76599-55-8; **10** (isomer 2), 76599-56-9; **12**, 76599-57-0; 3-chloropropene, 107-05-1; 2-methyl-3-chloropropene, 563-47-3; (*E*)-1-chloro-2-butene, 4894-61-5; 1-bromobutane, 109-65-9; 1,3-dibromopropane, 109-64-8; 1,4-dibromobutane, 110-52-1; 1,6-dibromohexane, 629-03-8; 1,10-dibromodecane, 4101-68-2; 2-bromopentane, 107-81-3; 1,4-dibromopentane, 626-87-9; 2-phenyl-1-bromoethane, 103-63-9; 3-chloro-1-heptene, 55682-98-9; 6-bromo-3-chloro-1-hexene, 76599-58-1; 7-bromo-3-chloro-1-heptene, 76599-59-2; 9-bromo-3-chloro-1-nonene, 76599-60-5; 13-bromo-3-chloro-1-tridecene, 76599-54-7; 3-chloro-4-methyl-1-heptene, 76599-61-6; 7-bromo-3-chloro-1-octene, 76599-62-7; 3-chloro-2-methyl-1-heptene, 71518-90-6; 3-chloro-2-methyl-5-phenyl-1-pentene, 76599-57-0; 6-bromo-3-chloro-2-methyl-1-hexene, 76599-63-8; 7-bromo-3-chloro-2-methyl-1-heptene, 76599-64-9; (*E*)-4-chloro-2-octene, 76599-65-0; (*E*)-8-bromo-4-chloro-2-octene, 76599-66-1; [3-(ethylenedioxy)-1-propyl]magnesium bromide, 76599-67-2.

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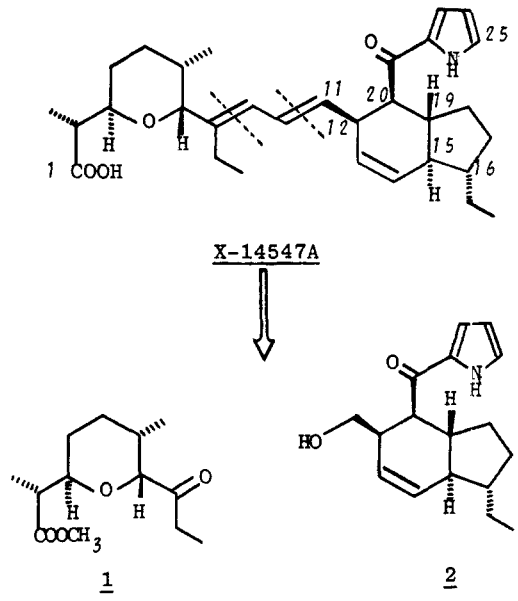
Ionophore Antibiotic X-14547A. Degradation Studies and Stereoselective Construction of the "Right Wing" (C_{11}-C_{25} Fragment) by an Intramolecular Diels-Alder Reaction[1]

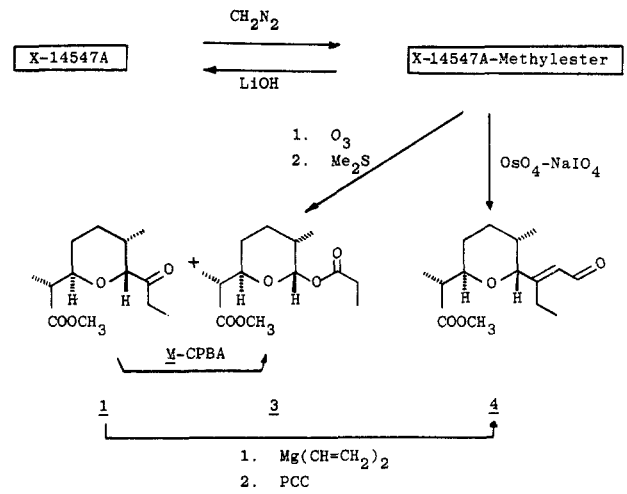
Summary: Studies directed toward the total synthesis of the ionophore antibiotic X-14547A are reported. Degradation methods led to a number of "left-wing" fragments, whereas synthetic operations led to a "right-wing" fragment, in a highly efficient and stereoselective manner via an intramolecular Diels-Alder reaction.

