Taxamycin Studies: $CrCl_2/NiCl_2$-Mediated Cyclizations and Unusual SeO_2 Oxidations

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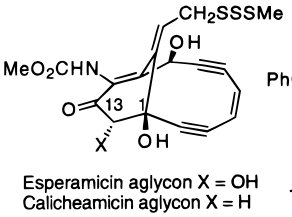
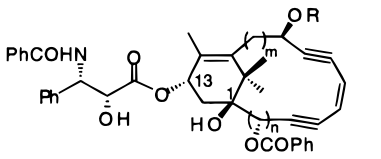
Received July 17, 1997 (Revised Manuscript Received September 10, 1997)

The enediyne family of anticancer antibiotics continues to be a topic of considerable current interest. This is a consequence of their novel mechanism of DNA cleavage involving cycloaromatization to benzyne diradicals and the synthetic challenge presented by the natural products themselves. This has also stimulated the design and synthesis of simpler analogues.[1] Hybrid structures that mimic esperamicin[2] and calicheamicin[3] include incorporation of part of the taxane framework (taxamycins),[4] the steroid nucleus (estramycins),[5] β-lactams (lactendiynes),[6] and enediynes linked to diethylstilbestrol.[7] In a continuation of our studies of the taxamycins **1**, we wish to report a more direct route to the taxamycin-12 compound **15** (eight fewer steps), the synthesis of the taxamycin-11 compound **16**, a study of $CrCl_2/NiCl_2$-mediated cyclizations, and an unusual SeO_2 oxidation of the α-acetylenic ethers **17** *via* an allene intermediate that may provide an alternative cycloaromatization route in appropriate systems.



Esperamicin aglycon X = OH
Calicheamicin aglycon X = H



1 Taxamycins-10, 11, 12, n = 0, 1, m = 0, 1

Aldehydes **2** and **4**[8] and enediyne **3** were prepared as previously described.[4] Condensation of the aldehyde **2** with the lithium acetylide derived from **3** afforded an 83% yield of the secondary alcohol diastereomer **5** (ratio 15:1) consistent with related systems[4,9] (Scheme 1). Subsequent steps provided the desired iodoacetylene **10** and oxidation with Dess−Martin periodinane afforded the aldehyde **13** (R = I) in 92% yield. Commencing with the related aldehyde **4**, a parallel condensation with the lithium salt derived from **3** gave the alcohol **7** as the major diastereomer in 86% yield (ratio 4:1) and further manipulation generated the iodo aldehyde **14** (R = I).

Several methods have been examined for the intramolecular ring closure of medium-sized cyclic enediynes, particularly for the 10-membered rings that mimic calicheamicin and esperamicin. These include ring contraction of a cyclic ether by [2,3]-Wittig rearrangement,[10] Nicholas-type cyclization of η^2-dicobalthexacarbonyl complexed propargylic cations with Lewis acid,[11] acetylenic anion−aldehyde condensations,[12] and fluoride-induced desilylation−condensation.[13] Our preferred method is the extension of the chromium(II)-mediated Nozaki−Kishi coupling[14] to intramolecular cyclizations of iodoacetylenes with aldehydes developed by Crevisy and Beau.[15]

In order to establish a reliable protocol, a number of experiments were conducted (table in the Supporting Information). Reactions f and l in Scheme 1 in THF,[16] using the $CrCl_2$(THF) complex,[17,18] represent the best cases. (DMF, useful for intermolecular examples, etc., failed.) The quantity of $NiCl_2$ was determined experimentally as the literature indicated that for some 10-membered ring systems nickel chloride was not required.[16] In other cases,[19] low yields were obtained with catalytic quantities and stoichiometric amounts were better.

Base-induced cyclization of **14** (R = H) with 2 equiv of potassium hexamethyldisilazide at −78 °C also provided the cyclized material **16** in variable yields of 15−25%.

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(17) Attempts to generate $CrCl_2$ in situ from $CrCl_3$ with $LiAlH_4$ and a catalytic amount of $NiCl_2$ resulted in low yields (5−10%) of cyclized material. SmI_2 coupling was also unsuccessful.

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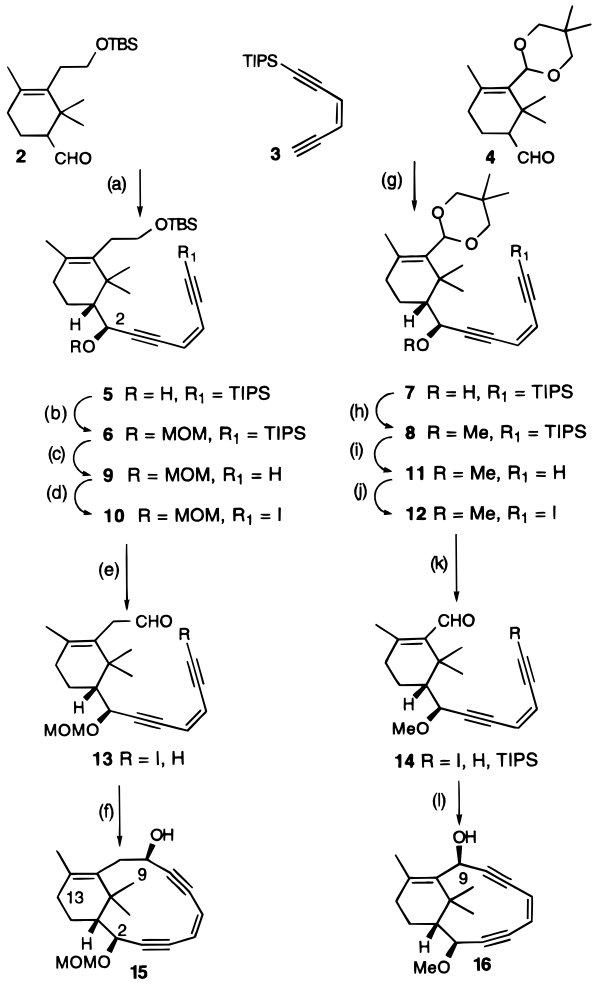
S0022-3263(97)01305-4 CCC: $14.00

