Tetrahedron Letters,Vol.29,No.4,pp 451-454,1988
Printed in Great Britain

0040-4039/88 $3.00 + .00
Pergamon Journals Ltd.

A SYNTHESIS OF 19-DEHYDROAMPHOTERONOLIDE B.†

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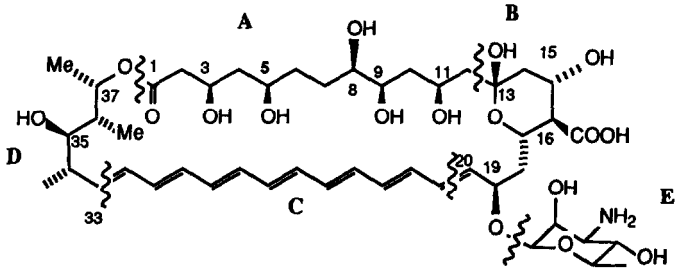
Summary: The four fragments A-D previously prepared for the synthesis of amphoteronolide B have been assembled to provide the titled compound. This assembly represents a formal synthesis of amphoteronolide B.

The unique structural and stereochemical features of the polyenemacrolide amphotericin B (1) have aroused the interest of synthetic chemists.[1,2] As a result, Nicolaou and collaborators have recently accomplished an elegant synthesis of this macrolide[2a,b] and we record herein the assembly of the three fragments A (5 in Scheme 1)[1a,b], B (2)[1c,d] and CD (13 in Scheme 3)[1e] prepared earlier in this laboratory. This assembly completes a synthesis of the titled compound (14 in Scheme 3) described in the preceding Note.

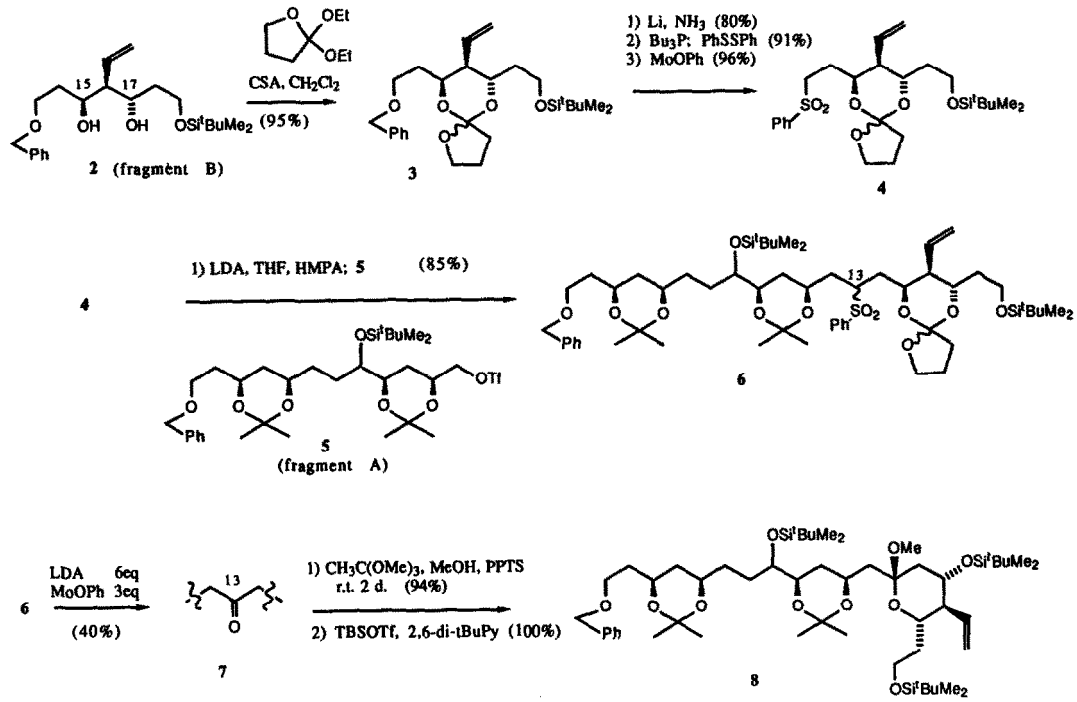


AMPHOTERICIN B (1)

