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EN ROUTE TO POLYENE MACROLIDE TOTAL SYNTHESIS; THE KEY CHIRAL SEGMENTS OF ROFLAMYCOIN‡

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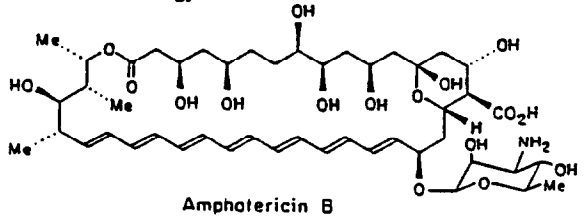
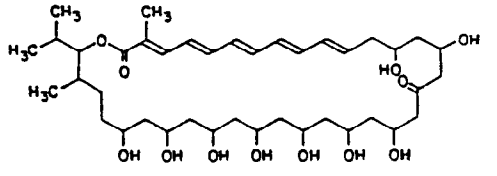
Abstract: Four sections of Roflamycoin, labeled A, B, D, and E, which correspond to 10 of the 11 chiral centers in this natural product, have been prepared.

The polyene macrolides, by virtue of their potent antifungal properties, constitute an important class of clinically valuable natural products.[2] Most of the attention in the synthetic area, not surprisingly, is directed toward Amphotericin B, 1,[3] the only one of many known examples[2] where even the issue of relative stereochemistry is known with certainty. However, based on the structure of 1,[4] as well as biosynthetic considerations,[5] efforts on related polyene macrolides have begun to surface.[6] Following our initial communication which described a simple, two step, reiterative method for 1,3-polyol construction of the all syn variety,[7] our attention became focused on the 36-membered macrolide Roflamycoin, 2.[8] We now report on the preparation of four key sections of 2, three of which successfully implement our earlier methodology.[7]



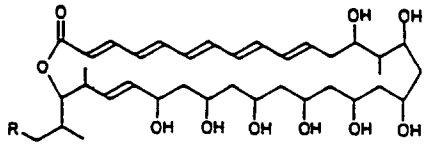
Amphotericin B

1



Roflamycoin

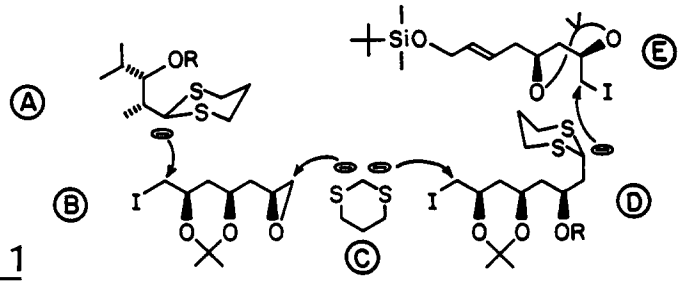
2



Mycoticin A (R = H)
Mycoticin B (R = CH_3)

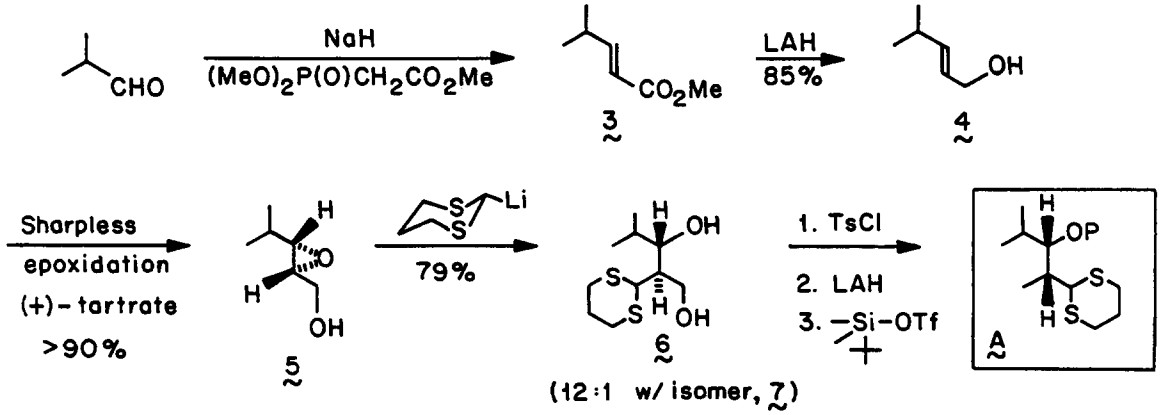
‡Dedicated to Professor Harry H. Wasserman on the occasion of his 65th birthday.

