 1255, 1105, 1050, 1000, 920, 845, 920, 735, 700 cm^{-1}; ^{1}H NMR δ 7.67 (m, 5 H, Ar), 7.32 (m, 10 H, Ar), 5.52 (m, 1 H, =CH), 5.10 (m, 1 H, =CH), 4.54 (dd, *J* = 10, 5 Hz, 0.6 H, CHO), 4.36 (s, 2 H, CH_2Ph), 4.24 (dd, *J* = 9, 6 Hz, 0.4 H, CHO), 3.60–3.40 (m, 1 H, CH_2O), 3.39–3.24 (m, 1 H, CH_2O), 2.64–2.49 (m, 2 H, CH_2O), 2.36–2.18 (m, 1 H, CHO), 2.02 (m, 2 H, $CHCH_3$), 1.04 and 1.02 (s, 9 H, $C(CH_3)_3$), 0.96 (d, *J* = 7 Hz, 1.8 H, CH_3), 0.90 (d, *J* = 6 Hz, 1.2 H, CH_3), 0.81 (d, *J* = 6.5 Hz, 1.2 H, CH_3), 0.49 (d, *J* = 6 Hz, 1.8 H, CH_3); mass spectrum, *m*/*e* (relative intensity) 499 ($M^+ - CH_3$, 0.2), 457 (1.5), 389 (1.6), 365 (9.9), 289 (11.7), 259 (15.1), 199 (15.6), 151 (13.6), 135 (22.6), 91 (base peak); HRMS, *m*/*e* calcd for $C_{33}H_{43}O_3Si$ ($M^+ + 1$) 515.2955, found 515.2972.

Preparation of Hydroxy Epoxide 19d. The epoxide **19d** obtained above (204 mg, 0.40 mmol) was dissolved in dry THF (0.4 mL) and treated with *n*-Bu_4NF (2 mL of a 1 M solution in tetrahydrofuran, 2.0 mmol) under argon and at 0 °C while stirring. Stirring was continued for 16 h at room temperature and then the reaction mixture was diluted with ether (150 mL), washed with water (2 × 20 mL) and brine (30 mL), and dried over $MgSO_4$. Filtration, evaporation, and purification by flash column chromatography (silica, 50% ether in petroleum ether) gave the hydroxy epoxide **19d** (110 mg, 97%) as an *E*/*Z* mixture. Pure *E* and *Z* components could be obtained either by flash column or preparative layer chromatography.

19d: *Z* compound; oil; R_f 0.29 (silica, 50% ether in petroleum ether); $[\alpha]^{25}_{D}$ +55.71° (*c* 0.015, $CHCl_3$); IR (neat) ν_{max} 3400, 3050, 3020, 2960, 2920, 2860, 1450, 1360, 1250, 1090, 1020, 920, 860, 730, 690 cm^{-1}; ^{1}H NMR δ 7.34 (s, 5 H, Ar), 5.48 (dd, *J* = 10, 8 Hz, 1 H, =CH), 5.40 (dd, *J* = 10, 9 Hz, 1 H, =CH), 4.53 (s, 2 H, CH_2Ph), 4.31 (br t, *J* = 7.5 Hz, 1 H, CHO), 3.64 (dd, *J* = 10, 5 Hz, 1 H, CH_2O), 3.50 (dd, *J* = 10, 7 Hz, 1 H, CH_2O), 3.48 (br s, 1 H, OH), 2.82 (m, 2 H, CHO), 2.72 (t, *J* = 3.5 Hz, 1 H, CH_2O), 2.55 (m, 2 H, CH_2O, $CHCH_3$), 1.94 (m, 1 H, $CHCH_3$), 1.07 (d, *J* = 8 Hz, 3 H, CH_3), 0.89 (d, *J* = 7.5 Hz, 3 H, CH_3); mass spectrum, *m*/*e* (relative intensity), 185 ($M^+ - CH_2Ph$, 2.8), 152 (10.6), 127 (11.5), 109 (10.8), 97 (15.0), 91 (base peak); HRMS, *m*/*e* calcd for $C_{17}H_{25}O_3$ ($M^+ + 1$) 277.1804, found 277.1802. Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.93; H, 8.76. Found: C, 73.74; H, 8.90.

19d: *E* compound; oil; R_f = 0.20 (50% ether in petroleum ether); $[\alpha]^{25}_{D}$ +11.80° (*c* 0.61, $CHCl_3$); IR (neat) ν_{max} 3440, 3030, 2960, 2870, 1490, 1470, 1450, 1400, 1360, 1255, 1200, 1090, 970, 925, 880, 815, 730, 690 cm^{-1}; ^{1}H NMR 7.34 (s, 5 H, Ar), 5.68 (dd, *J* = 15, 7 Hz, 1 H, =CH), 5.56 (dd, *J* = 15, 6 Hz, 1 H, =CH), 4.52 (s, 2 H, CH_2Ph), 4.01 (dt, *J* = 7 Hz, 1 H, CHO), 3.62 (dd, *J* = 8, 4 Hz, 1 H, CH_2O), 3.47 (dd, *J* = 8, 7 Hz, 1 H, CH_2O), 3.38 (d, *J* = 3 Hz, 1 H, OH), 2.84 (m, 1 H, CHO), 2.73 (t, *J* = 4 Hz, 1 H, CH_2O), 2.55 (dd, *J* = 5, 4 Hz, 1 H, CH_2O), 2.19 (m, 1 H, $CHCH_3$), 1.92 (m, 1 H, $CHCH_3$), 1.06 (d, *J* = 8 Hz, 3 H, CH_3), 0.89 (d, *J* = 7 Hz, 1 H, CH_3); mass spectrum, *m*/*e* (relative intensity), 185 ($M^+ - CH_2Ph$, 1.0), 152 (1.9), 127 (2.6), 109 (1.5), 97 (1.5), 91 (base peak); HRMS, *m*/*e* calcd for $C_{17}H_{25}O_3$ ($M^+ + 1$) 277.1804, found 277.1825.

(2*S*,3*R*,6*S*,7*S*)-1-(Benzyloxy)-7,8-epoxy-2,6-dimethyl-3-octanol (20). The hydroxy epoxide **19d** (*E*/*Z* mixture, 87 mg, 0.32 mmol) was dissolved in ethyl acetate (3 mL) and the flask was flushed with argon. 5% Pd/C (20 mg) was introduced, the flask was flushed with argon again, and the mixture was stirred under a hydrogen atmosphere at 25 °C for 2 h. The reaction mixture was then flushed with argon and filtered through Celite. Evaporation and purification by flash column chromatography (silica, 50% ether in petroleum ether) gave compound **20** (60 mg, 70%).

20: oil; R_f 0.25 (silica, 50% ether in petroleum ether); $[\alpha]^{25}_{D}$ +23.55° (*c* 0.9, $CHCl_3$); IR (neat) ν_{max} 3470, 3030, 2960, 2920, 2860, 1455, 1410, 1365, 1255, 1200, 1090, 1025, 925, 735, 695 cm^{-1}; ^{1}H NMR δ 7.36 (m, 5 H, Ar), 4.53 (s, 2 H, CH_2Ph), 3.70–3.40 (m, 4 H, CHO, CH_2O, OH), 2.72 (m, 2 H, CH_2–epoxide), 2.47 (dd, *J* = 5, 3 Hz, 1 H, CH–epoxide), 1.98–1.20 (m, 6 H, $CHCH_3$, CH_3), 0.93 (d, *J* = 6 Hz, 3 H, CH_3), 0.90 (d, *J* = 7 Hz, 3 H, CH_3); mass spectrum, *m*/*e* (relative intensity) 278 (M^+, 0.4), 247 (1.8), 173 (2.8), 141 (3.6), 108 (14.2), 91 (base peak); HRMS, *m*/*e* calcd for $C_{17}H_{26}O_3$ (M^+) 278.1882, found 278.1892.

(2*R*,3*S*,6*R*)-6-[(1*S*)-2-(Benzyloxy)-1-methylethyl]tetrahydro-3-methyl-2*H*-pyran-2-ol (20a). Compound **20** (55 mg, 0.20 mmol) was azeotropically dried with benzene (3 × 10 mL) and dissolved in dry methylene chloride (10 mL) under an argon atmosphere. Dry *dl*-camphorsulfonic acid (2.3 mg, 0.01 mmol) was added with stirring at room temperature and stirring was continued for 4 h at that temperature. The reaction mixture was then diluted with ether (150 mL), washed with 5% aqueous $NaHCO_3$ (2 × 10 mL), water (10 mL), and brine (20 mL), and dried ($MgSO_4$). Filtration, evaporation, and purification by flash column chromatography (silica, 50% ether in petroleum ether) afforded **20a** (52 mg, 95%).

20a: oil; R_f 0.14 (silica, 30% ether in petroleum ether); $[\alpha]^{25}{}_D$ –20.38° (*c* 1.3, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3440, 3060, 3030, 2930, 2870, 1455, 1365, 1275, 1200, 1170, 1075, 1025, 950, 900, 850, 735, 695 cm^{-1}; ^1H NMR δ 7.32 (m, 5 H, Ar), 4.52 (2 H, AB, CH_2Ph), 4.04–3.84 (m, 2 H, CHO, CH_2O), 3.77 (dd, $J = 9, 5$ Hz, 1 H, CH_2O), 3.60–3.36 (m, 3 H, CHO, CH_2O, OH), 3.32 (dd, $J = 8, 4$ Hz, 1 H, CH_2O), 2.08–1.20 (m, 6 H, $CHCH_3$, CH_2), 0.95 (d, $J = 6$ Hz, 3 H, CH_3), 0.81 (d, $J = 7$ Hz, 3 H, CH_3); mass spectrum, *m/e* (relative intensity), 278 (M^+, 0.3), 247 (2.7), 155 (2.2), 141 (5.2), 129 (9.1), 111 (5.0), 99 (6.8), 91 (base peak); HRMS, *m/e* calcd for $C_{17}H_{26}O_3$ (M^+) 278.1837, found, 278.1882.

(2*R*,3*S*,6*R*)-6-[(1*S*)-2-(Benzyloxy)-1-methylethyl]tetrahydro-3-methyl-2*H*-pyran-2-carboxaldehyde (21) and (2*R*,3*S*,6*R*)-6-[(1*S*)-2-(Benzyloxy)-1-methylethyl]-α-ethyltetrahydro-3-methyl-2*H*-pyran-2-methanol (21a). The hydroxytetrahydropyran derivative **20a** (55 mg, 0.20 mmol) was dissolved in dry methylene chloride (4.9 mL) under argon and at 25 °C, and recrystallized $CrO_3 \cdot HCl \cdot pyr$ (80 mg, 0.40 mmol) was added, followed by NaOAc (40 mg). Stirring was continued for 2.5 h, and then the reaction mixture was poured into ether (50 mL). The ethereal solution was filtered through florisil and concentrated in vacuo to afford an oily residue which was purified by chromatography on silica plates (two plates, 0.5 mm × 25 cm × 25 cm) with benzene as eluent leading to **21** (40 mg, 80%) which was immediately taken to the next step as follows. Aldehyde **21** (100 mg, 0.36 mmol) was dissolved in dry toluene (0.8 mL) under an argon atmosphere and cooled to –78 °C. Ethylmagnesium bromide (0.24 mL of a 3 M solution in tetrahydrofuran, 0.72 mmol) was added with stirring and stirring was continued for 1 h at –30 °C. The solution was quenched by the addition of saturated aqueous NH_4Cl (2 mL) and the reaction mixture was extracted with ether (3 × 50 mL), washed with saturated aqueous NH_4Cl (10 mL) and brine (10 mL), and dried ($MgSO_4$). Filtration, evaporation, and purification by flash column chromatography (silica, 40% ether in petroleum ether) gave compound **21a** (90 mg, 80%).

