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STUDIES ON THE TOTAL SYNTHESIS OF ANTIBIOTIC X-14547A
THE PENTAENE APPROACH

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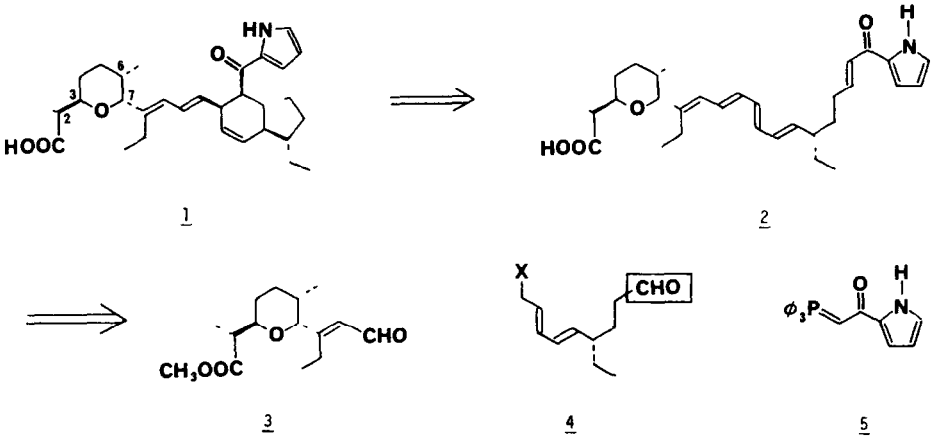
Summary A nine-step synthesis of X-14547A model compound 14 is described.

X-14547A (1), an unusual antibiotic of the polyether class,[2] has attracted much interest since its structure was first reported in 1978.[3] One total synthesis[4] and a number of syntheses of "left" and "right" hand fragments have now been recorded.[5] All approaches to the right-hand perhydroindene ring system have utilized intramolecular Diels-Alder reactions as the key transformation, whereas the syntheses of the left hand tetrahydropyranyl fragment have relied on the principle of internal asymmetric induction[6] to control independently the stereochemical relationship between C 2-C 3 and C.6-C.7. The problem of coupling of the two halves has not been adequately solved, however.

