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The Esperamicin- Calicheamicin Aglycones: Ring Closure of a Simple Strained System Mediated by Chromium(II)-Nickel(II) Salts

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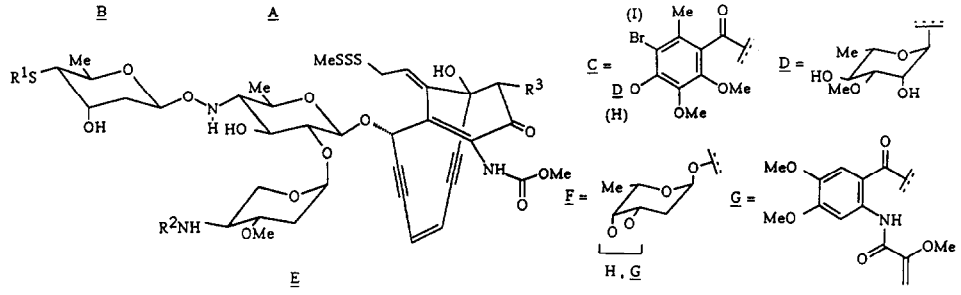
Key Words: esperamicin-calicheamicin aglycone model; chromium acetylide; Bergman aromatization

Abstract: *2,6-Diyne-4-cyclodecen-1-ol, a highly simplified and isolable monocyclic analogue of the bicyclic aglycone of esperamicins and calicheamicins, has been obtained by an intramolecular cyclocondensation of 1-iodo-1,5-diyne-3-decen-10-al mediated by chromium(II)-nickel(II) salts.*

The structural novelty of two very potent antitumor antibiotic series, esperamicins[1] and calicheamicins[2], has stimulated intense synthetic and mechanistic studies specially directed to the 1,5-diyn-3-ene strained ring system, culminating with the entire construction of the calichaemicin γ_1 aglycone recently disclosed by Danishefsky[3]. This unique structure is currently thought to be at the origin of the ability for these substances to impair double-stranded DNA. Bioreductive cleavage of the trisulfide linkage triggers an intramolecular conjugate addition to the bicyclic enone. The enediyne then undergoes a Bergman[4] cycloaromatization thus producing a benzenoid biradical which is capable of abstracting hydrogen atoms from the deoxyribose moities of the nucleic acids when positioned in the minor groove of DNA[5].

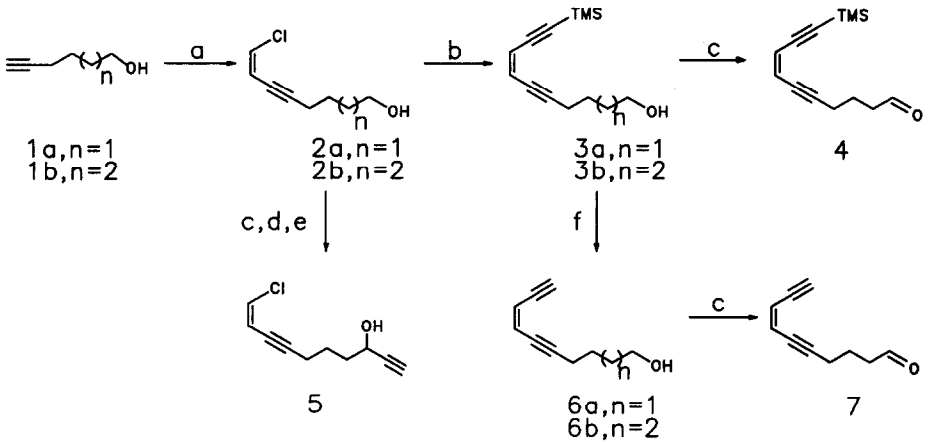


	R^1	R^2	R^3
calicheamicins	C	Me, Et or *i*Pr	H
esperamicins	Me	Et or *i*Pr	F

The construction of simple monocyclic 1,5-diyn-2-ene 10-membered rings[6,7], simulation of their cycloaromatization[6b,7], and *in vitro* tests of their ability to damage DNA[6b] have already been studied. All of these monocyclic structures are missing the propargylic hydroxy group, a mimic of the hydroxy group at C-12, on which the oligosaccharidic appendage is linked. We considered important to build up the simplest cyclodecenediyne bearing this functionality thus making possible the attachment of structural elements able to recognize DNA double-strand sequences. Ring closure of adapted acyclic precursors was however expected to be strongly unfavorable due to the highly strained features of this 10-membered ring system and because of the anticipated instability of the product.

We assumed that the recently developed coupling reaction of allylic[8], alkenyl[9] or alkynyl[10] halides or triflates with aldehydes mediated by chromium(II) salts, used in intramolecular versions[11] might fonction as well for ring closure of *strained* systems. A very recent report by Wender[12] prompted us to disclose our own results.

The palladium-catalyzed coupling reaction of (Z)-1,2-dichloroethylene with 5-hexyn-1-ol [$Pd(PPh_3)_4$-CuI-*n*-$PrNH_2$][13] gave 78% of enyne **2a**[14] on which a second coupling with trimethylsilyl acetylene provided silylated diynene **3a** (82%, Scheme 1). Pyridinium chlorochromate oxidation (83%) or desilylation prior to oxidation (75%) of **3a** furnished aldehydes **4** or **7**. Propargylic alcohol **5** was also prepared by oxidation, lithium trimethylsilyl acetylide addition, and desilylation of **2a**.