21a: diastereomeric mixture; oil; R_f 0.17 (silica, 30% ether in petroleum ether); IR (neat) ν_{max} 3420, 3060, 3020, 2960, 2920, 2870, 1490, 1450, 1370, 1360, 1100, 1205, 1080, 1060, 1020, 970, 900, 730, 690 cm^{-1}; ^1H NMR δ 7.33 (m, 5 H, Ar), 4.59, 4.53, and 4.51 (s, 2 H, CH_2Ph), 3.94–3.27 (m, 5 H, CHO, CH_2O), 2.35–1.14 (m, 9 H, $CHCH_3$, CH_2, OH), 1.06–0.76 (m, 9 H, CH_3); mass spectrum, *m/e* (relative intensity) 305 ($M^+ - H$, 0.2), 248 (1.4), 199 (3.7), 181 (6.1), 157 (20.4), 139 (12.5), 99 (14.2), 91 (base peak); HRMS, *m/e* calcd for $C_{19}H_{31}O_3$ ($M^+ + 1$) 307.2274, found 307.2277.

Preparation of Diol 21b. The alcohol **21a** (57 mg, 0.19 mmol) and ethanol (4 mL) were placed in a round-bottom flask and flushed with argon. 10% Pd/C (7 mg) was introduced and again argon was flushed through the flask. Hydrogen was bubbled through the stirred solution, and the hydrogen atmosphere was maintained while stirring for 16 h. The reaction mixture was then flushed with argon and filtered through Celite. Evaporation and purification by flash column chromatography (silica, 75% ether in petroleum ether) furnished diol **21b** (40 mg, 98%).

21b: diastereomeric mixture; oil; R_f 0.17 (silica, 75% ether in petroleum ether; IR (CCl_4) ν_{max} 3420, 2970, 2940, 2880, 1460, 1370, 1220, 1120, 1060, 975, 905, 875 cm^{-1}; ^1H NMR δ 3.78–3.48 (m, 5 H, CHO, CH_2O), 2.78 (br s, 1 H, OH), 2.22–1.20 (m, 9 H, $CHCH_3$, CH_2, OH), 1.12–0.81 (m, 9 H, CH_3); mass spectrum, *m/e* (relative intensity) 199 ($M^+ - OH$, 0.3), 184 (1.4), 157 (30.7), 139 (27.1), 121 (31.7), 109 (22.4), 95 (34.6), 85 (23.0), 81 (83.9), 69 (94.1), 55 (base peak); HRMS, *m/e* calcd for $C_{12}H_{25}O_3$ ($M^+ + 1$) 217.1805, found 217.1819.

Methyl (α*R*,2*R*,5*S*,6*R*)-Tetrahydro-α,5-dimethyl-6-propionyl-2*H*-pyran-2-acetate (3). The diol **21b** (37.4 mg, 0.17 mmol) was dissolved in dry acetone (5 mL) and cooled to –40 °C under argon. A solution of Jones' reagent (0.2 mL of 1.87 M solution; prepared from 111.25 g of CrO_3, 450 mL of H_2O, and 96.7 mL of concentrated H_2SO_4) was dropwise added and the reaction mixture was stirred at –20 °C for 2 h. Upon completion (TLC) excess ethereal diazomethane was added until gas evolution ceased and then the excess diazomethane was removed by bubbling argon through the solution. The mixture was then diluted with ether (80 mL) and the organic phase washed with 20% $NaHSO_3$ solution (2 × 10 mL), water (10 mL), and brine (25 mL), dried ($MgSO_4$), and evaporated. Chromatography on two silica plates (0.25 mm × 25 cm × 25 cm) with 25% ether in petroleum ether as solvent gave the keto ester **3** (31.6 mg, 85%) identical in all respects with the degradation product (see above for properties).

(±)-3-Ethyltetrahydro-2*H*-pyran-2-one (31). δ-Valerolactone (1.0 g, 10 mmol) was dissolved in anhydrous THF (10 mL) and dropwise added to a cold (–78 °C) LDA solution (12 mmol in 12 mL of THF) under argon and with stirring. After additional 30 min of stirring at –78 °C, ethyl iodide (1.64 mL, 20 mmol) dissolved in anhydrous HMPA (3.94 mL, 22 mmol) was dropwise added and the reaction mixture was stirred at –78 °C for 6 h (TLC monitoring). Quenching of the reaction with saturated aqueous NH_4Cl solution (50 mL) at –78 °C followed by warm-up and extraction of the mixture with methylene chloride (3 × 100 mL), washing of the combined organic phase with water (2 × 50 mL), 5% $NaHCO_3$ (50 mL), and brine (50 mL), drying ($MgSO_4$), filtration, and concentration gave an oily residue. Flash column chromatography (silica, ether–petroleum ether 1:1) led to ethyl-δ-valerolactone (896 mg, 70% yield) as a colorless oil.

31: oil; R_f 0.21 (silica, 50% ether in petroleum ether); IR (neat) ν_{max} 2980 (s), 2930 (s), 2870 (s), 1730 (lactone, s), 1455 (m), 1380 (m), 1350 (w), 1260 (m), 1130 (s), 970 (m) cm^{-1}; ^1H NMR δ 4.30 (m, 2 H, CH_2O), 2.42 (m, 1 H), 2.13 (m, 1 H), 1.90 (m, 3 H), 1.55 (m, 2 H), 1.00 (t, $J = 7.0$ Hz, 3 H, CH_3).

3-Ethyltetrahydro-2*H*-pyran-2-ol (31a). The lactone **31** (1.28 g, 10 mmol) was dissolved in CH_2Cl_2 (20 mL) and cooled to –78 °C under argon. DIBAL (6.0 mL, 10.5 mmol, 1.74 M in toluene) was added dropwise at –78 °C, and after it was stirred for 1 h at –78 °C, the mixture was quenched by the addition of CH_3OH (425 μL, 10.5 mmol) and then allowed to reach 25 °C. Dilution with ethyl acetate (100 mL) followed by washing with saturated solution of sodium potassium tartrate (50 mL), reextraction of the aqueous phase with ethyl acetate (3 × 50 mL), and washing of the combined organic fractions with brine (50 mL) gave a solution which was dried ($MgSO_4$) and concentrated, affording **31a** as an oily residue (1.30 g, 100% yield) pure enough for the next step.

31a: oil; R_f 0.31 (silica, 75% ether in petroleum ether); IR (neat) ν_{max} 3400 (OH, br s), 2920 (s), 2870 (s), 2720 (w), 1725 (s), 1450 (s), 1375 (m), 1280 (m), 1140 (s), 1070 (s), 970 (s) cm^{-1}; ^1H NMR δ 5.15 (s, 1 H, OCHO), 4.54–4.00 (m, 2 H, CH_2O), 3.70 (s, 1 H, OH), 1.90 (m, 1 H), 1.80–1.15 (m, 6 H), 9.15 (t, $J = 7.0$ Hz, CH_3); mass spectrum, *m/e* (relative intensity), 130 (M^+, 1), 112 ($M^+ - H_2O$, 15), 101 (9), 95 (7), 89 (7), 79 (14), 75 (base peak); HRMS, *m/e* calcd for $C_7H_{12}O_1$ 112.0822, found, 112.0835.

(*S*)-5-(*tert*-Butyldimethylsiloxy)-2-ethylvaleraldehyde (27). The crude lactol **31a** (3.95 g, 30.4 mmol) was dissolved in dry DMF (30 mL) and cooled to 0 °C. While stirring, imidazole (3.1 g, 45.5 mmol) was slowly added under an argon atmosphere followed by *tert*-butyldimethylsilyl chloride (6.89 g, 45.5 mmol). After 30 min stirring at 0 °C, the reaction mixture was allowed to reach room temperature and stirred for 1 h. The resulting mixture was then diluted with ether (200 mL), washed with water (2 × 50 mL) and brine (50 mL), dried ($MgSO_4$), and concentrated. Flash column chromatography (silica, 5% ether in petroleum ether) afforded in order of polarity the desired aldehyde **27** (5.19 g, 70% yield) and the isomeric closed form **31b** (protected lactol **31b**, 2.08 g, 28%).

(±)-27: oil; R_f 0.18 (silica, 5% ether in petroleum ether); IR (neat) ν_{max} 2980 (s), 2925 (s), 2700 (m), 1725 (CHO, s), 1460 (s), 1380 (s), 1250 (s), 1100 (br s), 830 (s), 780 (s) cm^{-1}; ^1H NMR δ 9.65 (d, $J = 3.5$ Hz, 1 H, CHO), 3.62 (t, $J = 5.5$ Hz, 2 H, CH_2O), 2.20 (m, 1 H), 1.75–1.45 (m, 6 H), 0.91 (t, $J = 7.0$ Hz, 3 H, CH_3), 0.86 (s, 9 H, $SiC(CH_3)_3$), 0.07 (s, 6 H, $Si(CH_3)_2$); mass spectrum, *m/e* (relative intensity), 187 (8), 185 (10), 131 (10), 83 (17), 75 (base peak); HRMS, *m/e* calcd for $C_{12}H_{23}O_2Si$ 227.1468, found 227.1475.

31b: oil; R_f 0.29 (silica, 5% ether in petroleum ether); IR (neat) ν_{max} 2960 (s), 2925 (s), 2850 (s), 1460 (s), 1390 (s), 1360 (w), 1250 (s), 1160 (s), 1100 (m), 1075 (s), 1040 (s), 870 (s), 835 (s), 775 (s) cm^{-1}; ^{1}H NMR δ 5.10 (m, 1 H, HCOO), 3.81 (t, J = 5.5 Hz, 2 H, H_2CO), 1.81–1.40 (m, 7 H), 0.95 (t, J = 7.0 Hz, 3 H, CH_3), 0.86 (s, 9 H, $SiC(CH_3)_3$), 0.07 (s, 6 H, $Si(CH_3)_2$); mass spectrum, *m/e* (relative intensity), 244 (M^+, 1), 203 (11), 185 (18), 83 (21), 75 (base peak); HRMS, *m/e* calcd for $C_7H_{12}O$ 112.0822, found 112.0838.

Alkylation of (+)-SAMP Hydrazone 25 to Product 26. The hydrazone **25** (5.0 g, 27.0 mmol) in dry ether (5 mL) was dropwise added to a precooled (−78 °C) LDA solution (3.8 mL diisopropylamine in 50 mL of Et_2O, 19.25 mL of 1.48 M *n*-BuLi in hexane; 27.0 mmol) under argon. The solution was allowed to reach 0 °C and kept at that temperature for 17 h, then recooled to −78 °C, and while stirring treated dropwise with 3-iodo-1-(*tert*-butyldimethylsiloxy)propane (8.4 g, 28.0 mmol) in ether (10 mL). The reaction mixture was brought up to 0 °C and stirred for 2 h before quenching with saturated NH_4Cl aqueous solution (30 mL). Separation of the organic phase followed by reextraction of the aqueous layer with ether (3 × 50 mL), combination of the extracts, washing with water (30 mL) and brine (30 mL), and drying ($MgSO_4$) afforded a solution of the product. Concentration followed by flash column chromatography (silica, ether–petroleum ether mixtures) gave pure **26** (6.9 g, 85% yield).

