Total Synthesis of Ionophore Antibiotic X-14547A. 1. Enantioselective Synthesis of the Tetrahydropyran and Tetrahydroindan Building Blocks

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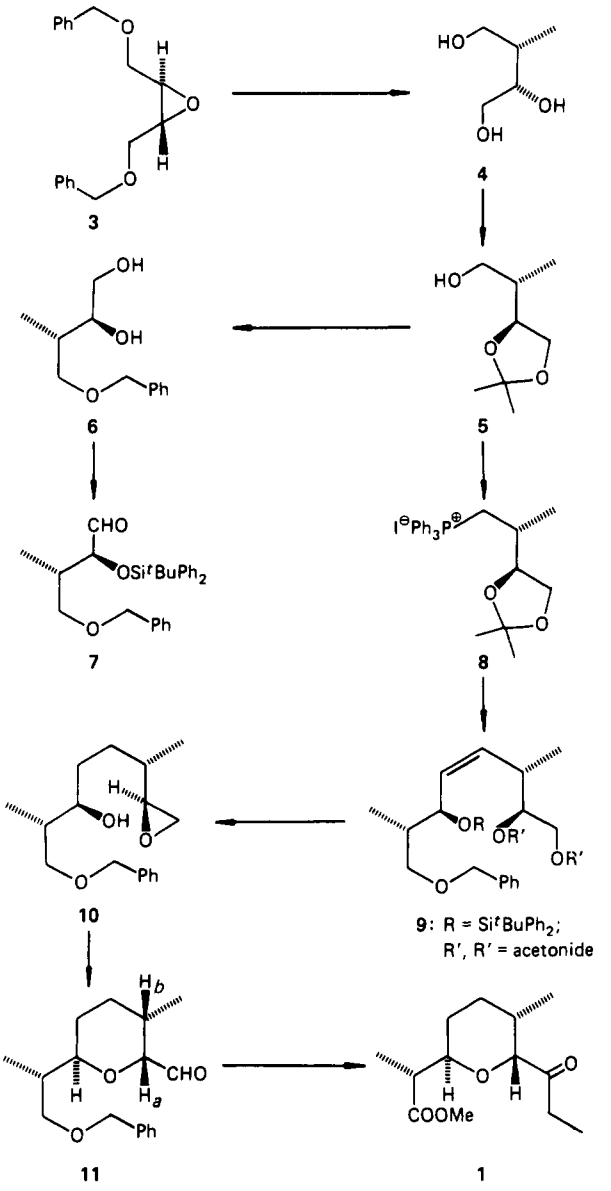
The ionophore class of antibiotics represents a biologically and commercially important group of compounds, whose number and utility continues to increase.[1,2] The intense interest in these compounds stems from their ability to complex cations and exert a variety of biological activities.[1,2] Lasalocid A,[3] monensin,[4] and calcimycin (A23187)[5] are three examples of these molecules, the total syntheses of which have recently been reported.

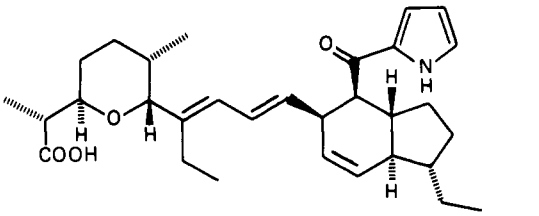
Among the naturally occurring ionophores, X-14547A,[6] a Hoffman-La Roche compound isolated from *Streptomyces antibioticus NRRL 8167*, represents a structurally unique molecule in that, although it contains fewer oxygens than the other members of this family, it possesses an array of rather rare and challenging features, including a *trans*-butadienyl moiety, a trans-fused tetrahydroindan system, and a ketopyrrole grouping (the last also found in calcimycin). The complete molecular structure, including absolute stereochemistry, of X-14547A has been determined through spectroscopic and X-ray techniques by Westley's group.[6] Its properties include complexation of both mono- and divalent cations, exhibition of antibiotic, antitumor, and antihypertensive capabilities, and promotion of growth in ruminants by improving feed utilization.[6]

