Pergamon

Tetrahedron Letters 39 (1998) 6139–6142

TETRAHEDRON LETTERS

Taxamycin Studies: Synthesis of Taxoid-Calicheamicin Hybrids

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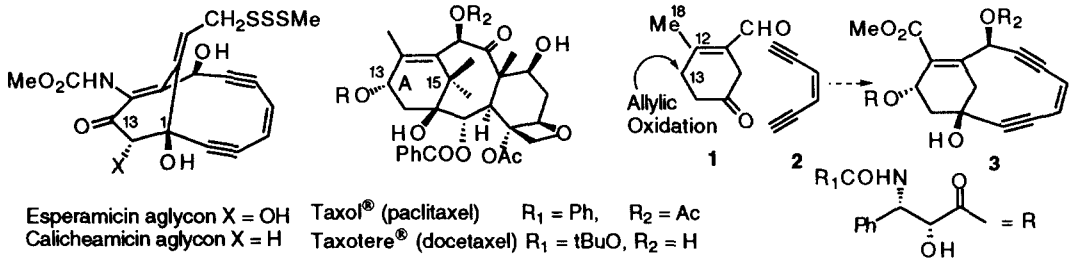
Received 1 May 1998; accepted 11 June 1998

Abstract: The synthesis of the bicyclic enediyne compounds **14-18** is described. The bicyclo[7.3.1]trideca-4,9-dien-2,6-diynes (**21**) are calicheamicin-taxoid mimics, that possess the Taxotere® side chain and an enediyne core. Cyclization of the iodo-aldehyde **13** [$CrCl_2(THF)_2$] afforded the bicyclic alcohol **14** as a single diastereomer (76%) and allylic oxidation (SeO_2) followed by reaction with the oxazolidine intermediate **19**, resolution and hydrolysis provided the taxamycins **21**.

Taxol® and Taxotere® are important drugs for the treatment of ovarian and breast cancer, while esperamicin[1] and calicheamicin[2] are key members of the enediyne family of anticancer antibiotics. The novel mechanism of action of these natural products have stimulated the synthesis of simpler less toxic analogues and mimics[3,4] and delineation of their mode of action by cycloaromatization and tubulin polymerization studies.[5]



Esperamicin aglycon X = OH
Calicheamicin aglycon X = H

Taxol® (paclitaxel) R_1 = Ph, R_2 = Ac
Taxotere® (docetaxel) R_1 = tBuO, R_2 = H

We have designed a new family of potential anti-tumor agents that combine aspects of the important pharmacophores in these families in which suitable functionality should facilitate tubulin binding and cycloaromatization would induce cell damage. For proper evaluation, the synthesis of these taxoid mimics (taxamycins)[6] requires the incorporation of a paclitaxel or docetaxel side chain at C_{13} of the bicyclic enediyne framework. This was not feasible in the methyl substituted 11 and 12 membered ring systems.[6c] In a continuation of our studies, we wish to report the synthesis of **14-18** which contain the bicyclo[7.3.1]trideca-4,9-dien-2,6-diyne core structure possessed by both esperamicin and calicheamicin and the normethyltaxamycin-10 compounds **21a-d** with the docetaxel (Taxotere®) side chain attached.

The Taxol® side chain has been attached to modified nuclei with retention of respectable tubulin binding.[7] Other enediyne hybrids incorporate the steroid nucleus (estramycins),[8] β-lactams (lactendiynes),[9] and enediynes linked to diethylstilbestrol.[10]

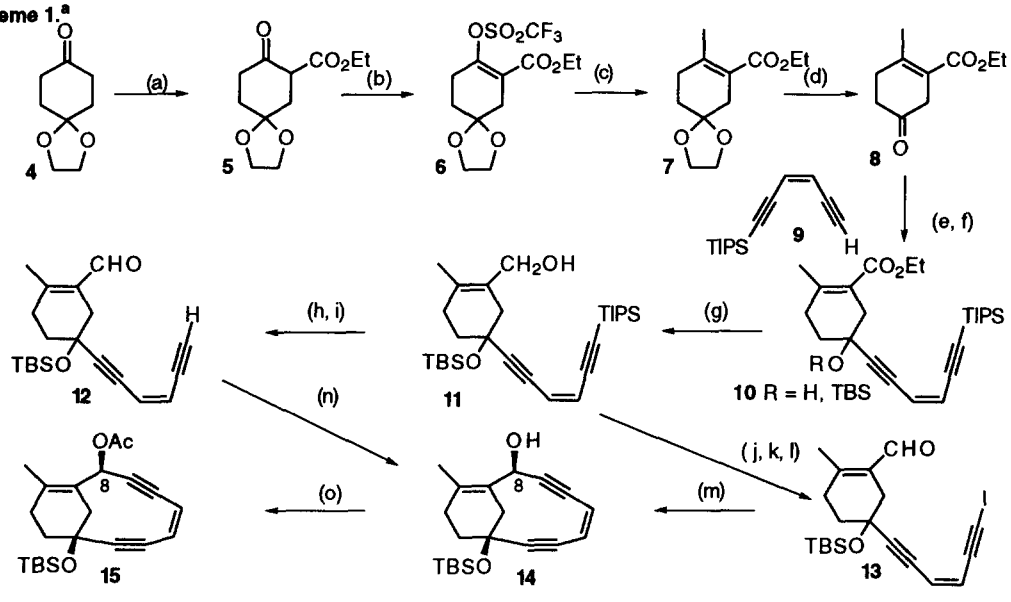
Our previous experience suggested that addition of a suitable enediyne building block **2** to a dicarbonyl substituted cyclohexene (**1**) would lead to the bicyclic system **3** in which oxygen functionality at C_{13} and at the