26: 50:1 diastereomerically pure by ^{1}H NMR ($Eu(fod)_3$); colorless oil; R_f 0.15 (silica, 20% ether in petroleum ether); $[\alpha]^{25}_D$ −4.20° (c 2.0, $CHCl_3$); IR (neat) ν_{max} 2960, 2930, 2860, 1608 (C=N), 1480, 1460, 1380, 1360, 1340, 1250, 1100, 830, 770 cm^{-1}; ^{1}H NMR δ 0.05 (s, 6 H, $Si(CH_3)_2$), 0.85 (t, J = 7.0 Hz, 3 H, CH_3), 0.9 (s, 9 H, *t*-Bu), 1.45 (m, 6 H, CH_2), 1.95 (m, 4 H, CH_2), 2.10 (m, 1 H, allyl CH), 2.70 (m, 1 H, NCH_2) 3.35 (s, 3 H, OCH_3), 3.40 (m, 3 H, NCH_2, OCH_2), 3.60 (m, 3 H, CH_2, NCH), 6.45 (d, J = 7.0 Hz, 1 H, vinyl CH); HRMS, *m/e* calcd for $C_{19}H_{40}O_2N_2Si$ (M^+) 356.2859, found 356.3864.

Ozonolysis of Hydrazone 26. A solution of hydrazone **26** (1.0 g, 0.33 mmol) in dry methylene chloride (20 mL) was cooled to −78 °C and ozonized until complete reaction (ca. 10 min, TLC). The solution was then flushed with argon and allowed to reach 25 °C before concentration under vacuum. Flash column chromatography (silica, ether–petroleum ether mixtures) afforded, in order of elution, optically active aldehyde **27** (71 mg 100% yield), spectroscopically and chromatographically identical with racemic **27** obtained from α-valerolactone, and (−)-(S)-2-(2-hydroxymethyl)-1-nitrosopyrolidine. Recombination of the aldehyde **27** obtained above with (+)-SAMP hydrazine gave back **20** of the same 50:1 diastereomeric ratio indicating the absence of racemization in these manipulations.

Methyl (2*E*,4*E*,6*S*)-9-(*tert*-Butyldimethylsiloxy)-6-ethyl-2,4-nonadienoate (27a). To a cold (−78 °C) solution of LDA (6.13 mmol, prepared from 857 μL, 6.13 mmol diisopropylamine in 7.30 mL THF, and 4.10 mL of 1.5 M *n*-BuLi solution in hexane) was added methyl 4-(dimethylphosphono)crotonate (1.85 mL, 6.73 mmol) under argon and in a dropwise fashion while stirring. After 10 min of stirring at −78 °C, the azeotropically dried aldehyde **27** (1.45 g, 5.11 mmol) in THF (5 mL) was slowly introduced and the reaction mixture was allowed to reach 0 °C, stirred for 1 h, then brought to 25 °C, and stirred at that temperature for 1 h. The reaction mixture was then diluted with ether (150 mL) and water (50 mL) and acidified with oxalic acid to pH 5. The organic layer was separated, combined with a second extract (100 mL of ether) of the aqueous phase and washed with water (50 mL) and brine (50 mL) before drying ($MgSO_4$). Evaporation followed by flash column chromatography (silica, ether–petroleum ether mixtures) afforded, in order of polarity, the *E* dienoate **27a** (1.58 g, 95% yield) and ca. 2% of its *E*,*Z* isomer.

27a: oil; R_f 0.15 (5% ether in petroleum ether); IR (neat) ν_{max} 2950 (s), 2920 (s), 2825 (m), 1719 (ester, s), 1640 (m), 1610 (w), 1550 (w), 1430 (w), 1250 (s), 1100 (s), 830 (s) cm^{-1}; ^{1}H NMR (360 MHz) δ 7.28 (dd, J = 10.0, 16.7 Hz, 1 H, HC=), 6.19 (dd, J = 10.0, 13.3 Hz, 1 H, HC=), 5.85 (dd, J = 8.3, 16.7 Hz, 1 H, HC=), 4.79 (d, J = 13.3 Hz, 1 H, HC=), 4.25 (s, 3 H, OCH_3), 3.55 (t, J = 6.6 Hz, 2 H, CH_2O), 2.00 (m, 1 H), 1.70–1.25 (m, 6 H), 0.82 (triplet obscured by singlet, 3 H, CH_3), 0,85 (s, 9 H, $SiC(CH_3)_3$), 0.08 (s, 6 H, $Si(CH_3)_2$); mass spectrum, *m/e* (relative intensity), 326 (M^+, 1), 311 ($M^+ - CH_3$, 1), 270 (10), 269 ($M^+ - C(CH_3)_3$, 50), 237 (70), 107 (40), 93 (52), 91 (30), 89 (base peak); HRMS, *m/e* calcd for ($C_{17}H_{31}O_3Si$) 311.2042, found 311.2063.

(2*E*,4*E*,6*S*)-9-(*tert*-Butyldimethylsiloxy)-6-ethyl-2,4-nonadien-1-ol (27b). Purified **27a** (1.80 g, 5.52 mmol) was dissolved in methylene chloride (10 mL) and cooled to −78 °C under an argon atmosphere. While stirring, DIBAL (6.67 mL of a 1.74 M solution in toluene, 11.60 mmol) was dropwise added and the reaction mixture was treated exactly as in the reduction of **31** to **31a** to afford, after flash column chromatography (silica, 50% ether in petroleum ether) the alcohol **27b** (1.63 g, 99%).

27b: oil; R_f 0.45 (silica, 50% ether in petroleum ether); IR (neat) ν_{max} 3380 (OH, br s), 2960 (s), 2930 (s), 2855 (s), 1650 (w), 1470 (m), 1460 (m), 1385 (m), 1360 (m), 1255 (s), 1100 (s), 985 (s), 835 (s), 750 (s) cm^{-1}; ^{1}H NMR δ 6.15 (dd, J = 10.0, 15.5 Hz, 1 H, HC=), 6.00 (dd, J = 10.0, 15.5 Hz, 1 H, HC=), 5.66 (dt, J = 15.5, 7.0 Hz, 1 H, HC=), 5.37 (dd, J = 8.5, 15.5 Hz, 1 H, HC=), 4.20 (d, J = 6.3 Hz, 2 H, CH_2O), 3.57 (ill-defined t, J = 6.5 Hz, 3 H, CH_2OSi, OH), 1.88 (m, 1 H), 1.54–1.07 (m, 7 H), 0.91 (s, 9 H, $SiC(CH_3)_3$), 0.85 (t, J = 7.0 Hz, 3 H, CH_3), 0.07 (s, 6 H, $Si(CH_3)_2$); mass spectrum, *m/e* (relative intensity) 298 (M^+, 1), 241 (3), 213 (3), 159 (13), 109 (14), 105 (15), 95 (26), 81 (27), 75 (base peak); HRMS, *m/e* calcd for $C_{13}H_{25}OSi$ 298.9071, found 298.9069.

Preparation of Bis(silyl ether) 27c. The alcohol **27b** (130 mg, 0.44 mmol) was dissolved in dry DMF (1.0 mL) and cooled to 0 °C. Imidazole (45 mg, 0.67 mmol) and *tert*-butyldiphenylsilyl chloride (176 mg, 0.67 mmol) were sequentially added with stirring and the reaction mixture was allowed to stir at room temperature for 1 h. Workup according to the procedure described for the preparation of **27** followed by flash column chromatography (silica, ether–petroleum ether mixtures) furnished the bis(silyl ether) **27c** (224 mg, 95% yield).

27c: oil; R_f 0.27 (silica, 5% ether in petroleum ether); IR (neat) ν_{max} 3050 (m), 2950 (s), 2925 (s), 2850 (s), 1650 (w), 1580 (w), 1470 (s), 1460 (s), 1430 (m), 1380 (m), 1360 (w), 1110 (s), 980 (s), 835 (s), 775 (m), 740 (s), 700 (s) cm^{-1}; ^{1}H NMR δ 7.68 (m, 4 H, Ar), 7.38 (m, 6 H, Ar), 6.22 (dd, J = 10.0, 15.5 Hz, 1 H, HC=), 6.00 (dd, J = 10.0, 15.5 Hz, 1 H, HC=), 5.65 (dt, J = 15.5, 6.0 Hz, 1 H, HC=), 5.38 (dd, J = 10.0, 15.5 Hz, 1 H, HC=), 4.22 (d, J = 5.5 Hz, 2 H, CH_2O), 3.58 (t, J = 7.0 Hz, 2 H, CH_2O), 1.90 (m, 1 H), 1.60–1.20 (m, 6 H), 1.08 (s, 9 H, $SiC(CH_3)_3$), 0.88 (s, 9 H, $SiC(CH_3)_3$), 0.82 (t, J = 7.0 Hz, 3 H, CH_3), 0.05 (s, 6 H, $Si(CH_3)_2$); mass spectrum, *m/e* (relative intensity), 536 (M^+, 1), 479 ($M^+ - C(CH_3)_3$, 5), 313 (10), 271 (19), 211 (13), 209 (33), 199 (base peak); HRMS, *m/e* calcd for $C_{29}H_{41}O_2Si_2$ 479.0193, found 479.0197.

Preparation of Mono(silyl ether) 27d. The bis(silyl ether) **27c** (236 mg, 0.44 mmol) was mixed with AcOH/THF/H_2O (3:2:2, 10 mL) and stirred at 25 °C for 1 h (TLC check). Dilution with CH_2Cl_2 (100 mL) followed by washing with water (3 × 25 mL), 5% $NaHCO_3$ (25 mL), and brine (50 mL), drying ($MgSO_4$), and evaporation afforded an oily product which was purified by flash column chromatography (silica, ether–petroleum ether) yielding **27d** (137 mg, 74% yield).

27d: oil; R_f 0.33 (silica, 50% ether in petroleum ether); IR (CCl_4) ν_{max} 3610 (w), 3400 (br w), 3060 (w), 2980 (s), 2930 (s), 2850 (s), 1470 (m), 1460 (m), 1425 (s), 1375 (m), 1110 (s) cm^{-1}; ^{1}H NMR δ 7.70 (m, 4 H, Ar), 7.38 (m, 6 H, Ar), 6.24 (dd, J = 10.0, 15.5 Hz, 1 H, HC=), 6.00 (dd, J = 10.0, 15.5 Hz, 1 H, HC=), 5.66 (dt, J = 15.5, 7.0 Hz, 1 H, HC=), 5.37 (dd, J = 8.5, 15.5 Hz, 1 H, HC=), 4.30 (d, J = 6.3 Hz, 2 H, CH_2O), 3.57 (t, J = 6.5 Hz, 2 H, CH_2O), 1.88 (m, 1 H), 1.54–1.12 (m, 6 H), 1.06 (s, 9 H, $SiC(CH_3)_3$), 0.85 (t, J = 7.0 Hz, 3 H, CH_3); mass spectrum, *m/e* (relative intensity), 422 (M^+, 1), 365 ($M^+ - C(CH_3)_3$, 5), 299 (10), 237 (6), 197 (10), 121 (10), 105 (12), 97 (25), 89 (50), 75 (base peak). Anal. Calcd for $C_{27}H_{38}O_2Si$: C, 76.73; H, 9.07. Found: C, 76.47; H, 8.90.

Preparation of Aldehyde 27e. Compound **27d** (1.00 g, 2.37 mmol) and pyridinium chlorochromate (764 mg, 3.56 mmol) were added to dry methylene chloride (5 mL) and stirred at room temperature for 2 h (TLC check). The reaction mixture was diluted with ether (50 mL) and filtered through a florisil (5 g, 100–200 mesh) pad (thorough wash with ether), and the resulting solution was then evaporated to afford the crude aldehyde **27e** (996 mg, 100%). Although the crude product was good enough for the next step, flash column chromatography (silica, ether–petroleum ether mixtures) could furnish pure aldehyde **27e** (960 mg, 95%).