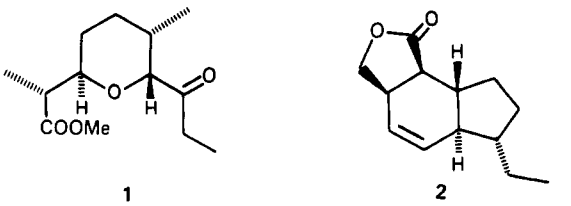
Our retrosynthetic analysis of this rather complex molecule recognized and required solutions to the following problems: (i) enantioselective construction of the tetrahydropyran and tetrahydroindan systems **1** and **2**, (ii) coupling of these two fragments and stereoselective formation of the *trans*-butadienyl moiety, and (iii) selective generation of the ketopyrrole unit. A previous publication from these laboratories[7] reported on some retrosynthetic studies leading to the isolation of **1** from the natural product and on methodology leading to the synthesis of racemic **2**.[8] In the present communication we wish to describe the total and enantioselective construction of both the tetrahydropyran (**1**) and tetrahydroindan (**2**) building blocks and in the following communication reveal the details of the first total synthesis of X-14547A in its optically active form by coupling the two segments

Scheme I



1 and **2** and constructing the *trans*-butadienyl and ketopyrrole systems.





The synthesis of the tetrahydropyran unit **1** (Scheme I) in its optically active form involves convergence from the (*S,S*)-epoxide **3**[9] to intermediates **7** and **8** followed by coupling and elaboration

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

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

(2) Pressman, B. C. *Annu. Rev. Biochem.* **1976**, *45*, 501.

(3) (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. Ireland, R. E.; McGarvey, G. J.; Anderson, R. C.; Badoud, R.; Fitzimmons, B.; Thaisrivongs, S. *Ibid.* **1980**, *102*, 6178.

(4) (a) Schmid, G.; Fukuyama, T.; Akasaka, K.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 259. Fukuyama, T.; Wang, C.-L. J.; Kishi, Y. *Ibid.* **1979**, *101*, 260. Fukuyama, T.; Akasaka, K.; Karenewsky, D. S.; Wang, C.-L. J.; Schmid, G.; Kishi, Y. *Ibid.* **1979**, *101*, 262. (b) Collum, D. B.: McDonald, J. H., III; Still, W. C. *Ibid.* **1980**, *102*, 2117, 2118, 2120.

(5) (a) Evans, D. A.; Sacks, C. F.; Kleschick, W. C.; Taber, T. R. *J. Am. Chem. Soc.* **1979**, *101*, 6789. (b) Grieco, P. A.; Williams, E.; Tanaka, H.; Gilman, S. *J. Org. Chem.* **1980**, *45*, 3537.

(6) (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 4 100 171, 1978. (e) Westley, J. W., personal communication.

(7) Nicolaou, K. C.; Magolda, R. L. *J. Org. Chem.* **1981**, *4*, 1506.

(8) Methodology for the synthesis of the tetrahydroindan system of X-14547A by an intramolecular Diels–Alder reaction has also been reported by Professors Roush and Ley: (a) Roush, W. R.; Myers, A. G. *J. Org. Chem.* **1981**, *46*, 1509. (b) Edwards, M. P.; Ley, S. V.; Lister, S. G. *Tetrahedron Lett.* **1981**, 361.