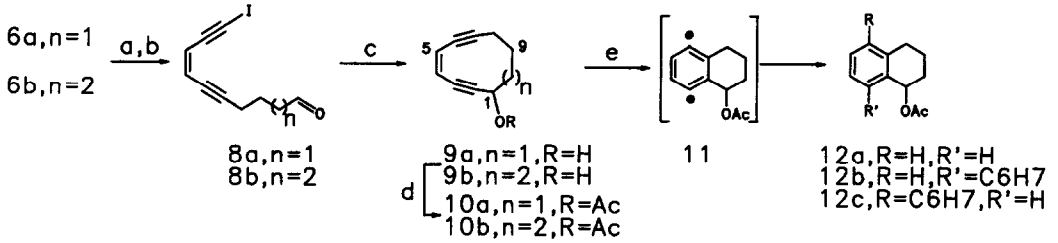


Scheme 1: *(a)* $C_2H_2Cl_2$, 1.25 equiv., $Pd(PPh_3)_4$, 1.7%, CuI, 4%, *n*-$PrNH_2$, 1.7 equiv., PhH, 40°C, 78% for **2a**, 60% for **2b**; *(b)* ≡—TMS, 1.3 equiv., same conditions as with *(a)*, 25°C, 82% for **2a**, 83% for **3b**; *(c)* PCC, 3.0 equiv., CH_2Cl_2, room temp., 75-85%; *(d)* Li—≡—TMS, 1.3 equiv., THF, -78°C, 65%; *(e)* Bu_4NF, 0.5 equiv., THF, 0°C, 85%; *(f)* K_2CO_3, 1.1 equiv., MeOH, room temp., 90%.

Attempts at cyclization by an "anhydrous" tetrabutylammonium fluoride-mediated reaction[15] on **5** or a palladium-catalyzed cyclocondensation[16] failed to give the desired cyclic product. Moreover, slow addition of **7** to a solution of lithium hexamethylsilyl amide under the conditions described by Tius[17] for intramolecular cyclization of an acetylide anion onto an *enolizable* aldehyde did provide the cyclized product, albeit in very low yield (0-10%).

When iodinated aldehyde **8a**, prepared by iodination and oxidation of alcohol **6a**, was slowly added to a suspension of $CrCl_2$-$NiCl_2$[10] in THF, the expected ten-membered enediynol **9a**[19] was produced in 34% yield[20], transformed into its acetate **10a** (Scheme 2). The same sequence of reactions starting from 6-heptyn-1-ol produced the eleven-membered compound **9b** (76% in the cyclocondensation step).

While **10a,b** were stable as expected from previous studies, **10b**[21] underwent a Bergman rearrangement[4] to **12a** (major product) and regioisomers **12b,c**[22] (minor products) by heating a benzene solution of **10b** in the presence of an excess of 1,4-cyclohexadiene[6a]. This transformation, followed by proton n.m.r. proceeded with a half-life of ~28 h at 37°C. This work is now in progress to produce other models including chiral bicyclic enediyne congeners and to evaluate the biological activity of these types of substances.



Scheme 2: *(a)* I_2-morpholine, PhH, 45°C, 80%; *(b)* PCC, 3.0 equiv., CH_2Cl_2, room temp., 83% for **8a**, 74% for **8b**; *(c)* $CrCl_2$, 5-8 equiv., $NiCl_2$, 0.07-0.1 equiv., THF, room temp., 34% for **9a**; 76% for **9b**; *(d)* Ac_2O, pyridine, 59% for **10a**, 90% for **10b**; *(e)* 1,4-cyclohexadiene, 100 equiv., PhH, see text.

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19. Selected ^{1}H-n.m.r. data ($CDCl_3$; for numbering system see Scheme 2): **9a:** δ 5.92 (dt, $J_{4,5}$ 9.5, $J_{5,8} = J_{5,8'}$ ~1.2 Hz, H-5); 5.86 (m, $J_{4,5}$ 9.5 Hz, H-4); 4.59 (m, H-1). **10a**: δ 5.92 (dtd, $J_{4,5}$ 9.5, $J_{5,8} = J_{5,8'}$ ~1.4, $J_{1,5}$ ~0.5 Hz, H-5); 5.85 (ddt, $J_{4,5}$ 9.5, $J_{1,4}$ 1.5, $J_{4,8} = J_{4,8'}$ ~0.7 Hz, H-4); 5.49 (dddd, $J_{1,10}$ 8.5, $J_{1,10'}$ 2.7, $J_{1,4}$ 1.5, $J_{1,5}$ ~0.5 Hz, H-1); 2.44 (m, H-8,8'); 2.08 (s, Ac). **9b**: δ 5.88 (m, $J_{4,5}$ 10.0 Hz, H-5); 5.83 (m, $J_{4,5}$ 10.0 Hz, H-4); 4.70 (m, $J_{1,11}$ 8.6, $J_{1,11'}$ 4.0 Hz, H-1); 2.48 (m, H-8,8'). **10b**: δ 5.89 (dtd, $J_{4,5}$ 10.0, $J_{5,8} = J_{5,8'}$ = 1.8, $J_{1,5}$ ~0.5 Hz, H-5); 5.82 (dd, $J_{4,5}$ 10.0, $J_{1,4}$ 1.2 Hz, H-4); 5.61 (dddd, $J_{1,11}$ 7.9, $J_{1,11'}$ 5.0, $J_{1,4}$ 1.2, $J_{1,5}$ ~0.5 Hz, H-1); 2.48 (m, H-8,8'); 2.08 (s, Ac).
20. Important losses upon workup were due to the instability of **9a** which can be stored in benzene or DMSO solutions at -20°C.
21. No clear-cut results could be obtained with the less stable **9a** which undergoes, besides cycloaromatization, other unidentified transformations.
22. 1,4-Cyclohexadiene hydrogen abstraction by biradical **11** may produce a solvent-caged radical pair which combined within the cage to give **12b,c**. For comparison (^{1}H-n.m.r., ms, hplc) compound **12a** was made available from commercial 1,2,3,4-tetrahydro-1-naphthol.

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