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PALLADIUM CATALYZED COUPLINGS OF ENOL TRIFLATES WITH ALKYNES UNDER VERY MILD CONDITIONS - THE STEREOSELECTIVE SYNTHESIS OF DIENEDIYNES FROM BIS(ENOLTRIFLATES)

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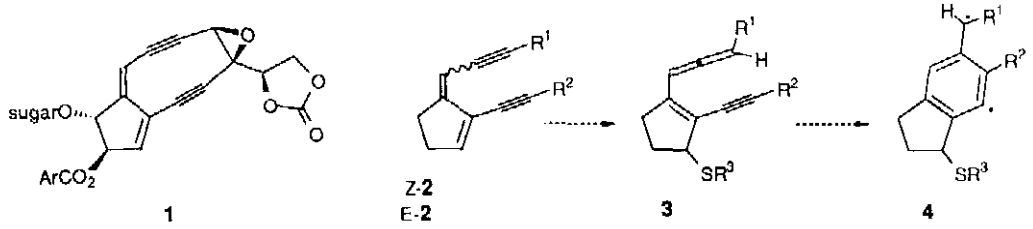
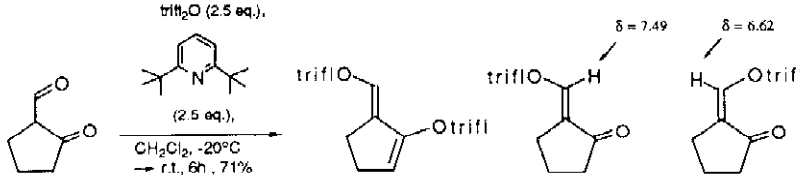
Summary: The stereoselectively accessible *E*-bis(enoltriflate) **6** couples under Pd(0)/CuI catalysis with two equiv. of alkyne giving *E* configuration dienediynes **7** with complete retention of stereochemistry.

There is much current interest in the highly unsaturated antitumor antibiotics neocarzinostatin chromophore (**1**) [1], esperamicin [2], calichemicin [2], and dynemicin [2]. These compounds, except the first one, are substituted cyclic 3-hexene-1,5-diynes which - upon Bergman cyclization [3] to a highly reactive benzene-1,4-diyl σ,σ-diradical - cleave DNA. Neocarzinostatin (**1**) can furnish - through thiol mediated vinylogous S_N2' type ring opening of the conjugated oxirane - a short-lived highly unsaturated 10-membered ring exhibiting in conjugation a triple bond, a double bond, and a 1,2,3-butatriene unit [4]. Cyclization of this intermediate gives a styrene-α,3-diyl π,σ-diradical in a reaction *commemorative* of the Bergman process; this diradical then cleaves DNA.



Since the structure elucidation of the aforementioned antibiotics, a number of highly unsaturated systems *different* from those encountered in nature have been conceived which - again by cyclization/aromatization - might cleave DNA, too. Nicolaou *et al.* reflected whether S,S-dipropargylsulfones cleave DNA via thiophene based π,π-diradicals [5]. (4*Z*)-1,2,4-Heptatrien-6-yne furnishes toluene-α,3-diyl - a π,σ-diradical - upon gentle heating according to a report by Myers *et al.* [6]. Substituted (4*Z*)-1,2,4-heptatrien-6-ynes behave similarly [7]. Terashima *et al.* pointed out that *E* and *Z* configuration dienediynes **2** might also lead to such toluen-α,3-diyl π,σ-diradicals (here: **4**) if a 1,6-addition of thiol generates the 1,2,4-heptatrien-6-yne derivative **3** initially; one representative each of *Z*-**2** and *E*-**2** was synthesized to substantiate this idea [8].

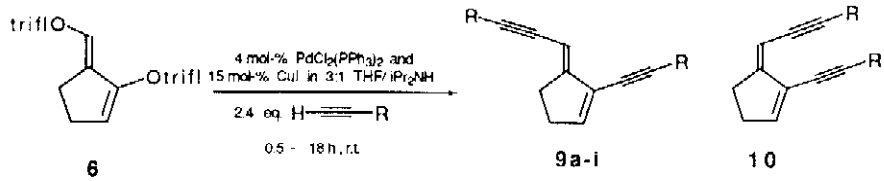


5 6 7 8

We presented a straightforward synthesis of *Z*-**2** ($R^1 = R^2$) in 3 steps from formylcyclopentanone (**5**) in the preceding report [9]. In the present communication, in an extension of efforts directed at the synthesis of analogs of the neocarzinostatin chromophore **1**, we disclose a rapid and versatile synthesis of the *E*-configuration isomers *E*-**2** ($R^1 = R^2$) *requiring only 2 steps* from formylcyclopentanone. As in the case of *Z*-**2**, we planned to form the ene/yne linkages of *E*-**2** by the palladium catalyzed coupling of two - later possibly different - alkynes with a sterically defined bis(enoltriflate). The latter (**6**) was prepared from formylcyclopentanone **5** [10] and triflic anhydride / 2,6-di-*tert*-butylpyridine [11] in 71% yield (6h). When the reaction was worked up prior to completion, i.e., after 30 min, we obtained 19% of bistriflate **6** along with 46% of *one* monotriflate **7**. The *E* configuration of its C=C bond follows from the lowfield shift δ = 7.49 of the olefinic proton compared to δ = 6.62 in the *Z*-isomer **8** [9]. Obviously, the monotriflate does *not* preserve the *Z* configuration of 2-(hydroxymethylene)cyclopentanone which is the prevalent - (12:1 ratio in $CDCl_3$) - tautomer of formylcyclopentanone [10,12].

