NMR spectra were run at the CUA Chemical Instrumentation Center.

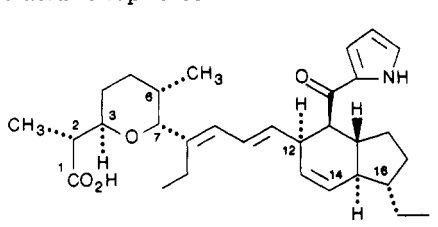
**Registry No.** **1a**, 10493-98-8; **1c**, 10481-34-2; 1d, 3400-89-3; **2a**, 77426-28-9; **2a** (brosylate), 77426-30-3; **2a** (dimethylcarbamate), 104994-76-5; **2a** (phenylthionocarbonate), 104994-77-6; **2c**, 104994-72-1; **2d**, 104994-73-2; **3a**, 10316-66-2; **3b**, 104994-78-7; **3c**, 50870-61-6; **3d**, 3400-88-2; **4a**, 104994-71-0; **4d**, 104994-74-3; **5a**, 86137-11-3; **5d**, 104994-75-4; dimethylthiocarbamoyl chloride, 16420-13-6.

**Anthony A. Ponaras,* Ömer Zaim**
*Department of Chemistry*
*The Catholic University of America*
*Washington, D.C. 20064*
*Received July 21, 1986*

## An Efficient Enantioselective Total Synthesis of (-)-X-14547A (Indanomycin)

*Summary:* A highly efficient and stereocontrolled enantioselective total synthesis of the antibiotic ionophore X-14547A (indanomycin) (1) is described. A particularly concise approach to the key pyranaldehyde intermediate **3** features the use of reductive lithiation to append the axial C(7) pyran side chain. A Wittig reaction was employed to couple the two major subunits **3** and **4** followed by intramolecular [4 + 2] cycloaddition to complete the framework.

*Sir:* The ionophoric antibiotics represent a stereochemically complex and synthetically challenging class of biologically important molecules.[1] In 1978, X-14547A (indanomycin), a novel member of this group of ionophores, was isolated at Hoffmann-LaRoche, and the structure and absolute configuration were established by Westley.[2] X-14547A exhibits activity against Gram-positive bacteria as well as antitumor and antihypertensive activity and functions as an effective growth promoter for ruminants.[5b] X-14547A also has the ability to complex and transport mono-, di-, and trivalent metal cations, an uncommon property among antibiotics except for a small number of carboxylic acid ionophores.

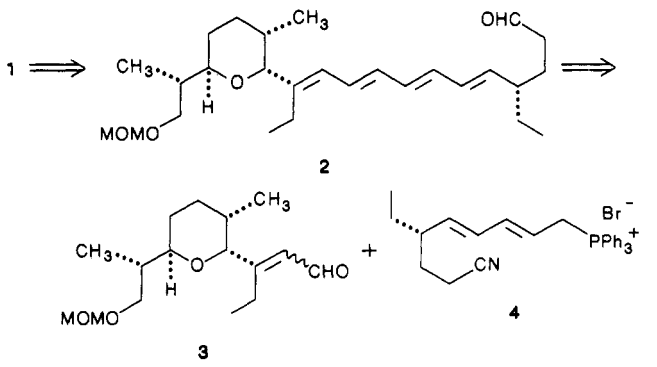


**1**

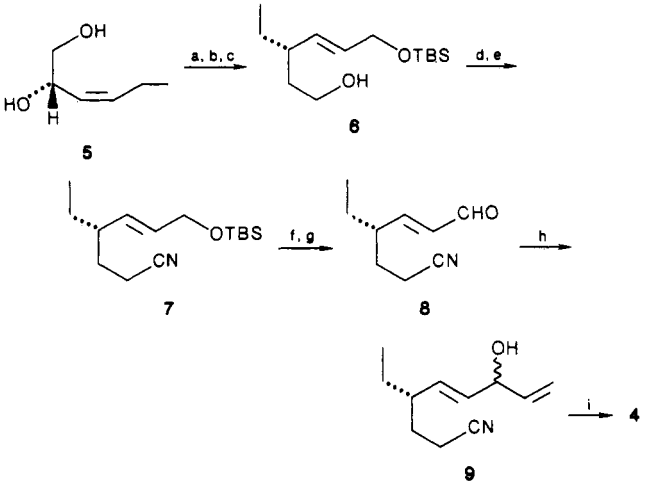
The unusual structural features of X-14547A, such as the 1(*E*),3(*E*)-butadienylhexahydroindene unit (one of two natural products to contain a trans-fused hexahydroindene ring system[3]) and the $\alpha$-acylpyrrole (common to only a few other ionophores such as calcimycin (A-23187)[4]), have stimulated a number of recent synthetic studies, two of which have culminated in a total synthesis.[5i,l]

