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METHODOLOGY FOR THE POLYENE AND RELATED ANTIBIOTICS — ENANTIOSPECIFIC SYNTHESIS OF CHIRAL STRUCTURAL UNITS OF AMPHOTERICIN B FROM A COMMON PROGENITOR: THE C_{14}-C_{20} AND C_{32}-C_{38} SEGMENTS

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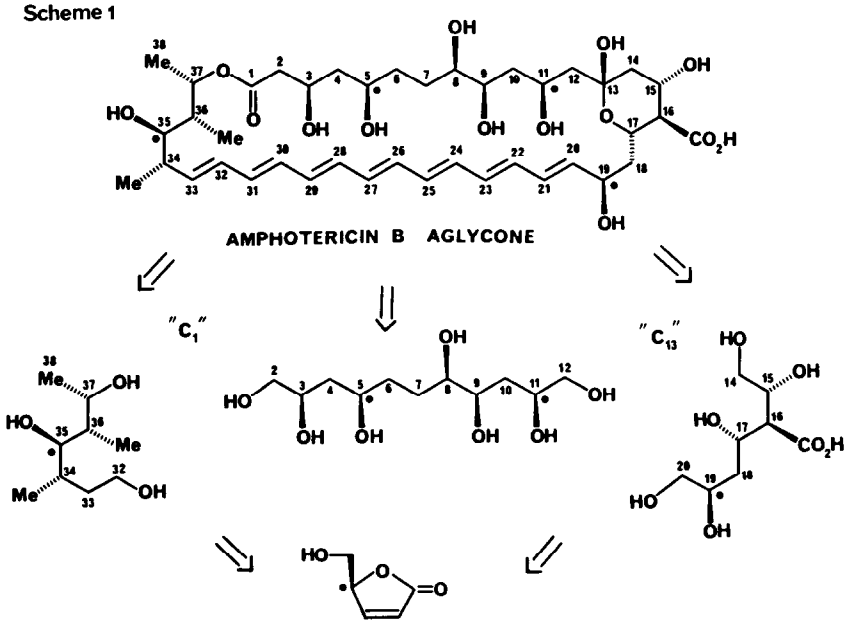
Summary - Structural units corresponding to the C_{14}-C_{20} and C_{32}-C_{38} segments of amphotericin B were synthesized from a single chiral progenitor.

In the previous paper,[1] we described an efficient and convergent synthesis of the C_1-C_{13} segment of amphotericin B[2] starting with (S)-4-hydroxymethyl butyrolactone which is readily available from L-glutamic acid,[3] D-ribonolactone,[4] or D-mannitol.[5] In this paper, we report enantiospecific syntheses of the C_{14}-C_{20} and C_{32}-C_{38} segments of this polyene antibiotic, utilizing the same starting material, namely L-glutamic acid. Recent publications have described other approaches to these two segments based on aldol methodology,[6,7] on asymmetric alkylation of chiral β-aminoacyl butyrolactones[8] and the utilization of carbohydrates.[9] A semi-synthetic approach for the assembly of amphotericin B is also available.[10]

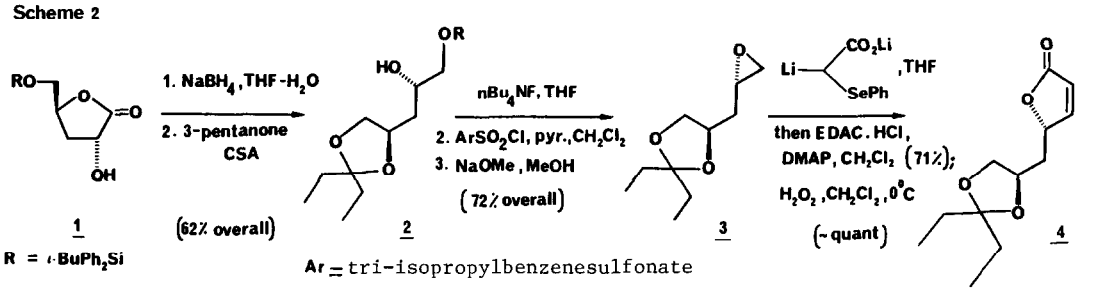
Our novel strategy takes advantage of the replicating lactone technology,[11,12] which permits the systematic functionalization of 4-substituted butyrolactones and butenolides.[13] Applying this powerfully predictive strategy, it is possible to synthesize stereochemically and functionally defined subunits that match the C_1-C_{13}, C_{14}-C_{20} and C_{32}-C_{38} segments of amphotericin B from a single chiral progenitor.