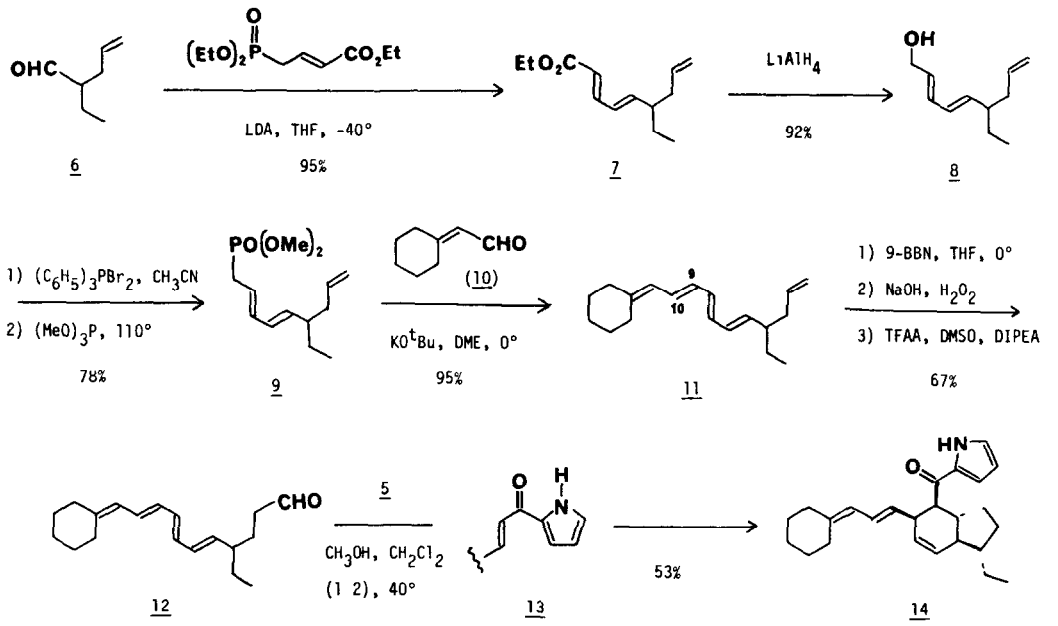
Scheme I



Our solution to this problem has its genesis in the hypothesis[5c] that the biosynthesis of 1 might involve an internal cyclization of a pentaene intermediate such as 2 (Scheme I).[7] Not only did we imagine that 2 would be a suitable synthetic precursor to 1, we also recognized that this intermediate could be assembled from precursors 3, 4, and 5 by a sequence in which all of the functionality of 2 (and hence 1) would be fully differentiated and be mutually compatible at every stage of the synthesis. We illustrate the viability of this approach by

describing a short (8 step) synthesis of pentaene 13 and its facile cyclization to X-14547A model compound 14 (Scheme II).

Scheme II



Treatment of aldehyde 6[8] with the lithium anion of triethylphosphonocrotonate at -40°C with warming to room temperature afforded diene ester 7[9a,b] in 95% yield. Reduction of 7 ($LiAlH_4$, Et_2O, 0°C, 92% yield) afforded alcohol 8,[9a,b] bromination ($(C_6H_5)_3PBr_2$, CH_3CN, 0°C) of which provided the expected bromide in excellent yield. The latter compound was then treated with trimethylphosphite in hot toluene (110°C) to give phosphonate 9[9a,b] in 78% yield from 8. A mixture of 9 (1.0 equiv.) and aldehyde 10[10] (1.0 equiv.) in DME was added dropwise to a solution of KO^tBu (2.0 equiv.) in DME at 0°C and the resulting solution was stirred at this temperature for 1.5 h. In this manner pentaene 11,[9a] a 95 5 mixture of stereoisomers with respect to the newly formed double bond, was obtained in 95% yield. This olefination procedure proved to be far superior to all of the alternative methods examined.[11] It should be noted as well that the sensitive nature of 11 towards radical induced polymerization reactions necessitated that all subsequent transformations be performed in the presence of BHT. Hydroboration of 11 with 9-BBN in THF at 0°C (alkaline H_2O_2 workup) afforded the expected primary alcohol[9a] as the sole reaction product (84% yield after chromatography).[12,13] This intermediate was then oxidized with a Swern reagent (TFAA, DMSO, diisopropylethylamine, CH_2Cl_2, -78° → 23°C) to afford aldehyde 12[9a] in 80% yield.[14] Finally, treatment of 12 with phosphorane 5[5c] in a 2 1 CH_2Cl_2-CH_3OH cosolvent mixture (39 h, 40°C) afforded X-14547A model compound 14[9a,b] directly in 53% yield together with 17% of a mixture of cis-fused products.[15]

Only one trans-fused cycloadduct was isolated from this Diels-Alder reaction. The stereochemistry of this compound, 14,[16] was assigned by comparison of its ^{1}H and ^{13}C NMR data to that of X-14547A and the perhydroindene fragments reported in our previous communication.[5c] The diastereoselectivity of the thermal cyclization of 13, therefore, appears to parallel the simpler cases previously reported.[5] Attempts to suppress the formation of the cis-fused by-products, however, by use of Lewis acidic reagents ($EtAlCl_2$, CH_2Cl_2, 0°C, $MgCl_2$ or $CaCl_2$ in aqueous CH_3OH, etc.) in the cyclization step (using purified 13)[15b] have thus far proven unsuccessful. In spite of this shortcoming, we believe that the sequence outlined in Scheme II is ideally suited for use in a synthesis of 1. Such studies are in progress and will be reported upon in due course.

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7 No experimental evidence exists regarding this hypothesis. Intramolecular Diels-Alder reactions have, however, been postulated in the biosynthesis of a number of natural products. For a discussion of this topic, see Ciganek, E. Org. Reactions, in press, and the literature cited therein.

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9. (a) The spectroscopic properties (NMR, IR, mass spectrum, and UV (where appropriate)) of this compound were fully consistent with the assigned structure. (b) A satisfactory combustion analysis (±0.3% for C and H) was obtained for this compound.