Scheme 1[a]

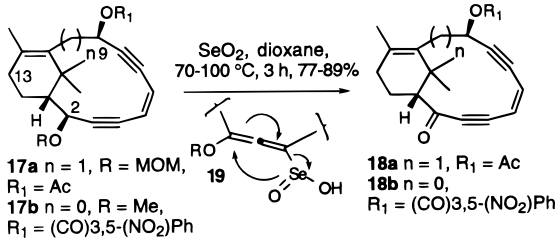


[a] Reagents: (a) *n*-BuLi, THF, −78 to +21 °C, 15 h, 83% (15:1); (b) MOMCl, (*i*-Pr)$_2$NEt, CH_2Cl_2, 0−21 °C, 15 h, 85%; (c) TBAF, THF, −78 to +21 °C, 3 h, 99%; (d) I_2, morpholine, C_6H_6, 60−70 °C, 3 h, 83%; (e) Dess−Martin periodinane, CH_2Cl_2, 21 °C, 30 min, 92%; (f) $CrCl_2$ (THF) (6 equiv), $NiCl_2$ (1.6 equiv), THF, 30 min, 40%; (g) *n*-BuLi, −78 to +21 °C, 15 h, 86% (4:1); (h) NaH, MeI, THF, 0−21 °C, 5 h, 89%; (i) TBAF, THF, −78 to +21 °C, 1 h, 91%; (j) I_2 morpholine, C_6H_6, 60−70 °C, 3 h, 75%l (k) 3:1 THF/4% aqueous HCl, 3 h, 91%; (l) $CrCl_2$(THF) (8 equivf), $NiCl_2$ (0.06 equiv), THF, 21 °C, 45 min, 37%.

Anhydrous fluoride sources such as tetrabutylammonium difluorotriphenylstannate[20] caused desilylation and no cyclization of **14** (R = TIPS). The new secondary alcohols in **15** and **16** were syn relative to the C_2 ether groups, a stereochemical result that was consistent with related intramolecular cases in which the same geometric preference was observed for closure to 10-membered rings.[12d]

It was anticipated, by analogy with taxoid systems, that allylic oxidation would introduce the desired oxygen at C_{13} (taxane numbering)[9c,21] for attachment of the appropriate side chain. However, oxidants such as CrO_3 or PCC resulted only in recovery of starting material.

Scheme 2



Treatment of the acetate **17a** with selenium dioxide in dioxane at 60−70 °C afforded exclusively the C_2 ketone **18a** in 89% yield. The strain and lack of orbital overlap in this ring system is reflected in the carbonyl IR band at 1740 cm^{-1}. Initially it appeared that the acidity of the reaction had resulted in hydrolysis of the MOM ether followed by oxidation of the resulting alcohol. However, this was not the case, as a parallel oxidation of the methyl ether **17b** with excess SeO_2 also gave the corresponding ketone **18b** in a yield of 77% (NMR COSY). Consistent with the accepted mechanism of selenium dioxide oxidations,[22] these reactions likely proceeded via an ene reaction to form the allene intermediate **19** followed by sigmatropic rearrangement to an acetal and hydrolysis to the ketones upon aqueous workup. The double bond in the A ring is hindered by both the enediyne bridge on one face and by the sterically demanding *gem* dimethyl group on the other. These features apparently inhibit the approach of the SeO_2, and thus, the rearrangement pathway is observed. In principle, the generation of the allene should facilitate the cycloaromatization (Meyers cyclization), but this was not observed due to the presence of the bridgehead olefin. However, this oxidation sequence may have potential as a trigger mechanism in other cases.

In summary, general methods have been developed for the synthesis of these challenging bridged enediyne systems using chromium/nickel-mediated coupling. These cyclizations are difficult due to the strained rings produced in addition to the steric hindrance provided by the geminal methyl groups. Investigations in progress have demonstrated that in less demanding cases the yields are improved under the conditions developed above. These results will be reported in due course.

Acknowledgment. We are grateful to the Natural Sciences and Engineering Research Council of Canada and Torcan Chemical Ltd. for financial support of this research, to S. Gambarotta for a gift of the $CrCl_2$(THF) complex, and to S. Woo and P. D. Wilson and the reviewers for helpful advice. C.W.H. thanks NSERC for a Postgraduate Scholarship, and S.P. thanks the Association Française pour la Recherche for a Postdoctoral Fellowship.

Supporting Information Available: Experimental procedures and spectral data (24 pages).

JO9713058

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