27e: oil; R_f 0.21 (silica, 10% ether in petroleum ether); IR (neat) ν_{max} 3050 (m), 2955 (s), 2915 (s), 2850 (m), 2710 (w), 1715 (aldehyde, s), 1650 (w), 1460 (m), 1425 (m), 1380 (w), 1360 (w), 1265 (s), 1110 (s), 990 (m), 890 (w), 815 (w), 730 (s), 700 (s) cm^{-1}; ^{1}H NMR (350 MHz) δ 9.61 (t, J = 5.0 Hz, 1 H, CHO), 7.55 (m, 4 H, Ar), 7.52 (m, 6 H, Ar), 6.20 (dd, J = 15.0, 10.0 Hz, 1 H, HC=), 5.98 (dd, J = 15.0 Hz, 10.0 Hz, 1 H, HC=), 5.48 (dt, J = 15.0, 7.0 Hz, 1 H, HC=), 5.28 (dd, J = 15.0, 10.0 Hz, 1 H, HC=), 4.19 (d, J = 7.0 Hz, 2 H, CH_2CO), 3.50 (m, 1 H), 2.31 (m, 3 H), 1.88–1.11 (m, 5 H), 0.94 (s, 9 H, $SiC(CH_3)_3$), 0.78 (t, J = 7.0 Hz, 3 H, CH_3); mass spectrum, *m/e* (relative intensity) 420 (M^+, 1), 405 ($M^+ - CH_3$, 1), 863 ($M^+ - C(CH_3)_3$, 7), 200 (19), 199 (base peak); HRMS, *m/e* calcd for $C_{23}H_{27}O_2Si$ 363.1780, found 363.1809.

Methyl (2*E*,6*S*,7*E*,9*E*)-9-(*tert*-butyldiphenylsiloxy)-6-ethyl-2,7,9-undecatrienoate (28). Methyltriphenylphosphonium acetate (1.19 g, 3.56 mmol), was added directly to a magnetically stirred toluene (2.5 mL) solution of freshly prepared aldehyde **27e** (996 mg, crude) at 25 °C under argon. Stirring was continued for 12 h and then the reaction mixture was diluted with ether (100 mL) and concentrated in vacuo. Purification by flash column chromatography (silica, ether–petroleum ether mixtures) afforded, in order of polarity, the Diels–Alder precursor **28** (947 mg, 90% yield from **27d**) together with minor amounts of its *Z* isomer.

28: oil; R_f 0.38 (silica, 20% ether in petroleum ether); IR (neat) ν_{max} 3080 (m), 2960 (s), 2930 (s), 2850 (s), 1735 (ester, s), 1650 (m), 1450 (m), 1370 (m), 1360 (s), 1110 (s), 910 (s), 735 (s), 700 (s) cm^{-1}; ^{1}H NMR δ 7.70 (m, 4 H, Ar), 7.80 (m, 6 H, Ar), 6.96 (dt, J = 7.5, 15.5 Hz, 1 H, HC=), 6.23 (dd, J = 10.0, 15.5 Hz, 1 H, HC=), 6.02 (dd, J = 10.0, 15.0 Hz, 1 H, HC=), 5.82 (d, J = 15.5 Hz, 1 H, HC=), 5.68 (dt, J = 15.0, 6.5 Hz, 1 H, HC=), 5.35 (dd, J = 15.0, 10.0, Hz, 1 H, HC=), 4.25 (d, J = 6.5 Hz, 2 H, CH_2O), 3.72 (s, 3 H, OCH_3), 2.18 (m, 2 H), 1.91 (m, 1 H), 1.60–1.15 (m, 4 H), 1.05 (s, 9 H, $SiC(CH_3)_3$), 0.95 (t, J = 7.0 Hz, 3 H, CH_3); mass spectrum, *m/e* (relative intensity) 476 (M^+, 1), 445 ($M^+ - OCH_3$, 1), 421 (9), 420 (6), 419 ($M^+ - C(CH_3)_3$, 19), 213 (84), 199 (base peak); HRMS, *m/e* calcd for $C_{30}H_{40}O_3Si$ 476.2747, found 476.2738. Anal. Calcd for $C_{30}H_{40}O_3Si$: C, 75.63; H, 8.40. Found: C, 75.64; H, 8.33.

Methyl (1*S*,3a*R*,4*S*,5*R*,7a*S*)-5-(*tert*-Butyldiphenylsiloxy)-1-ethyl-3a,4,5,7a-tetrahydro-4-indancarboxylate (29). A reusable sealed tube (Sennital glass, 1 × 10 cm), containing a degassed (argon, bubbled for 20 min) toluene (7.2 mL) solution of **28** (640 mg, 1.44 mmol), was heated to 130 °C for 48 h. Concentration of the reaction mixture in vacuo and purification by flash column chromatography afforded **29** (448 mg, 70%), starting material (**28**, 57 mg, 9%), and an isomer of **29** (**29a**, 92 mg, 14%) presumed to be epimeric at C-16 (X-14547A numbering).

29: oil; R_f 0.50 (silica, 10% ether in petroleum ether); IR (neat) ν_{max} 3075 (m), 3050 (m), 2970 (s), 2925 (s), 2880 (s), 1733 (ester, s), 1650 (w), 1590 (w), 1460 (m), 1430 (m), 1360 (m), 1265 (s), 1190 (m), 1160 (m), 1110 (s), 940 (w), 820 (w), 780 (w), 735 (s), 700 (s) cm^{-1}; ^{1}H NMR (360 MHz) δ 7.65 (m, 4 H, Ar), 7.38 (m, 6 H, Ar), 5.95 (d, J = 10.0 Hz, 1 H, HC=), 5.69 (dt, J = 10, 3.5 Hz, 1 H, HC=), 4.20 (m, 2 H, CH_2O), 3.48 (s, 3 H, OCH_3), 2.80 (m, 1 H, HCC=), 2.65 (dd, J = 6.7, 11.0 Hz, 1 H, HCCOO), 2.00–1.20 (m, 9 H), 1.00 (s, 9 H, $SiC(CH_3)_3$), 0.82 (t, J = 7.0 Hz, 3 H, CH_3); mass spectrum, *m/e* (relative intensity), 461 ($M^+ - CH_3$, 1), 445 ($M^+ - OCH_3$, 2), 421 (9), 420 (30), 419 ($M^+ - C(CH_3)_3$, 87), 213 (base peak); HRMS, *m/e* calcd for $C_{26}H_{31}O_3Si$ 419.2043, found 419.2061. Anal. Calcd for $C_{30}H_{40}O_3Si$: C, 75.63; H, 8.40. Found: C, 75.42; H, 8.45.

29a: oil; R_f 0.45 (silica, 10% ether in petroleum ether); IR (neat) ν_{max} 3065 (m), 3050 (m), 2950 (s), 2930 (s), 2860 (s), 1737 (ester, s), 1650 (w), 1455 (m), 1438 (m), 1360 (m), 1250 (m), 1060 (m), 1010 (s), 820 (m), 700 (s) cm^{-1}; ^{1}H NMR (360 MHz) 7.50 (m, 4 H, Ar), 7.38 (m, 6 H, Ar), 5.88 (dt, J = 10.0, 3.5 Hz, 1 H, HC=), 5.68 (br d, J = 10 Hz, 1 H, HC=), 3.57 (s, OCH_3), 3.52 (m, 2 H, H_2CO), 2.58 (m, 1 H), 3.40–3.20 (m, 2 H), 2.00–1.13 (m, 8 H), 1.05 (s, 9 H, $SiC(CH_3)_3$), 0.90 (t, J = 7.0 Hz, 3 H, CH_3); mass spectrum, *m/e* (relative intensity), 476 (M^+, 1), 445 ($M^+ - OCH_3$, 1), 421 (6), 420 (9), 419 ($M^+ - C(CH_3)_3$, 25), 213 (base peak); HRMS, *m/e* calcd for $C_{26}H_{31}O_3Si$ 419.2061, found 419.2093.

(3a*R*,5a*S*,6*S*,8a*R*,8b*S*)-6-Ethyl-3,3a,5a,6,7,8,8a,8b-octahydro-1*H*-indeno[4,5-*c*]furan-1-one (4). A solution of **29** (444 mg, 1.0 mmol) in anhydrous THF (1.0 mL), cooled to 0 °C, was treated with either n-Bu_4NF (1.50 mL of 1 M THF solution, 1.50 mmol) or HF–pyridine (2.50 mL of 1 M THF solution, 2.50 mmol) and was allowed to stir at room temperature until TLC analysis revealed completion of the reaction. Dilution with ether (75 mL), washing with water (2 × 25 mL) and brine (25 mL), drying ($MgSO_4$), filtering, and evaporation afforded lactone **4** (173 mg, 100%) as a crystalline solid and essentially pure. Further purification could be achieved by flash column chromatography (silica, ether–petroleum ether mixtures) and/or recrystallization (ether–petroleum ether mixtures).

(±)-4: colorless rods; mp 68–68.5 °C; R_f 0.40 (silica, 50% ether in petroleum ether. Optically enriched (+)-**4**: $[\alpha]^{25}_D$ +113.00° (c 0.20, $CHCl_3$); IR (CCl_4) ν_{max} 3010 (w), 2950 (s), 2900 (s), 2960 (s), 1785 (s), 1650 (w), 1550 (m), 1538 (m), 1455 (w), 1360 (w), 1290 (w), 1200 (w), 1180 (s), 1145 (w), 1030 (m), 1000 (m) cm^{-1}; ^{1}H NMR δ 6.05 (d, J = 10.0 Hz, 1 H, HC=), 5.70 (dt, J = 10.0, 3.5 Hz, 1 H, HC=), 4.50 (dd, J = 8.6, 7.2 Hz, 1 H, H_2CO), 3.90 (dd, J = 8.6, 10.0 Hz, 1 H, CH_2O), 3.20 (m, 1 H, HCC=), 2.55 (dd, J = 7.2, 11.1 Hz, 1 H, HCCOO), 2.06–1.90 (m, 2 H), 1.78–1.15 (m, 7 H), 0.95 (t, J = 7.0 Hz, 3 H, CH_3); mass spectrum, *m/e* (relative intensity), 206 (M^+, 7), 177 (17), 161 (20), 152 (46), 131 (19), 119 (21), 117 (14), 112 (18), 107 (15), 105 (45), 95 (96), 92 (43), 91 (base peak); HRMS, *m/e* calcd for $C_{13}H_{18}O_2$ 206.1307, found 206.1337. Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.68; H, 8.80. Found: C, 75.81; H, 8.81. X-ray analysis revealed that the crystals were orthorhombic, space group $P2_1nb$, with a = 6.659 (2) Å, b = 11.272 (3) Å, c = 18.110 (5) Å, and d_{calcd} = 1.186 g cm^{-3} for Z = 4 ($C_{13}H_{18}O_2$, M = 206.28). Intensity data were measured on a Hilger-Watts diffractometer (Ni filtered Ca Kα radiation, θ–2θ scans, pulse height discrimination). The crystal used measured 0.02 × 0.15 × 0.25 mm and 727 reflections were observed [$I > 2.5\ \sigma(I)$].

Reaction of γ-Butyrolactone with MeMgBr–Pyrrole System. MeMgBr (10.7 mL of a 2.8 M THF solution, 30.0 mmol) was added to cooled (0 °C) toluene (87.0 mL) under argon followed by freshly distilled (P_2O_5) pyrrole (2.04 g, 30.0 mmol). The reaction mixture was heated to 55 °C under argon for 1 h giving a greenish solution to which anhydrous γ-butyrolactone (**32**) (2.58 g, 30.0 mmol) in toluene (5.0 mL) was dropwise added with stirring. TLC analysis revealed rapid formation of amide **33**. Excess of MeMgBr–pyrrole reagent (>2 equiv) and prolonged heating at 110 °C (12–24 h) resulted in the almost exclusive formation of the ketopyrrole **33** as revealed by TLC. The reaction mixture was cooled (25 °C) and diluted with CH_2Cl_2 (200 mL), saturated NH_4Cl solution (100 mL), and 10% aqueous HCl solution to pH 6.0. The organic phase was separated and the aqueous layer was reextracted with CH_2Cl_2 (2 × 75 mL) and the combined organic solution washed with water (3 × 50 mL) and brine (50 mL). Drying ($MgSO_4$) followed by evaporation and flash column chromatography (silica, ether) afforded pure amide **33** (138 mg, 90%) or ketopyrrole **34** (138 mg, 90%).