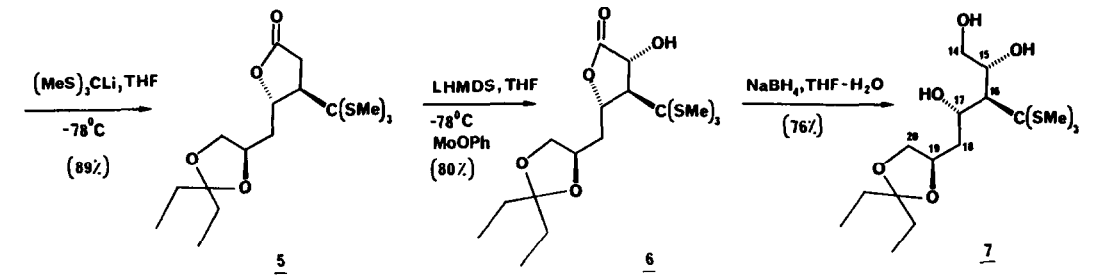
Scheme 1



The C_{14}-C_{20} segment - Lactone 1 which is readily available from (S)-4-hydroxymethyl butyrolactone,[12] was converted into the protected tetrol 2 $[\alpha]_D$ -8.6° (c 1, $CHCl_3$) via a standard sequence shown in Scheme 2.[14]

Scheme 2





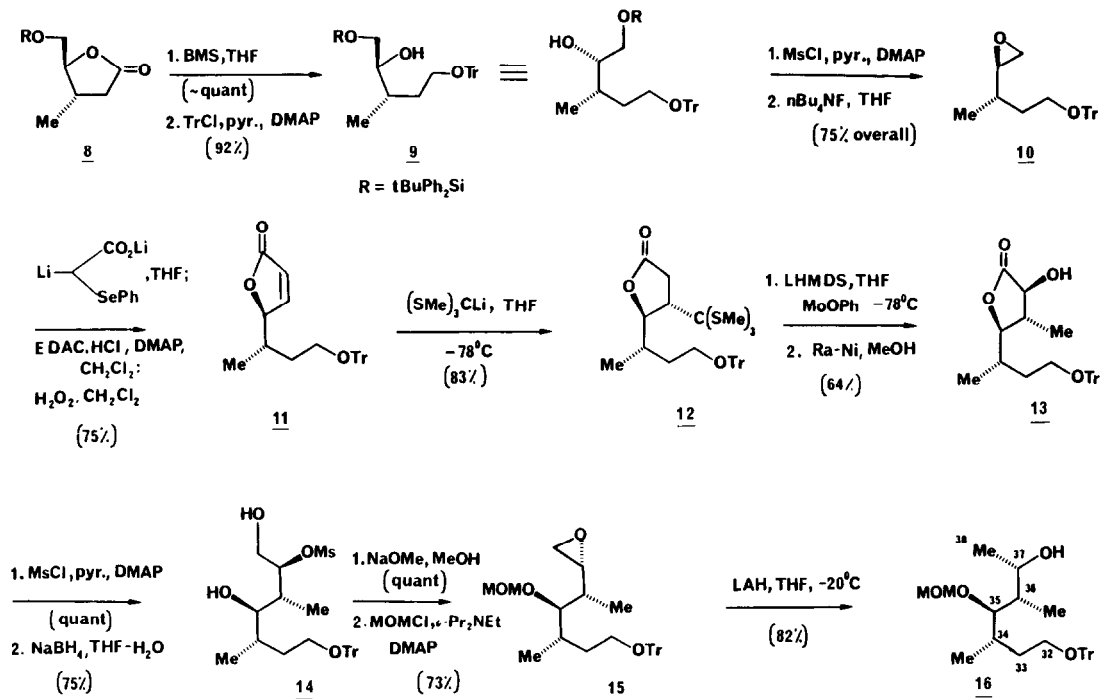
Desilylation, selective sulfonylation and treatment with base gave the epoxide 3, $[\alpha]_D$ -22.4° (c 1, $CHCl_3$). Application of the two-carbon extension procedure[11,12] with dilithio phenylselenoacetate,[15,16] followed by lactonization and elimination gave the replicated butenolide 4, $[\alpha]_D$ 89.3° (c 1, $CHCl_3$). Having thus assembled the desired length of the intended C_{14}-C_{20} carbon chain, we were faced with the task of a stereocontrolled introduction of two vicinal anti substituents at C_{15} and C_{16}. We reasoned that the bulk of the C_4 substituent would greatly favor conjugate attack on the butenolide from the less congested side, particularly if the nucleophile itself were also bulky. Treatment of 4 with lithium tris(methylthio)methane[17] afforded the corresponding adduct 5 as the sole product in excellent yield, $[\alpha]_D$ -3.7° (c 0.75, $CHCl_3$). Hydroxylation of the enolate of 5 with MoOPH,[12,18] gave 6 as the only product. Finally reduction of 6 afforded the triol 7 $[\alpha]_D$ 12.1° (c 1, $CHCl_3$) which corresponds to the C_{14}-C_{20} segment of the intended target and constitutes a functionally versatile precursor.

