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## The First 6-Membered/10-Membered Ring Analogues of the Dienediyne Core of Neocarzinostatin Chromophore<sup>1</sup>

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Abstract: The Z-configurated enoltriflate 16 and ortho-ethinyl benzaldehyde were coupled giving the (trimethylsilyl)ethinyl aldehyde 17 which cyclized ( $\rightarrow$  tricyclic dienediyne 14; 21%) in the presence of CsF, Ac<sub>2</sub>O, and 18-crown-6. A similar coupling allowed to prepare iodoalkinyl aldehyde 21. It gave the tricyclic dienediyne 13 (53%) in a Nozaki-Hiyama reaction with stoichiometric NiCl<sub>2</sub>.

Neocarzinostatin is a highly potent anti-tumor chromoprotein whose biological activity stems from its exceedingly labile chromophore  $1^2$ . The unique structure of 1 as a whole and its extremely strained epoxybicyclo[7.3.0]-1(12),8-dodecadiene-2,6-diyne core continue to attract the attention of synthetic chemists. While the simplest analogue 2 of this compound was prepared as early as 1988 by Wender and associates <sup>3</sup> a fully functionalized analogue has not yet been obtained. The closest approach is due to the Myers group where the epoxydienediyne 3 was prepared <sup>4</sup>. Nonetheless, many syntheses of simpler dienediyne models 4 of chromophore 1 were realized during the last years in which the unsaturated system was incorporated into acyclic, mono- or oligocyclic frameworks. Further dienediyne models which contain the natural 5-membered/9-membered-ring core are compounds 5 from Wender's laboratory <sup>5</sup> and 6 from Takahashi and Doi <sup>6</sup>. Dienediyne models with the unnatural 5-membered/10-membered ring core are more abundant and include compounds 7 <sup>7</sup> and 8 <sup>8</sup> from the Hirama group, 9 from Myers and Dragovich <sup>9</sup>, 10 from Terashima and coworkers <sup>10</sup>, 11 from our own group <sup>11</sup>, and 12 from Ueda *et al* <sup>12</sup>. However, most if not all of these compounds are still quite unstable. With the goal of increasing the stability of neocarzinostatin chromophore models we have prepared its first 6-membered/10membered ring dienediyne analogues 13 and 14 and describe there obtention in Schemes 1 and 2, respectively <sup>1</sup>.



2-Formylcyclohexanone was converted via mono(enoltriflate)  $16^{13}$  and Pd catalyzed C,C coupling with *ortho*ethinylbenzaldehyde into the Z-dienediyne 17 (Scheme 1). It did not cyclize to dienediynol 13 when exposed to fluoride ions<sup>14</sup>, but gave the corresponding acetate 14 when acetic anhydride was additionally present<sup>15, 16</sup>. The alternative of a cyclization of the desilylated alkinyl aldehyde 18 with LiHMDS<sup>17</sup> and CeCl<sub>3</sub> failed.



However, the target dienediyne 13 was accessible by the route of Scheme 2. There, monotriflate 16 was coupled with *ortho*-HC=C-C<sub>6</sub>H<sub>4</sub>-CH<sub>2</sub>OH ( $\rightarrow$ 19; 82%) to provide, after desilylation <sup>18</sup>, hydroxyalkyne 20 (80%). We oxidized the C<sub>sp</sub> -H bond <sup>19</sup>, then the OH group <sup>20</sup>, and obtained via iodoalkyne 22 (95%) the (iodoalkinyl) aldehyde 21 (87%). The Nozaki-Hiyama reaction <sup>21</sup> has become a powerful tool for the cyclization of iodinated 3-ene-1,5-diynes <sup>19, 22</sup>. Therefore, we felt encouraged to test it for the first in the cyclization of an iodinated dienediyne (21). The usual conditions (CrCl<sub>2</sub>, *catalytic* NiCl<sub>2</sub>) gave mediocre yields of the desired cyclization product 13. Gratifyingly, 53% of compound 13 were isolable when NiCl<sub>2</sub> was employed stoichiometrically. Since - according to thin layer chromatography - the cyclization itself went to completion the loss of material is almost only due to decomposition during flash chromatography on SiO<sub>2</sub>. E.g., the dienediyne model 13 was not as stable as we had hoped (and its acetate 14 neither).