Retrosynthetically, we envisioned suitable disconnections as shown in Scheme 1. After sectioning the pentaene in a (3 + 1) sense,[9] portions A, B, D, E remain, along with the need for a one-carbon lynchpin (e.g., dithiane C).[10]



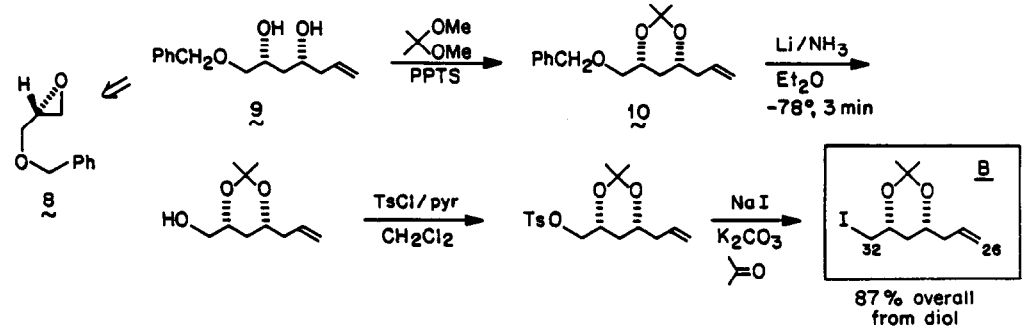
Scheme 1

A strategy for preparing section A, which contains two chiral centers of assumed stereochemistry, requires that all four enantiomers be available without significant alterations in the route to each. Scheme 2 illustrates our use of Sharpless technology[11] to fulfill this important criterion. The product of Horner-Emmons olefination, 3, reduces readily to allylic alcohol 4 with LAH in THF. Tartrate-controlled epoxidation leads to epoxy alcohol 5, R=H, which by high field NMR analysis on the derived acetate showed essentially one isomer under the influence of a chiral shift reagent ($Eu(hfc)_3$). Tetrahydropyranylation of alcohol 5, dithiane opening over 2 days in the presence of 5 equiv HMPA (~80%),[12] and subsequent hydrolysis gave a ca. 5:1 mix of regioisomers 6 and 7. To avoid use of HMPA, time delays, a mediocre ratio of isomers, and a protection/deprotection sequence, alcohol 5 was treated with 2 equiv of lithio dithiane in THF containing 5 equiv DMPU.[13] This minor modification afforded directly a 12:1 ratio of 6 to 7 (79%) in just a few hours at -20°C. Selective tosylation and thence LAH reduction gave A, P=H, which required TBDMS-OTf[14] to effect silyl etherification, ultimately completing the preparation of this three carbon piece (i.e., C-33 to C-35, A, P=Si(t-Bu)Me_2, $[\alpha]_D^{24}$ = +5.02° (c 5.48, $CHCl_3$)).