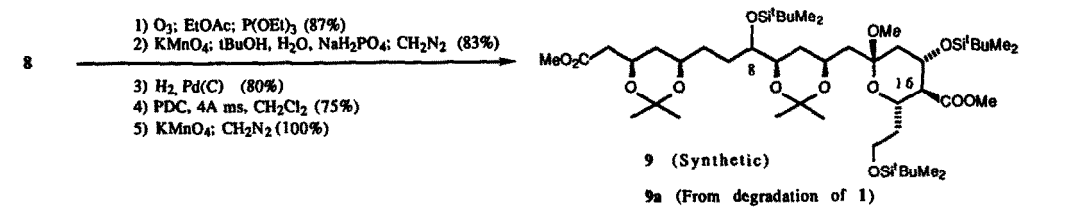
The reaction sequence with reagents and yields used to couple fragments A and B are shown in Scheme 1. Of the many protecting groups for the C(15), C(17)-diol in 2 (fragment B), the cyclic orthoester shown in 3[3] fulfilled the requirements necessary to effect three subsequent reactions: i) effective coupling of 4 and 5, ii) selective removal of the orthoester in the conversion of 7 to 8 and, iii) concommitant ketalization at C(13) to form 8 effected with the aid of trimethyl orthoacetate which rapidly scavenged water unavoidably present in the reaction medium.[4] The overall yield of the conversion of 5 to 8 is ca. 30%. It should be noted that only one methoxy anomer results from this cyclization.

Scheme 2 outlines functional group manipulation of the AB fragment 8. The sequence of reactions indicated in the scheme converted both the C(16)-vinyl and C(1)-benzyloxy groups into the methoxycarbonyl groups of 9. It is noted that oxidation of the aldehydes to the corresponding carboxylic acids involved in this sequence was best executed with $KMnO_4$ in a buffered solution.[1g]

