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PROGRESS TOWARD ROFLAMYCOIN; SYNTHESIS OF THE C-12 TO C-35 SECTION IN HOMOCHIRAL FORM

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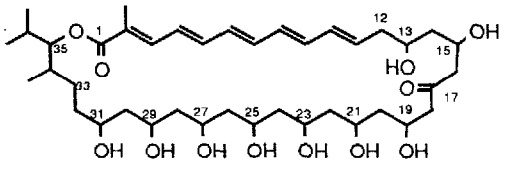
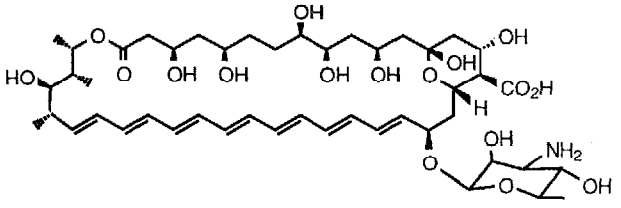
Abstract: A 24 carbon fragment containing 11 chiral centers has been prepared in optically pure form en route to the polyene macrolide roflamycoin.

Roflamycoin (1), a 36-membered polyene macrolide, represents one of over 200 known examples of this class of natural products.[4] In addition to displaying significant antifungal properties, roflamycoin is part of a select subgroup, the members of which (including Amphotericin B (2), Nystatin, and Mycoheptin) have demonstrated channel forming antibiotic properties via interactions with phospholipid-sterol membranes.[5] Unlike the other three, however, roflamycoin is devoid of a sugar appendage.



1, Roflamycoin



2, Amphotericin B

The stereochemistry of the eleven chiral centers in 1 is presently unknown. An all-syn relationship between the polyhydroxyl section has been assumed by analogy to 2,[6] as well as from biosynthetic proposals.[7] Elegant structural assignments on lienomycin by Nakanishi,[8] and for the mycoticins by Schreiber[9] have shown that alternative arrays do indeed occur, while more recent work on the C-1 to C-10 portion of nystatin A_1 by Beau[10] concluded than the all-syn configuration prevails for this section of the molecule. The implication here is that

no apparent common denominator exists among these polyacetate/polypropionate-derived macrolides, and that each one of interest may well require individual assessment. Our prospects for related chemical/spectroscopic experiments on natural 1 are unfortunately not encouraging.[11] Nonetheless, in pursuit of synthetic roflamycoin, or at least what would constitute the all-syn polyol form of 1 should the assumption of all syn stereochemistry prove valid in this case, we now describe the preparation of the C-12 to C-35 segment of 1 in suitably protected, optically pure form.

The goal of attaching readily obtained[6] fragments of 1 together was anticipated using three dithiane units corresponding to carbons 17, 25, and 33, these locations chosen due to symmetry features in roflamycoin. With homochiral precursors 3 and 4 available from prior efforts,[6] initial construction of the C-33, C-34 bond was pursued following conversion of 4 to 5 in a 2-pot procedure. Metalation of 3 required both n-BuLi and TMEDA at 0° for 2.5 h (0.23 M) along with DMPU (3 equiv)[12] to assist in the alkylation with 5 (1.25 equiv) to afford 6.[13] Protection of the free hydroxyl at C-31 as the SEM ether 7[14] proceeded smoothly at room temperature in CH_2Cl_2 provided that n-Bu_4NI (1.1 equiv) was present. Reductive removal of the dithiane moiety with Raney nickel was extremely problematic under typical conditions.[15] Prior debenzylation made little difference. Ultimately, the critical parameter turned out to be the solvent, as switching to THF (room temp. → reflux) lead to reduction of both the dithiane and benzyl ether groups giving 8 quantitatively. Conversion of 8 to coupling partner 9 then followed the usual protocols.

Introduction of C-25 via lithiodithiane[16] was surprisingly inefficient. Isolation of olefinic by-products pointed to competitive SET processes.[17] Use of Seebach's[18] distannylated analog 10 (1.25 equiv) not only lead to alkylated product 11 in high yield, but also facilitated the subsequent re-metalation, which likewise underwent coupling with epoxide 5 (1.25 equiv) to arrive at the C-18 to C-35 portion 12. Control of stereochemistry at C-25 was realized, after dithiane hydrolysis,[19] by virtue of the Merck modification[20] of Narasaka's procedure[21] for syn-1,3-diol formation. A conservative ratio of > 25:1 syn-13:anti-13 was determined from HPLC analyses[22] with samples obtained from stereorandom reduction with $NaBH_4$.