As our retrosynthetic analysis of **1** illustrates (Scheme I), we elected to utilize a tandem Wittig reaction-intramolecular Diels-Alder cycloaddition sequence to assemble the hexahydroindene framework late in the synthesis. A similar strategy was successfully employed by Roush and co-workers in their recent partial synthesis.[5g,j] It was thus envisioned that tetraene **2**, the required substrate for the Wittig-cycloaddition process, would become available via

**Scheme I**



**Scheme II**[a]



[a] Reagents: (a) TBDSCl (1.1 equiv), $Et_3N$ (1.5 equiv), DMAP (catalytic), $CH_2Cl_2$, 23 °C, 10 h; (b) $CH_3C(OCH_3)_3$ (2.8 equiv), $CH_3CH_2CO_2H$ (catalytic), xylenes, $\Delta$, 19 h; (c) *i*-$Bu_2AlH$ (2.2 equiv), THF, -70 → 23 °C, 1.5 h; (d) *p*-TsCl (1.1 equiv), pyridine-$CH_2Cl_2$ (1:1), 23 °C, 10 h; (e) KCN (2.1 equiv), $Me_2SO$, 55 °C, 5 h; (f) *n*-$Bu_4NF$ (1.04 equiv), THF, 0 °C, 20 min; (g) PDC (2 equiv), $CH_2Cl_2$, 23 °C, 12 h; (h) $CH_2$=$CHMgBr$ (3 equiv), THF, -78 → 23 °C, 30 min; (i) $Ph_3P$-HBr (1.1 equiv), $CH_2Cl_2$, 23 °C, 10 min.

(1) (a) Wierenga, W. In *The Total Synthesis of Natural Products*; Apsimon, J., Ed.; Wiley: New York, 1981; Vol. 4, p 363. (b) Dobler, M. In *Ionophores and Their Structures*; Wiley: New York, 1981. (c) *Polyether Antibiotics*; Westley, J. W., Ed.; Marcel Dekker: New York, 1983.

(2) (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.; 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. *J. Antibiot.* **1979**, *32*, 100.

(3) For the second natural hexhahydroindene, ircinianin, see: Hofheinz, W.; Schonholzer, P. *Helv. Chim. Acta* **1977**, *60*, 1367.

(4) Chaney, M. O.; Demarco P. V.; Jones, N. D.; Occlowitz, J. L. *J. Am. Chem. Soc.* **1973**, *96*, 1932.

(5) (a) Edwards, M. P.; Ley, S. V.; Lister, S. G. *Tetrahedron Lett.* **1981**, *22*, 361. (b) Roush, W. R.; Meyers, A. G. *J. Org. Chem.* **1981**, *46*, 1509. (c) Nicolaou, K. C.; Claremon, D. A.; Paphatjis, D. P. *Tetrahedron Lett.* **1981**, *22*, 4647. (d) Nicolaou, K. C.; Magolda, R. L. *J. Org. Chem.* **1981**, *46*, 1506. (e) Nicolaou, K. C.; Papahatjis, D. P.; Claremon, D. A.; Dolle, R. E., III. *J. Am. Chem. Soc.* **1981**, *103*, 6967. (f) Nicolaou, K. C. Caremon, D. A.; Papahatjis, D. P.; Magolda, R. L. *J. Am. Chem. Soc.* **1981**, *103*, 6969. (g) Roush, W. R.; Peseckis, S. M. *Tetrahedron Lett.* **1982**, *23*, 4879. (h) Edwards, M. P.; Ley, S. V.; Lister, S. G.; Palmer, B. D. *J. Chem. Soc., Chem. Commun.* **1983**, 630. (i) Edwards, M. P.; Ley, S. V.; Lister, S. G.; Palmer, B. D.; Williams, D. J. *J. Org. Chem.* **1984**, *49*, 3503. (j) Roush, W. R.; Peseckis, S. M.; Walts, A. E. *J. Org. Chem.* **1984**, *49*, 3429. (k) Burke, S. D.; Armistead, D. M.; Fevig, J. M. *Tetrahedron Lett.* **1985**, *26*, 1163. (l) Nicolaou, K. C.; Papahatjis, D. P.; Claremon, R. L.; Magolda, R. L.; Dolle, R. E. *J. Org. Chem.* **1985**, *50*, 1440.

