Taxamycins: A New Enediyne Family Constructed from Versatile Disilyl-Substituted Building Blocks

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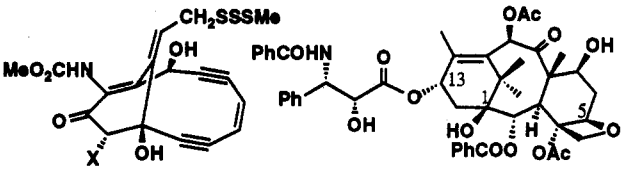
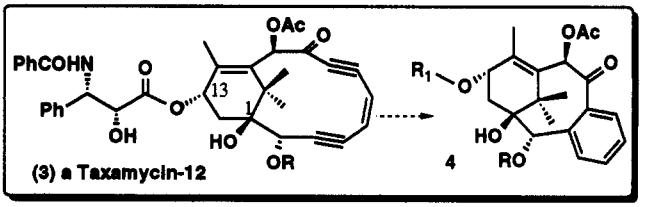
Summary: The Pd(0)-based synthesis of two disilyl synthons [(*Z*)-1-(trimethylsilyl)-6-(*tert*-butyldiphenylsilyl)hex-3-ene-1,5-diyne (**7**) and (*Z*)-1-(trimethylsilyl)-6-(triisopropylsilyl)hex-3-ene-1,5-diyne (**8**)], selective removal of the trimethylsilyl group (K_2CO_3, MeOH) to afford **13** and **14**, and the construction of the taxamycin-12 compound **25** (16,17,18-trimethyl-2-(monomethyloxy)-9-hydroxybicyclo[9.3.1]pentadec-5-ene-3,7-diyne) by intramolecular Nozaki condensation of the iodoalkyne **24** (1,3,3-trimethyl-2-(2-oxoethyl)-4-((*Z*)-1-(monomethyloxy)-7-iodohept-4-ene-3,6-diynyl)cyclohexene) is described.

The enediyne, antitumor antibiotics such as esperamicin A (**1**)[1] and calicheamicin (**2**)[2] have generated widespread interest due to their novel mechanism of DNA cleavage[3] and the synthetic challenge these structures represent. Consequently, considerable effort is being devoted both to the synthesis of the natural products themselves[4,5] and a variety of structural analogues.[6-13] In a similar manner the potent antitumor agent taxol[14] has also stimulated recent synthetic chemistry[15] due to its mode of action and scarcity of supply. It has been established that in certain cases the taxol side chain may be attached to modified nuclei with retention of respectable tubulin activity.[16,17] Consequently, a new family of biologically active agents (taxamycins) may be envisaged. Structure **3** is representative, but many variations are possible depending upon the ring sizes and substitution patterns. These systems hold promise for the rapid construction of aromatic taxanes and related compounds as illustrated by the implicit conversion of **3** into **4**. Several current approaches for the

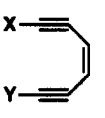


(1) Esperamicin A aglycon X = OH
(2) Calicheamicin aglycon X = H

Taxol



(3) a Taxamycin-12



5 X = Y = H
6 X = Me_3Si, Y = Me_3Sn
7 X = Me_3Si, Y = $^tBuPh_2Si$
8 X = Me_3Si, Y = $^iPr_3Si$

total synthesis of taxol utilize benzenoid intermediates for the preparation of the C ring.[18-20] In addition, lower homologues of **3** may possess interesting therapeutic potential, provided the appropriate side chain and suitable functionality to trigger aromatization in the cell are present. To investigate these possibilities including the synthetic utility of the Bergman cycloaromatization[21] and the factors responsible for biradical formation in this series we desired a versatile enediyne synthon. We wish to report the synthesis of two suitable building blocks, (*Z*)-1-(trimethylsilyl)-6-(*tert*-butyldiphenylsilyl)hex-3-ene-1,5-diyne (**7**) and (*Z*)-1-(trimethylsilyl)-6-(triisopropylsilyl)-hex-3-ene-1,5-diyne (**8**), and the use of **8** for the preparation of **25**, a member of the parent taxamycin-12 ring system (where the number represents the size of the ring containing the enediyne unit).