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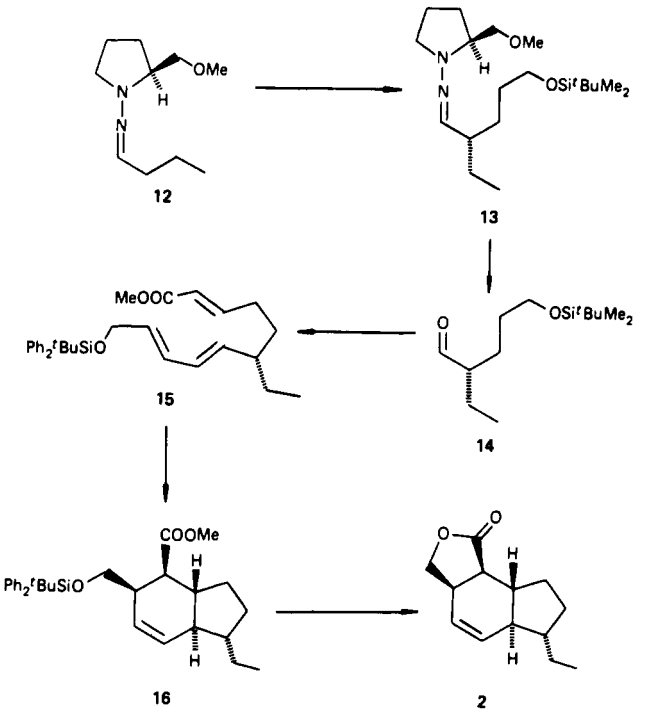
to the final target via an epoxide opening-ring closure reaction accompanied by one inversion, a sequence that sets all four asymmetric centers in their correct stereochemistry. Reaction of the epoxide **3**[9,10] with excess $LiCuMe_2$ (Et_2O, −78 → −40 °C) followed by hydrogenolysis of the benzyl ethers (10% Pd–C, EtOH, 25 °C) furnished the triol **4** in essentially quantitative yield (overall from **3**). Exposure of **4** to dimethoxyacetone–benzene (5:1) in the presence of catalytic amounts of camphorsulfonic acid (CSA) at 25 °C for 15 h followed by brief treatment with CSA in methanol at 25 °C led selectively to the acetonide **5** in 98% yield. This material then served as a common intermediate for the synthesis of both fragments **7** and **8** required for the Wittig step of the sequence. Thus, the phosphonium salt **8**[11] was prepared from the corresponding iodide (PPh_3, CH_3CN–$(EtO)_3CH$, 4:1, 75 °C, 48 h, 80% yield) which was obtained from **5** via the tosylate [(1) 2 equiv of TsCl in pyridine, 0–25 °C, 100%; (2) excess NaI in acetone, 25 °C, 48 h, 85%], whereas conversion of **5** to **7**[11] involved the following steps: (i) benzylation (NaH–$PhCH_2Br$, 1·3 equiv each, DME, 0–65 °C, 90%), (ii) deprotection of the 1,2-diol system (amberlite IR-120, ethylene glycol–DME, 2:1, 45 °C, 80%), (iii) differentiation of the primary and secondary hydroxyls [(1) 1·2 equiv of $(CH_3)_3CCOCl$–pyridine, 0–25 °C; (2) 1·3 equiv of imidazole, 1·2 equiv of *t*-$BuPh_2SiCl$, DMF, 0–25 °C; 2·0 equiv of DIBAL, CH_2Cl_2, −78 °C; 85% overall yield], and (iv) oxidation (2·0 equiv of CrO_3·HCl·pyr, 4-Å molecular sieves, CH_2Cl_2, 25 °C, 85%).

