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STUDIES DIRECTED TOWARD THE PREPARATION OF POLYENE MACROLIDE MIMICS

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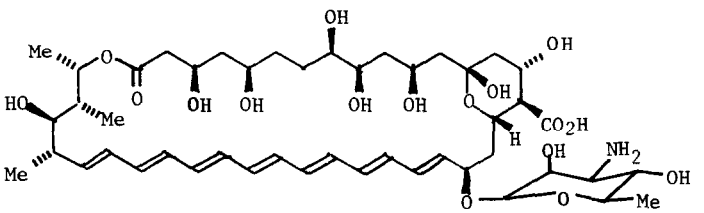
Summary: Cyclodimerization of two symmetrical but dissimilar fragments provides a facile route to macrocyclic dilactones containing conjugated polyolefins. Methods have been developed for the stereoselective synthesis of cis-2,4,6-triacetoxyheptanedial and the simple acylation of alcohols with dimethyl phosphonoacetic acid.

The polyene macrolides, such as amphotericin B (1) are an important class of antibiotics which display potent antifungal activity.[1] Their mode of action involves the disruption of normal membrane function by complexation of membrane bound sterols.[2] However, the lack of selectivity between ergosterol and cholesterol, typical of fungi and mammals respectively, can result in severe toxicity. We describe here our initial results in developing methodology to prepare potential polyene macrolide mimics in order to identify factors important to sterol complexation and intrinsic bioactivity.



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We set as our initial target macrocycle 6 to determine the best methods for cyclizing two dissimilar but symmetrical halves. The requisite triene-diol 5 was prepared by treating the diphosphonate 2[3] with 2 mole equivalents of s-butyl lithium at -78°C in THF followed by the addition of aldehyde 3[4] and warming to ambient temperature to afford 4 in 60% yield. Deprotection of 4 (p-TsOH,MeOH,RT) gave 5 in 80% yield.

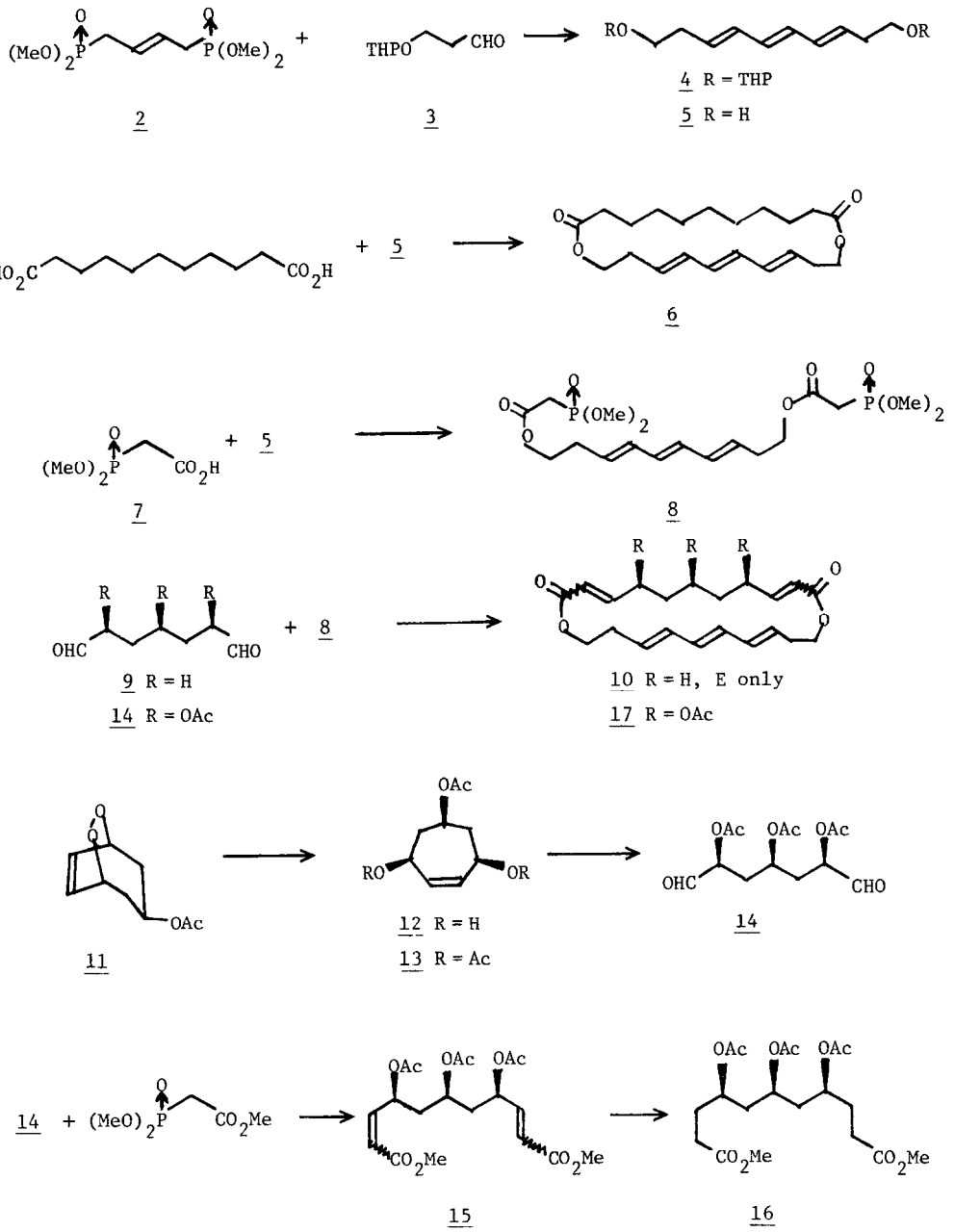
The cyclization of 5 with undecanedioic acid at 10^{-3}M under a variety of standard conditions[5] gave 6 in only 10-20% yield after chromatographic purification. Since most of these procedures require elevated temperatures, the low yields were attributed to the thermal instability of the triene 5.[6]