SCHEME 1



SCHEME 2

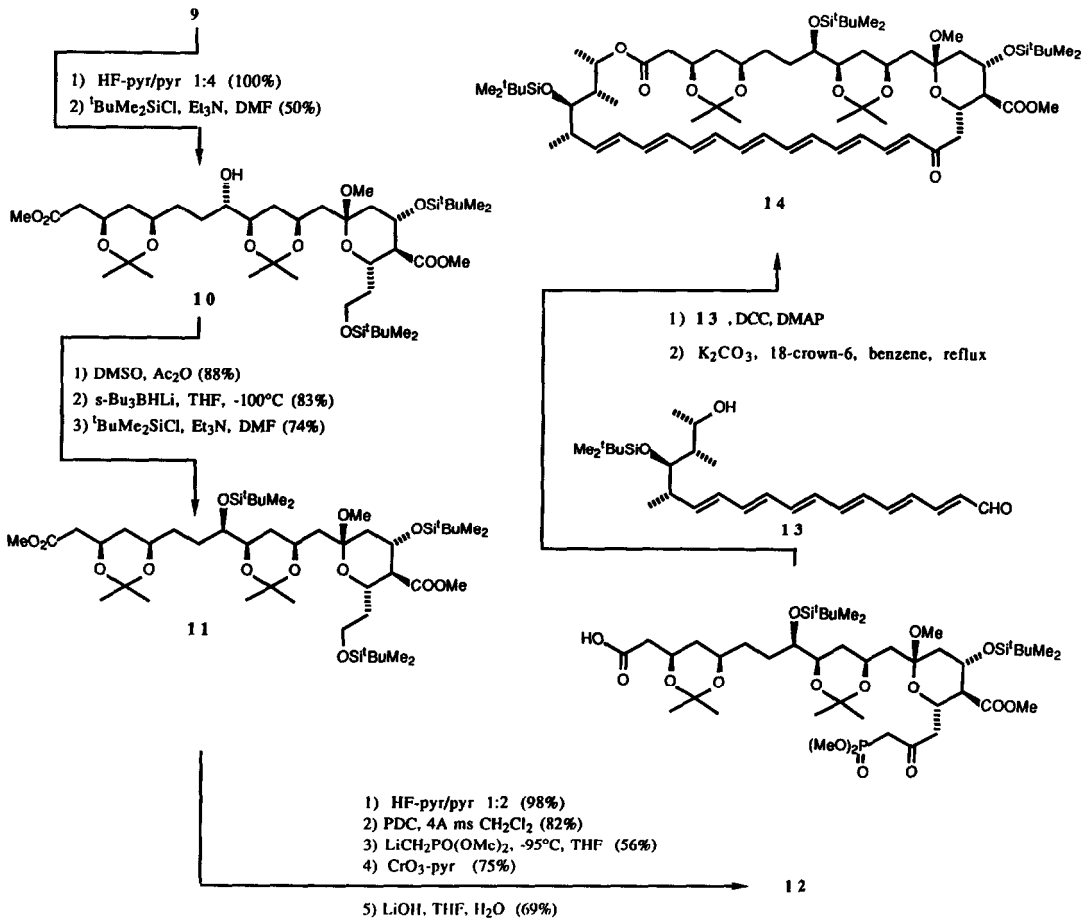


The preceding Note describes the preparation of 9a from 1,[5] and 9a was compared with synthetic material 9. To our surprise (and disappointment) there were minor but observable differences between the two compounds, although high resolution mass spectra indicated that 9 and 9a were of the same molecular weight. (i) Thin layer chromatography showed that they had different mobilities on silica gel. (ii) ^{1}H NMR spectra were very similar, but not identical. The C(16) protons of both 9 and 9a showed the same chemical shift and coupling pattern (2.22 ppm, $J_{15,16} = J_{16,17} = 10.3$ Hz) indicative of the three equatorial substituents [C(15-17)] on the pyran ring. The C(13) methoxy group had the same chemical shift in both compounds and was presumably axial. One multiplet (δ 3.5 ppm) in the ^{1}H NMR spectrum of 9 was shifted 0.05 ppm downfield from that of 9a. As a result of the unique chemical shift of this proton and those to which it was coupled, this proton was assigned to the C(8) position. Therefore, it was concluded that 9 was epimeric to 9a at the C(8) stereogenic center, despite evidence presented earlier strongly favoring "syn" C(8)-C(9) stereochemistry of 9.[1b,6]

Scheme 3 outlines inversion of the C(8) stereochemistry of 9. This was accomplished by mild cleavage of the silyl ethers, selective silylation at C(15,19), oxidation-reduction[2b] of the C(8) alcohol, and finally, silylation of the resultant "syn" alcohol. Compound 11 was compared to 9a and was found to be identical. The C(19) center was converted to a keto-phosphonate by selective addition of lithium methyl dimethylphosphonate to the C(19) aldehyde and oxidation of the β-hydroxyphosphonate. The C(1) methyl ester was saponified last in order to obtain pure material in the preceding steps.

Following the proceedure described earlier,[2b] the AB fragment (12) and the CD fragment (13) were coupled by DCC mediated esterification and subsequent macro-Wittig cyclization[7] to provide the 19-dehydroamphoteronolide derivative 14, which was, again, found to be identical to material derived from oxidative degradation[8] of amphotericin B. Since 14 has been converted to amphoteronolide B,[2b] this work constitutes a formal total synthesis of the same.

SCHEME 3



Acknowledgements. We thank the National Institutes of Health for financial support. RMK was an NIH postodctoral fellow.

References and Footnotes

† Presented at the annual meeting of the Japan Chemical Society, April 3, 1987; Abstract pp. 1144-1145.

1. Contributions from this laboratory, see (a) Ma, P.; Martin, V.S.; Masamune, S.: Sharpless, K.B.; Viti, S.M. J. Org. Chem. 1982, 47, 1378. (b) Masamune, S.; Ma, P.; Okumoto, H.; Ellingboe, J.W.; Ito, Y. Ibid. 1984, 49, 2843. (c) Masamune, S.; Kaiho, T.; Garvey, D.S. J. Am. Chem. Soc. 1982, 104, 5521. (d) Boschelli, D.; Ellingboe, J.W.; Masamune, S. Tetrahedron Lett. 1984, 25, 3395. (e) Boschelli, D.; Takemasa, T.; Nishitani, T.; Masamune, S. Ibid. 1985, 26, 5239. (f) Blanchette, M.A.; Choy, W.; Davis, J.T.; Essenfield, A.P.; Masamune, S.; Roush, W.R.; Sakai, T. Ibid. 1984, 25, 2183. (g) Abiko, A.; Roberts, J.C.; Takemasa, T.; Masamune, S. Ibid. 1986, 27, 4537.