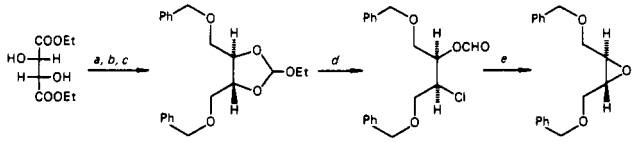
Combination of the ylide derived from **8** (Me_2SO, dimsylsodium) with aldehyde **7** (benzene) at 25 °C resulted in the formation of olefin **9** (*E*/*Z* mixture ca. 2:1) in 77% yield. Since the double bond is saturated later in the synthesis, this stereoisomerism is of no consequence, and therefore, separation is not required although it could be achieved at this stage for characterization purposes [$R_f(E)$ = 0.38, $R_f(Z)$ = 0.46, silica, 2.5% ethyl acetate in benzene]. Transformation of **9** to the key intermediate **10**[11] was smoothly performed by (i) removing the acetonide (amberlite IR-120, ethylene glycol–DME, 2:1, 45 °C, 80%), (ii) tosylation of the primary hydroxy group (1·1 equiv of TsCl–pyridine, −20 → 25 °C, 75%), (iii) exposure to freshly prepared sodium methoxide in methanol (1·1 equiv, 25 °C, 100%), (iv) desilylation (2·0 equiv of *n*-Bu_4NF, THF, 25 °C, 100%), and (v) selective hydrogenation of the double bond (H_2, 5% Pd–C, EtOAc, 70%). The crucial cyclization of the hydroxy epoxide **10** was found to proceed under acidic (CSA catalyst) conditions at 25 °C with complete regio- (tetrahydropyran ring) and stereoselectivity (inversion of epoxide center) and in high yield (95%), affording a hydroxytetrahydropyran derivative. Mild oxidation of this derivative (2·0 equiv of CrO_3·HCl·pyr, NaOAc, CH_2Cl_2, 25 °C) led smoothly to the aldehyde **11** (80% yield, R_f = 0.45, silica, 30% ether in petroleum ether). The stereochemistry of this aldehyde (**11**) was evident from the coupling constant J_{AB} = 6·0 Hz (suggesting a cis relationship for H_A and H_B) and was proven by the successful conversion to the target molecule (**1**) by the following sequence: (i) ethylmagnesium bromide addition (2·0 equiv, toluene, −78 °C, 80%), (ii) deprotection of the alcohol (H_2, 10% Pd–C, EtOH, 100%), (iii) Jones oxidation (acetone −40 → −20 °C, 90%), and (v) methylation (CH_2N_2, Et_2O, 0 °C). Synthetic **1**, $[\alpha]^{25}_D$ −21.96° ($CHCl_3$, *c* 0.85), R_f = 0.58, silica, 50% ether in petroleum ether) was identical (NMR, IR, MS, $[\alpha]_D$, TLC) with the material derived from natural X-14547A as described previously.[7]

A highly enantioselective synthesis of the tetrahydroindan building block **2** (Scheme II) was designed along similar lines to our previously reported construction of racemic **2**[7] and taking advantage of the elegant method of Enders[12] for the asymmetric alkylation of aldehydes via optically active SAMP hydrazones. Thus, targeting the sequence for **2** in its optically active form, we chose the SAMP-hydrazone **12**[12] as a suitable and readily available starting material. Thus, lithiation (1·1 equiv of LDA, Et_2O, 0 °C, 17 h) of **12** followed by quenching with 3-iodo-1-(*tert*-butyldimethylsilyl)oxypropane[13] ($ICH_2CH_2CH_2OSi$-*t*-$BuMe_2$, 1·1 equiv, −78 → 0 °C, 2 h) furnished product **13**[11] in 85% chemical

Scheme II



(9) The (S,S)-epoxide **3** was prepared from (−)-diethyl D-tartrate in 70–75% overall yield by the following sequence: (a) $(EtO)_3CH$–camphorsulfonic acid–toluene, Δ; (b) $LiAlH_4$–THF, 0 °C; (c) $PhCH_2Br$–NaH–DME, 0–65 °C; (d) PCl_5–CH_2Cl_2, 0–25 °C; (e) K_2CO_3–MeOH, 25 °C.



(10) All new compounds were fully characterized by spectroscopic means (^1H NMR, IR, MS) and exhibited satisfactory analytical and/or high-resolution mass spectral data. Yields refer to isolated, chromatographically and spectroscopically, homogeneous materials.