The use of the dilithio salt derived from **5** to insert the endiyne chromophore has been examined previously with mixed results.[22] Our initial attempts to prepare **6** with different elements (Si and Sn) at the terminal acetylenes were disappointing, but the different rates of base-induced cleavage of silylalkynes, mediated in part by their relative

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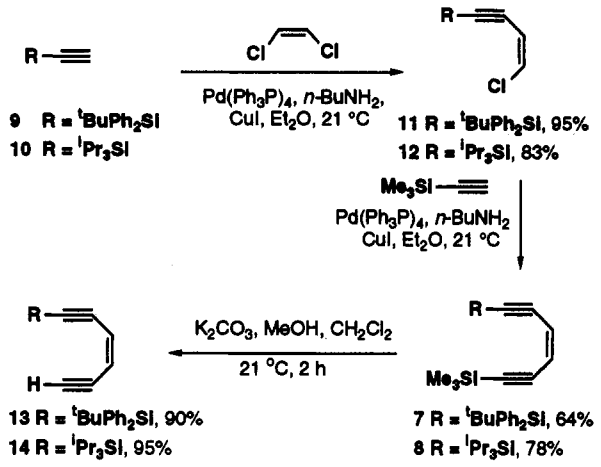
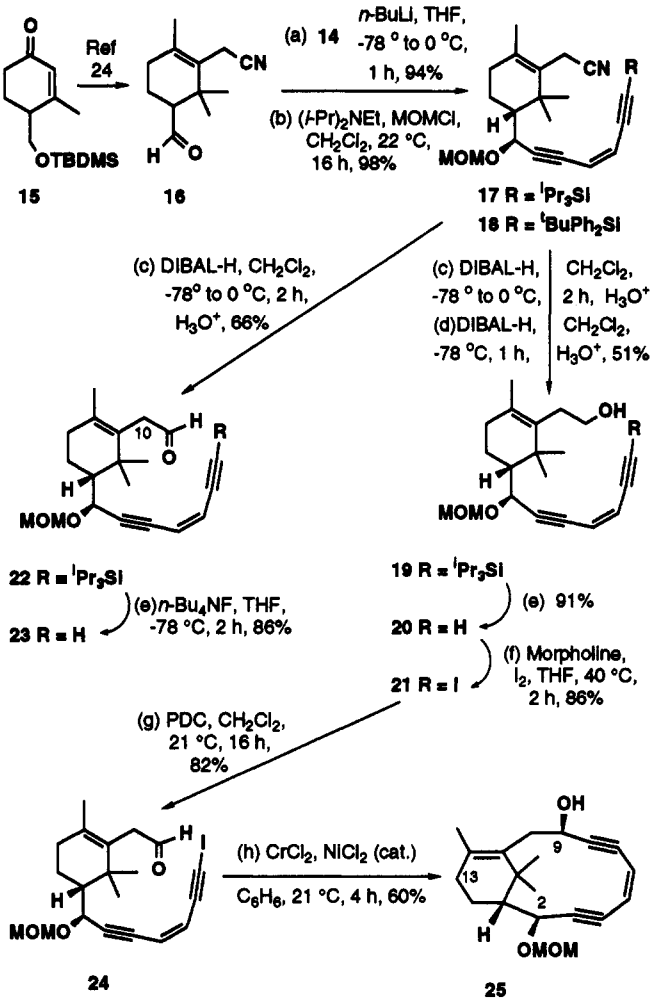
Scheme I. Synthesis of Enediyne Synthons



steric bulk, should allow selective protection and release. [relative rates: Et_3Si (1), Ph_3Si (12), $EtMe_2Si$ (49), Me_3Si (277)].[23] Thus, **7** and **8** were synthesized by repetitive Pd(0)-based couplings followed by removal of the trimethylsilyl group in K_2CO_3–methanol as outlined in Scheme I. The triisopropyl system **14** has proven more useful than **13**, since in some cases, such as the fluoride induced deprotection of **18**, chromatographic separation of the product and the *tert*-butyldiphenylsilyl system was troublesome.