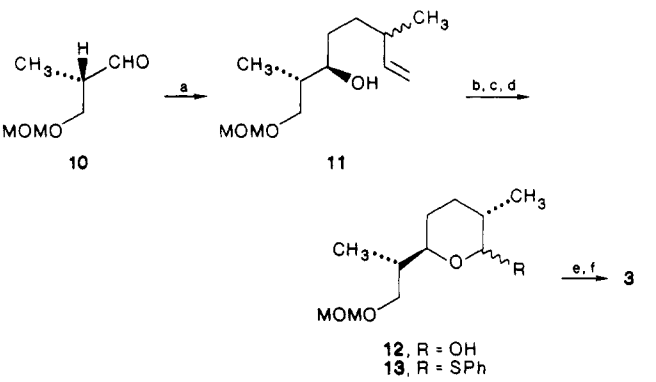
0022-3263/86/1951-4743$01.50/0 

the Wittig coupling of the left-hand pyran subunit **3** and the right-hand subunit, phosphonium salt **4**, in which the aldehyde group required for **2** is masked as a nitrile.

Preparation of the first of the two major subunits in optically pure form is outlined in Scheme II. The sequence to phosphonium salt **4** was initiated from the known diol **5**[6] ($[\alpha]_D^{23}$ +8.9° (*c* 5.05, *i*-PrOH)) by selective silylation of the primary hydroxyl group.[7] The crucial *S* configuration for the ethyl appendage (at C(16) in **1**) was next established via an ortho ester Claisen rearrangement which provided the expected $\gamma,\delta$ unsaturated ester upon treatment of the monoprotected diol with trimethyl orthoacetate in refluxing xylenes in the presence of a catalytic amount of propionic acid.[8] Reduction of the crude methyl ester with diisobutylaluminum hydride afforded exclusively (NMR analysis) the *E* olefinic alcohol **6** in 87% overall yield for the three-step process.[9,10] Homologation of **6** by tosylation and displacement with cyanide under standard conditions provided nitrile **7** in 88% yield (from **6**).[9] Elaboration of the (*E,E*)-diene unit commenced with desilylation of **7** by *n*-$Bu_4NF$ and oxidation of the resulting alcohol with pyridinium dichromate (PDC) in $CH_2Cl_2$ which smoothly produced the $\alpha,\beta$ unsaturated aldehyde **8** in 67% yield over two steps.[9] Homologation directly to the required *E,E* phosphonium salt employed a process adapted from technology developed originally for carotinoid synthesis.[11] Treatment of **8** with vinylmagnesium bromide in THF at −78 °C produced the sensitive pentadienyl alcohol **9** as a 1:1 mixture of diastereomers, which upon reaction with $Ph_3P$–HBr, generated exclusively the key (*E,E*)-dienylphosphonium salt **4** in 87% yield (from **8**) presumably via $S_N2'$ displacement.[9,12]