Diol 13 was next transformed to iodide 14 by the straightforward series: a) acetonide formation; b) debenzylation; c) tosylation; d) iodide displacement, in an overall yield of 81%. Coupling of 14 with the lithio dianion of 16 (2 equiv), itself prepared from epoxide 15[6] as shown, proceeded remarkably well (93%) to give 17, thus completing construction of the desired all syn polyol array.[23] Formation of the iodide 19 via 18 as before sets the stage for the beginning phase of polyene insertion prior to cyclization.

In summary, the lynchpinning of three homochiral building blocks (i.e., 3, 5, and 16) to arrive at the polyhydroxylated portion of roflamycoin has been accomplished. Construction of the requisite polyene, attachment to 18, and macrolactonization are presently under investigation.

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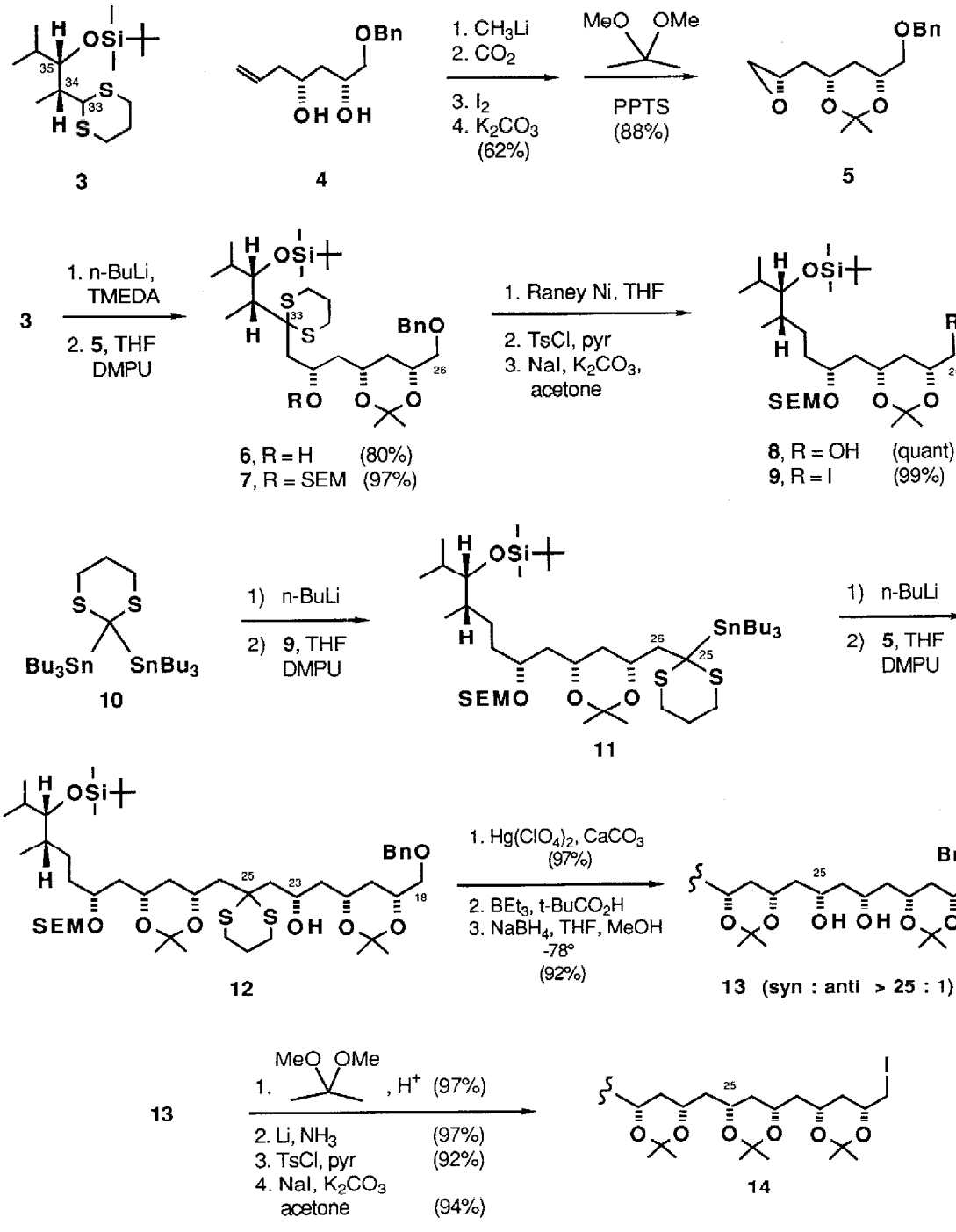
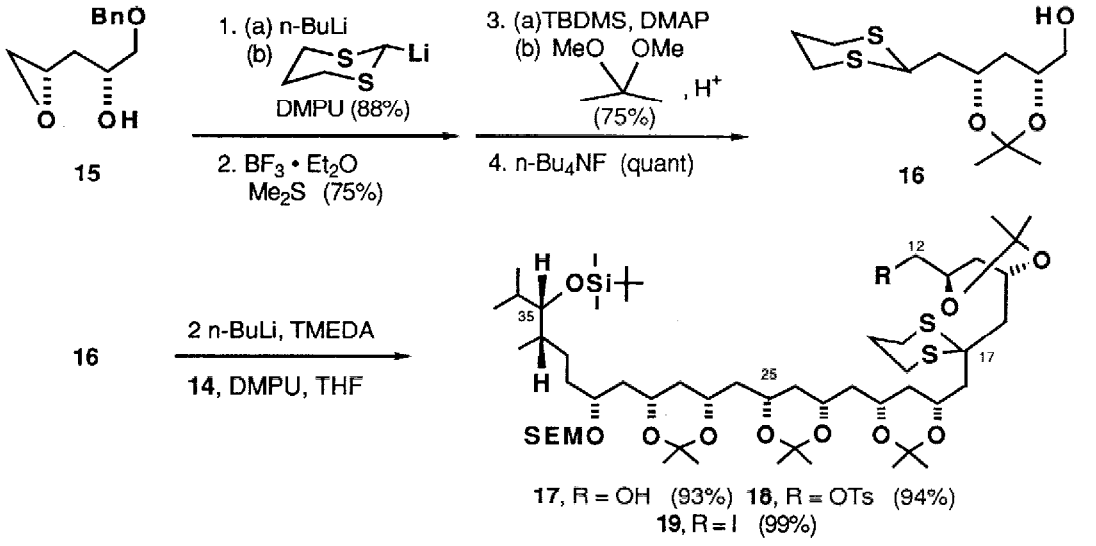