(11) ^1H NMR data of selected key intermediates (250 MHz, $CDCl_3$, Me_4Si): **7**, δ 0.88 (d, *J* = 7 Hz, 3 H, CH_3), 1.11 (s, 9 H, $C(CH_3)_3$), 2.36 (m, 1 H, CH), 3.32 (dd, *J* = 9.5 Hz, 1 H, C*H*HO), 3.65 (t, *J* = 9 Hz, 1 H, CH*H*O), 4.03 (m, 1 H, CHO), 4.46 (s, 2 H, CH_2Ph), 7.36 (m, 10 H, aromatic), 7.65 (m, 5 H, aromatic), 9.57 (d, *J* = 1 Hz, 1 H, CHO); **8**, δ 0.84 (d, *J* = 7 Hz, CH_3), 1.29 and 1.34 (s, 3 H each, acetonide-$(CH_3)_2$), 2.10 (m, 1 H, CH), 3.52 (t, *J* = 8 Hz, 1 H, C*H*HO), 4.10 (dd, *J* = 8, 7 Hz, 1 H, CH*H*O), 3.94 (m, 2 H, CH_2P), 4.32 (bq, *J* = 7 Hz, 1 H, C*H*O), 7.67–8.03 (m, 15 H, aromatic); **10**, δ 0.90 (d, *J* = 7 Hz, 3 H, CH_3), 0.93 (d, *J* = 6.0 Hz, 3 H, C*H*$_3$), 1.20–1.98 (m, 6 H, CH_2, CH), 2.47 (dd, *J* = 5, 3 Hz, 1 H, C*H*-epoxide), 2.72 (m, 2 H, C*H*-epoxide), 3.40–3.70 (m, 4 H, CH_2O, CHO, OH), 4.53 (s, 2 H, CH_2Ph), 7.37 (m, 5 H, aromatic); **11**, δ 0.97 (d, *J* = 7 Hz, 3 H, C*H*$_3$), 1.13 (d, *J* = 7 Hz, 3 H, CH_3), 0.86–2.10 (m, 6 H, CH_2, CH), 3.44 (dd, *J* = 9, 7 Hz, 1 H, CH_2O), 3.60 (dd, *J* = 9, 4.5 Hz, 1 H, C*H*$_2$O), 3.67 (b, t, *J* = 8 Hz, 1 H, C*H*O), 4.10 (*J* = 6 Hz, 1 H, OCHC=O), 4.50 (s, 2 H, CH_2Ph) 7.27 (m, 5 H, aromatic), 9.83, (s, 1 H, CHO); **13**, δ 0.04 (s, 6 H, $Si(CH_3)_2$), 0.82 (s, 9 H, $SiC(CH_3)_3$, 0.82 (t, *J* = 7.0 Hz, 3 H, CH_3), 1.26–2.12 (m, 11 H, CH_2, CH), 2.66 (m, 1 H, C*H*HN), 3.30 (s, 3 H, OCH_3), 3.22–3.58 (m, 6 H, CH_2O, CH*H*N, C*H*N), 6.37 (d, *J* = 7.5 Hz, 1 H, C*H*=N); **15**, δ 0.95 (t, *J* = 7.0 Hz, 3 H, CH_3), 1.05 (s, 9 H, $SiC(CH_3)_3$), 1.15–1.60 (m, 4 H, CH_2), 1.91 (m, 1 H, CHC=), 2.18 (m, 2 H, C*H*$_2$C=C), 3.72 (s, 3 H, $COOCH_3$), 4.25 (d, *J* = 6.5 Hz, 2 H, CH_2O), 5.35 (dd, *J* = 15.0, 10.0 Hz, 1 H, CH=C), 5.68 (dt, *J* = 15.0, 6.5 Hz, 1 H, CH=C), 5.82 (d, 15.5 Hz, 1 H, CH=C), 6.02 (dd, *J* = 15.0, 10.0 Hz, 1 H, C*H*=C), 6.23 (dd, *J* = 15.5, 10.0 Hz, 1 H, CH=C), 6.96 (dt, *J* = 15.5, 7.5 Hz, 1 H, CH=C), 7.70 (m, 4 H, aromatic), 7.80 (m, 6 H, aromatic); **16** (360 MHz), δ 0.82 (t, *J* = 7.0 Hz, 3 H, CH_3), 1.00 (s, 9 H, $SiC(CH_3)_3$), 1.20–2.00 (m, 9 H, CH_2, CH), 2.65 (dd, *J* = 11.0, 6.7 Hz, 1 H, CHCOO), 2.80 (m, 1 H, CHC=), 3.48 (s, 3 H, $COOCH_3$), 4.20 (m, 2 H, CH_2O), 5.69 (dt, *J* = 10.0, 3.5 Hz, 1 H, CH=C), 5.95 (d, *J* = 10.0 Hz, 1 H, CH=), 7.38 (m, 6 H, aromatic), 7.65 (m, 4 H, aromatic).