It was desirable to convert bistriflate **6** into dienediynes **9** under very mild conditions because **6** decomposes rapidly even at room temperature. Also, one will require complete regiocontrol in our future objective of coupling two different alkynes with **6**. A literature survey revealed that conjugated enynes have been prepared from an enol triflate and a (trimethylstannyl)alkyne with $Pd(PPh_3)_4$/LiCl *under reflux* in THF [13]. Likewise, 1,3-enynes result from enol triflates and terminal alkynes R-C≡C-H using the same catalyst or $PdCl_2(PPh_3)_2/NEt_3$ (0.5 - 24h) *at 75°C* in DMF [14]. Cacchi *et al.* [15], however, realized couplings employing $PdCl_2(PPh_3)_2$ in the presence of CuI and $HNEt_2$ *at room temperature* in DMF [16].

We were pleased to find that the couplings of bis(enoltriflate) **6** could be effected at room temperature, too. We followed a modified Cacchi protocol, i.e., worked in THF/iPr_2NH mixtures (3:1) in the presence of $PdCl_2(PPh_3)_2$ and CuI as catalysts. Reaction times between 0.5 h for nucleophilic alkynes [(1-hydroxycyclohexyl)acetylen → **9b**; 1,1-dimethyl-2-propin-1-ol → **9c**] and 16 - 18 h for less nucleophilic alkynes [(trimethylsilyl)acetylen → **9a**; propargyl(*tert*-butyldiphenyl)silylether → **9d**] afforded dienediynes **9** with complete stereocontrol in good and sometimes quantitative yields (cf. scheme). Where comparisons with their *Z*-isomers **10** are possible [9], *E*-**9** reveals a slight lowfield shift ($\Delta\delta$ = +0.07 - +0.17 ppm) of the exocyclic vinylic proton [17] and a slight highfield shift of the endocyclic vinylic proton ($\Delta\delta$ = -0.04 - -0.17 ppm). As expected, the *E*-isomer **9f** - upon irradiation of the exocyclic sp^2-H - revealed *no* NOE at either of its ring methylene resonances while the corresponding *Z*-isomer **10f** [9] produced a NOE of 2.6% at δ_H = 2.61-2.64 (m) under similar conditions.

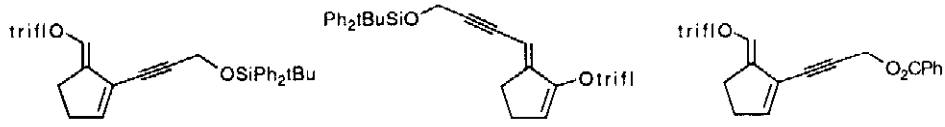


6 9a-i 10

9	R	Yield	$\delta_9(sp^2\text{-}H)$[a]		$\delta_9(sp^2\text{-}C_{tert})$[a]		$\delta_9\text{-}\delta_{10}(sp^2\text{-}H)$[b]	
			exoc.	*endoc.*	*exoc.*	*endoc.*	*exoc.*	*endoc.*
a	$SiMe_3$	97%	5.66	6.54	98.69	147.26	+0.11	-0.17
b	$C(OH)(CH_2)_5$	84%	5.63	6.49	97.95	146.15	+0.14	-0.04
c	$CMe_2\text{-}OH$	98%	5.57	6.46	97.75	145.99	+0.13	-0.07
d	$CH_2\text{-}O\text{-}SiPh_2tBu$	63%	5.54	6.43	98.35	146.31		
e	tBu	100%	5.58	6.32	98.49	143.27	+0.07	-0.17
f	nBu	83%	5.59	6.33	98.67	143.55	+0.17	-0.11
g	cC_6H_{11}	77%	5.63	6.34	98.65	143.36	+0.17	-0.13
h	$CH_2\text{-}OTHP$	26%[c]	5.63	6.51	98.13	146.91		
i	$CH_2\text{-}OMe$	43%[d]	5.64	6.52	97.96	146.97	+0.16	-0.10

[a] In ppm downfield from TMS at 200 MHz in $CDCl_3$.- [b] δ_{10} values from Ref. 9.- [c] Along with 26% of one monocoupling product.- [d] Along with 42% of monocoupling product after 96 h.-

The first triflate moiety of bistriflate **6** *coupled much faster with the alkyne than the second.* Thus, when a mixture of **6** and $H\text{-}C{\equiv}C\text{-}CH_2\text{-}OSiPh_2tBu$ (1.1 equiv.) was exposed to the catalysts for a couple of minutes, 98% of essentially one monocoupling product was isolated. Surprisingly, this compound (contaminated by 6% of the the isomeric monocoupling product) seems to be **11** and not **12**, i.e., resulting from substitution of the endocyclic rather than the exocyclic triflate function. This is inferred from the OCH_2 *singlet* (δ = 4.51) in the ^{1}H-NMR spectrum of **11**, since a *doublet* - due to long-range coupling across the C≡C bond - would be expected in **12**: At least, the corresponding *bis*coupling product **9d** displays such a doublet (δ = 4.54, ^5J = 2 Hz) for one of its CH_2 groups; the other OCH_2 signal is a singlet (δ = 4.51). While monocoupling product **11** delivered biscoupling product **9d** when *resubmitted* to the coupling conditions (overnight; 24%), the monocoupling product **13** obtained from **6** and propargyl benzoate [72 h; 44%; $\delta(OCH_2)$ = 5.10 (s)] did not couple a second time even with a large excess of the alkyne.



11 12 13

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