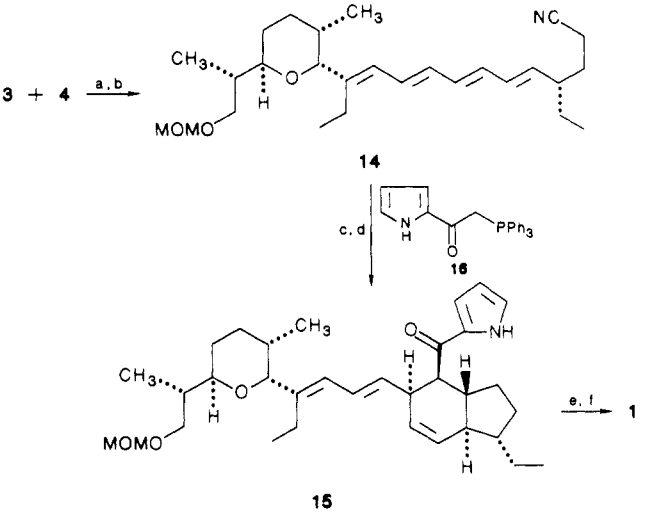
The left-hand pyran subunit was elaborated as shown in Scheme III. Thus, the optically active aldehyde **10** ($[\alpha]_D^{23}$ +15.09° (*c* 7.59, $CHCl_3$)) was prepared via three well-precedented steps in 73% overall yield from commercially available (*S*)-(+)-methyl 3-hydroxy-2-methyl-

**Scheme III**[a]




[a] Reagents: (a) $LiCu((CH_2)_2CHCH_3CH{=}CH_2)_2$ (1.1 equiv), $Et_2O$, −48 → −40 °C, 20 min; (b) $O_3$ (excess), $CH_2Cl_2$, −78 °C, 15 min; then $(CH_3)_2S$ (excess), −78 → 25 °C, 20 min; (c) $K_2CO_3$ (excess), $CH_3OH$, 23 °C, 3 h; (d) PhSH (1.5 equiv), $BF_3$–$Et_2O$ (1.4 equiv), $CH_2Cl_2$, −78 °C, 10 min; (e) LiDBB (2 equiv) (until green color persists), −78 °C, 10 min; then $CH_3CH_2COCH{=}CHOCH_3$ (1.1 equiv), THF, −78 °C, 10 min; (f) PPTS (catalytic), $CH_2Cl_2$, −40 °C, 1 h.

**Scheme IV**[a]




[a] Reagents: (a) *t*-BuOK (1.7 equiv), DMF, −23 (1 h) → 0 °C (35 min); (b) $I_2$ (catalytic), hexanes, $Cs_2CO_3$, $K_2CO_3$, 23 °C, 20 min; (c) *i*-$Bu_2AlH$ (2.0 equiv), −78 (6 min) → 0 °C (25 min), quench at −78 °C with $CH_3OH$; (d) **16** (5 equiv), $ClCH_2CH_2Cl$, BHT, $SrCO_3$, $Cs_2CO_3$, 45 °C, 96 h; then 65 °C, 48 h; (e) $Me_3SiI$ (excess), $CHCl_3$, −78 → −60 °C, 10 min; (f) $CrO_3$ (excess), acetone, −23 °C, 1 h.

The left-hand pyran subunit was elaborated as shown in Scheme III. Thus, the optically active aldehyde **10** ($[\alpha]_D^{23}$ +15.09° (*c* 7.59, $CHCl_3$)) was prepared via three well-precedented steps in 73% overall yield from commercially available (*S*)-(+)-methyl 3-hydroxy-2-methyl-

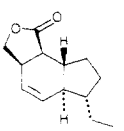
(6) Boeckman, R. K., Jr.; Napier, J. J.; Thomas, E. W.; Sato, R. I. *J. Org. Chem.* **1983**, *48*, 4152.

(7) Chaudhary, S. K.; Hernandez, O. *Tetrahedron Lett.* **1979**, 99.

(8) For a review on this subject, see: Ziegler, F. E. *Acc. Chem. Res.* **1977**, *10*, 227.

