Tetrahedron Letters,Vol.26,No.40,pp 4891-4894,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

POLYENE SYNTHESIS: A COMPARATIVE STUDY

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ABSTRACT: As part of an effort to synthesize the polyene macrolide antibiotics, a comparison of several methods of polyene synthesis has been carried out with the finding that superior results were obtained using the Wollenberg vinyl ether method.

The polyene macrolide antibiotics are a structurally complex class of compounds that possess potent fungicidal activity which has been exploited in the treatment of human mycoses.[1] Common to all members of this class is a macrocyclic structure featuring clearly defined hydrophilic (polyol) and hydrophobic (polyene) regions, as illustrated by amphotericin B (Figure 1.). As part of an effort to develop a general synthetic strategy to the

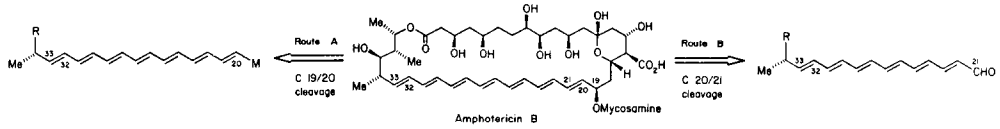
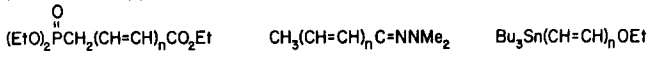


Figure 1.

polyene macrolide antibiotics,[2] we required a method of preparing polyenes that was mild enough to tolerate allylic asymmetry and sensitive functionality, as well as sufficiently flexible to allow preparation of chromophores ranging from four to seven double bonds to accommodate the variation found within this class of compounds. Following a preliminary survey of available olefination methods, we focused our attention on reagents 1 - 3 as applied to the synthetic approaches outlined in Figure 1.



1 2 3

Route A. The strategy depicted by route A was envisioned as a convergent insertion of the intact polyene unit through an olefination reaction to form the C32-C33 double bond followed by the condensation of a vinyl organometallic species with an aldehyde to result in the C19-C20 bond. With this in mind, stannyl phosphonium salt 4 was targeted to implement this strategy (Figure 2.). Unfortunately, all attempts to execute this plan were frustrated by the instability of intermediates en route to 4. Representative of the problems encountered, condensation of the anion of phosphonate 1 (n=1)[3] with stannyl acrolein 5[4] led to the desired trienyl ester 6 contaminated with substantial amounts of ethyl benzoate (Figure 2.). Following chromatographic purification, compound 6 was observed to quantitatively convert

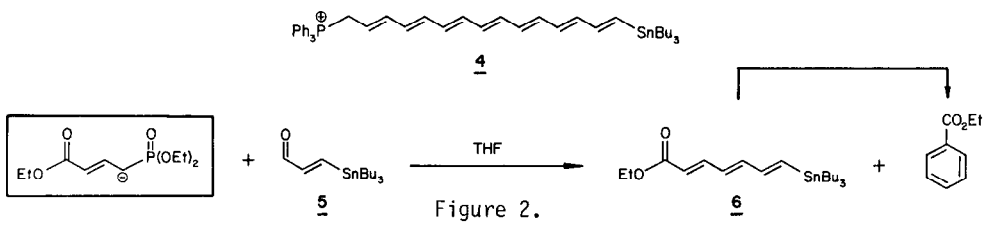


Figure 2.

to ethyl benzoate upon storing at room temperature. This transformation probably occurs through electrocyclic ring closure followed by aromatization via loss of nBu_3SnH.[5]

Route B. In an effort to minimize problems due to the handling of unstable intermediates, a more linear approach was adopted in the study of this route. Given the preliminary results of Brooks and Kellogg using a reagent of type 1 (n=1),[2b] we chose to explore a Wittig-Horner sequence to the desired polyene aldehyde. To increase the overall efficiency of the route, we sought to reduce the number of iterations required through the use of phosphonate 1 (n=2).[3] A model olefination sequence was carried out using isobutyraldehyde in Figure 3. Although the desired hexanenyl species could be obtained, the overall yield was disappointingly low.

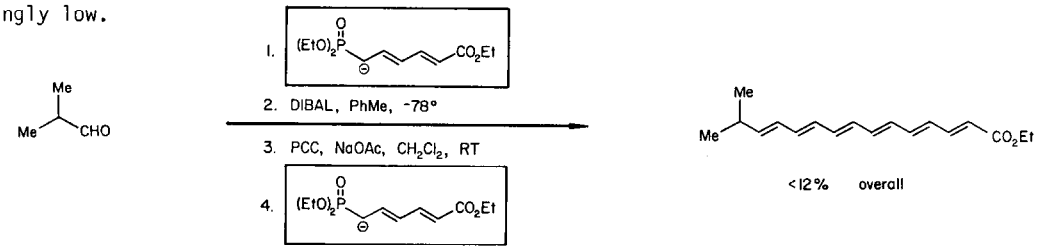


Figure 3.