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

(13) Prepared from 3-chloro-1-propanol by sequential treatment with *tert*-butyldimethylsilyl chloride/Et_3N/DMAP in CH_2Cl_2 and sodium iodide in acetone [80% overall yield, bp 102–105 °C (15 mmHg)].

yield and in excess of 95% diastereomeric purity as determined by ^{1}H NMR–Eu(fod)$_3$ techniques ($[\alpha]^{25}_D$ −4.2° (*c* 2.00, $CHCl_3$), R_f = 0.48, silica, 50% ether in petroleum ether). This mixture was carried through the following sequence until the coupling with the optically pure tetrahydropyran fragment allowed convenient separation of diastereoisomers. Ozonolysis of hydrazone **13** (CH_2Cl_2, −78 °C, 15 min) proceeded smoothly and in quantitative yield producing the aldehyde **14** from which the synthesis proceeds essentially as we described previously,[7] namely, (**14** → **15**, 60% overall yield) (i) condensation with the lithio salt of methyl-4-(dimethylphosphono)crotonate, (ii) reduction with excess DIBAL, (iii) protection with *tert*-butyldiphenylsilyl chloride, (iv) selective hydrolysis of the *tert*-butyldimethylsilyl ether, (v) oxidation with CrO_3·HCl·pyr, and (vi) condensation with (carbomethoxy)-methylenetriphenylphosphorane; **15** → **16**, 70%: Δ, toluene; **16** → **2**, 100%: *n*-Bu_4NF. Synthetic lactone **2** ($[\alpha]^{25}_D$ +113.00° (c 0.20, $CHCl_3$), R_f 0.40, silica, 50% ether in petroleum ether) obtained by this route exhibited identical spectroscopic and chromatographic properties as the racemic compound previously obtained and fully characterized by spectroscopic and X-ray crystallographic analysis.[7]

With the two important building blocks **1** and **2** at hand, the stage was set for their coupling and the conclusion of the total synthesis of X-14547A. The remaining operations are described in the accompanying communication.[14,15]

(14) Nicolaou, K. C.; Claremon, D. A.; Papahatjis, D. P.; Magolda, R. L. *J. Am. Chem. Soc.*, following paper in this issue.

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Total Synthesis of Ionophore Antibiotic X-14547A. 2. Coupling of the Tetrahydropyran and Tetrahydroindan Systems and Construction of the Butadienyl and Ketopyrrole Moieties