(9) All new substances exhibited spectroscopic data (IR, $^1H$ NMR (300 MHz), MS) consistent with the assigned structures and acceptible combustion or high-resolution mass spectral analytical data. $^1H$ NMR data (in $\delta$ at 300 MHz in $CDCl_3$ unless otherwise indicated): (**2**) 9.73 (s (br), 1 H), 6.45 (m, 1 H), 6.25–5.90 (m, 5 H), 5.35 (dd, $J_1$ = 14 Hz, $J_2$ = 10 Hz, 1 H), 4.59 (s, 2 H), 4.12 (s (br), 1 H), 3.59 (m, 2 H), 3.33 (m, 1 H), 3.31 (s, 3 H), 2.40 (m, 2 H), 2.25 (m, 2 H), 2.00–1.20 (m, 11 H), 1.10–0.90 (m, 12 H); (**3**) 10.03 (d, $J$ = 8.2 Hz, 1 H), 6.07 (d, $J$ = 9.2 Hz, 1 H), 4.56 (s, 2 H), 4.21 (s (br), 1 H), 3.65 (m, 1 H), 3.50 (m, 1 H), 3.35 (m, 1 H), 3.30 (s, 3 H), 2.72 (m, 1 H), 2.32 (m, 1 H), 2.24 (m, 1 H), 2.02–1.86 (m, 3 H), 1.50 (m, 2 H), 1.15 (t, $J$ = 7.7 Hz, 3 H), 0.91 (d, $J$ = 6.7 Hz, 3 H), 0.82 (d, $J$ = 6.9 Hz, 3 H); (**4**) 7.90–7.50 (m, 15 H), 6.55 (m, 1 H), 5.90 (dd, $J_1$ = 15 Hz, $J_2$ = 10 Hz, 1 H), 5.30 (m, 2 H), 4.85 (m, 2 H), 2.19 (m, 2 H), 1.94 (m, 1 H), 1.70 (m, 1 H), 1.37 (m, 2 H), 1.20 (m, 1 H), 0.78 (t, $J$ = 9 Hz, 3 H); (**6**) (90 MHz) 5.46 (m, 2 H), 4.12 (d, $J$ = 4 Hz, 2 H), 3.63 (t, $J$ = 6 Hz, 2 H), 2.30–1.00 (m, 6 H), 0.89 (m (br), 12 H), 0.07 (s, 6 H); (**7**) (400 MHz) 5.64–5.57 (dt, $J_1$ = 15 Hz, $J_2$ = 5 Hz, 1 H), 5.33–5.23 (dd, $J_1$ = 15 Hz, $J_2$ = 9 Hz, 1 H), 4.16 (dd, $J_1$ = 4.7 Hz, $J_2$ = 1.4 Hz, 2 H), 2.37–2.31 (m, 1 H), 2.30–2.23 (m, 1 H), 2.03 (m, 1 H), 1.81–1.69 (m, 1 H), 1.56–1.40 (m, 2 H), 1.34–1.27 (m, 2 H), 0.91 (s, 9 H), 0.88 (t, $J$ = 7 Hz, 3 H), 0.07 (s, 6 H); (**8**) 9.50 (d, $J$ = 9 Hz, 1 H), 6.55 (dd, $J_1$ = 15 Hz, $J_2$ = 10 Hz, 1 H), 6.15 (dd, $J_1$ = 15 Hz, $J_2$ = 8 Hz, 1 H), 2.34 (m, 3 H), 1.90 (m, 1 H), 1.70 (m, 1 H), 1.59 (m, 1 H), 1.48 (m, 1 H), 0.95 (t, $J$ = 9 Hz, 3 H); (**9**) 5.90 (m, 1 H), 5.62 (m, 1 H), 5.39 (m, 1 H) 5.22 (m, 2 H), 4.63 (m, 1 H), 2.18 (m, 2 H), 2.07 (m, 1 H), 1.81 (m, 1 H), 1.74 (m (br), 1 H), 1.55 (m, 1 H), 1.48 (m, 1 H), 1.35 (m, 1 H), 0.95 (m, 3 H); (**10**) 9.72 (d, $J$ = 2 Hz, 1 H), 4.60 (s, 2 H), 3.74 (d, $J$ = 7 Hz, 2 H), 3.33 (s, 3 H), 2.62 (m, 1 H), 1.13 (d, $J$ = 9 Hz, 3 H); (**11**) 5.65 (m, 1 H), 4.90 (m, 2 H), 4.58 (s, 2 H), 3.62 (m, 1 H), 3.48 (m, 2 H), 3.34 (s, 3 H), 2.86 (s (br), 1 H), 2.09 (m, 1 H), 1.76 (m, 1 H), 1.55–1,20 (m, 4 H), 0.97 (m, 3 H), 0.92 (m, 3 H); (**13**) 7.45–7.13 (m, 5 H), 5.48 (d, $J$ = 4.5 Hz, 1 H) 4.44 (dd, $J_1$ = 6.5 Hz, $J_2$ = 6.3, 2 H), 4.03 (m, 1 H), 3.47 (m, 1 H), 3.25 (s, 3 H), 3.22 (m, 1 H), 2.11 (m, 1 H), 1.79–1.23 (m, 5 H), 1.00 (d, $J$ = 6.8 Hz, 3 H), 0.91 (d, $J$ = 6.8 Hz, 3 H); (**14**) 6.48 (m, 1 H), 6.15 (m, 4 H), 6.00 (m, 1 H), 5.29 (dd, $J$ = 12 Hz, $J_2$ = 8 Hz, 1 H), 4.60 (s, 2 H), 4.15 (s (br), 1 H), 3.60 (m, 2 H), 3.17 (s on m, 4 H), 2.33 (m, 4 H), 1.95 (m, 6 H), 1.45 (m, 4 H), 1.15 (m, 1 H), 1.05–0.85 (m, 12 H); (**15**) 9.66 (s (br), 1 H), 6.90 (s, 1 H), 6.84 (s, 1 H), 6.22 (dd, $J_1$ = 5 Hz, $J_2$ = 2 Hz, 1 H), 5.94 (d, $J$ = 9 Hz, 1 H), 5.83 (m, 2 H), 5.48 (dt, $J_1$ = 8 Hz, $J_2$ = 3 Hz, 1 H), 5.38 (dd, $J_1$ = 13 Hz, $J_2$ = 9 Hz, 1 H), 4.62 (s, 2 H), 3.95 (d, $J$ = 3 Hz, 1 H), 3.50 (m, 2 H), 3.36 (s, 3 H), 3.33 (m, 2 H), 2.20–1.00 (m, 17 H), 0.95–0.70 (m, 12 H).

