Tetrahedron Letters,Vol.28,No.11,pp 1143-1146,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

METHODOLOGY FOR THE POLYENE AND RELATED ANTIBIOTICS—ENANTIOSPECIFIC SYNTHESIS OF CHIRAL STRUCTURAL UNITS OF AMPHOTERICIN B FROM A COMMON PROGENITOR: THE C_1-C_{13} POLYOL SEGMENT

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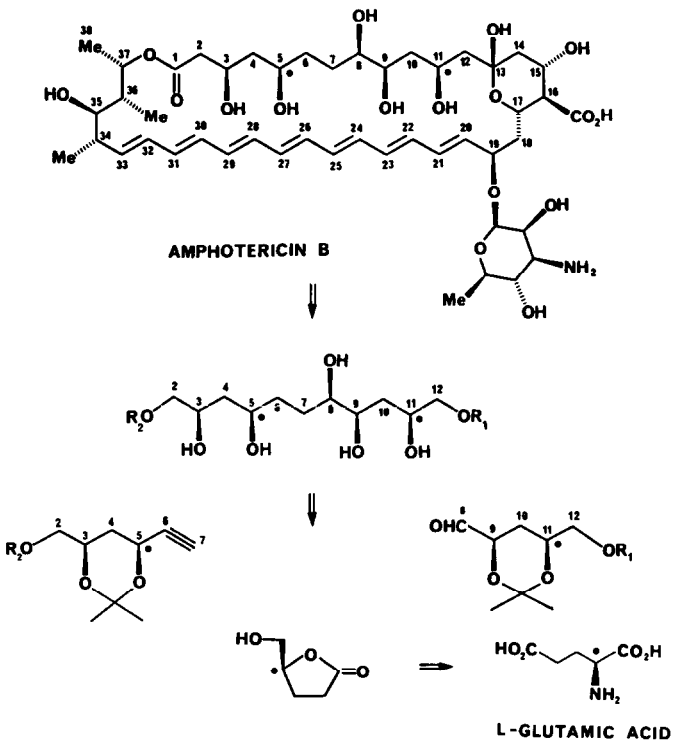
Summary - The optically pure C_1-C_{13} subunit of amphotericin B encompassing five asymmetric centers was synthesized from a readily available chiron derived from L-glutamic acid.

Amphotericin B, a member of the antifungal group of polyene antibiotics[1] possesses a unique array of functional and stereochemical features which presents a veritable challenge in synthetic design and assembly. Several approaches that address these issues have been recently reported in the literature,[2] culminating with a cleverly executed degradation-reconstruction protocol by Nicolaou and coworkers,[3] who demonstrated the feasibility of assembling such complex structures with remarkable facility from appropriate subunits obtained via degradation of the antibiotic. In this and the following paper we present a tactically and operationally novel strategy for the systematic construction of appropriate segments of amphotericin B in enantiomerically pure form, utilizing a common precursor.[4] This paper describes convergent and efficient approaches to the C_1-C_{13} polyol segment starting with (S)-4-hydroxymethyl butyrolactone which is readily available from L-glutamic acid.[5,6]

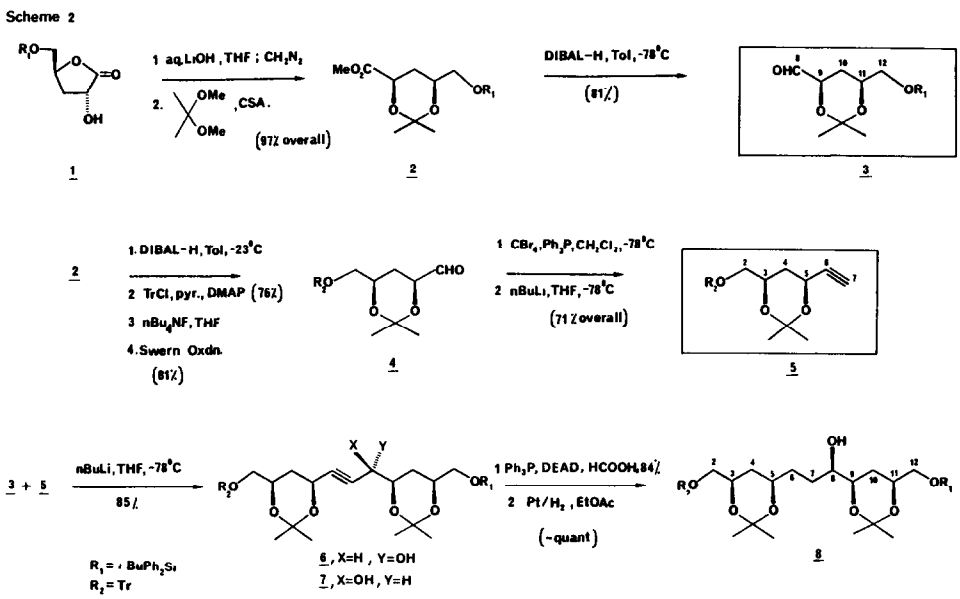
Scheme 1



Central to the stereochemical decoding operation was the expectation that the sole asymmetric center in (S)-4-hydroxymethyl butyrolactone could control the stereochemical outcome of subsequent bond forming processes. This hypothesis was experimentally realized.