In an effort to streamline this sequence through a reduction in the number of required manipulations, we examined reagents which would afford unsaturated carbonyl compounds in the aldehyde oxidation state directly. With this in mind, the utility of metalated N,N-dimethylhydrazones as introduced by Corey and co-workers was investigated.[6] Using isobutyraldehyde as a model, the lithium anion of the reagent derived from sorbaldehyde (2,n=2) smoothly condensed to afford 7 (Figure 4.). Unfortunately, numerous attempts to effect the conversion

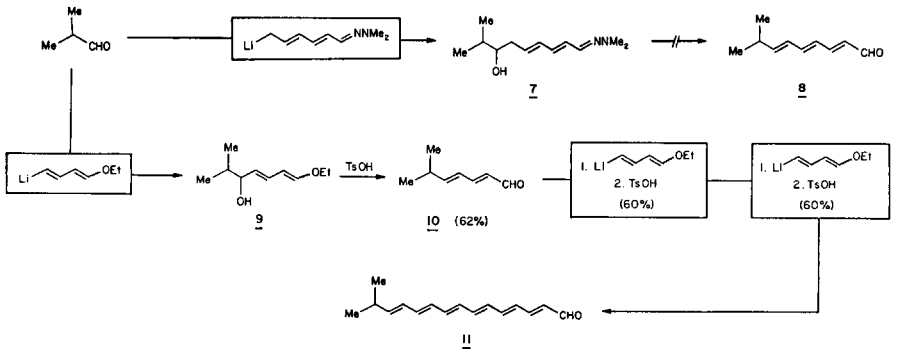


Figure 4.

of 7 to trienal 8 resulted in the formation of complex mixtures of products.[7]

These disappointing results led us to turn our attention to a reagent introduced by Wollenberg (3,n=2), which has been shown to effect similar homologations.[8] To date, this reagent has only rarely been applied to structurally complex carbonyl compounds and has seen limited use in the preparation of aldehydes possessing highly extended conjugation.[9] The lithium salt derived from 3(n=2) via transmetalation[8] cleanly condensed with isobutyraldehyde (THF,-78°C) to give 9 as an oil stable to chromatographic purification (SiO_2). The desired dienal 10 was obtained as a single isomer following exposure to TsOH (cat.) in aqueous THF at room temperature.[10] Repetition of this sequence twice conveniently produced a single hexaenyl aldehyde 11 in respectable overall yield. Adding to the attractiveness of this approach is the ready availability of the reagent 2(2=1),[11] thus allowing the preparation of polyolefins possessing an odd number of conjugated double bonds.

To demonstrate the viability of this strategy for polyene macrolide synthesis, we applied this olefination sequence to the protected propionate region of amphotericin B(12[12], Figure 5.). As indicated, the desired key intermediate 13 was obtained in very good overall yield as a single isomer (^1H and ^{13}C NMR),[13] provided the Corey modification for unmasking the dienal is applied to the sensitive adduct in the first iteration.[9a,b] As a result, we now have in hand a reliable route to produce quantities of 13 suitable for completion of the total synthesis of amphotericin B.[14]

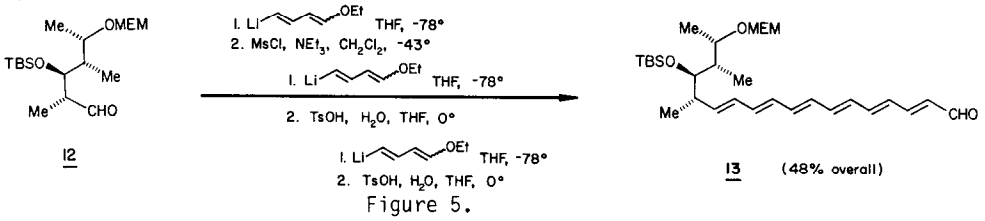


Figure 5.

In this comparative study on the relative merits of methods of preparing unbranched polyolefinic aldehydes, we have found an iterative strategy based upon the Wollenberg vinyl ether methodology to be the most promising in terms of generality and ease of operation. The incorporation of this strategy in the synthesis of the polyene macrolide antibiotics, as well as other highly unsaturated natural products, will be reported in due course.

Acknowledgement is made to the National Institutes of Health for their generous support of this work.

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12. Full experimental details will be reported shortly.
13. The all trans geometry was assigned to 13 based upon the magnitude of the J values for the completely resolved vinylic protons in the dienyl and tetraenyl precursors (J's≈9-16 Hz) and the partially resolved spectrum for 13[12]: ^1H NMR ($CDCl_3$, 360 MHz) δ 0.02 (s,3H), 0.05 (s,3H), 0.85 (d,J=7.0 Hz,3H), 0.92 (s,9H), 1.04 (d,J=6.9 Hz,3H), 1.08 (d,J=6.2 Hz, 3H), 1.90 (m,1H), 2.46 (m,1H), 3.40 (s,3H), 3.50-3.60 (m,3H), 3.69 (m,2H), 3.90 (m, 1H), 4.70 (d,J=7.5 Hz, 1H), 4.75 (d,J=7.5 Hz,1H), 5.82 (dd,J=7.9, 15.5 Hz, 1H), 6.05-6.60 (m,9H), 6.72 (dd,J=10.0, 14.3 Hz, 1H), 7.14 (dd, J=11.3, 15.1 Hz, 1H), 9.56 (d, J=7.9 Hz, 1H).
14. Compound 13 may serve as a substrate for a mild olefination procedure recently reported by Masamune, Rousch and co-workers.[2k]

(Received in USA 1 July 1985)