0040-4039/98/$ - see front matter
PII: S0040-4039(98)01297-0

vinyl methyl group could be introduced by allylic oxidation to facilitate the required functionalization and facilitate cycloaromatization.

As outlined in Scheme 1, the *mono*-ethylene ketal of 1,4-cyclohexanedione (**4**) was treated with LDA followed by ethyl cyanoformate,[11] to generate the β-keto-ester **5** (60%). Exposure of **5** to KHMDS and $PhN(SO_2CF_3)_2$ gave the corresponding triflate **6** in quantitative yield. The vinyl methyl group was introduced with Me_2CuLi[12] to give the cyclohexene **7** and the ketal removed with 35% aqueous CF_3COOH (3 d) to provide the keto-ester **8** in 80% yield.

Scheme 1.[a]



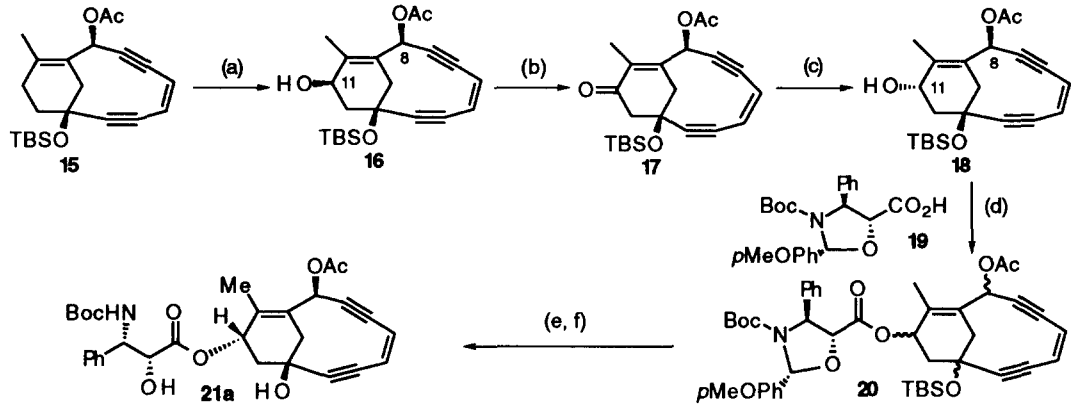
[a]Reagents: (a) LDA, THF, -78 °C, to -15 °C, 1 h; EtOCOCN, HMPA , -78 °C, 30 min, 60%; (b) KHMDS, THF, -78 °C, 30 min; $PhN(SO_2CF_3)_2$, -78 °C to 21 °C, 1 h 99%; (c) MeLi, CuI, Et_2O, 0 °C, 15 min, -78 °C to 21 °C, 99%; (d) 35% aq. CF_3CO_2H, $CHCl_3$, 21 °C, 3 d, 80%; (e) *t*-BuLi, $CeCl_3$,THF, -78 °C, 10 min, 84%; (f) TBSCl, Et_3N, CH_2Cl_2, 0 °C to 21 °C, 98%; (g) DIBAL-H, CH_2Cl_2, -78 °C to -60 °C, 2 h, 99%; (h) Dess-Martin periodinane, CH_2Cl_2, 21 °C, 1 h, 99%; (i) CsF, Ac_2O, $NaHCO_3$, CH_3CN, mol. sieves, 4 d, 48%; (j) TBAF, THF, -78 °C to 0 °C, 4 h, 93%; (k) I_2, morpholine, benzene, 60 °C, 2 h, 69%; (l) Dess-Martin periodinane, CH_2Cl_2, 21 °C, 1 h, 98%; (m) $[CrCl_2(THF)_2]$ (8 equiv.), THF, 30 min, 76%; (n) KHMDS, THF, -78 °C, 60%; (o) Ac_2O, DMAP (cat.), Py, 21 °C, 15 h, 99%.