Sir: The ionophore antibiotics are becoming an increasingly interesting class of naturally occurring substances with regard to both biology[2] and synthesis.[3] X-14547A is a novel member of this family of compounds, recently isolated from *Streptomyces antibioticus* NRRL8167 by Westley et al.[4] and fully characterized by spectroscopic and X-ray techniques. Its biological properties include antibiotic activity against gram-positive bacteria, antihypertensive and antitumor activities, and improvement of ruminant feed utilization.[4,5] Structurally, X-14547A is a rather unique assembly of functionalities, including the rare frameworks of pyrrolylcarbonyl[6] and trans-fused tetrahydroindan systems.

Scheme I



Scheme II



A possible retrosynthetic analysis of X-14547A leads to a convergent scheme requiring the construction and coupling of fragments **1** and **2** (Scheme I). In this communication we report (I) the first degradation studies on X-14547A leading to the "left-wing" fragment **1** and (II) synthetic studies leading stereoselectively to the "right-wing" fragment **2**. The degradation studies provide useful information for an eventual total synthesis, whereas the synthetic work indicates solutions to the stereoselective construction of the novel tetrahydroindan and pyrrolylcarbonyl systems of X-14547A.

(I) Degradation Studies. A number of asymmetric centers of X-14547A are potentially vulnerable to epimerization, and it was of crucial interest to us to determine whether any damage to the stereochemistry was inflicted during hydrolysis of X-14547A methyl ester to the natural product. To answer this question we prepared the methyl ester of the antibiotic (CH_2N_2, ether, 0 °C, 100%) and subjected it to basic hydrolysis (10 equiv of LiOH, 1:1

(1) This work was first described at the 2nd Chemical Congress of the North American Continent, Las Vegas, Aug 1980, Abstract No. ORGN 156.

(2) Reviews: (a) Westley, J.W. *Adv. Appl. Microbiol.* **1977**, *22*, 177; (b) Pressman, B.C.; *Annu. Rev. Biochem.* **1976**, *45*, 501.

(3) Lasalocid A: (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. Monensin: (c) Schmid, G.; Fukuyama, T.; Akasaka, K., Kishi, Y, *Ibid.* **1979**, *101*, 259; Fukuyama, T.; Wang, C-L.J.; Kishi, Y. *Ibid.* **1979**, *101*, 260; Fukuyama, T.; Akasaka, K.; Karanewsky, D. S.; Wang, C.-L. J.; Schmid, G.; Kishi, Y. *Ibid.* **1979**, *101*, 262; (d) Collum, D. B.; McDonald, J. H., III; Still, W. C. **1980**, *102*, 2117; Collum, D. B.; McDonald, J. H., III; Still, W. C. *Ibid.* **1980**, *102*, 2118; Collum, D. B.,; McDonald, J. H., III; Still, W. C. *Ibid.* **1980**, *102*, 2120. Calcimycin (A-23187): (e) Evans, D. A.; Sacks, C. F.; Kleschick, W. A.; Taber, T. R. **1979**, *101*, 6789; (f) Grieco, P. A.; Williams, E.; Tanaka, H.; Gilman, S. *J. Org. Chem.* **1980**, *45*, 3537.