3
4
1. CH3Li
2. CO2
3. I2
4. K2CO3
(62%)
MeO OMe
PPTS
(88%)
5
1. n-BuLi,
TMEDA
2. 5, THF
DMPU
6, R = H (80%)
7, R = SEM (97%)
1. Raney Ni, THF
2. TsCl, pyr
3. NaI, K2CO3,
acetone
8, R = OH (quant)
9, R = I (99%)
10
1) n-BuLi
2) 9, THF
DMPU
11
1) n-BuLi
2) 5, THF
DMPU
12
1. Hg(ClO4)2, CaCO3
(97%)
2. BEt3, t-BuCO2H
3. NaBH4, THF, MeOH
-78°
(92%)
13 (syn : anti > 25 : 1)
13
1. , H+ (97%)
2. Li, NH3 (97%)
3. TsCl, pyr (92%)
4. NaI, K2CO3
acetone (94%)
14



References and Notes

1. A.P. Sloan Fellow, 1984-1988; Dreyfus Teacher-Scholar, 1984-1989.
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3. President's Undergraduate Fellow, 1987-1988.
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22. Analyses were performed on a Perkin-Elmer Series 4 HPLC with a DuPont Zorbex Sil (4.6mm x 25cm) column (hexanes/EtOAc, 7:3) at 2 mL/min [R_t = 6.85 (major) and 8.55 (minor) min].
23. All intermediates gave satisfactory IR, NMR, MS, and where possible, HRMS data. Combustion analyses were successfully (±0.3%) performed on 7, 12, 13 (acetonide) and 17 by Spang Microanalytical Labs.

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