33: colorless crystals, mp 54–55 °C (ether–petroleum ether); R_f 0.32 (silica, ether); IR ($CHCl_3$) ν_{max} 3610 (m), 3450 (br m), 3010 (s), 2950 (s), 2980 (m), 1710 (amide, s), 1465 (s), 1410 (m), 1370 (m), 1335 (m), 1270 (s), 1205 (s), 1118 (s), 1072 (s), 1015 (w), 925 (m), 910 (s), 860 (w) cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 7.30 (m, 2 H, HC=), 7.14 (m, 2 H), 3.60 (t, J = 6.0 Hz, 2 H, H_2CO), 3.34 (t, J = 6.0 Hz, 2 H, H_2CCCO), 2.00 (m, 2 H); mass spectrum, *m/e* (relative intensity), 153 (M^+, 7), 67 (base peak); HRMS, *m/e* calcd for $C_8H_{11}NO_2$ 157.0784, found 153.0787. Anal. Calcd for $C_8H_{11}NO_2$: C, 62.71; H, 7.24; N, 9.15. Found: C, 62.86; H, 7.30; N, 9.09.

4-Hydroxy-1-pyrrol-2-yl-1-butanone (34). Colorless crystals, mp 62–62.5 °C (ether–petroleum ether); R_f 0.22 (silica, ether); IR ($CHCl_3$) ν_{max} 3450 (s), 3300 (br w), 3010 (s), 2970 (m), 2920 (m), 2870 (s), 1638 (ketone, s), 1540 (s), 1405 (s), 1320 (w), 1290 (m), 1205 (s), 1100 (s), 1040 (m), 1010 (m), 920 (m) cm^{-1}; ^{1}H NMR δ 9.40 (br s, 1 H, NH), 7.10 (m, 1 H, HC=), 6.95 (m, 1 H, HC=), 6.30 (m, 1 H, HC=), 3.70 (t, J = 7.0 Hz, 2 H, H_2COH), 2.95 (t, J = 7.0 Hz, 2 H, H_2CO), 2.00 (p, J = 7.0 Hz, 2 H, H_2C), 1.70 (br s, 1 H, OH); mass spectrum, *m/e* (relative intensity), 153 (M^+, 2), 135 ($M^+ - H_2O$, 10), 109 (27), 94 (39), 62 (base peak); HRMS, *m/e* calcd for $C_8H_{11}O_2N$ 153.0789, found 153.0788. Anal. Calcd for $C_8H_{11}O_2N$: C, 62.71; H, 7.24. Found: C, 26.81; H, 7.30; N, 9.09.

(1*S*,3a*R*,4*S*,5*R*,7a*S*)-1-Ethyl-3a,4,5,7a-tetrahydro-5-(hydroxymethyl)-4-indanyl Pyrrol-2-yl Ketone (30). To a toluene (150 μL) solution of methylmagnesium chloride (70 μL, of a 2.8 M in THF, 0.20 mmol) was slowly added in a dropwise fashion pyrrole (12.6 μL, 0.20 mmol) at 0 °C under an atmosphere of argon. The mixture was heated at 50 °C for 1 h and then azeotropically (benzene) dried lactone **4** (20 mg, 0.10 mmol) dissolved in toluene (50 μL) was introduced maintaining the solution at 50 °C. Initial TLC analysis indicated what was presumed to be amide formation although attempts to isolate it were unsuccessful. Prolonged heating of the reaction mixture resulted in the eventual formation of the ketopyrrole **30**. The reaction mixture was cooled to 25 °C, diluted with ether (50 mL), and quenched with a saturated solution of NH_4Cl (25 mL). The organic phase was separated, the aqueous solution was reextracted with ether (2 × 25 mL), and the extracts were combined and washed with water (25 mL) and brine (25 mL) and dried ($MgSO_4$). Concentration followed by preparative layer chromatography (0.5 mm, 20 × 20 cm, silica plate) provided pure ketopyrrole **30** (25 mg) (93% yield) along with minor amounts of starting material (1.0 mg, 4%).

30: oil; R_f 0.21 (silica, 75% ether in petroleum ether); IR (neat) ν_{max} 3430 (OH, br s), 3280 (br s), 3050 (m), 3005 (w), 2950 (s), 2920 (m), 2870 (s), 1620 (s), 1542 (m), 1460 (m), 1425 (m), 1410 (s), 1295 (m), 1265 (s), 1100 (m), 1045 (s), 1015 (m), 830 (w), 730 (s) cm^{-1}; ^1H NMR δ 9.47 (br s, 1 H, NH), 7.09 (m, 1 H, HC=), 7.00 (m, 1 H, HC=), 6.32 (m, 1 H, HCN), 6.10 (d, J = 10.0 Hz, 1 H, HC=), 5.58 (dt, J = 10.0, 3.5 Hz, 1 H, HC=), 3.60 (m, 3 H), 3.44 (dd, J = 7.0, 11.0 Hz, 1 H, HCCO), 2.72 (m, 2 H), 2.15–0.90 (m, 7 H), 0.92 (t, J = 7.0 Hz, 3 H, CH_3); mass spectrum, m/e (relative intensity), 255 ($M^+ - H_2O$, 23), 254 (7), 253 (11), 94 (base peak); HRMS, m/e calcd for $C_{17}H_{21}NO$ 255.1623, found 255.1648. Anal. Calcd for $C_{17}H_{23}O_2N$: C, 74.68; N, 5.13; H, 8.49. Found: C, 74.81; N, 5.26; H, 8.58.

(1*S*,3a*R*,4*S*,5*R*,7a*S*)-1-Ethyl-3a,4,5,7a-tetrahydro-5-[(phenylthio)methyl]-4-indancarboxylic Acid (4a). Lithium thiophenoxide (5.34 mmol) was generated in dry DMF by adding thiophenol (0.60 mL, 5.89 mmol) to a magnetically stirred suspension of LiH (43.0 mg, 5.34 mmol) in dry DMF (2.20 mL) at 25 °C under an argon atmosphere (45 min). This solution was then added to optically enriched lactone **4** (220.0 mg, 1.07 mmol in 0.20 mL of DMF) *via* syringe. The mixture was then stirred at 110 °C for 3 h, then cooled (0 °C), acidified with 1.2 N aqueous HCl, and extracted with ether (2 × 60 mL). The ether extracts were washed with H_2O (50 mL) and brine (30 mL), dried ($MgSO_4$), filtered, and flash chromatographed (silica, 20% ether in petroleum ether) yielding carboxylic acid **4a** (320 mg, 95%). An identical reaction was carried out on racemic lactone.

4a: oil; $[\alpha]^{25}{}_D$ −46.6° (c 1.6, $CHCl_3$); R_f 0.22 (silica, 20% ether in petroleum ether); IR (neat) ν_{max} 3500–2400 (br, CO_2H), 2960 (s), 1710 (s, C=O), 1580 (m), 1480 (m), 1440 (m), 1290 (m), 1220 (m), 1090 (w), 1020 (w), 910 (m) cm^{-1}; ^1H NMR δ 7.30 (m, 5 H, Ar), 5.92 (m, 2 H, $\mathit{H}C{=}C\mathit{H}$), 3.18 (m, 1 H, $HCCO_2$), 2.70–3.00 (m, 3 H, $C\mathit{H}_2S$, $\mathit{H}CC{=}$), 1.90–2.20 (m, 9 H, CH, CH_2), 0.91 (t, J = 7.0 Hz, 3 H, $C\mathit{H}_3CH_2$); mass spectrum, m/e (relative intensity) 316.2 (M^+, 8.5), 269.2 (2.5), 206.1 (2.1), 177.1 (2.6), 161.1 (5.5), 123.0 (base peak); HRMS, m/e calcd for $C_{19}H_{24}O_2S$ 316.1497, found 316.1504.

Methyl (1*S*,3a*R*,4*S*,5*R*,7a*S*)-1-Ethyl-3a,4,5,7a-tetrahydro-5-[(phenylthio)methyl]-4-indancarboxylate (4b). A solution of **4a** (280.0 mg, 0.89 mmol) (optically enriched) in ether (2.0 mL) was magnetically stirred and cooled (0 °C). Ethereal diazomethane was added dropwise until gas evolution ceased and a yellow color remained. The excess diazomethane was removed by bubbling argon through the solution. Rotary evaporation afforded 294.0 mg (100%) of crude methyl ester **4b**. Preparative layer chromatography (silica, 20% ether in petroleum ether) furnished an analytical sample. A similar reaction on the racemic material was carried out.

4a: oil; $[\alpha]^{25}{}_D$ −32.6° (c 1.05, $CHCl_3$); R_f 0.27 (silica, 5% ether in petroleum ether); IR (neat) ν_{max} 3000 (w), 2950 (s), 1735 (s), 1580 (m), 1480 (m), 1460 (w), 1430 (m), 1330 (w), 1190 (m), 1140 (m), 1090 (m) cm^{-1}; ^1H NMR δ 7.12–7.40 (m, 5 H, Ar), 5.95 (d, J =10.0 Hz, 1 H, HC=), 5.82 (m, 1 H, HC=), 3.70 (s, 3 H, CH_3O), 2.65–3.02 (m, 4 H, SCH_2, $CHCO_2$, HCC=), 1.02–2.08 (m, 9 H, CH, CH_2), 0.91 (t, J = 7.0 Hz, 3 H, CH_3CH_2); mass spectrum, m/e (relative intensity) 330.9 ($M^+ + 1$, 3.6), 329.9 (M^+, 16.9), 161.0 (23.7), 147.0 (23.0), 122.9 (base peak); HRMS m/e calcd for $C_{20}H_{26}O_2S$ 330.1703, found 330.1652.

(1*S*,3a*R*,4*S*,5*R*,7a*S*)-1-Ethyl-3a,4,5,7a-tetrahydro-5-[(phenylthio)methyl]-4-indanmethanol (37). A solution of crude, optically enriched methyl ester **4b** (280.0 mg, 0.85 mmol) in 10 mL of dry ether was magnetically stirred under argon at 0 °C. $LiAlH_4$ (33.0 mg, 0.85 mmol) was added in one portion and stirring was continued until the reaction was complete (TLC). Ether (75 mL) was saturated with H_2O and added dropwise to the cold mixture over 10 min. When all the excess $LiAlH_4$ was neutralized and a white precipitate of aluminum salts formed, the mixture was dried ($MgSO_4$) and filtered. The filter cake was washed with dry ether (150 mL) and the ether was evaporated to afford a white solid which crystallized from ether, yielding **37** (257 mg, 100%). An identical reaction was carried out with racemic material.

37: colorless solid, mp (racemic) 80.0–81.5 °C (ether), mp (optically active) 93.0–94.5 °C (ether); $[\alpha]^{25}{}_D$ −38.9° (c 0.90, $CHCl_3$); R_f 0.53 (silica, 60% ether in petroleum ether); IR ($CHCl_3$) ν_{max} 3360 (OH, m), 3050 (w), 3005 (m), 2950 (s), 1580 (m), 1470 (m), 1435 (m), 1080 (w), 920 (m) cm^{-1}; ^1H NMR δ 7.10–7.45 (m, 5 H, Ar), 5.90 (d, J = 10.0 Hz, 1 H, HC=), 5.76 (m, 1 H, HC=), 3.68 (m, 2 H, CH_2O), 3.20 (m, 1 H), 2.60–2.87 (m, 2 H), 2.27 (br s, 1 H, OH), 1.00–2.04 (m, 10 H, CH_2, CH), 0.87 (t, J = 7.0 Hz, 3 H, $C\mathit{H}_3CH_2$); mass spectrum, m/e (relative intensity), 302.9 ($M^+ +$ 1, 6.3), 301.9 (M^+, 25.8), 175.0 (9.8), 161.0 (47.1), 147.0 (13.2), 123.9 (26.6), 122.9 (base peak); HRMS, m/e calcd for $C_{19}H_{26}OS$: 302.1754, found 302.1683.