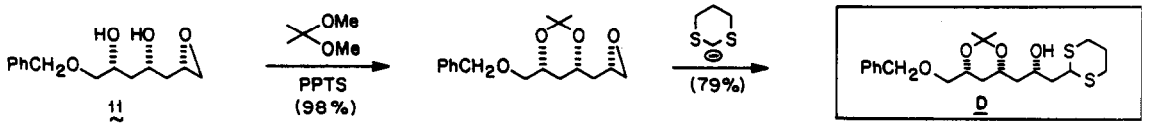


Scheme 2

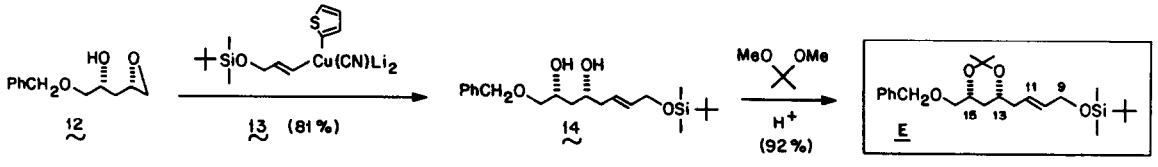
Sections B, D, and E all derive from diol 9 ($[\alpha]_D^{22}$ = -1.2° (c 10, $CHCl_3$), prepared earlier from epoxide 8. Primary iodide B, which represents the C-26 to C-32 fragment, was realized by straightforward manipulation of acetonide 10. Lithium in NH_3 reduction (-78°C, 3 min, MeOH quench) gave the free alcohol, which was converted to B via the tosylate (CH_2Cl_2/pyr, rt, overnight; then NaI/acetone, 0.25 equiv K_2CO_3, reflux).



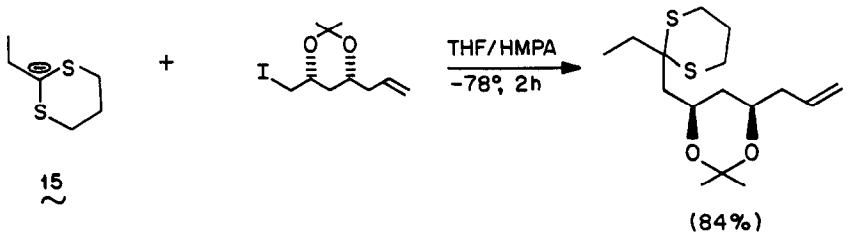
In place of the conversion of 9 to iodide B, re-epoxidation[7] led to 11, the diol of which was treated with dimethoxypropane. Dithiane opening of the monosubstituted epoxide gave the required C-17 to C-24 segment, D.



Rather than reacting epoxy alcohol 12 with the cuprate prepared from CuCN and 2 equiv of vinyllithium,[15] as discussed en route to B and D, 12 was exposed to the mixed thienyl cuprate 13,[16] which delivers C-9 to C-11 (macrolide numbering) possessing the needed functionality at C-9 for eventual macrolactonization across the 8,9 positions.[17] Conversion to E upon treatment of 14 with dimethoxypropane/cat. TsOH proceeded without incident.



Finally, to test the viability of B as an electrophilic partner toward dithiane alkylation, a model study was carried out with dithioacetal 15. Metalation of 15 proceeded as expected[18] at -20°C over 2h using n-BuLi in THF. After cooling to -78°C, HMPA (1 equiv) was introduced, followed by iodide B via cannula, which had been dried azeotropically (toluene) and precooled in THF to -78°C. Stirring for 2h at this temperature afforded, after the usual workup, product 16 in 84% isolated yield.



15

In summary, four fundamental sections of Roflamycoin have been prepared. The polyol portions derive from a H.O. vinyl cuprate opening of a chiral epoxide/re-epoxidation sequence. The two centers at C-34 and C-35 have been realized *via* a Sharpless epoxidation/dithiane opening, which implies that all four enantiomers of this western zone of as yet undetermined stereochemistry should be available by controlling both double bond geometry and choice of tartrate. The adjoining of these subunits, following triene construction,[19] as well as a related polyol strategy (using cuprates formed from E or Z propenyllithium) which may be applied to macrolides, e.g., the Mycoticins,[20] composed of occasional propionate units, form the basis of ongoing studies.

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References and Notes

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