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RAPID AND STEREOSELECTIVE CONSTRUCTION OF DIENEDIYNES RELATED TO THE NEOCARZINOSTATIN CHROMOPHORE

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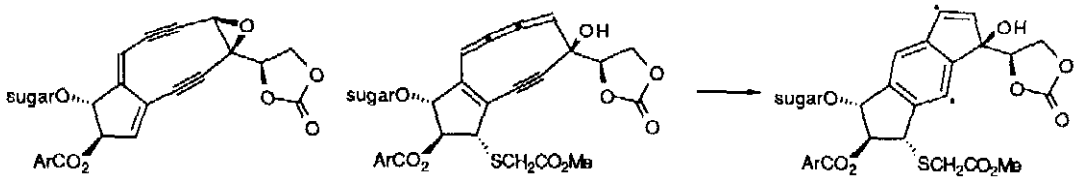
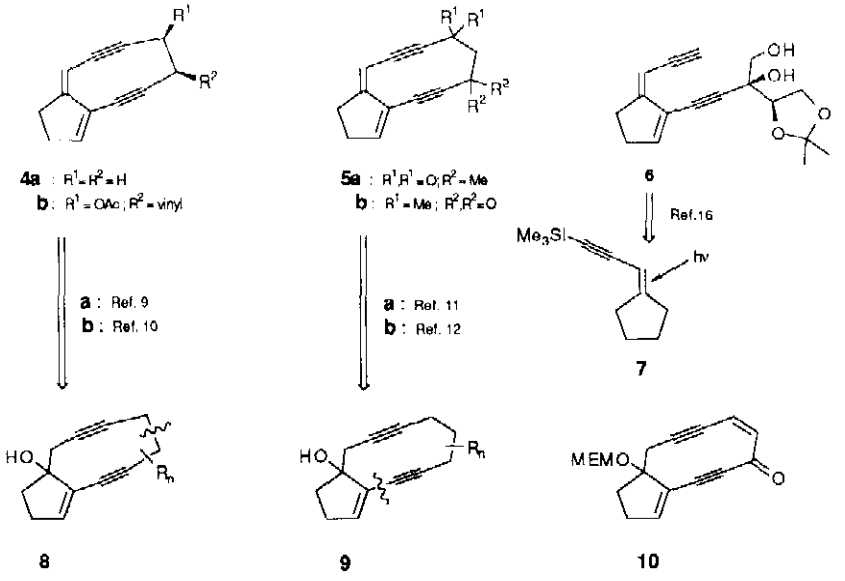
Summary: Formylcyclopentanone was transformed into Z configuration dienediynes **15** in three steps. As the key step served Pd catalyzed stereoselective couplings of the isomerically pure bis(enoltriflate) **13** with two equiv. of alkyne.

Neocarzinostatin is a highly potent antitumor chromoprotein from *Streptomyces* [1]. Its biological activity can be traced back to chromophore **1** which is extremely labile towards temperature, light, acid, or base, once the apoprotein is removed. The structure of **1** was elucidated in 1985 [2] the complete stereochemical assignment following shortly later [3]. The antitumor activity of **1** seems to be primed by a thiol mediated S_N2' type ring opening of the hexa-3,5-diene-1-yn-1-yl oxirane substructure giving a highly strained cumulene intermediate **2**. Cyclization of **2** furnishes diradical **3** capable of abstracting hydrogen atoms from DNA and cleaving it thereby [4]. This mode of action is related to those responsible for DNA clevage by the hexa-1,5-diyne-3-ene containing antitumor antibiotics esperamicin [5], calichemicin [6], or dynemicin [7].

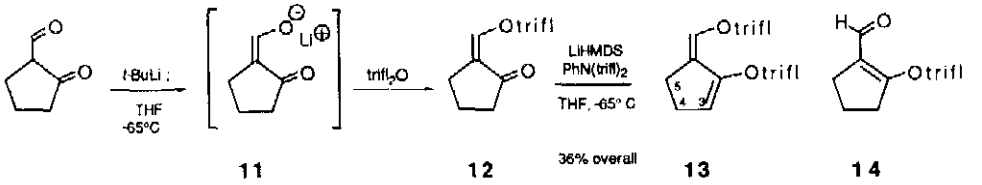


1 **2** **3**

The continuing need for the development of anti cancer medicals warrants the development of methodology for the synthesis of **1** or less complex yet still active model compounds. Five groups have addressed this goal to date [8]. Wender *et al.* assembled the carbon frameworks **4a** [9] and **4b** [10] of the neocarzinostatin bicyclic core. Hirama *et al.* prepared the 10-membered homologs **5a** [11] and **5b** [12]. In both syntheses, the *stereogenic* C=C bond was introduced *after* closure of the cycloalkadiyne (through elimination of H_2O from **8** or **9**, respectively), a transformation which Krebs *et al.* will still have to add to the synthesis of *their* 10-membered analog **10** [13]. This *modus operandi* transpires also from Krebs' earlier approach towards **1** [14] and is seemingly envisaged in the scheme of Myers *et al.* [15], too. This is because, following this strategy, one obviates the difficulty which Terashima *et al.* [16] encountered in their synthesis of the monocyclic dienediyne analog **6**: Devoid of the constraints imposed by a *preformed* ring, the stereogenic C=C bond in its precursor **7** is introduced initially with the wrong = more stable *E* configuration; it had to be subsequently adjusted - albeit only in a 1:2 ratio - through irradiation.



