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AN EXPEDITIOUS SYNTHESIS OF THE OPEN-CHAIN (E)- AND (Z)-DIENEDIYNE SYSTEMS RELATED TO NEOCARZINOSTATINE CHROMOPHORE

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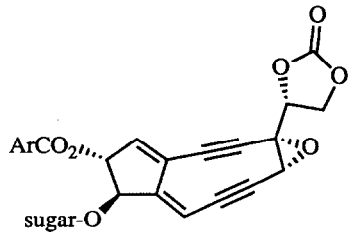
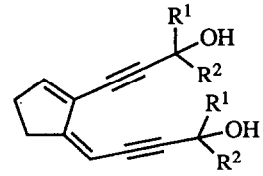
Summary: The title (E)- and (Z)-dienediyne systems could be successfully prepared by means of palladium-catalyzed double coupling reaction of (E)- and (Z)-dienolditriflates with various propargyl alcohols.

Neocarzinostatine chromophore **1** (NCS-Chr) has attracted much attention because of its notable bicyclo[7.3.0]dodecadienediyne system and strong DNA-cleaving activity. The intriguing biochemical property has been recognized as a result of hydrogen abstraction from sugar backbone of DNA by phenylenediradical species generated from NCS-Chr *via* Bergman-type cyclization of the eneyne cumulene system.[1] Although



NCS-Chr **1**



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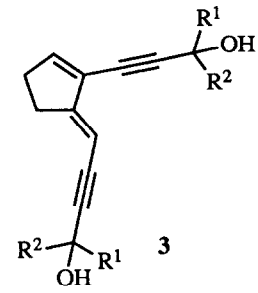
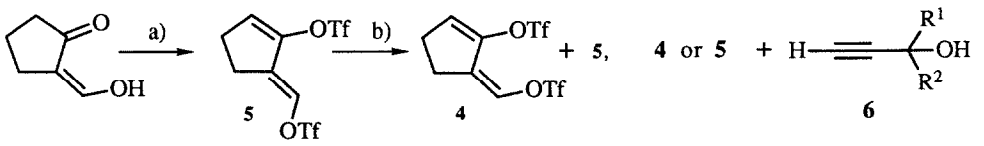


3

NCS-Chr analogues which can undergo Bergman-type cyclization, have been extensively investigated,[2] only a few analogues carrying open-chain dienediyne systems have so far been reported due to the lack of effective methodologies to construct such molecules.[3] In this communication, we wish to disclose an expeditious synthesis of the stereodefined open-chain (E)- and (Z)-dienediyne systems with common acetylenic functionalities (**2** and **3**) related to **1**.

One of the simplest methods to synthesize **2** and **3** could be realized by utilizing palladium-catalyzed double coupling reaction of (E)- and (Z)-dienolditriflates with various propargyl alcohols. As shown in the next page, the (E)- and (Z)-dienolditriflates were readily prepared from 2-formyl-cyclopentanone.[4] Thus, treatment of 2-formyl-cyclopentanone with triflic anhydride and 2,6-di-*tert*-butyl-4-methylpyridine afforded (E)-dienolditriflate (**5**)[5] in 63% yield.[6] Photo-induced isomerization of **5** was effected by irradiating with a high pressure mercury lamp to give the (Z)-dienolditriflate (**4**)[7] in 37% yield accompanied with recovered **5** (48%).[8] The key double coupling reaction could be achieved in good to excellent isolated yields by treating **4** or **5** with propargyl alcohols (**6**) (2.5eq) in DMF at room temparature for 2 to 4 hr in the presence of $PdCl_2(PPh_3)_2$ (5mol%), CuI (10mol%) and Et_2NH (3eq), giving rise to **2** or **3**[9,10] after florisil column chromatography under argon atmosphere.



		2 yield (%)	3 yield (%)
c) → 2 or 3	a : $R^1 = R^2 = Me$	73	91
	b : $R^1 = R^2 = Ph$	63	98
	c : $R^1, R^2 = -(CH_2)_4-$	72	79
	d : $R^1, R^2 = -(CH_2)_5-$	71	91

a) Tf_2O, 2,6-di-^{t}butyl-4-methylpyridine, CH_2Cl_2, rt, 1d, 63% b) hν, acetone, rt, 30min, 37%
c) see the text.

Thus, we have succeeded in expeditiously preparing the stereodefined open-chain (Z)- and (E)-dienediynes such as **2** and **3**, which may be useful for studying the phenylenediradical formation and DNA cleavage. Furthermore, the explored synthetic route may hold promise for exploring prominent anticancer agents.[11]

References and Notes

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5. **5**; ^{1}H-NMR ($CDCl_3$): 2.63 - 2.68 (m, 2H), 2.79 - 2.83 (m, 2H), 6.20 (t, 1H, J = 2.9Hz, CH_2CH), 6.83 (m, 1H, *CH*OTf). HRMS calculated for $C_8H_6F_6O_6S_2$, 375.9509; found 375.9506.
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7. **4**; ^{1}H-NMR ($CDCl_3$): 2.60 - 2.65 (m, 2H), 2.72 - 2.77 (m, 2H), 6.22 (m, 1H, CH_2CH), 6.53 (m, 1H, *CH*OTf). HRMS calculated for $C_8H_6F_6O_6S_2$, 375.9509; found 375.9518.
8. While both **4** and **5** were fairly unstable oils, they can be stored in the dark in a form of hexane solution without decomposition.
9. Isomerization of the *exo*-olefinic double bond was not observed.
10. The ^{1}H- NMR spectra of **2a** and **3a** were shown as representative examples **2a**; ^{1}H-NMR ($CDCl_3$): 1.56 (s, 2x3H), 1.58 (s, 2x3H), 2.50 (m, 2H), 2.65 (m, 2H), 3.3 - 3.8 (br, 2H), 5.44 (m, 1H), 6.53 (m, 1H). **3a**; ^{1}H-NMR ($CDCl_3$): 1.57 (s, 4x3H), 1.9 - 2.2 (br, 2H), 2.59 (m, 2H), 2.74 (m, 2H), 5.58 (m, 1H), 6.47 (t, 1H, J = 3.0Hz).
11. These (Z)- and (E)-dienediynediols (**2** and **3**) showed the following IC_{50} values (mM) when subjected to *in vitro* cytotoxicity assay against P388 murine leukemia. **2a**, 4.2×10^{-3}; **3a**, 4.8×10^{-3}; **2b**, 4.2×10^{-3}; **3b**, 4.1×10^{-3}; **2c**, 1.5×10^{-2}; **3c**, 2.6×10^{-3}; **2d**, 2.4×10^{-3}; **3d**, 2.8×10^{-3}.

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