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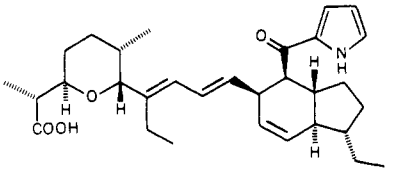
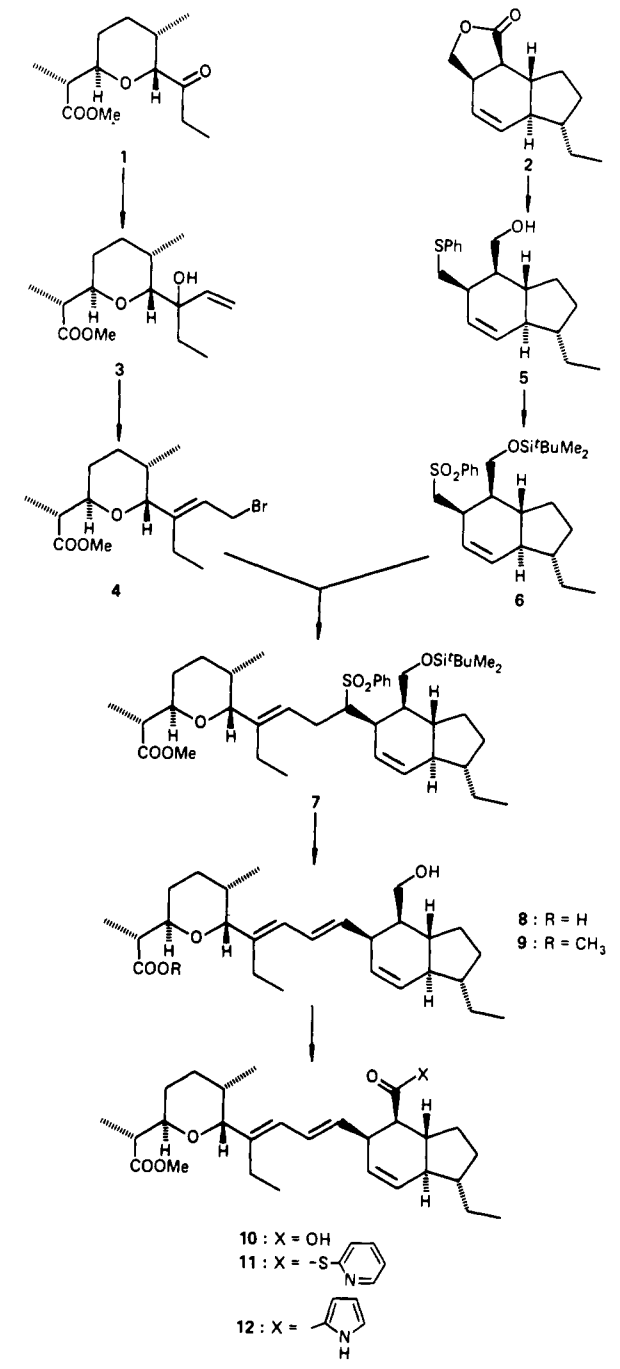
In the preceding paper,[1] we described enantioselective syntheses of the tetrahydropyran and tetrahydroindan building blocks (**1** and **2**, Scheme I) for the total synthesis of the ionophore antibiotic X-14547A. This communication deals with the successful conclusion of the total synthesis of X-14547A, describing a highly efficient coupling of the two fragments **1** and **2** and a two carbon unit and stereoselective constructions of the butadienyl and ketopyrrole systems.



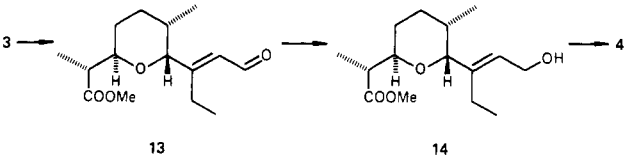
X-14547A

The location of the ketopyrrole unit and the unsaturation in the tetrahydroindan system impose some complications on the coupling of the two fragments and the regioselective formation of the *trans*-butadienyl chromophore due to persistent interference from these systems.[2] It was after considerable experimentation

Scheme I



Scheme II



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that we decided to postpone the construction of the ketopyrrole appendage until the end and to utilize the phenyl sulfone 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 used is outlined in Scheme I.

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

(1) Nicolaou, K. C.; Papahatjis, D. P.; Claremon, D. A.; Dolle, R. E., III, *J. Am. Chem. Soc.*, preceding paper in this issue.

(2) Wittig-type approaches for the coupling of the two segments of the molecule and construction of the butadienyl system were originally explored but proved unsuccessful, presumably due to the propensity of the carbonyl compounds involved toward rapid enolization.

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