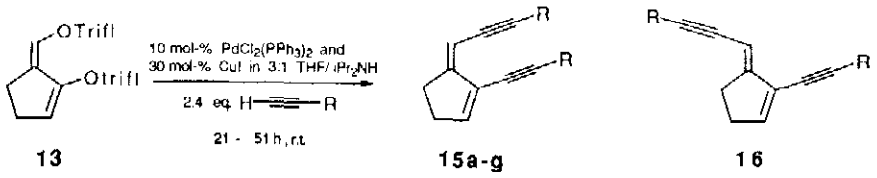
We conceived of forming the ene/yne linkages of neocarzinostatin chromophore model compounds by a transition metal mediated coupling of a diene precursor endowed with the required *Z* configuration *beforehand*. As such we chose the bis(enoltriflate) **13**. It was derived from the mono(enoltriflate) **12** which in turn was obtained in 55% yield from formylcyclopentanone [17] by deprotonation with *tert*-BuLi and by triflic anhydride quench of the resulting *Z*-configuration lithium enolate **11**. *Z*-**12** was distinguished from the corresponding *E*-isomer [18] by the highfield shift of its exocyclic =CH- proton (δ 6.62 vs. 7.49 ppm); **12** is distinguishable from its isomer **14** by the absence of an aldehyde resonance.



Conversion of **12** into bis(enoltriflate) **13** with triflic anhydride / 2,6-di-*tert*-butylpyridine [19] suffered from loss of most of the stereochemical integrity. However, sulfonylation of the corresponding lithium enolate (LiHMDS) with N,N-bis(trifluoromethanesulfonyl)aniline [20] gave isomerically pure **13** in 47% yield [δ_H = 2.63-2.65 (m, 4-H_2), 2.73-2.76 (m, 5-H_2), 6.23 (bt, $J_{3,4}$ = 3.1 Hz, $^5J_{3,1-=CH}$ not resolved, 3-H), 6.54 (bs, $^5J_{1-=CH,3}$ not resolved, 1-=CH)].

Bis(enoltriflate) **13** was coupled with terminal alkynes at room temperature under modified [18] Cacchi conditions [21], i.e., in a mixture of THF and $HNiPr_2$ in the presence of catalytic amounts both of CuI and

$PdCl_2(PPh_3)_2$. The desired dienediynes **15a-g** resulted in moderate to fair yields (cf. scheme). During these couplings, the *Z* configuration was preserved entirely as shown by ^{1}H-NMR spectroscopic comparison with the corresponding *E* configuration dienediynes **16** [18].

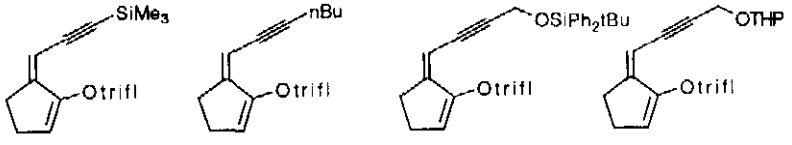


13 **15a-g** **16**

15	R	Yield	δ(sp^2-H)[a]		δ(sp^2-C$_{tert}$)[a]	
			exoc.	*endoc.*	*exoc.*	*endoc.*
a	$SiMe_3$	63%[b]	5.55	6.71	98.95	153.08
b	$C(OH)(CH_2)_5$	45%	5.49	6.53	98.30	149.18
c	CMe_2-OH	81%	5.44	6.53	98.10	149.42
d	tBu	69%[c]	5.49	6.49	98.89	149.57
e	nBu	36%	5.42	6.44	98.78	147.70
f	cC_6H_{11}	62%	5.46	6.47	98.85	148.13
g	CH_2-OMe	42%	5.48	6.62	98.12	150.32

[a] In ppm downfield from TMS at 300 or 400 MHz in $CDCl_3$.- [b] Mixed with 7% **17**.- [c] Mixed with 26% tBu-C≡C-C≡C-tBu.-

Interestingly, the exocyclic triflate moiety of **13** couples faster than its endocyclic counterpart. When **13** was treated, for example, with 1.1 eq. of $HC{\equiv}C\text{-}SiMe_3$, we could isolate 76% of a 4:1 mixture of the monocoupling product **17** and what is presumed to be its "regioisomer" (coupling at the *endocyclic* C-O bond). The ^{1}H-NMR shifts of the olefinic protons of **17** (δ = 5.49, 6.23) are identical with those reported by Terashima *et al.* who obtained **17** from 2-(ethoxycarbonyl)cyclopentanone in 8 steps [16]; the corresponding δ values for the minor product were distinctly different (6.48, 6.59). The regiochemistry of **17** was assigned by analogy to that of the *only* monocoupling product **18** which resulted - in 18% yield - from bistriflate **13** and 1-hexyne at incomplete conversion. **18** reveals splitting of the peak of its exocyclic sp^2-H (δ = 5.45) *inter alia* by a coupling ^5J = 2.5 Hz across the C≡C bond; in the regioisomer no such splitting would be observed.



17 **18** **19** **20**

Since monocoupling products like **19** and **20** were similarly accessible - as ca. 10:1 and 12:1 mixtures with structurally unassigned alkynes, respectively - the present strategy should lend itself also to the regiocontrolled coupling of two *different* alkynes to bistriflate **13**, a goal which is currently pursued in our laboratories.

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