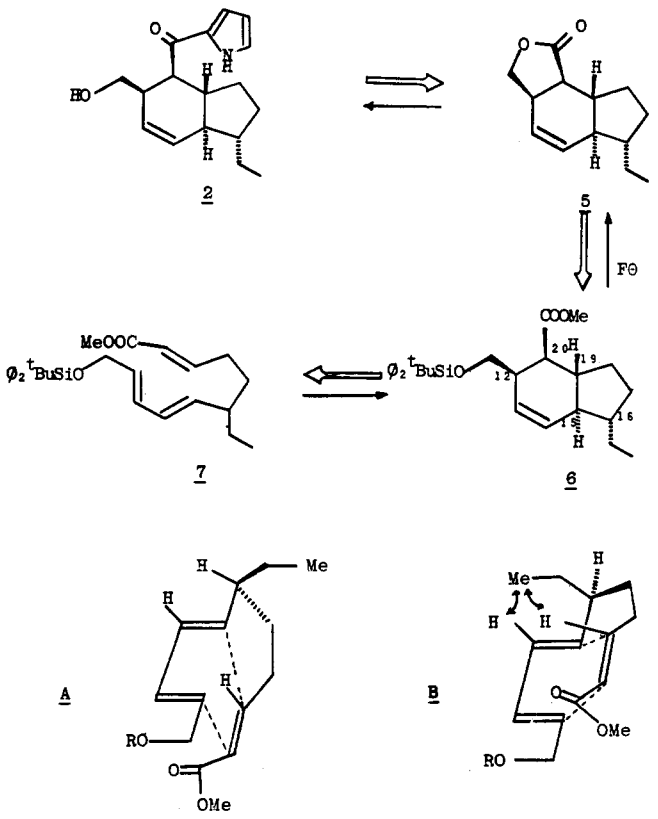
(4) (a) Westley, J. W.; Evans, R. H., Jr.; Liu, C.-M; Hermann, T.; Blount, J. F. *J. Am. Chem. Soc.* **1978**, *100*, 6786. (b) Liu, C.-M; Hermann, T. E.; Liu, M.; Bull, D. N.; Palleroni, N. J.; Prosser, B. L. T.; Westley, J. W.; Miller, P. A. *J. Antibiot.* **1979**, *32*, 95. (c) Westley, J. W.; Evans, 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.

(5) Westley, J. W., personal communication.

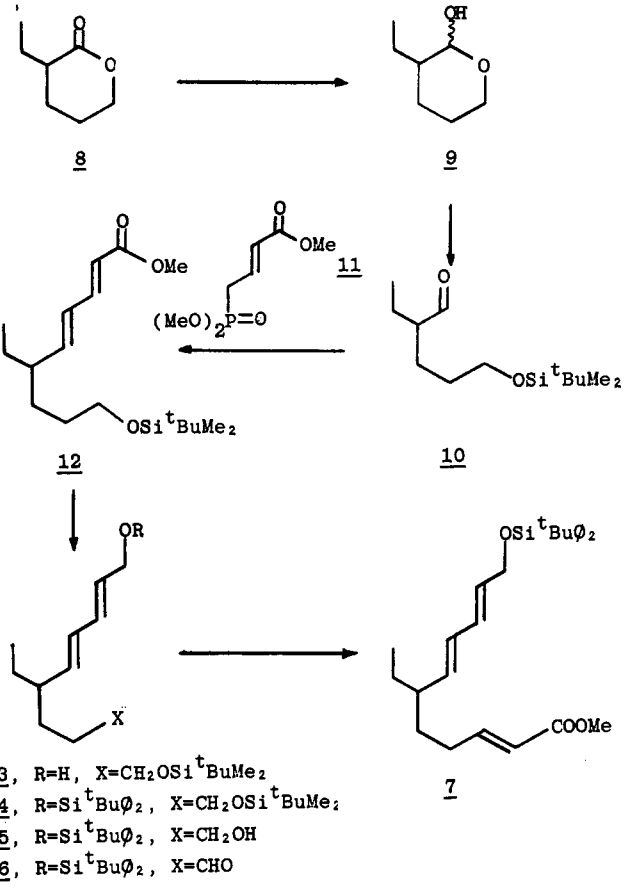
(6) The only other known polyether antibiotic containing the pyrrolylcarbonyl functionality is calcimycin (A-23187): Chaney, M. O; Demaro, P. V.; Jones, N. D.; Occolowitz, J. L. *J. Am. Chem. Soc.* **1974**, *96*, 1932.

0022-3263/81/1946-1506$01.25/0

Scheme III



Scheme IV



13, R=H, X=$CH_2OSi^tBuMe_2$
14, R=$Si^tBu\phi_2$, X=$CH_2OSi^tBuMe_2$
15, R=$Si^tBu\phi_2$, X=CH_2OH
16, R=$Si^tBu\phi_2$, X=CHO

THF–H_2O, 25 °C, 7 days). Although relatively slow, the saponification proceeded *without epimerization at any asymmetric center*, leading cleanly (98%) to X-14547A. On comparison of NMR spectra of X-14547A, *significant changes in* ^1H and ^{13}C *NMR chemical shifts*[7] *were observed at different concentrations*, a rare phenomenon, presumably due to strong dimeric complexation of the compound in solution.[8]