The cyano aldehyde **16** was prepared from cyclohexenone **15** as described recently for the synthesis of the taxane nucleus by an intramolecular Diels–Alder approach.[24] The lithium acetylide derived from **14** was condensed with **16** (Scheme II), and the major diastereomer of the resulting alcohol (4:1, established by X-ray of a related system[24]) protected as the monomethyl ether **17** (98%). Diisobutylaluminum hydride reduction of the nitrile in **17** could be terminated at the aldehyde stage to generate **22** directly or reduced further to the primary alcohol **19**. The fluoride-mediated, concurrent desilation–condensation was examined,[25] in view of the potential difficulty caused by the acidity of the C_{10} hydrogens (taxol numbering) in **23**, relative to the acetylenic hydrogen under basic conditions. Silyl replacement proceeded smoothly with either CsF in THF or tetrabutylammonium fluoride in THF to generate **23**, but no significant cyclization to **25** occurred. Completely anhydrous fluoride sources also suppressed desilation. Unfortunately, neither the use of the corresponding acid chloride under different conditions including Pd(0) nor tin triflate based cyclization of **23** was successful, and attempts to form the dimethoxy acetal with cerium trichloride in order to effect acetal based ring closure also failed. Thus, the $CrCl_2$–$NiCl_2$ based coupling of vinyl triflates and iodides with aldehydes, developed

Scheme II. Synthesis of the Taxamycin-12 Compound 25



OTBDMS = OSi^{t}BuMe$_2$ MOMCl = CH_3OCH_2Cl DIBAL-H = ^{i}BuAlH

by Nozaki and co-workers,[26,27] which has been effective in other enediyne systems, was examined.[11,28] Conversion of the alkyne **20** into the alkynyl iodide **21** was accomplished with morpholine and iodine (86%) and the primary alcohol oxidized to the aldehyde **24** with pyridinium dichromate (82%). The desired ring closure was effected smoothly with this nickel-catalyzed chromium-based procedure to provide the bicyclo[9.3.1]pentadecadienediyne

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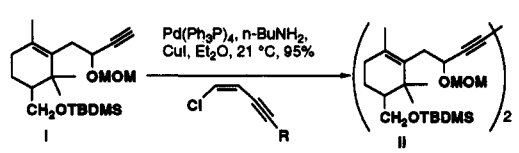
(25) Attempts to build the desired ring system in a "clockwise" fashion from **i** were not successful, instead palladium coupling gave high yields of the dimer **ii** but none of the required enediyne!



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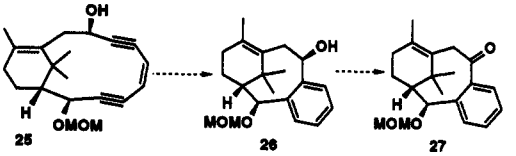
(29) The reviewers have recommended that a comment on the cycloaromatization of **25** be included. The remaining sample of **25** was heated for a total of 4 h (8 × 30 min, sealed tube, toluene, 1,4-cyclohexadiene) in a microwave oven (Lei, B.; Fallis, A. G. *J. Org. Chem.* **1993**, *58*, 2186) in an effort to effect the conversion to **26**. The products were oxidized with pyridinium dichromate to provide ketone **27** for comparison with an authentic sample of **27** prepared by an independent Diels–Alder route.[24] In spite of the aromatic signals (^{1}H NMR) in the δ 7–7.6 region expected for **27**, we have been unable to characterize the material to our satisfaction, and currently the yield is low (3–10%).



system **25** in 60% isolated yield. A single diastereomer was formed. On the basis of molecular models preferential attack from the bottom (*si* face) was anticipated, and thus it seems likey the new secondary alcohol at C_9 is syn relative to the C_2 MOM group.

In conclusion, the directness of this approach to enediyne systems, using the disilyl–enediyne unit **8** followed by an intramolecular Nozaki condensation, should prove beneficial for a variety of synthetic objectives. The importance of aromatic species as key taxol intermediates for total synthesis is well recognized.[15,18-20,24] Thus, cycloaromatization of various taxamycins should facilitate the preparation of useful synthons in a straighforward manner.[29] Future reports will describe conformational studies, molecular mechanics calculations, the cycloaromatization of more highly functionalized skeletons to aromatic taxoids, and the synthesis of ring-contracted taxamycin-10 nuclei that should mimic their esperamicin and calicheamicin relatives.

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Supplementary Material Available: Experimental procedures for the preparation of compounds **7–9**, **11–14**, **17**, and **19–25** including spectral data (26 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.