(1*S*,3a*R*,4*S*,5*R*,7a*S*)-1-Ethyl-3a,4,5,7a-tetrahydro-5-[(phenylsulfonyl)methyl]-4-indanmethanol (37a). To a solution of optically enriched hydroxy sulfide **37** (200.0 mg, 0.66 mmol) in CH_2Cl_2 (1 mL) and ether (5 mL) was added diphenyl diselenide (226.0 mg, 0.72 mmol). The mixture was magnetically stirred at 0 °C and 30% H_2O_2 (0.40 mL, 4.0 mmol) was added dropwise via a Teflon-brand needle (10 min). The cooling bath was removed and the reaction mixture was allowed to stir at 25 °C for 7 h (TLC). The reaction mixture was diluted with CH_2Cl_2 ether (1:2, 100 mL) and washed with saturated aqueous $NaHCO_3$ (2 × 30 mL), 10% aqueous sodium thiosulfate (2 × 30 mL), and brine (50 mL), dried ($MgSO_4$), filtered, and evaporated. The crude sulfone was flash chromatographed (silica, 75% ether in hexane) to yield pure **37a** (180 mg, 82% yield). An identical reaction was carried out on racemic material.

37a: oil; $[\alpha]^{25}{}_D$ −37.6° (c 0.95, $CHCl_3$); R_f 0.30 (silica, 70% ether in petroleum ether); IR ($CHCl_3$) ν_{max} 3510 (OH, m), 3020 (m), 3000 (m), 2960 (s), 2870 (s), 1580 (w), 1480 (w), 1450 (m), 1448 (s), 1400 (m), 1475 (m), 1300 (SO_2, S), 1145 (SO_2, S), 1080 (s), 1030 (m), 945 (m) cm^{-1}; ^1H NMR δ 7.96 (m, 2 H, Ar), 7.62 (m, 3 H, Ar), 5.78 (d, J = 10.0 Hz, 1 H, HC=), 5.60 (m, 1 H, HC=), 3.40–3.82 (m, 3 H), 2.85–2.12 (m, 2 H), 2.52 (m, 1 H, OH), 1.00–2.10 (m, 10 H, CH, CH_2), 0.88 (t, J = 6.0 Hz, 3 H, $C\mathit{H}_3CH_2$); CI mass spectrum (isobutane), m/e (relative intensity) 334.6 (M^+, 34.8), 316.6 (35.0), 175.1 (base peak). Anal. Calcd for $C_9H_{26}O_3$: C, 68.23; H, 7.84; S, 9.59. Found: C, 68.03; H, 7.90; S, 9.45.

***tert*-Butyl[[(1*S*,3a*R*,4*S*,5*R*,7a*S*)-1-ethyl-3a,4,5,7a-tetrahydro-5-[(phenylsulfonyl)methyl]-4-indanyl]methoxy]dimethylsilane (38).** To optically enriched hydroxy sulfone **37a** (150 mg, 0.45 mmol) in dry CH_2Cl_2 (1.0 mL) were added Et_3N (93 μL, 0.66 mmol) and 4-(dimethylamino)pyridine (2.9 mg, 0.023 mmol). The mixture was magnetically stirred under argon at 25 °C and *tert*-butyldimethylsilyl chloride (74 mg, 0.49 mmol) was introduced in one portion. Stirring was continued until completion was indicated by TLC (20 h), and the mixture was then diluted with ether (110 mL), washed with 1.2 N aqueous HCl (30 mL), H_2O (30 mL), 5% aqueous $NaHCO_3$ (30 mL), and brine (30 mL), dried ($MgSO_4$), filtered, and evaporated. The crude silyl ether was flash chromatographed (silica, 20% ether in petroleum ether) to give pure **38** (192 mg, 95%). An identical reaction was carried out on racemic material.

38: oil; $[\alpha]^{25}{}_D$ −38.6° (c 0.90, $CHCl_3$); R_f 0.57 (silica, 25% ether in petroleum ether); IR (neat) ν_{max} 3060 (w), 3020 (m), 2960 (s), 2860 (s), 1580 (w), 1470 (m), 1460 (m), 1445 (m), 1385 (w), 1300 (SO_2, S), 1250 (SO_2, S), 1140 (s), 1980 (s), 1000 (w), 900 (w), 830 (s) cm^{-1}; ^1H NMR δ 7.88 (m, 2 H, Ar), 7.54 (m, 3 H, Ar), 5.99 (br d, J = 10.0 Hz, 1 H, HC=), 5.88 (d, J = 10.0 Hz, 1 H, CH=), 3.56 (m, 2 H, $CH\mathit{H}O$, $C\mathit{H}CH_2SO_2$), 3.40 (dd, J = 9.0, 8.0 Hz, 1 H, $C\mathit{H}HO$), 2.98 (m, 2 H, CH_2SO_2), 0.98–1.95 (m, 9 H, CH_2, CH), 0.84 (t, J = 7.0 Hz, 3 H, CH_3), 0.75 (s, 9 H, $SiC(CH_3)_3$), −0.07 and −0.08 (s, 3 H each, $Si(CH_3)_2$); CI mass spectrum (isobutane), m/e (relative intensity) 449.0 ($M^+ + 1$, 45.2), 391.0 ($M^+ - t$-Bu, 32.6), 317.0 (21.4), 198.9 (15.7), 175.0 (base peak); HRMS, *m*/*e* calcd for $C_{25}H_{41}O_3SiS$ 449.2596, found 449.2522.

Coupling of Bromide 36 and Sulfone 38. Preparation of Compounds 39 and 39′. To sulfone **38** (172 mg, 0.38 mmol, dried in vacuo over P_2O_5 for 48 h) was added dry THF (0.30 mL) under an argon atmosphere. This magnetically stirred solution was cooled (−78 °C) and dropwise treated with LDA (0.9 mL of 0.5 M solution, generated by addition of *n*-BuLi (1 mL of 1.5 M in hexane) to 2.2 mL of THF and 0.24 mL of diisopropylamine at −78 to 0 °C, 45 min). The reaction mixture was stirred for 10 min at −78 °C and then 0.15 mL of HMPA (distilled from CaH_2) was added and stirring continued until the HMPA dissolved (flask removed from cooling bath, 1 min). The flask was recooled to −78 °C and allylic bromide **36** (200 mg, 0.61 mmol) in THF (300 μL) was added in one portion. The reaction was allowed to stir for 25 min at −78 °C (TLC indicated completion in 10 min). Saturated aqueous NH_4Cl solution was added (5 mL) and the mixture allowed to reach room temperature. Extraction with ether (3 × 60 mL), washing with 1.2 N HCl (20 mL), 5% aqueous $NaHCO_3$ (10 mL), and brine (20 mL), drying ($MgSO_4$), filtration, evaporation, and flash column chromatography (silica, 20% ether in petroleum ether) afforded **39** and its diastereoisomer **39′** in pure form (261 mg, 98% total yield). The ratios of diastereoisomers starting from optically enriched lactone **38** was 9:1 (slow/fast) and from racemic lactone 1:1 indicating that these were the diastereoisomers resulting from the right wing **38** and not from sulfone epimers.

39: oil; $[\alpha]^{25}{}_D$ −49.5° (*c* 2.10,m $CHCl_3$); R_f 0.28 (silica, 25% ether in petroleum ether); IR (neat) ν_{max} 3060 (w), 3020 (w), 2945 (s), 2850 (s), 1738 (C═O, s), 1460 (m), 1375 (m), 1350 (m), 1300 (m), 1350 (m), 1200 (m), 1140 (s), 1080 (s), 900 (m), 830 (s) cm^{-1}; ^{1}H NMR δ 7.88 (d, *J* = 7.0 Hz, 2 H, Ar), 7.52 (m, 3 H, Ar), 6.02 (d, *J* = 10.0 Hz, 1 H, CH═), 5.86 (br d, *J* = 10.0 Hz, 1 H, CH═), 5.12 (t, *J* = 7.0 Hz, 1 H, CH═), 4.08 (br s, *J* = 10.0 Hz, 1 H, ═CCHO), 3.65 (m, 3 H, CHO, $CHSO_2$, C*H*$CHSO_2$), 3.47 (s, 3 H, CH_3O), 3.40 (d, *J* = 10.0 Hz, 2 H, CH_2O), 2.84 (m, 1 H, C*H*CO_2CH_3), 2.55 (t, *J* = 6.5 Hz, 2 H, ═CHC$H_2$$CSO_2$), 1.00–2.00 (m, 17 H, C$H_2$C*H*), 1.02 (d, *J* = 7.0 Hz, 3 H, CH_3), 0.86 (t, *J* = 7.0 Hz, 3 H, CH_3), 0.85 (s, 9 H, $SiC(CH_3)_3$), 0.82 (t, *J* = 7.0 Hz, 3 H, CH_3), 0.74 (d, *J* = 7.0 Hz, 3 H, CH_3), 0.01 (s, 6 H, $Si(CH_3)_2$); CI mass spectrum (isobutane), *m*/*e* (relative intensity) 702.2 (M^+ + 2, 26.0), 701.2 (M^+ + 1, 49.1), 700.2 (M^+, 6.9), 543.2 (M^+ − *t*-Bu, 12.8), 569.0 (17.7), 559.1 (18.0), 427.1 (41.5), 257.1 (24.9), 171.1 (23.7), 71.0 (65.3), 61.0 (base peak). Anal. Calcd for $C_{40}H_{64}O_6SSi$: C, 68.52; H, 9.20; S, 4.57. Found: C, 68.67; H, 9.25; S, 4.69.

39′: oil; $[\alpha]^{25}{}_D$ +16.1° (*c* 2.16, $CHCl_3$); R_f 0.36 (silica, 25% ether in petroleum ether); IR (neat) ν_{max} 3060 (w), 3020 (w), 2945 (s), 2830 (s), 1735 (C═O, s), 1580 (w), 1460 (s), 1440 (s), 1375 (m), 1360 (m), 1300 (s), 1255 (s), 1200 (s), 1140 (s), 1080 (s), 900 (s), 830 (s) cm^{-1}; ^{1}H NMR δ 7.88 (m, 2 H, Ar), 7.50 (m, 3 H, Ar), 6.00 (br d, *J* = 10.0 Hz, HC═), 5.90 (m, 1 H, HC═), 5.18 (t, *J* = 7.0 Hz, 1 H, HC═), 4.05 (s, br s, 1 H, ═CCHO), 2.54 (s, 3 H, OCH_3), 3.34–3.80 (m, 5 H, CH_2O, CHO, $CHSO_2$, C*H*$CHSO_2$), 2.83 (m, 1 H, $HCCO_2$), 2.36–2.70 (m, 2 H, ═$CHCH_2CSO_2$), 0.95–2.00 (m, 17 H, CH_2, CH), 0.83 (s, 9 H, $SiC(CH_3)_3$), 0.80 (t, *J* = 6 Hz, 6 H, C$H_3$$CH_2$), 0.66 (d, *J* = 6.0 Hz, 3 H, CH_3), 0.01 (s, 6 H, $Si(CH_3)_2$); CI mass spectrum (isobutane), *m*/*e* (relative intensity) 701.1 (M^+ + 1, 24.7), 700.1 (M^+, 2.8), 543.1 (M^+ − *t*-Bu, 6.8), 559.0 (12.7), 427.1 (23.0), 349.0 (13.3), 317.0 (22.5), 257.1 (21.2), 171.1 (14.1), 149.0 (12.9), 143.0 (18.0), 123.0 (12.6), 91.0 (59.9), 61.0 (base peak). Anal. Calcd for $C_{40}H_{64}O_6SSi$: C, 68.52; H, 9.20; S, 4.57. Found: C, 68.55; H, 9.22; S, 4.54.