(10) The optical purity of nitrile **7** ($[\alpha]_D^{23}$ +34.9° (*c* 1.77, $CHCl_3$)) was demonstrated by conversion to the key tricyclic lactone intermediate i ($[\alpha]_D^{25}$ +134.0° (*c* 0.32, $CHCl_3$)) employed by Nicolaou and Ley (lit.[5] $[\alpha]_D^{25}$ +136° (*c* 1.02, $CHCl_3$)).



(11) Rosenberger, M.; McDougle, P.; Bahr, J. *J. Org. Chem.* **1982**, *47*, 2130.

(12) $^1H$ NMR homonuclear decoupling experiments (at 300 MHz) established unequivocally that the dienylphosphonium salt **4** possessed the required *E* geometry at both olefins.

propionate.[13,14] Reaction of **10** with the lithium dialkylcuprate prepared in the usual fashion[15] from 1-(bromomethyl)-4-pentene[16] established the crucial threo relationship between the hydroxyl and methyl substituents in **11** (C(2)–C(3) in **1**) via the presumed intermediacy of a copper chelate.[17] The expected mixture (1:1) of diastereomeric alcohols **11** was obtained in 93% yield.[9,18] Oxidative cleavage of the terminal olefin of **11** by ozonolysis, followed by reductive workup ($(CH_3)_2S$) and subsequent base-catalyzed epimerization of the adjacent secondary methyl group (C(6) in **1**, afforded **12** as an ~1:3 mixture of anomeric lactols ($\alpha$:$\beta$) accompanied by a minor amount of the acyclic aldehyde. This mixture was directly treated with thiophenol in $CH_2Cl_2$ at −78 °C in the presence of $BF_3$–$Et_2O$ to produce the $\alpha$-(phenylthio)pyran **13** also as a mixture (~3:1, $\alpha/\beta$) of anomers in 47% overall yield from **11**.[9] The mixture was next subjected to reductive lithiation with lithium 4,4′-di-*tert*-butylbiphenylide[19] (2.0 equiv) in THF at −78 °C which presumably generates the axial $\alpha$-lithiopyran.[20,21] Condensation of this intermediate with 1-methoxy-1(*E*)-penten-3-one[22] afforded the expected 1,2-adduct, possessing the required axial appendage (at C(7) in **1**), which was treated without purification with pyridinium *p*-toluene sulfonate (catalytic) in $CH_2Cl_2$ at −40 °C to give the key pyranaldehyde subunit **3** in 42% overall yield (from **13**) as an ~3:1 (*E*/*Z*) mixture of geometric isomers. Thus, optically active **3** is available by a stereocontrolled sequence of only eight steps from commercially available materials.