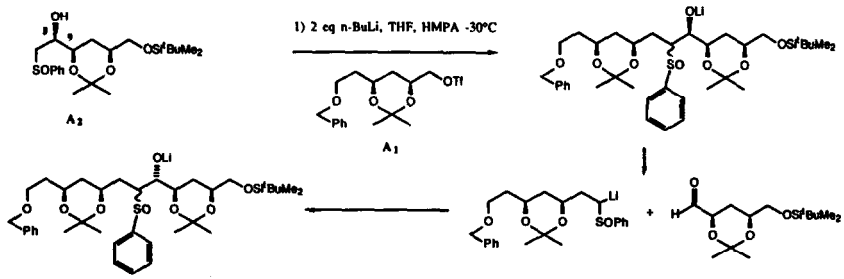
2. From other groups, see (a) Nicolaou, K.C.; Daines, R.A.; Uenishi, J.; Li, W.S.; Papahatjis, D.P.; Chakraborty, T.K. J. Am. Chem. Soc. 1987, 109, 2205. (b) Nicolaou, K.C.; Daines, R.A.; Chakraborty, T.K.; Ibid. 1987, 109, 2208. (c) Hannessian, S.; Sahoo, S.P.; Botta, M. Tetrahedron Lett. 1987, 28, 1143 and 1147. (d) Hannessian, S.; Botta, M. Ibid. 1987, 28, 1151. (e) Solladie, G.; Hutt, J. Ibid. 1987, 28, 797. (In this reference the authors misquote the yield of the coupling reaction used to construct Fragment A of our synthesis, reference 3b.) (f) Williams, J.M.; McGarvey, G.J. Ibid. 1985, 26, 4891. (g) McGarvey, G.J.; Williams, J.M.; Hiner, R.N.; Matsubara, Y.; Taeboem, O. J. Am. Chem. Soc. 1986, 108, 4943. (h) Liang, D.; Pauls, H.W.; Fraser-Reid, B. J. Chem. Soc. Chem. Commun. 1984, 1123. (i) Hirama, M.; Ueni, M. Tetrahedron Lett. 1982, 23, 5307. (j) Brooks, D.W.; Kellog, R.P. Ibid. 1982, 23, 4991. (k) Lipshutz, B.H.; Kotsuki, H.; Lew, W. Ibid. 1986, 27, 4825. (l) Floyd, D.M.; Fritz, A.W. Ibid. 1981, 2847.

3. Compound 3 is a 1:1 mixture of separable epimeric orthoesters and the reaction series in Scheme 1 were carried out with the mixture and also with either single isomer. The yields recorded are for the mixture series.

4. Use of trimethyl orthoformate, for instance, reduced the yield of 8 (with the C(15), C(19)-OH) to ca. 50%. Water apparently participates in this orthoester hydrolysis to produce an acyclic ester which does not cyclize to the pyran.

5. See compound 9 in the preceding Note.

6. Synthesis of fragment A was reported in ref 1b. It is believed that the crucial coupling step of subunits A_1 and A_2 provided the anti-configuration at C(8)-C(9) by equilibration of the alkylation product, as shown below.



7. The macro-Wittig cyclization was documented earlier by Masamune S.; Bates, G.S.; Corcoran, J.W. Angew. Chem. Int. Ed. Engl. 1977, 16, 585 and was later modified by Stork, G.; Nakamura, E. J. Org. Chem. 1979, 44, 4010 and Nicolaou, K.C.; Seitz, S.P.; Pavia, M.R.; Petasis, N.A. Ibid. 1979, 44, 4011.

8. See compound 13 in the preceding Note.

(Received in USA 12 November 1987)