Preparation of Compound 41. Sulfone **39** (50 mg, 0.071 mmol) was dissolved in 40% Triton B (benzyltrimethyl ammonium hydroxide in MeOH, 5 mL) and stirred at 25 °C under argon for 2 h. The reaction was then heated at 45 °C for 33 h. The mixture was cooled (0 °C) and acidified with 30% aqueous $NaHSO_4$ to pH 5. Ethereal diazomethane was added until the yellow color persisted. The mixture was bubbled with argon and then extracted with ether (3 × 50 mL). The ether extracts were washed with H_2O (3 × 30 mL) and brine (30 mL), dried ($MgSO_4$), filtered, and evaporated. The product was separated from hydroxy sulfone by flash chromatography (silica, 40% ether in petroleum ether → 75% ether in petroleum ether) yielding 12 mg (40%; 80% based on 50% conversion of olefin **41** and 20 mg (50%) of hydroxy sulfone **39a** contaminated with 10% impurity. This mixture was not purified but recycled under identical reaction conditions as above for 25 h at 45 °C. The total yield after one recycle was 18 mg (57%; 80% based on recovered hydroxy sulfone) of **39a**.

41: oil; $[\alpha]^{25}{}_D$ −192.4° (*c* 0.58, $CHCl_3$); R_f 0.18 (silica, 40% ether in petroleum ether); IR (neat) ν_{max} 3480 (OH, m), 3010 (m), 2950 (s), 2870 (s), 1740 (C═O, s), 1640 (w), 1450 (m), 1445 (m), 1380 (m), 1360 (m), 1268 (m), 1210 (m), 1160 (m), 1120 (m), 1060 (m), 1020 (m), 980 (m), 960 (m) cm^{-1}; ^{1}H NMR δ 6.12 (dd, *J* = 15.0, 10 Hz, 1 H, CH═), 5.94 (d, *J* = 10.0 Hz, 1 H, CH═), 5.88 (d, *J* = 10.0 Hz, 1 H, CH═), 5.59 (d, *J* = 15.0, 10.0 Hz, 1 H, CH═), 5.44 (dt, *J* = 10.0, 2.5 Hz, 1 H, CH═), 4.23 (br s, 1 H, ═CCHO), 3.89 (m, 1 H, CHO), 3.58 (s, 3 H, CO_2CH_3), 3.42–3.68 (m, 3 H, CH_2O, OH), 3.10 (m, 1 H, ═CCHC═), 3.03 (m, 1 H, C*H*CO_2CH_3), 1.05–2.30 (m, 18 H, CH_2, CH), 1.05 (d, *J* = 7.5 Hz, 3 H, CH_3), 0.96 (t, *J* = 7.5 Hz, 3 H, CH_3), 0.90 (t, *J* = 7.0 Hz, 3 H, CH_3), 0.83 (d, *J* = 7.0 Hz, 3 H, CH_3); mass spectrum, *m*/*e* (relative intensity) 444.1 (M^+, 13.4), 415.1 (16.0), 265.1 (72.6), 226.0 (27.7), 190.0 (17.4), 185.1 (31.2), 159.1 (22.1), 105.0 (40.8), 91.0 (74.7), 55.0 (base peak); HRMS, *m*/*e* calcd for $C_{28}H_{44}O_4$ 444.3239, found 444.3213.

Preparation of Compound 41′. This compound was prepared from sulfone **39′** in a similar fashion and yield as compound **41**.

39′: oil; $[\alpha]^{25}{}_D$ +129.75° (*c* 0.80, $CHCl_3$); R_f 0.45 (silica, 60% ether in petroleum ether); IR (neat) ν_{max} 3450 (OH, m), 3005 (m), 2950 (s), 2860 (s), 1735 (C═O, s), 1460 (m), 1430 (m), 1375 (m), 1350 (m), 1260 (m), 1205 (m), 1160 (m), 1120 (m), 1050 (m), 1020 (m), 980 (m), 960 (m) cm^{-1}; ^{1}H NMR δ 5.35 (dd, *J* = 10.0, 15.0 Hz, 1 H, HC═), 4.62 (dd, *J* = 10.0, 15.0 Hz, 1 H, HC═), 4.47 (m, 1 H, HC═), 4.27 (br s, 1 H, ═CCHO), 3.46–4.02 (m, 3 H, CHO, C*H*$_2$O*H*), 3.62 (m, 3 H, CH_3O), 2.95–3.20 (m, 2 H, $HCCO_2$, ═CCHC═), 1.00–2.30 (m, 17 H, CH, CH_2), 1.07 (d, *J* = 6.0 Hz, 3 H, CH_3), 0.99 (t, *J* = 8.0 Hz, 3 H, CH_3), 0.92 (t, *J* = 7.0 Hz, 3 H, CH_3), 0.83 (d, *J* = 7.5 Hz, 3 H, CH_3); mass spectrum, *m*/*e* (relative intensity) 444.3 (M^+, 18.3), 415.3 (24.1), 265.3 (base peak), 239.2 (11.5), 226.2 (34.4), 190.1 (18.7), 185.1 (39.9), 171.1 (23.0), 159.1 (21.5), 153 (25.7), 147.1 (20.9), 133.1 (20.6), 121.1 (21.4), 105.1 (38.5), 95 (82.1); HRMS, *m*/*e* calcd for $C_{28}H_{44}O_4$ 444.3239, found 444.3271.

Preparation of Compound 42. Alcohol **41** (4.0 mg, 0.009 mmol) was dissolved in dry, freshly distilled acetone (from $KMnO_4$, 1 mL), stirred, and cooled (−20 °C). This was treated with Jones's reagent (20 μL, prepared by adding 96.7 mL of concentrated H_2SO_4 to a cold (0 °C) stirring solution of 111.25 g of CrO_3 in 450 mL of H_2O) and was allowed to reach −5 °C over a 3-h period. Aqueous sodium bisulfite (20%, 0.5 mL) was added dropwise upon completion of the reaction (TLC) and the mixture was extracted with ether (3 × 25 mL). The combined ether extracts were washed with H_2O (3 × 25 mL) and brine (25 mL), dried ($MgSO_4$), filtered, and concentrated to approximately 2 mL. Petroleum ether was added (2 mL) and the solution was processed by flash column chromatography (silica, 50% ether in petroleum ether–ether) to yield analytically pure carboxylic acid **42** (3.5 mg, 85% yield).

42: oil; $[\alpha]^{25}{}_D$ −152.4° (*c* 0.75, $CHCl_3$); R_f 0.30 (silica, 50% ether in petroleum ether); IR (neat) ν_{max} 3600–2400 (CO_2H, br m), 3010 (w), 2950 (s), 1738 (C═O ester, s), 1700 (C═O, acid, s), 1460 (m), 1430 (m), 1370 (m), 1350 (m), 1260 (m), 1160 (m), 1120 (m), 1060 (m), 960 (m), 905 (m) cm^{-1}; ^{1}H NMR δ 6.28 (dd, *J* = 15.0, 11.0 Hz, 1 H, CH═), 5.91 (br d, *J* = 10.0 Hz, 1 H, HC═), 5.51 (m, 1 H, HC═), 4.21 (d, *J* = 3.0 Hz, 1 H, ═CHCO), 3.81 (m, 1 H, HCO), 3.59 (s, 3 H, OCH_3), 3.30 (m, 1 H), 2.92 (m, 1 H), 2.82 (m, 1 H), 1.00–2.20 (m, 17 H, CH_2, CH), 1.05 (d, *J* = 8.0 Hz, 3 H, CH_3), 0.94 (*J* = 7.5 Hz, 3 H, CH_3), 0.90 (t, *J* = 7.0 Hz, 3 H, CH_3), 0.82 (d, *J* = 7.8 Hz, 3 H, CH_3); mass spectrum, *m*/*e* (relative intensity) 459.3 (M^+ + 1, 6.5), 458.3 (M^+, 20.1), 430.3 (10.3), 429.3 (35.3), 265.2 (85.3), 225.2 (17.0), 185.1 (20.2), 171.1 (20.5), 147.1 (19.6), 119.1 (23.7), 55.1 (base peak); HRMS, *m*/*e* calcd for $C_{28}H_{42}O_5$ 458.3032, found 458.3028.

Preparation of Compound 42′. Compound **42′** was prepared from alcohol **41′** as described above for **42**.

42′: oil; $[\alpha]^{25}{}_D$ +125.5° (*c* 0.25, $CHCl_3$); R_f 0.30 (silica, 50% ether in petroleum ether); IR (neat) ν_{max} 3600–2350 (OH, br m), 3020 (m), 2960 (s), 2860 (s), 1740 (C═O, ester, s), 1710 (C═O, acid, s), 1460 (m), 1430 (m), 1380 (m), 1350 (m), 1265 (m), 1210 (m), 1160 (m), 1120 (m), 1060 (m), 960 (m) cm^{-1}; ^{1}H NMR δ 6.28 (dd, *J* = 13.0, 15.0 Hz, 1 H, CH═), 5.90 (br d, *J* = 10.0 Hz, 1 H, HC═), 5.50 (m, 1 H, HC═), 4.22 (br s, 1 H, ═CHCO), 3.84 (m, 1 H, HCO), 3.58 (s, 3 H, OCH_3), 3.30 (m, 1 H), 2.96 (m, 1 H), 2.71 (dd, *J* = 6.0, 11.0 Hz, 1 H, *H*CCO_2H), 0.80–2.22 (m, 17 H, C*HCH*$_2$), 1.05 (d, *J* = 7.0 Hz, 3 H, CH_3), 0.94 (t, *J* = 8.0 Hz, 3 H, CH_3), 0.89 (t, *J* = 6.0 Hz, 3 H, CH_3), 0.81 (d, *J* = 7.0 Hz, 3 H, CH_3); mass spectrum, *m/e* (relative intensity) 459.3 (M^+ + 1, 6.9), 458.3 (M^+, 33.1), 430.3 (12.8), 429.3 (39.6), 266.2 (20.7), 265.2 (92.6), 226.2 (20.3), 225.2 (18.3), 185.1 (25.3), 171.1 (23.8), 159.1 (21.1), 147.1 (19.6), 137.1 (23.7), 119.1 (23.7), 55.1 (base peak); HRMS, *m/e* calcd for $C_{28}H_{42}O_5$ 458.3032, found 458.3039.

X-14547A Methyl Ester (2). A solution of acid **42** (2.5 mg, 0.0055 mmol) which was dried in vacuo (over P_2O_5, 4 h, 25 °C) in dry toluene (0.20 mL) was magnetically stirred under an argon atmosphere and treated at 25 °C with 2,2′-dipyridyl disulfide (1.8 mg, 0.0082 mmol) and triphenylphosphine (recrystallized from ether–hexane, 2.2 mg, 0.0082 mmol). The reaction mixture was stirred at 25 °C before additional reagents (3.6 mg; 0.016 mmol of 2,2′-dipyridyl disulfide and 4.3 mg, 0.016 mmol, of triphenylphosphine) were added. Stirring was continued for another 25 h at which time TLC indicated complete formation of the thio ester. This mixture was cooled under argon (−78 °C) and then was treated (with stirring) with pyrrylmagnesium chloride (0.40 mL of 0.30 M in toluene) (this pyrrylmagnesium chloride was prepared from 0.89 mL of 2.8 M MeMgCl in THF, 0.25 mL of freshly distilled pyrrole in 6.5 mL of toluene, −40 → 0 °C, 10 min). The reaction was complete in 1 h at −78 °C as indicated by TLC and was then quenched at −78 °C with saturated aqueous NH_4Cl solution (5 mL). This mixture was extracted with ether (3 × 25 mL), and the ether extracts were washed with 10% aqueous K_2CO_3 (2 × 30 mL), H_2O (30 mL), and brine. After the mixture was dried ($MgSO_4$), filtered and evaporated, the crude product was obtained as an oil. Purification by flash column chromatography (silica, 20% ether in petroleum ether) afforded pure X-14547A methyl ester (**2**) (2.3 mg, 95%).