Seeking milder cyclization conditions we next examined the possibility of ring closure using phosphonate stabilized anions as demonstrated by Burri in his vermiculine synthesis.[7] Resetting our target to macrocycle 10 we set out to prepare the diphosphonate 8. The mildest method for obtaining 8 directly from 5 would be to employ dimethyl phosphonoacetyl chloride in a simple acylation reaction although related acid chlorides required several steps to prepare.[8] A more direct approach was found using dimethyl phosphonoacetic acid (7) which was obtained by hydrolysis of trimethyl phosphonoacetate (1 eq KOH, 1M, 16 hr) followed by ion exchange chromatography (Dowex 50W-X8, H^+, 10 eq).[9] Anhydrous acid 7 was obtained in essentially quantitative yield by azetropic removal of residual water with toluene under reduced pressure. Treatment of 7 with 1 equivalent of oxalyl chloride in methylene chloride-DMF (10:1) and the addition of crude diol 5 gave 8 in 72% overall yield from the bis-THP ether 4.[10] The slow addition of a 1:1 mixture of 8 and dial 9 to a stirred slurry of sodium hydride in THF gave the desired macrocycle 10 in 70% isolated yield. Hydrogenation of macrocycles 10 and 6 gave the same saturated dilactone (m p = 58-59°C).

Based on the structure of 1,[11] the hydroxyl groups of a model polyol region should have a cis-1,3 relationship. In a previous report we described the stereoselective preparation of endoperoxide 11 as a possible precursor to an all cis-1,3 polyol unit.[12] Cleavage of the peroxide with zinc-zinc chloride in cold methanol gave the triol monoacetate 12 (m p = 135-135.5°C) in quantitative yield. Acetylation of 12 with acetic anhydride in cold pyridine gave analytically pure 13 (m p = 121°C) in 75% yield. Ozonolysis of 13 at -78°C in ethyl acetate followed by reductive workup (H_2, Pd/C, 0°C) gave crude dial 14 which was treated with an excess of lithio trimethyl phosphonoacetate in THF (RT, 4 hours) to yield crude 15 as a mixture of olefinic isomers. Hydrogenation of 15 (Pd/C, MeOH, RT) followed by column chromatography gave a 52% yield of 16 based on the amount of 13 initially employed. Pure dial 14 was obtained in 49% yield upon flash chromatography of the crude ozonolysis product. Both 14 and 16 were shown to be single isomers by ^1H and ^{13}C NMR analysis demonstrating that the stereochemical relationship of the oxygen functionalities was retained throughout the ozonolysis and homologation sequence.