Ozonolysis of X-14547A methyl ester in CH_2Cl_2 at −78 °C followed by Me_2S decomposition of the ozonide produced the ketone **1**[9,10] (50%) and the ketal ester **3**[11] (30%; Scheme II) as the only two major products. The presence of acetic acid (2 equiv) during ozonolysis surpressed almost completely the formation of **3**, leading to **1** in greater than 95% yield. Baeyer–Villiger oxidation (1.2 equiv of *m*-CPBA) of **1** afforded **3**. Cleavage of the C_{10}–C_{11} bond while preserving the C_9–C_{10} double bond was achieved when X-14547A methyl ester was exposed to $NaIO_4$ (2.4 equiv) and OsO_4 (0.01 equiv) in *t*-BuOH–H_2O (1:1) at 25 °C, furnishing the α,β-unsaturated aldehyde **4** (25% yield) as the only recognizable material. Ketone **1** was converted to aldehyde **4** in a highly stereoselective manner[12] by a two-step sequence (a, 1.1 equiv of vinylmagnesium bromide, THF, −78 °C; b, 5 equiv of CrO_3·pyr·HCl, CH_2Cl_2, 40 °C) in 70% overall yield. While these degradation studies provided the "left-wing" intermediates **1**, **3**, and **4**, the "right side" of the molecule did not survive. The C_{11}–C_{25} fragment was constructed by a total synthesis as described below.

(II) Synthetic Studies. Scheme III outlines strategic bond disconnections and retrosynthetic analysis of the C_{11}–C_{25} segment (**2**) of X-14547A. This analysis leads sequentially to intermediates **5**–**7** and requires as key steps (a) a stereoselective construction of the tetrahydroindan system by an intramolecular Diels–Alder reaction and (b) a regioselective attachment of the pyrrole unit to form the pyrrolylcarbonyl functionality. Consideration of the Diels–Alder rules and two alternative endo transition states A and B (Scheme III) encouraged us to expect a favorable outcome of this cycloaddition reaction via the sterically preferred transition state A. With regard to the formation of the pyrrolylcarbonyl group, it was felt that the alternative pathway leading to an amide by C–N bond formation should be reversible, particularly due to the strategic position of the liberated alkoxy group, and, therefore, under the proper experimental conditions the desired product should be predominating as the thermodynamically most stable product. To test and apply those hypotheses to the total synthesis of X-14547A, we undertook the synthesis of precursor **7** and its conversion to **2**.

(7) The "dense electronic clouds" of the molecule are presumably responsible for the changes in the electromagnetic environment of certain sides as the compound dimerizes, thus providing a "shift reagent effect".

(8) This phenomenon is currently under further investigation and more details will be reported in due course.

(9) All new compounds exhibited satisfactory IR, ^1H NMR, and mass spectral properties, as well as analytical and/or exact mass data. Yields refer to isolated, chromatographically homogeneous materials.

(10) ^1H NMR data (250 MHz, $CDCl_3$) are as follows. For **1**: τ 5.82 (d, J = 5.0 Hz, 1 H, H-7), 6.28 (m, 1 H, H-3), 6.30 (s, 3 H, $COOCH_3$), 7.25 (m, 1 H, H-2), 7.52 (m, 2 H, CH_2CO), 7.90–8.75 (m, 5 H, CH, CH_2), 8.90 (d, J = 7.2 Hz, 3 H, CH_3) 8.95 (t, J = 7.0 Hz, 3 H, CH_3), 9.02 (d, J = 6 Hz, 3 H, CH_3). For **5**: 3.95 (d, J = 10.0 Hz, 1 H, olefin), 4.30 (dt, J = 10.0, 3. 5 Hz, 1 H, olefin), 5.48 and 6.10 (2 t, J = 8.6 Hz, 1 H each, CH_2O), 6.82 (m, 1 H, H-12), 7.45 (dd, J = 7.2, 11.2 Hz, 1 H, H-20), 7.94–8.85 (m, 9 H, CH, CH_2), 9.05 (t, J = 7.0 Hz, 3 H, CH_3). For **2**: 0.53 (br s, 1 H, NH), 2.91, 3.00, 3.68 (3 m, 1 H each, pyrrole), 3.90 (d, J = 10.0 Hz, 1 H, olefin), 4.42 (dt, J = 10.0, 3.5 Hz, 1 H, olefin), 6.40 (m, 2 H, CH_2O), 6.54 (dd, J = 11.0, 7.0 Hz, 1 H, H-20), 6.45 (br s, 1 H, OH), 7.29 (m, 2 H), 7.85–9.10 (m, 7 H), 9.08 (t, J = 7.0 Hz, 3 H, CH_3).