2: oil; $[\alpha]^{25}_D$ −174.6° (*c* 0.11, $CHCl_3$); R_f 0.17 (silica, 10% ether acetate in petroleum ether); IR (neat) ν_{max} 3270 (NH, m), 3010 (m), 2960 (s), 2910 (s), 2860 (m), 1730 (C=O, ester, s), 1640 (C=O, ketone, s), 1540 (w), 1455 (m), 1430 (m), 1410 (s), 1380 (m), 1350 (m), 1300 (m), 1260 (m), 1210 (s), 1160 (m), 1120 (m), 1100 (m), 1040 (m), 1020 (m), 960 (m) cm^{-1}; ^1H NMR δ 9.64 (br s, 1 H, NH), 7.03 (m, 1 H, pyrrole CH), 6.87 (m, 1 H, pyrrole CH), 6.27 (m, 1 H, pyrrole CH), 5.96 (d, *J* = 10.0 Hz, 1 H, CH=), 5.70–5.88 (m, 2 H, CH=), 5.50 (dt, *J* = 10.0, 3.0 Hz, 1 H, CH=), 5.42 (dd, *J* = 12.5, 8.0 Hz, 1 H, CH=), 4.12 (d, *J* = 5.0 Hz, 1 H, =CCHO), 3.74 (m, 1 H, CHO), 3.68 (s, 3 H, OCH_3), 3.38 (m, 2 H, CHCO, =CC*H*C=), 2.80 (m, 1 H, C*H*CO_2CH_3), 1.00–2.10 (m, 13 H, CH_2, CH), 1.10 (d, *J* = 7.0 Hz, 3 H, CH_3), 0.95 (t, *J* = 7.5 Hz, 3 H, CH_3), 0.82 (d, *J* = 7.0 Hz, 3 H, CH_3), 0.78 (t, *J* = 7.5 Hz, 3 H, CH_3); mass spectrum, *m/e* (relative intensity) 508.3 (M^+ + 1, 1.5), 507.3 (M^+, 4.5), 265.2 (23.3), 127.1 (11.9), 126.1 (10.1), 109.1 (11.7), 94 (base peak); HRMS, *m/e* (calcd for $C_{32}H_{45}O_4N$ 507.3348, found 507.3341. Anal. Calcd for $C_{32}H_{45}O_4N$: C, 75.69; H, 8.94; N, 2.76. Found: C, 75.41; H, 8.68; N, 2.47.

Preparation of X-14547A Derivative 45. An identical procedure as for the preparation of **2** above was carried out using dried acid **42′** leading to the corresponding thio ester **43′** and then to the isomer of X-14547A methyl ester compound **45** in 90% yield.

45: oil; $[\alpha]^{25}_D$ +141.8° (*c* 0.11, $CHCl_3$); R_f 0.15 (silica, 10% ethyl acetate in petroleum ether); IR (neat) ν_{max} 3270 (NH, m), 3015 (w), 2960 (s), 2920 (s), 2860 (s), 1740 (C=O, ester, s), 1640 (C=O, ketone, s), 1540 (w), 1460 (m), 1430 (m), 1410 (s), 1380 (m), 1260 (m), 1210 (m), 1160 (m), 1100 (m), 1040 (m), 960 (m) cm^{-1}; ^1H NMR δ 9.13 (br s, 1 H, NH), 6.95 (m, 1 H, pyrrole CH), 6.88 (m, 1 H, pyrrole CH), 6.26 (m, 1 H, pyrrole CH), 5.76–6.00 (m, 2 H, HC=), 5.50 (dt, *J* = 10.0, 3.0 Hz, 1 H, HC=), 5.40 (dd, *J* = 13.0, 10.0 Hz, 1 H, CH=), 3.78 (m, 1 H, CHO), 4.15 (d, *J* = 4.0 Hz, 1 H, =CCHO), 4.15 (d, *J* = 4.0 Hz, 1 H, =CC*H*O), 3.78 (m, 1 H, CHO), 3.58 (s, 3 H, OCH_3), 3.38 (m, 2 H, CHCO, =CCHC=), 2.90 (m, 1 H, C*H*CO_2CH_3), 0.80–2.05 (m, 16 H, CH_2, CH), 1.04 (d, *J* = 7.0 Hz, 3 H, CH_3), 0.93 (t, *J* = 7.0 Hz, 3 H, CH_3), 0.80 (d, *J* = 7.0 Hz, 3 H, CH_3), 0.76 (t, *J* = 7.0 Hz, 3 H, CH_3); mass spectrum *m/e* (relative intensity) 508.3 (M^+ + 1, 5.6), 507.3 (M^+, 16.5), 266.2 (10.0), 265.2 (51.5), 111.1 (12.6), 109.1 (11.9), 99.1 (10.6), 97.1 (20.2), 94.0 (base peak); HRMS, *m/e* calcd for $C_{32}H_{45}NO_4$ 507.3032, found 507.3371.

Preparation of X-14547A Derivative 44. Synthetic or natural X-14547A methyl ester (**2**) (20 mg, 0.40 mmol) in toluene (2 mL) was treated with pyrrolmagnesium chloride (0.67 mL of 0.34 M in toluene–THF, 0.23 mmol) at 100 °C for 10 min. The reaction mixture was cooled to 25 °C and then was treated with saturated aqueous NH_4Cl (5 mL).

The mixture was extracted with ether (3 × 40 mL) and the ether portions were washed with H_2O (3 × 30 mL) and brine (30 mL). Drying ($MgSO_4$), filtration, and evaporation afforded crude diketopyrrole **44** which was flash chromatographed (silica, 30% ether in petroleum ether) yielding pure **44** (20 mg, 95%).

44: oil; $[\alpha]^{25}_D$ −205.0° (*c* 0.65, $CHCl_3$); R_f 0.21 (silica, 50% ether in petroleum ether); IR (neat) ν_{max} 3270 (NH, m), 3010 (w), 2960 (s), 2930 (s), 2870 (m), 1635 (C=O, s), 1540 (m), 1455 (m), 1420 (m), 1405 (s), 1385 (m), 1300 (w), 1120 (m), 1100 (m), 1040 (m), 1015 (m), 960 (m), 910 (m) cm^{-1}; ^1H NMR δ 9.67 and 9.93 (br s, 1 H each, NH), 7.05 (m, 2 H, pyrrole CH), 6.94 (m, 1 H, pyrrole CH), 6.89 (m, 1 H, pyrrole CH), 6.25 (m, 2 H, pyrrole CH), 5.97 (d, *J* = 10.0 Hz, 1 H, CH=), 5.62–5.84 (m, 2 H, CH=), 5.49 (dt, *J* = 10.0, 3.0 Hz, 1 H, CH=), 5.36 (dd, *J* = 13.0, 7.0 Hz, 1 H, CH=), 4.04 (d, *J* = 5.0 Hz, 1 H, =CCHO), 4.0 (m, 1 H, CHO), 3.40 (m, 3 H, CHCO, =CC*H*C=), 1.10–2.10 (m, 16 H, CH_2, CH), 1.15 (d, *J* = 7.5 Hz, 3 H, CH_3), 0.95 (t, *J* = 7.5 Hz, 3 H, C*H*$_3$), 0.83 (d, *J* = 7.0 Hz, 3 H, C*H*$_3$), 0.95 (t, *J* = 7.5 Hz, 3 H, CH_3), 0.83 (d, *J* = 7.0 Hz, 3 H, CH_3), 0.58 (t, *J* = 7.5 Hz, 3 H, CH_3); mass spectrum, *m/e* (relative intensity) 542.1 (M^+, 2.7), 300.1 (27.2), 123 (14.2), 94 (base peak); HRMS, *m/e* calcd for $C_{35}H_{46}N_2O_3$ 542.3508, found 542.3520.

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Registry No. 1, 66513-28-8; **2**, 76567-01-6; **3**, 76566-84-2; (±)-4, 88244-69-3; 4, 76566-89-7; **4a**, 95671-28-6; **4b**, 95532-30-2; **5**, 76566-86-4; **6**, 76566-87-5; **10**, 80183-15-9; **10a**, 95532-11-9; **11**, 13811-71-7; **11a**, 95588-28-6; **11b**, 95532-12-0; **12**, 80109-48-4; **13**, 80109-49-5; **14**, 74213-64-2; **15**, 74243-88-2; **15a**, 74243-90-6; **15b**, 74243-92-8; **15c**, 95588-29-7; **16**, 80184-02-7; **16a**, 95532-13-1; **16b**, 95532-14-2; **16c**, 95532-15-3; **17**, 80109-41-7; **18**, 95532-16-4; (*E*)-**19**, 80109-43-9; (*Z*)-**19**, 80183-17-1; (*E*)-**19a**, 95532-17-5; (*Z*)-**19a**, 95588-30-0; (*E*)-**19b**, 95532-18-6; (*Z*)-**19b**, 95588-31-1; (*E*)-**19c**, 95532-19-7; (*Z*)-**19c**, 95588-32-2; (*E*)-**19d**, 95588-33-3; (*Z*)-**19d**, 95532-20-0; **20**, 80109-44-0; **20a**, 81444-68-0; **21**, 95532-21-1; **21a** (isomer 1), 95532-22-2; **21a** (isomer 2), 95532-31-3; **21b** (isomer 1), 95532-23-3; **21b** (isomer 2), 95532-24-4; **25**, 95671-30-0; **26**, 80145-50-2; (±)-**27**, 80109-46-2; **27**, 91109-67-0; (±)-**27a**, 95588-34-4; **27a**, 95532-32-4; (±)-**27b**, 95588-35-5; **27b**, 91053-85-9; (±)-**27c**, 95588-36-6; **27c**, 95532-33-5; (±)-**27d**, 95588-37-7; **27d**, 95532-34-6; (±)-**27e**, 95588-38-8; **27e**, 95532-35-7; **28**, 80183-16-0; (±)-**28**, 95588-43-5; **29**, 76566-90-0; (±)-**29**, 95588-44-6; **29a**, 95532-25-5; (±)-**29a**, 95588-45-7; **30**, 76566-85-3; (±)-**31**, 65618-03-3; **31a**, 76566-93-3; **31b**, 91053-83-7; **32**, 96-48-0; **33**, 95532-26-6; **34**, 27472-39-5; **35**, 80109-50-8; **36**, 80109-51-9; **37**, 80109-52-0; (±)-**37**, 95588-46-8; **37a**, 95532-27-7; (±)-**37a**, 95588-47-9; **38**, 80109-53-1; (±)-**38**, 95588-48-0; **39**, 80109-54-2; **39a**, 95532-28-8; **41**, 80109-56-4; **41′**, 95588-39-9; **42**, 80109-57-5; **42′**, 95588-40-2; **43**, 80109-58-6; **43′**, 95588-41-3; **44**, 95532-29-9; **45**, 95588-42-4; $(EtO)_3CH$, 122-51-0; $I(CH_2)_3OSi$-*t*-$BuMe_2$, 78878-05-4; $(MeO)_2P(O)CH_2CH{=}CHCOOMe$, 76566-95-5; $Ph_3P{=}CHCOOMe$, 2605-67-6; $Cl(CH_2)_3OH$, 627-30-5; δ-valerolactone, 542-28-9; pyrrole, 109-97-7.