Saponification of the readily available lactone 1,[5,6] followed by acetonide formation afforded the ester 2, $[\alpha]_D$ 4.2° (c,1)[7] in high overall yield (Scheme 2). This pivotal chiron could be functionalized in such a way so as to provide a nucleophilic and an electrophilic component required for the assembly of the intended target. Reduction of 2 with one equivalent of DIBAL-H at -78° gave the aldehyde 3, $[\alpha]_D$ 7.6° (c,2) which corresponds to C_8-C_{12} segment of the target.

Scheme 2

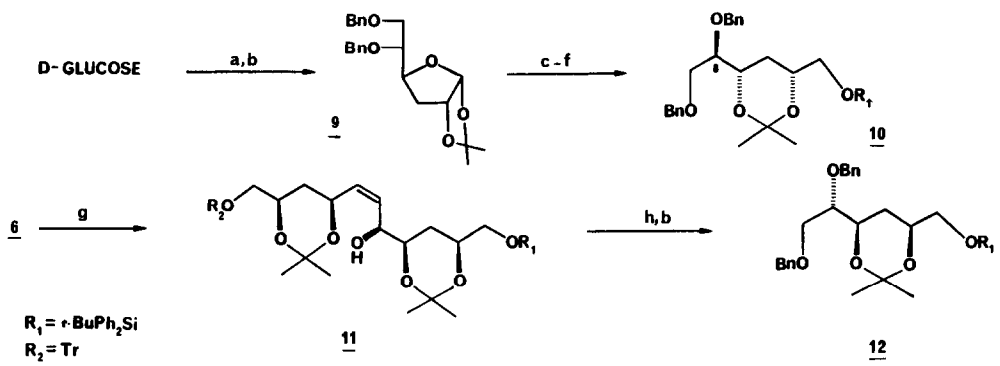


On the other hand, reduction at -23°, tritylation and desilylation gave the corresponding alcohol $[\alpha]_D$ 29.9° (c, 1). Oxidation afforded the aldehyde 4 which has an enantiomeric relationship to 3, except for the nature of the protective group on the primary alcohol. Application of the Corey-Fuchs procedure[8] led to the acetylene derivative 5, $[\alpha]_D$ 17.1° (c, 0.9) which represents the C_2-C_7 subunit of amphotericin B. With chirons 3 and 5 in hand, we were ready to address their coupling en route to the intended subtarget. Addition of the aldehyde 3 to the lithium salt of 5, afforded a 12:1 mixture of propargylic alcohols 6 and 7 respectively in 85% yield. The major isomer 6, $[\alpha]_D$ 13.4° (c, 1) was found to be the incorrect (8S)-isomer (vide infra). Several attempts to reverse the stereoselection (addition of lithium chloride, formation of the Grignard reagent from 5, or inverse addition), were not successful. The situation was easily rectified by treatment of 6 under the conditions of the Mitsunobu reaction,[9] which afforded the inverted alcohol 7, $[\alpha]_D$ 17.8° (c, 1.93), in 84% yield.[10] Reduction of 7 afforded the optically pure C_2-C_{12} subunit 8, $[\alpha]_D$ 15.2° (c, 1.4) in excellent overall yield.

Because of the propensity of oxygen bearing substituents in 3 and 5, it is difficult to rationalize the origin of the stereoselection leading to 6. Inspection of molecular models reveals that a Li-coordinated intermediate involving the aldehyde carbonyl and the C_9 oxygen atoms cannot unambiguously account for the observed bias. This is consistent with a recent observation made in the reaction of an acetylenic Grignard reagent with an α-alkoxy aldehyde.[11] On the other hand, lithium coordination was invoked by Masamune and coworkers[4] to explain the stereoselection observed in the reaction of a C_7 sulfoxide anion related to 5 with 3 (as the t-butyldimethylsilyl ether).[12]

In order to secure definitive proof for the correct sense of chirality at C_8 in the acetylenic alcohol 6, we carried out the sequence shown in Scheme 3. Thus, the known[13] 3-deoxy-1,2-O-isopropylidene-D-xylohexofuranose was transformed into the dibenzyl ether 9, which was subjected to hydrolysis, reduction and protection of the hydroxy groups to give 10, $[\alpha]_D$ 2.2° (c 0.65). Alternatively, Lindlar reduction of 6, followed by ozonolysis, reductive workup and benzylation gave the fragment 12, $[\alpha]_D$ -2.2° (c, 1.35), which was enantiomeric with 10 obtained by an unambiguous route from D-glucose (Scheme 3).