Condensation of the cerium acetylide of enediyne **9**[6] with **8** afforded the corresponding alcohol **10** (R = H) in 84% yield. The alcohol was protected, and the ester function was reduced (*i*-Bu_2AlH,-78 °C) in quantitative yield. Subsequent removal of the triisopropylsilyl group (*n*-Bu_4NF) generated the corresponding acetylene which was converted to the desired iodoacetylene **10** (R = I) with iodine and morpholine. This product was oxidized with Dess-Martin periodinane to provide iodoaldehyde **13** in an overall yield of 62% for the 4 steps.

The intramolecular coupling of the iodoacetylene proceeded readily based on our previous research.[6] Exposure of **13** to the freshly prepared $[CrCl_2(THF)_2]$ complex[13] in THF afforded the bicyclic system **14** as a single diastereomer in 76% yield. Reasonable yields (60-70%) were also obtained with commercial anhydrous (toluene azeotrope) $CrCl_2$. In contrast to the more sterically demanding cyclizations examined earlier,[6c]

catalytic $NiCl_2$ was not required in these decadiynene systems. This is consistent with related 10-membered ring enediyne cyclizations,[14] although the mechanistic role of Ni(II) in these reactions remains obscure, as many cases require a catalytic amount of $NiCl_2$.[15] A 60% yield of **14** was also achieved from treatment of the aldehyde **12** with KHMDS at -78 °C, although the anhydrous fluoride-mediated cyclization procedure[16] on the corresponding silylacetylene-aldehyde failed.

Scheme 2.[a]



[a]Reagents: (a) SeO_2, dioxane, 70 °C, 30 min, 66%; (b) Dess-Martin periodinane, CH_2Cl_2, 21 °C, 45 min., 99%; (c) $NaBH_4$, MeOH, $CeCl_3$, 0 °C, 41%; (d) DCC, **19**, DMAP (cat.), toluene, 21 °C, 30 min, 99%, (1:1); (e) PTSA, MeOH, 21°C, 1.5 h, 94%; (f) TBAF, THF, 21 °C, 30 min, 75%.

Conversion of **14** to its acetate **15** set the stage for oxygen introduction, by treatment of **15** with SeO_2 to provide the allylic alcohol **16** (Scheme 2) as a single diastereomer in a yield of 66%. Consistent with a related example,[17] this oxidation occurred from the top face as a consequence of the steric hindrance of the enediyne bridge. The diastereomeric alcohol **18** was prepared by oxidation of **16** with Dess-Martin periodinane to afford the crystalline cyclohexenone **17**. X-ray analysis of **17** confirmed the structures in these series.[18] Reduction of the ketone **17** with sodium borohydride in the presence of $CeCl_3$ resulted in the preferential formation of alcohol **18** accompanied by its diastereoisomer (60:40 ratio).

Independently the two alcohols **16** and **18** were coupled with the oxazolidine **19**[19] (a protected form of the Taxotere® side chain) to provide two separate diastereomeric mixtures (1:1) in quantitative yield represented by the heterocyclic ester **20.** Acid catalyzed ring opening afforded the four distinct esters that were resolved by chromatography (SiO_2). The individual silyl ether isomers were converted to their C_1 alcohols upon exposure to *n*-tetrabutylammonium fluoride in THF. For clarity only the taxamycin-10 **21a,** possessing the Taxotere® side chain, is illustrated. This compound's stereochemical and electronic features most closely mimic those of the natural products.

Compound **21a** displayed negligible effects on tubulin polymerization and in protecting against Ca^{2+} induced depolymerization compared to Taxol®. Cytotoxic activity with the HT-29 human cancer cell line[20] was also weak (70% cell death at 10^{-4} M; Taxol® 90% at 10^{-9} M). This cytotoxic activity should increase in the presence of a cycloaromatization initiator which removes the bridgehead double bond. This double bond was inert to hydrogenation, a feature consistent with hyperstable alkenes,[21] and activation by oxidation of the

vinyl methyl group failed (SeO_2, CrO_3, PCC). To circumvent this difficulty, potential triggering mechanisms which involve intramolecular reactions with the olefin are under investigation.

In summary, these studies have established a reliable strategy for the synthesis of bicyclic enediynes and examined the biological activity of taxamycin-10 systems. This information will help delineate the structural and functional features required for future investigation.

Acknowledgment. We are grateful to NSERC Canada, Torcan Chemical Ltd., the Canadian Breast Cancer Research Initiative, and the Saunders-Matthey Foundation for Breast Cancer Research for financial support of this research. We thank A. Commerçon (Rhône-Poulenc Rorer) for a generous gift of oxazolidine **19**.

References and Notes

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