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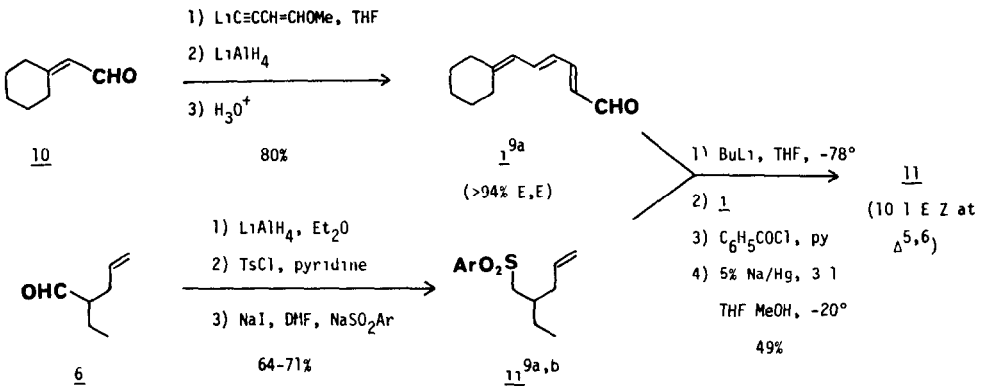
11. The phosphorane corresponding to 9 afforded under optimal conditions (nBuLi, THF, -78°C, LiBr (4 equiv.), addition of 10, -78°C → 25°C, quench with CH_3OH) a 78:22 mixture of 11 and its 9,10-(Z) olefin isomer in 86% yield. Improved product ratios (up to 95 5 selectivity with NaH, DME, 23°C, 37% yield) were obtained using the corresponding phosphine oxide but the product yields were substantially diminished (18-56%). The most successful (in terms of yield and stereoselectivity) alternative route to 11 involved an adaptation of Lythgoe's olefination procedure (Kocienski, P.J.; Lythgoe, B., Waterhouse, I. J. Chem. Soc., Perkin I 1980, 1045, and references cited therein). This sequence, however, is

longer and less convergent (especially if applied to 3) than the route outlined in Scheme II.



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13. The use of a vinyl group as a latent aldehyde precursor was turned to only after we experienced substantial setbacks with approaches involving standard aldehyde protecting groups. In large measure these difficulties are attributable to the sensitivity of the tetraene functionality towards acid catalyzed decomposition reactions, which precluded the use of dioxolane or dioxane protecting groups in this reaction sequence. Acyclic acetal protecting groups (e.g., a dimethylacetal) could not be used as a consequence of the sensitivity of such groups to the conditions needed for the synthesis of the requisite diene allylic bromide (another very sensitive functional group which readily liberates HBr).

14. Huang, S.L., Omura, K., Swern, D. Synthesis 1978, 297.

15. (a) The solubility problems previously noted[5c] for 5 are avoided by using a CH_3OH-CH_2Cl_2 cosolvent mixture. Remarkably, the reagent dissolves readily in this mixture at 40°C to give homogeneous solutions (0.1M) but not in either solvent alone. (b) The Wittig reaction of soluble 5 with 12 at room temperature (17 h) afforded 47% of pentaene 13[9a] together with 25% of cycloadducts and 10% of recovered 12. The longer reaction time and higher reaction temperature specified in the text were used simply to ensure complete cyclization of 13.

16. Spectroscopic data for 14 ^{1}H NMR (270 MHz, $CDCl_3$) δ 9.33 (br s, 1H, NH), 7.00, 6.92, 6.29 (3H, pyrrole CH), 5.97 (m, 2H), 5.65 (d, J = 10.4 Hz, 1H), 5.51 (dt, J = 9.9, 2.8 Hz, 1H), 5.40 (dd, J = 8.3, 7.2 Hz, 1H), 3.41 (m, 2H), 0.94 (t, J = 7.2 Hz, 3H, CH_3), ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 191.1, 142.0, 132.6, 130.5, 129.6, 129.1, 127.1, 124.1, 121.9, 115.2, 110.3, 52.5, 50.2, 44.8, 43.7, 40.7, 37.1, 29.7, 29.1, 28.3, 27.6, 27.3, 27.0, 26.8, 12.4, IR (CH_2Cl_2) 3425, 3010, 2925, 2850, 1640 (br), 1540 cm^{-1}, UV (EtOH) λ 291 (ε15,300), 244 (ε30,500), mass spectrum, m/e 363 (parent ion).

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