Scheme 3

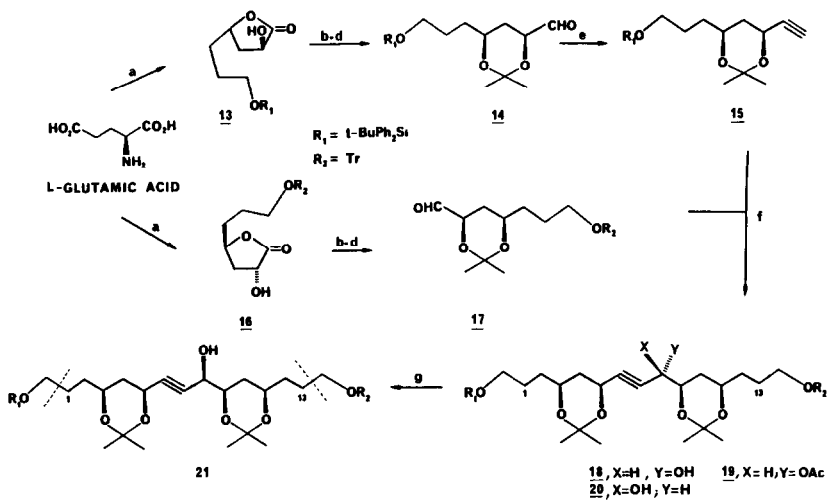


a. ref. 13; b. BnBr, NaH; c. aq. H_2SO_4; d. $NaBH_4$, MeOH; e. t-$BuPh_2SiCl$, DMF; f. 2,2-dimethoxypropane, CSA; g. Lindlar, EtOAc; h. O_3, CH_2Cl_2.EtOH; then $NaBH_4$

In an alternative approach to the C_1-C_{13} segment of amphotericin B, we prepared the aldehydes 14 and 17 (enantiomeric except for the nature of the protecting groups) from 13 $[\alpha]_D$ -28° (c, 2.18) and 16 $[\alpha]_D$ 26.6° (c, 1.23) respectively based on the replicating lactone technology already described.[5] Conversion[8] of 14 to the corresponding acetylene derivative 15, and condensation with 17 afforded the mixture of propargylic alcohols 18 (acetate 19, $[\alpha]_D$ 8.6°; c, 1) and 20 in a ratio of ~12:1. Separation and Mitsunobu reaction afforded the polyol 21 $[\alpha]_D$ 6° (c, 0.5) having the correct sense of chirality at C_8 (amphotericin numbering) (Scheme 4). Polyols 8 and 20 are useful precursors to the C_1-C_{13} segment of amphotericin B since the former can be chain-extended and the latter can be chain-shortened to the desired length.

The presently described route to the polyol segment of amphotericin B has a number of rewarding features which include efficiency of operation, stereochemical control, and convergence. The 12-step sequence can be realized in above 30% overall yield from the readily available lactone 1, and it is adaptable to large-scale operations.

Scheme 4



a. ref. 5; b. aq. LiOH, then CH_2N_2; c. 2,2-dimethoxypropane, CSA (87%, 3 steps); d. DIBAL-H, -78°, toluene, 90%; e. CBr_4, Ph3P, then BuLi, 56% (3 steps); f. n-BuLi, THF, -78°, add 17; 76%; g. Ph_3P, DEAD, HCO_2H, ether, 84%.

Acknowledgments - We wish to thank NSERCC and FCAR (Quebec) for generous financial assistance, Dr. Phan Viet Tan for assistance in highfield n.m.r. experiments and M. Evans for mass spectra. We also thank Roger Léger for technical assistance as a summer student.

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7. All new compounds were adequately characterized by spectral (400 MHZ ^1H n.m.r., mass) and microanalytical (crystalline compounds) techniques. Optical rotations were recorded in chloroform at 25°.
8. E.J. Corey and P.L. Fuchs, Tetrahedron Lett., 3769 (1972).
9. O. Mitsunobu, Synthesis, 1 (1981).
10. Alternatively, oxidation of the mixture of 6 and 7 (PCC, CH_2Cl_2, NaOAc) gave the corresponding ketone which upon reduction with L-selectride in THF gave a 7 and 6 respectively in a ratio of 7:3.
11. See for example, T. Takahashi, M. Miyazawa and J. Tsuji, Tetrahedron Lett., 26, 5139 (1985).
12. Coordination by other oxygen atoms was excluded but no compelling arguments were presented in favor of the Li-coordinated aldehyde and carbonyl C_9 oxygen atoms. The epimeric C_8 alcohol may also be a major product similar to our experience.
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(Received in USA 20 October 1986)