The reaction of 14 and diphosphonate 8 at 10^{-3}M in THF with 3 mole equivalents of sodium hydride gave the protected cyclic triol 17 in 30% yield after plc on silica as a mixture of isomers about the newly formed double bonds. From these results it is apparent that by employing acid labile protecting groups in place of the acetyl groups and applying the methods described above, the preparation of potential polyene macrolide mimics is feasible. The use of the

Horner-Emmons reaction to prepare macrocycles containing sensitive functionality may have general importance in the area of polyene macrolide synthesis.[13,14]



References

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2) Patterson, J.; Holland, J.; Bieber, L.L. J. Antib., 1979, 32, 646 and references. Bittman, R. Lipids, 1978, 13, 686.

3) German Patent 1,092,472. C.A., 1962, 413b. This would appear to be a much simpler procedure than employing the method of Lednicer. Lednicer, D. J. Org. Chem., 1971, 36, 3473.

4) Tufariello, J.J.; Tegeler, J.J. Tetrahedron Letters, 1976, 4037.

5) Typical thermal and Ag catalysed thio ester procedures as well as methods employing 1-methyl pyridinium salts were used. For leading references see Nicolaou, K.C. Tetrahedron, 1977, 33, 683.

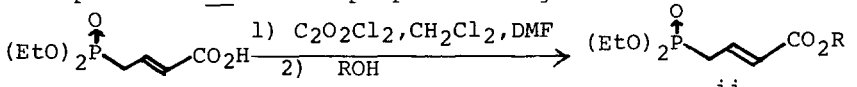
6) Serious decomposition of the triene 5 was observed upon refluxing in toluene at 10^{-3} molar for 10 hours.

7) Burri, K.F.; Cardone, R.A.; Chen, W.Y.; Rosen, P. J. Am. Chem. Soc., 1978, 100, 7069.

8) Bodnarchuk, N.D.; Maluvik, V.V.; Derkack, G.I.; Kirsunov, A.V. Z. Obsh. Khim. 1971, 41, 1470 (Eng). Subsequent to completion of these studies Meyers employed diethyl phosphonoacetyl chloride in a synthesis of N-methyl maysenine. Meyers, A.I.; Roland, D.M.; Comins, D.L.; Henning, R.: Fleming, M.P.; Shimizu, K. J. Am. Chem. Soc., 1979, 101, 4732.

9) Lombardo, L.; Taylor, R.J.K. Syn. Com., 1978, 8, 463.

10) We have also found that triethyl phosphonocrotonate readily affords the corresponding carboxylic acid i (m p = 85-86.5°C) and that high yields of acylated products ii can be prepared using the described methods.



i ii

R = 1°, 2° and 3°.

11) Ganis, P.; Auitabile, G.; Mechlinski, W.; Schaffner, C.P. J. Am. Chem. Soc. 1971, 93, 4560.

12) Floyd, D.M.; Cimarusti, C.M. Tetrahedron Letters, 1979, 4129.

13) Subsequent to the completion of these studies two papers appears further exploring the use of the Horner-Emmons reactions for the closure of macrocycles. Stork, G.; Nakamura, E. J. Org. Chem., 1979, 44, 4010. Nicolaou, K.C.; Seitz, S.P.; Pavic, M.R. Petasis, N.A. J. Org. Chem., 1979, 44, 4011

14) Spectral data for all compounds was consistent with assigned structures. All crystalline compounds gave satisfactory micro analysis. Compounds 5 and 10 were shown to be single isomers by ^{13}C NMR analysis: 5 (crude, olefin region) 133.6, 132.4, and 131.3 ppm in CD_3OD; 10 (purified, olefin region) 148.9, 133.4, 131.0, 129.8, and 121.6 ppm in $CDCl_3$. Both 15 and 17 were obtained as mixtures about the newly formed double bonds.

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