Scheme 1: a) tert-BuLi (1.0 equiv.), THF,  $-78^{\circ}C$ , 30 min;  $(F_3C-SO_2)_2O$ (1.0 equiv.), 30 min; 57% <sup>13</sup>.- b) LiHMDS (1.1 equiv.), THF, -78°C, 30 min; (F<sub>3</sub>C-SO<sub>2</sub>)<sub>2</sub>O (1.0 equiv.), 45 min;  $68\%^{13}$ .- c) H-C=C-SiMe<sub>3</sub> (1.15 equiv.), PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (5 mol-%), Cul (12 mol-%), Et<sub>2</sub>O/iPr<sub>2</sub>NH (3:1), -5°C, 18 h; 75 % after chromatographic separation<sup>23</sup> of a 97:3 mixture of regioisomers <sup>13</sup>.- d) ortho-Ethinylbenzaldehvde (1.2)eauiv.). PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (7 mol-%), CuI (17 mol-%), THF/ $iPr_2NH$  (3:1), room temp., 20 h, 70%.- e) I N NaOH, THF/MeOH (1:1), 30 h; 69%.- f) CsF (5 equiv.), Ac<sub>2</sub>O (1.5 equiv.), 18crown-6 (1 equiv.), THF, room temp., 20 h; 21%.- g) LiHMDS (3 - 30 equiv.), CeCl3 (3-6 equiv.), THF, - $78^{\circ}C$ , 3 h.- h) aq. NH<sub>3</sub> (24%) / THF (1:1), 18 h; or: NaOH, MeOH, 18 h.



Scheme 2: a) ortho-Ethinylbenzyl alcohol (1.3 equiv.),  $PdCl_2(PPh_3)_2$  (5 mol-%), CuI (12 mol-%), THF/iPr<sub>2</sub>NH (3:1), room temp., 4 h; 82 %.- b) NH<sub>4</sub>F (45% in H<sub>2</sub>O), Bu<sub>4</sub>NHSO<sub>4</sub> (0.25 equiv.), CH<sub>2</sub>Cl<sub>2</sub>, room temp., 1 h<sup>18</sup>; 80%.- c) I<sub>2</sub> (2.5 equiv.), morpholine (5.9 equiv.), THF, 40°C, 4 h<sup>19</sup>; 95%.d) Dess-Martin reagent (2.0 equiv.), CH<sub>2</sub>Cl<sub>2</sub>, room temp., 1 h<sup>20</sup>; 87%.- e) CrCl<sub>2</sub> (3 equiv.), NiCl<sub>2</sub> (1 equiv.), THF, -10 - -5°C, 5 h; 53%.



The structure of the novel 6-membered/10-membered ring analogues 13, 14 of the dienediyne moiety of neocarzinostatin is supported by their spectroscopic data <sup>16</sup> and particularly by the similarity of the <sup>1</sup>H and <sup>13</sup>C NMR data with those of the previously prepared 5-membered/10-membered ring analogue 11 <sup>11</sup> (Table 1).

	4-H	9-Н		13-H for 11, 14-H for 13 and 14	Ar-H	
11 (200 MHz) 11	5.86 (s)	5.49 (br. s)		6.09 (br. s)	6.90 and 7.02 (2 dt), 7.41 and 7.47 (2 dd)	
13 (300 MHz)	5.49 (d)	5.54 (d)		6.37 (td)	7.24-7.41 (m)	
14 (300 MHz)	6.70 (s)	5.56 (d)		6.41 (td)	7.28-7.33 (m) and 7.35-7.43 (m)	
	CH <sub>2</sub>		C-4	(	Sp2	C <sub>sp</sub>
11 (50 MHz) <sup>11</sup>	30.88 (2 ×)		65.79	100.04, 122.48, 127.71, 127.85, 128.49, 129.21, 131.98, 140.25, 146.22, 156.70		84.16, 93.75, 95.19, 95,42
13 (125 MHz)	22.36, 26.51, 33.41		65.88	105.35, 120.84, 121.52, 128.11, 128.52, 130.06, 131.82, 138.58, 142.05, 144.93		86.73, 89.02, 94.53, 95.07
14 (75 MHz)	22.28, 26.52, 33.35		66.52	105.45, 120.60, 123.16, 128.30, 128.61, 131.07, 131.89, 134.25, 143.07, 144.83		85.64, 86.71, 94.41, 94.99

Table 1: Characteristic dienediyne <sup>1</sup>H NMR data (CDCl<sub>3</sub>; splitting patterns in brackets) and <sup>13</sup>C NMR shifts (CDCl<sub>3</sub>)

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