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A Synthetic Approach to Polyene Macrolides.
Macrolide and Polyene Generation

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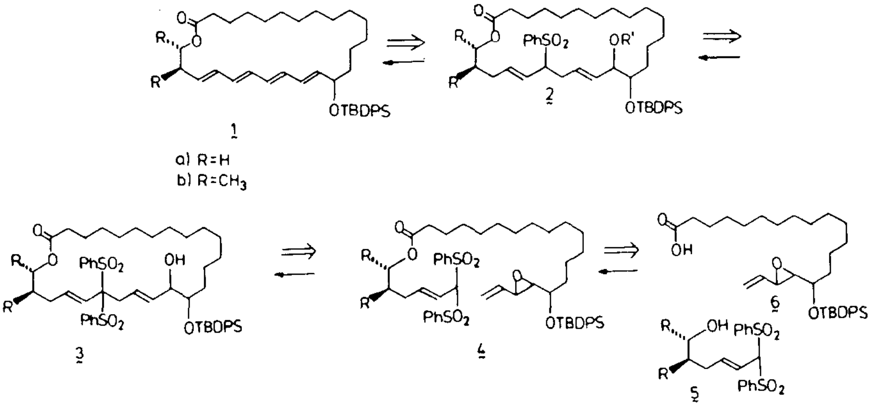
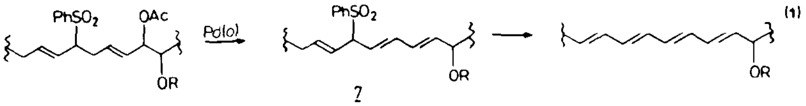
Summary: The 26-membered ring skeleton of tetrin-A has been synthesized using palladium based macrolactonization and elimination reactions.

Facilitation of macrocyclization[1] and elimination[2] reactions by palladium catalysts suggested such reactions would apply for the synthesis of the polyene macrolides. Using the tetraene macrolide 1 as a model for tetrin A, a synthetic strategy as summarized in the Scheme was envisioned. A key element in this route is a proposed sequential elimination of an allylic carboxylate and an allylic sulfone[3] which would be envisioned to proceed through the triene 7 (eq. 1) in which the alkoxy group would direct the deprotonation in the intermediate π-allylpalladium complexes

Scheme. Retrosynthetic Analysis and Synthesis of Tetrin A Model





away from itself.[4] The juxtaposition of functionality for the bis-elimination of the tetraene precursor 2 should derive from macrocyclization via isomerization using a vinyl epoxide[1b,5] in which the bis-sulfone is introduced as the pro-nucleophile as in 4 to adjust its pH in order to facilitate proton transfer in the intermediate π-allylpalladium complex of the cyclization reaction. In this letter, we report the success of palladium templates in realizing both of these goals.

The acyclic precursor 4 arises by esterification of the alcohol 5 with the acid 6 using DCC and DMAP[6] (>70%). Concentrations >1M were necessary; lower concentrations dramatically reduced the yields. Using our earlier derived homogeneous catalyst system for macrocyclizations of 5 mol% $(Ph_3P)_4Pd$ with added dppe,[7] a 10% yield of macrolide along with a complex product mixture resulted. Changing the second ligand to dppp and dppb gave some improvements. Using $Pd(OAc)_2$ and a reducing agent (either n-butyllithium or DIBAL-H) with dppp and dppb as ligands gave 30% and 43% yields respectively of the macrolide. In other work, we noted that improved yields sometimes resulted by using better π-acceptor ligands. Tri-isopropylphosphite represents one such ligand[8] which has the added advantage of also serving as a reducing agent for Pd(+2). Indeed, using this new system for macrocyclizations, a 70% yield of the 26-membered ring resulted. Increasing the scale of reaction led to a 92% isolated yield! Spectral data and combustion analysis confirm the structure. The presence of diastereomeric mixtures, since 6a and 6b were employed as diastereomeric mixtures, induced us to remove one of the stereogenic centers to simplify the nmr spectra (eq. 2). The vinyl region of these spectra now simplified [8: (R=H), δ 6.79 (dt, J=15.8, 5.5 Hz), 6.62 (d, J=15.8 Hz), 5.86 (dt, J=16.0, 6.2 Hz), 5.69 (d, J=16.0 Hz); 8: (R=CH_3), δ 6.72 (m), 6.57 (d, J=15.8 Hz), 5.86 (m), 5.69 (d, J=16.0 hz)] and establish the E, E nature of both double bonds in both cases.

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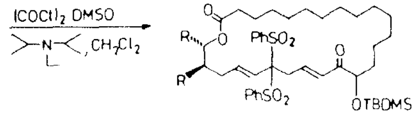

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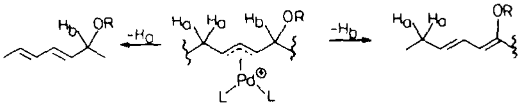
(2)

Desulfonylation and acylation of the hydroxyl group are now required to set the functionality for elimination. Attempts to desulfonylate 3 led to substantial destruction. On the other hand, initial acetylation of 3 (Ac_2O, DMAP, C_5H_5N, rt, 74-85%) permitted desulfonylation (6%Na(Hg), 3/1 THF/CH_3OH, HOAc, 0°, 78-80%) to proceed to the requisite elimination substrates 2 (R=H and CH_3).

The key double elimination of the relatively poor leaving groups, sulfone and acetoxy, also was designed to take advantage of palladium (0) activation. Prior work established that allylic acetates are much better leaving groups than allylic sulfones--a fact that suggests 7 (eq. 1) should be an intermediate. The double activation of the sulfone in 7[4] should facilitate its elimination relative to the simple allyl sulfone. In the event, in situ generation of a Pd(0) catalyst [Pd(OAc)$_2$, dppb, n-C_4H_9Li, $PhCH_3$] followed by addition of triethylamine and substrate led, after reflux for 4.5 h to tetraenes 1 (50-60% yields). For 1 ($R=CH_3$), laser desorption mass spectroscopy and combustion analysis established the elemental composition. The proton nmr spectra establishes the presence of the eight olefinic hydrogens. The all E configuration derives from comparison of the UV-spectrum [(C_2H_5OH). 279 nm (64, 530), 291 nm (65, 620), 307 nm (44, 150), 321 nm (40, 220)] to that of tetrin A.[9] Furthermore, subjection of the polyene to iodine or palladium salts, catalysts known to equilibrate polyenes to the thermodynamically more stable all E isomer,[10] have no effect on the product.

The successful realization of the synthesis of the polyene macrolide 1 offers a new strategy in which formation of the macrocycle sets up the system for polyene construction. The ability of palladium catalysts to activate poor leaving groups toward elimination provides sufficiently mild conditions that a sensitive polyene can be created. It is interesting to note the directive effect of the oxygen functionality on the regioselectivity of the elimination (eq. 3). While statistics favor the observed direction, an enhanced kinetic acidity of H_a relative to H_b arising from the differential activation by the unsymmetrical π-allylpalladium species and/or the direct effect of the oxygen substituent would also seem likely to play a role. The efficacy of the triisopropyl phosphite ligand in the macrocyclization is also noteworthy. While the notion was to enhance the electron deficiency on the allyl fragment with such π-acceptor ligands to increase the rate of nucleophilic attack with charge neutralization, a firm explanation must await more detailed studies of the by-products under the alternative conditions. Nevertheless, the practical consequence of the excellent yield in forming a 26-membered ring (up to 92%) suggest such ligands may be more generally important.



(3)

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