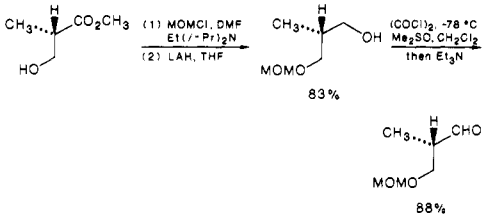
The final stages of the assembly of X-14547A were initiated by Wittig coupling of the two major subunits **3** and **4** as shown in Scheme IV. A mixture of **3** (E/Z (~3:1), 1 equiv) and **4** (1.5 equiv) was cooled to −23 °C in DMF and subjected to treatment with *t*-BuOK (1.7 equiv) over ~1.5 h which produced a complex mixture of geometric isomers of tetraenenitrile **14**. Without purification, this mixture was directly isomerized to the key *trans*-tetraenenitrile **14** by treatment with $I_2$ (catalytic) in hexanes in 79% overall yield from **3**.[9] The aldehyde precursor **2**, required for the tandem Wittig–[4 + 2] cycloaddition sequence, was then obtained in 83% yield by reduction of **14** with diisobutylaluminum hydride in toluene at −78 °C followed by slow warming to 0 °C and Rochelle salt workup.[9] Since the tetraenealdehyde **2** and nitrile **14** were somewhat unstable and had a tendency toward polymerization, all manipulations including reactions were carried out in the presence of a small amount of radical inhibitor (BHT). Moreover, the tetraene intermediates, aldehyde **2** and nitrile **14**, were particularly sensitive to the presence of traces of acid in the reaction medium which resulted in facile epimerization of the axial pyran side chain (C(7) in **1**). Therefore, traces of inorganic bases ($Cs_2CO_3$ and $SrCO_3$ or $K_2CO_3$) were employed in reactions of **2** and **14** to alleviate this difficulty. Aldehyde **2** (1 equiv) and the ketopyrrole stabilized ylide **16**[5g] (1.5 equiv) in 1,2-dichloroethane (~$10^{-3}$ M in both reactants) were heated at 45 °C for 96 h, followed by 48 h at 65 °C to produce the hexahydroindene **15** in 53% overall yield (from **2**).[9] Ketopyrrole **15** was indistinguishable from the natural C(1) methoxymethyl ether of the C(1) alcohol of X-14547A by comparison of their IR, $^1H$ NMR (300 MHz), and mass spectra, as well as TLC behavior.[23] Final conversion of **15** to (−)-**1** was effected by initial treatment of **15** with dilute trimethylsilyl iodide ($Me_3SiI$) in $CHCl_3$ resulting in cleavage of the C(1) methoxymethyl ether to the corresponding alcohol in 70% yield. Oxidation of this alcohol with $CrO_3$ (excess) in acetone at −23 °C then afforded synthetic (−)-X-14547A (**1**) in 79% yield.[24]

In summary, a convergent and enantioselective synthesis of the antibiotic X-14547A has been developed. Particularly noteworthy is the concise sequence featuring a reductive lithiation to establish the key C(7) asymmetric center. Further applications of related reductive lithiation reactions of $\alpha$-thiophenyl vinyl ether substrates are currently under study.[25]

**Acknowledgment.** We are very grateful to the National Science Foundation and the National Institute of General Medical Sciences of the National Institutes of Health for research grants (NSF, CHE-81-19823, and NIGMS, GM-30345) in support of this investigation. We also wish to acknowledge the award of an NSRA fellowship from the National Institutes of General Medical Sciences (GM-10495) to E.J.E. (1985–1987) and Sherman-Clarke Fellowships (University of Rochester) to D.M.D. and A. B.C.

