Tetrahedron Letters,Vol.27,No.47,pp 5691-5694,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

A Synthetic Approach to Polyene Macrolides: Synthesis of the Building Blocks

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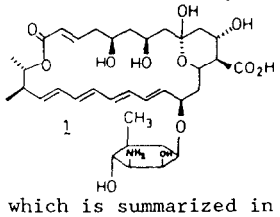
Summary: The two building blocks required to construct the 26-membered ring skeleton of tetrin-A have been synthesized.

The polyene macrolides are a major target of synthetic efforts due to their clinical utility in the treatment of local and systemic mycoses and their unusual structural features which consist of a highly polyunsaturated fragment imbedded into a functionalized macrolactone.[1] We initiated our studies directed toward the synthesis of tetrin A (1)[2,3] and chose as our initial target the polyene macrolide (2) to develop the basic methodology. The sensitivity of the polyene led us to



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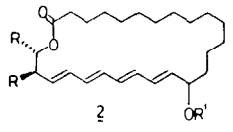
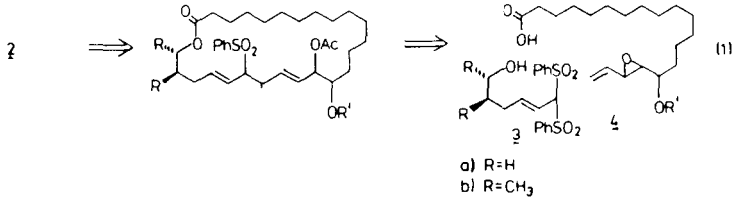


2
a) R=H
b) R=CH_3

develop a strategy, which is summarized in eq. 1, whereby this functionality would be introduced as late in the sequence as possible. To explore this strategy, we required the synthesis of the alcohols 3a and/or 3b, the latter being the exact

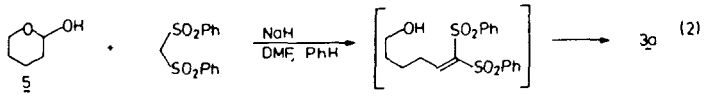


(1)

3
a) R=H
b) R=CH_3

fragment required for tetrin A, and the acid 4. In this letter, we record the syntheses of these building blocks.

The preparation of the allylic bis-sulfone 3a takes advantage of the fact that the equilibrium between a vinylidene bis-sulfone and an allylic bis-sulfone lies

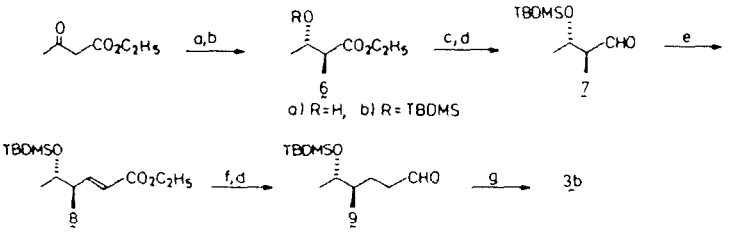


(2)

5

essentially completely (>99%) towards the latter. Thus, alcohol 3a is available in a single operation from the lactol 5 as shown in eq. 2.[4] In synthesizing 3b, we concentrated on a asymmetric synthesis since, in our construction of the natural product itself, an enantiomerically pure alcohol is required. While pulegone served as a readily available enantiomerically pure starting material,[5] a more satisfactory route takes advantage of the known Baker's yeast reduction of ethyl acetoacetate followed by methylation as outlined in Scheme 1.[6,7]

Scheme 1. An Asymmetric Synthesis of Alcohol 3b.