(11) The structure of this compound was clearly evident from its ^{13}C NMR spectrum ($CDCl_3$, Me_4Si): δ 93.98 (ketal carbon), 173.13 and 175.08 (ester carbonyl carbons).

(12) *E*/*Z* ratio of ca. 6:1 by ^1H NMR spectroscopy.

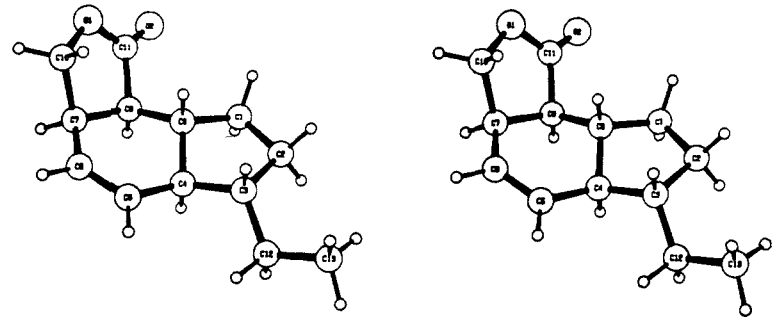


Figure 1. Stereoscopic view of the X-ray structure of lactone **5**.

Scheme IV outlines the synthesis of the requisite Diels–Alder precursor triene **7**. δ-Valerolactone was alkylated (LDA–EtI, THF–HMPA, −78 °C) to afford **8** (80%) which was then reduced (1.05 equiv of DIBAL, CH_2Cl_2, −78 °C) to lactol **9** (100%). Treatment of **9** with *t*-$BuMe_2SiCl$ (1.5 equiv) and imidazole (1.5 equiv) in DMF at 25 °C furnished the silyl ether aldehyde **10** in 70% yield.[13] Condensation of **10** with the lithio salt of methyl 4-(dimethylphosphono)crotonate (**11**; 1.2 equiv, generated from equimolar amounts of the phosphonate and LDA in THF at −78 °C) in THF at −78 °C furnished the (*E,E*)-dienoate **12** in 95% yield.[14] Reduction of **12** with DIBAL (2.1 equiv, CH_2Cl_2, −78 °C) led to the alcohol **13** (99% yield). Taking advantage of the higher stability of the *tert*-butyldiphenylsilyl ether relative to the *tert*-butyldimethylsilyl ether toward acid hydrolysis, we interchanged the protection of the diol **13** to **15** via **14** (a, 1.5 equiv of *t*-$BuPh_2SiCl$, 1.5 equiv of imidazole, DMF, 25 °C; b, 3:2:2 AcOH–THF–H_2O, 25 °C, 1 h) in 70% overall yield. Finally oxidation of **15** to **16** (1.5 equiv of CrO_3·pyr·HCl, CH_2Cl_2, 25 °C) followed by reaction with [(carbomethoxy)-methylene]triphenylphosphorane (1.5 equiv) in toluene at 25 °C afforded the triene **7** in 90% overall yield from **15**.

When triene **7** was heated in degassed toluene solution at 130 °C (sealed tube) for 48 h, there was obtained bicycle **6** as the major cycloadduct in 70% yield.[15] Exposure of **6** to *n*-Bu_4NF (1.1 equiv) in THF at 25 °C led directly and quantitatively to the tricyclic lactone **5**[10] which crystallized from hexane in colorless rods, mp 68–68.5 °C. The ^1H NMR spectroscopic data of **5** and **6** (**5**, $J_{12,20}$ = 7.2 Hz, $J_{19,20}$ = 11.2 Hz; **6**, $J_{12,20}$ = 6.7 Hz, $J_{19,20}$ = 11 Hz)[16] strongly pointed to the indicated stereochemistry at centers C-12, C-20, and C-19, in agreement with Roush's results,[16,17] but provided little information regarding the remaining asymmetric centers (C-15, C-16). The complete stereochemical picture was obtained from X-ray crystallographic analysis[18] which was performed on lactone **5** and which confirmed all five asymmetric centers as predicted and desired for X-14547A. Clearly the relative steric comfort enjoyed by transition state A (Scheme III) which is maintained in the final products is responsible for the observed stereoselectivity of this Diels–Alder reaction. A computer-generated structure of **5** based on the X-ray crystallographic data is shown in Figure 1.