**Supplementary Material Available:** Experimental procedures for preparation of compounds **1**–**11** and **13**–**15** and complete spectroscopic data (12 pages). Ordering information is given on any current masthead page.

(13) (*S*)-(+)-Methyl 3-hydroxy-2-methylpropionate (available from the Aldrich Chemical Co.) was first protected as its methoxymethyl ether and subsequently reduced with LAH to the corresponding alcohol shown in the equation. A Swern oxidation then afforded the desired aldehyde (+)-**10**.




(14) (a) Branca, Q.; Fischli, A. *Helv. Chim. Acta* **1977**, *60*, 925. (b) Nagota, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873.

(15) (±)-5-Bromo-3-methyl-1-pentene was converted to the homogeneous diorganocuprate by reaction with Li metal (containing 1% Na) (10 equiv) in $Et_2O$ at −8 → 0 °C (3.5 h) followed by slow addition (by cannula) of the resulting 0.58 M solution of the lithium reagent to a suspension of CuBr–$(CH_3)_2S$ (0.55 equiv) in $Et_2O$ at −40 °C and stirring at −40 (1 h) → −15 °C (1 h).

(16) Conviently prepared from (±)-3-methyl-4-penten-1-ol (available from Wiley Chemical Co.) by treatment with $Ph_3P$ and $CBr_4$ in dichloromethane followed by distillation (96%).

(17) Still, W. C.; Schneider, J. A. *Tetrahedron Lett.* **1980**, *21*, 1035.

(18) The optical purity of the mixture of diastereomeric alcohols **11** was established by conversion to a mixture of the corresponding Mosher esters (excess acid chloride was utilized to assure complete conversion). Examination of the mixture by $^1H$ NMR (300 MHz) confirmed the presence of only two diasteromers, indicating the optical purity of the two diastereomers **11** to be ≥98%.

(19) Freeman, P. K.; Huchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924.

(20) Cohen, T.; Lin, M. T. *J. Am. Chem. Soc.* **1984**, *106*, 1130.

(21) For recent related applications, see: Beau, J.-M.; Sinay P. *Tetrahedron Lett.* **1985**, *26*, 6185, 6189, 6193.

(22) Harayama, T.; Hidetsura, C.; Inubushi, Y. *Chem. Pharm. Bull.* **1978**, *26*, 1201.

(23) Natural (−)-X-14547A was converted to the natural (−)-C(1) methoxymethyl ether ($[\alpha]_D^{23}$ −315.4° (*c* 0.69, $CHCl_3$)) of the (−)-C(1) alcohol of X-14547A ($[\alpha]_D^{23}$ −298.4° (*c* 2.04, $CHCl_3$)) in 43% overall yield by the three-step sequence: (1) $ClCO_2CH_3$ (3.0 equiv), *i*-$Pr_2EtN$ (6.0 equiv), THF, −22 → 0 °C, 30 min; (2) $NaBH_4$ (3.0 equiv), anhydrous EtOH, 23 °C, 20 min; (3) $CH_3OCH_2Cl$ (3.0 equiv), *i*-$Pr_2EtN$ (5.0 equiv), DMF, 23 °C, 1.5 h.

(24) Synthetic (−)-X-14547A was identical with natural (−)-X-14547A by comparison of the $^1H$ NMR (300 MHz) spectrum and TLC behavior in three solvent systems.

(25) Boeckman, R. K., Jr.; Charette, A. B., unpublished results, 1986.

**Robert K. Boeckman, Jr.,* Eric J. Enholm**
**Donald M. Demko, André B. Charette**
*Department of Chemistry*
*University of Rochester*
*Rochester, New York 14627*
*Received July 16, 1986*