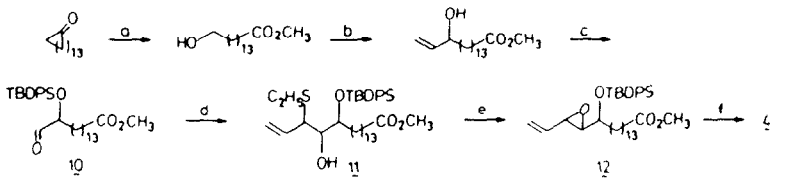


a) See ref. 7,8 b) TBDMS-Cl, imidazole, DMAP, DMF, 91% c) $LiBH_4$, THF, 77% d) DMSO, $(COCl)_2$, $(C_2H_5)_3N$, CH_2Cl_2 e) $(C_2H_5O)_2P(O)CH_2CO_2C_2H_5$, LiCl, DBU, CH_3CN, 90% over two steps f) Li, NH_3, t-C_4H_9OH, THF, 82% g) $(PhSO_2)_2CH_2$, NaH, DMF, PhH, 96% then HOAc, H_2O, THF

Diastereo- and enantiomerically pure (>95%) ester 6 could not be efficiently reduced directly to the aldehyde and thus required the two step procedure as shown. The oxidation of the alcohol to the aldehyde by either PCC or Swern conditions showed no detectable epimerization. Olefination of 7 proceeded by using either $Ph_3PCHCO_2C_2H_5$ or the Emmons-Wadsworth-Horner reagent, with the latter preferred. Only the E isomer 8 was detected. Simultaneous reduction of the double bond and the ester occurred using lithium in liquid ammonia. Swern oxidation of 8 set the stage for the bis-sulfone condensation as outlined in eq. 2, whereupon subsequent hydrolysis completed the synthesis of enantiomerically pure 3b, $[\alpha]_D^{25}o$ + 3.6° (c 0.90, $CHCl_3$).

Scheme 2 details the synthesis of the acid building block 4 (R'=TBDPS). The preparation of the α-siloxyaldehyde 10 from commercially available cyclopentadecanone proceeded straightforwardly as outlined.[10] Three routes to generate 4 were explored. The simplest, the direct condensation with allyltetrahydrothiophanium chloride under

Scheme 2. Synthesis of Carboxylic Acid 4



a) i. MCPBA, $CHCl_3$, reflux ii. KOH, H_2O, CH_3OH iii. TMS-Cl, CH_3OH, ether, hexane, 70% overall

b) i. $(COCl)_2$, DMSO, $(C_2H_5)_3N$, CH_2Cl_2, 97% ii. CH_2=$CHMgBr$, THF, 0^o

c) i. TBDPS-Cl, imidazole, DMF ii. O_3, CH_2Cl_2 then $(CH_3)_2S$, 71% from b. i

d) CH_2=$CHCH_2SC_2H_5$, t-C_4H_9Li, $Ti(OC_3H_7\text{-}i)_4$, THF, 90%

e) i. $CH_3OSO_2CF_3$, 2,6-(t-$C_4H_9)_2C_5H_3N_2$, 0^o ii. Cs_2CO_3, PhH, reflux 72%

phase transfer conditions,[9] failed to react at all. A five step sequence accomplished this task in quite satisfactory yield but a shorter sequence was desired. Using the method of Yamamoto,[11] a chemo- and regioselective addition of the anion derived from allylethyl sulfide gave a diastereomeric mixture of adducts 11. S-Alkylation occurred using methyl trifluoromethanesulfonate in the presence of 2,6-di-t-butylpyridine. Direct subjection of the crude hydroxysulfonium salt to various bases including aqueous sodium hydroxide, sodium hydride, and potassium carbonate in the presence or absence of 18-crown-6 gave low yields of the desired vinyl epoxide 12. On the other hand, use of cesium carbonate in refluxing benzene provided 12 in yields >70%. Simple base hydrolysis completed the sequence.

The routes outlined provide ready access to the necessary building blocks[12] for the polyene macrolide.

Acknowledgment: We wish to thank the National Institutes of Health, General Medical Sciences, for their generous support of our programs. We thank the DFG for a stipend for PM.

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(Received in USA 7 August 1986)