With the tetrahydroindan system built efficiently and with high stereochemical control, we then turned our attention to the construction of the pyrrolylcarbonyl side of the molecule, utilizing the γ-lactone functionality. Model studies with γ-butyrolactone revealed that the reagent derived from pyrrole and MeMgCl[19] in toluene solution at 25 °C leads to the hydroxy amide by C–N bond formation, whereas the same reagent at 110–110 °C leads to the corresponding (hydroxypyrrolyl)carbonyl exclusively by C–C bond formation. When these conditions were applied to the tricyclic intermediate **5** at 100–110 °C, the pyrrolylcarbonyl **2**[10] was obtained in 80–90% yield, whereas the corresponding hydroxy amide was only detectable by TLC at 25 °C, reverting back to lactone **5** too rapidly for chromatographic isolation.

With the methodology for creating the important trans-fused tetrahydroindan and pyrrolylcarbonyl systems stereo- and regioselectively and for generating X-14547A from its methyl ester with stereochemical integrity as well as with ample supplies of authentic and synthetic intermediates, the stage is now set for the total synthesis of this novel ionophore antibiotic.[20]

Acknowledgment. We thank Dr. J. W. Westley of Hoffman-La Roche for generous supplies of X-14547A and Dr. J. F. Blount, also of Hoffman-La Roche, for the X-ray analysis of lactone **5**. Our thanks are also due to Dr. George T. Furst of the Department of Chemistry, University of Pennsylvania, for helpful discussions on NMR data. This work was financially supported by the A. P. Sloan foundation and the University of Pennsylvania.

Registry No. **1**, 76566-84-2; **2**, 76566-85-3; **3**, 76566-86-4; **4** (*E* isomer), 76566-87-5; **4** (*Z* isomer), 76566-88-6; **5**, 76566-89-7; **6** (endo isomer), 76566-90-0; **6** (exo isomer), 76566-91-1; **7**, 76566-92-2; **8**, 32821-68-4; **9**, 76566-93-3; **10**, 76566-94-4; **11**, 76566-95-5; **12**, 76566-96-6; **13**, 76566-97-7; **14**, 76566-98-8; **15**, 76566-99-9; **16**, 76567-00-5; X-14547A, 66513-28-8; X-14547A methyl ester, 76567-01-6; δ-valerolactone, 542-28-9; *t*-$BuMe_2SiCl$, 18162-48-6; *t*-$BuPh_2SiCl$, 58479-61-1; [(carbomethoxy)methylene]triphenylphosphorane, 2605-67-6; pyrrole, 109-97-7; MeMgCl, 676-58-4; $Mg(CH{=}CH_2)_2$, 6928-74-1; CH_2N_2, 334-88-3.

(13) The remaining material was the lactol silyl ether, which after chromatographic separation and deprotection (3:2:2 AcOH–THF–H_2O, 45 °C) can be recycled.

(14) ^1H NMR spectroscopy revealed contamination with ca. 2–3% of the isomeric (*E,Z*)-dienoate which can be removed chromatographically.

(15) This cycloaddition reaction also produced an additional 15% of a mixture of products, the major of which is presumed to be the exo isomer of **6** on the basis of ^1H NMR data.[16]

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

(17) Similar progress toward the synthesis of the "right wing" of X-14547A by an intramolecular Diels–Alder reaction has been reported by Professor W. R. Roush at the 2nd Chemical Congress of the North American Continent, Las Vegas, Aug 1980.

(18) The X-ray crystallographic analysis of **5** was performed by Dr. J. F. Blount of Hoffman-La Roche; full details will be reported later.

(19) (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.

(20) Professor S. V. Ley of Imperial College London, informed us of similar studies on the synthesis of the X-14547A "right wing" in his laboratories.

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

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