The C_{32}-C_{38} segment

The alternating arrangement of vicinal methyl and hydroxy groups in this segment of amphotericin B offers a challenge in synthetic design, since it represents yet another pattern of substitution that arises from the propionate biosynthetic pathway. The readily available butyrolactone derivative 8,[11] was transformed into the epoxide 10, mp 62-63°; $[\alpha]_D$ - 1.6° (c 0.9, $CHCl_3$) in high overall yield. A two-carbon extension with dilithio phenylselenoacetate, followed by lactonization and oxidative elimination afforded the replicated butenolide 11, $[\alpha]_D$ - 48.4° (c 1.9, $CHCl_3$) (Scheme 3). Capitalizing on the template effect of the butenolide, we carried out a sequential conjugate addition with a

bulky methyl equivalent, followed by a stereocontrolled hydroxylation. Thus, treatment of 11 with the anion of tris(trimethylthio)methane gave 12 in high yield, $[\alpha]_D$ 16° (c 1.5 $CHCl_3$). Formation of the enolate, hydroxylation with MoOPH, followed by desulfurization gave the lactone 13, $[\alpha]_D$ -1.19° (c 1.17, $CHCl_3$). Having taken full advantage of the template effect of the butenolide in two successive stereocontrolled functionalizations, there remained for us to adjust the level of oxidation at the terminal carbon atom which was destined to become the C_{38} methyl group, and to invert the configuration at C_{37}. Mesylation of 13 followed by reduction with sodium borohydride gave the diol 14, which was converted into the epoxide 15, $[\alpha]_D$ 0.6° (c 1, $CHCl_3$) with concomitant inversion of configuration at C_{37}. Protection of the hydroxy group as the MOM ether, followed by reduction with lithium aluminum hydride gave the intended C_{32}-C_{38} segment 16, $[\alpha]_D$ 5.9° (c0.6, $CHCl_3$) with its full complement of substituents in enantiomerically pure form.

Scheme 3



In this and the preceding paper, we have presented a new strategy and an operationally novel approach for the enantiospecific and expedient synthesis of segments of amphotericin B from a single chiral progenitor. The replicating butenolide chiron strategy offers the merits of versatility and efficacy combined with high predictive power. It should find widespread use in the total synthesis of polyketide-derived and related natural products.

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