

## THE SYNTHESIS OF A 10-MEMBERED BENZO-OXADIYNE RING

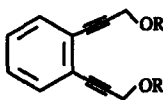
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**Abstract:** The synthesis of 10-membered benzo-oxadiyne **12** is described and its thermal stability is compared to that of its carbocyclic analogues **5** and **6**.

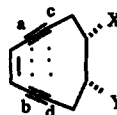
The highly unusual structures of the recently isolated calicheamicin<sup>1a</sup> and esperamicin<sup>1b</sup> and their powerful antitumor activities has prompted a number of model studies of these fascinating systems.<sup>2</sup> Our earlier work<sup>3</sup> involved an easy entry into *o*-benzodiyne systems of type **1** which are related to the enediyne system of calicheamicin, and the synthesis of 11, 12, and 13-membered ring systems **2-4**, which were stable in boiling cumene.

We wish to report the synthesis of the 10-membered benzo-oxadiyne **12**, which should be more strained than the recently described<sup>4,5</sup> decaendiyne **5** and **6**, since the C-O bond is shorter than a C-C bond.



**1** R = H  
**2** R, R = CO

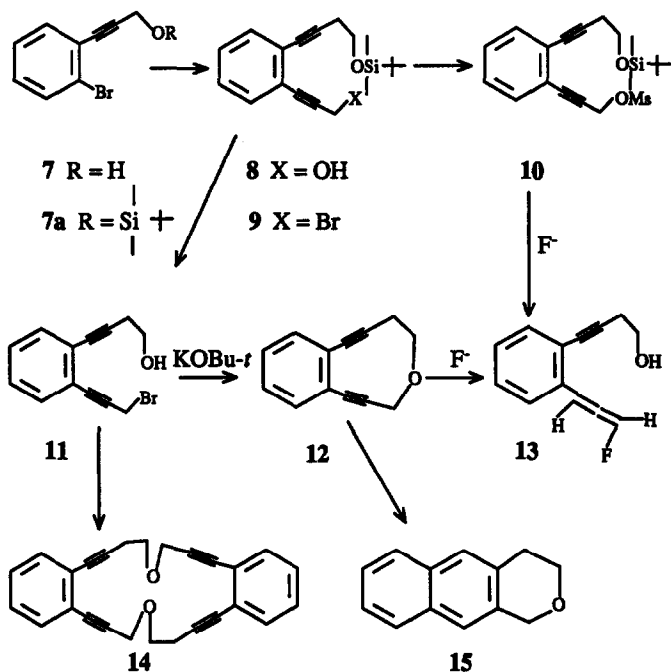
**3** R, R = COCO  
**4** R, R = COCH<sub>2</sub>CO



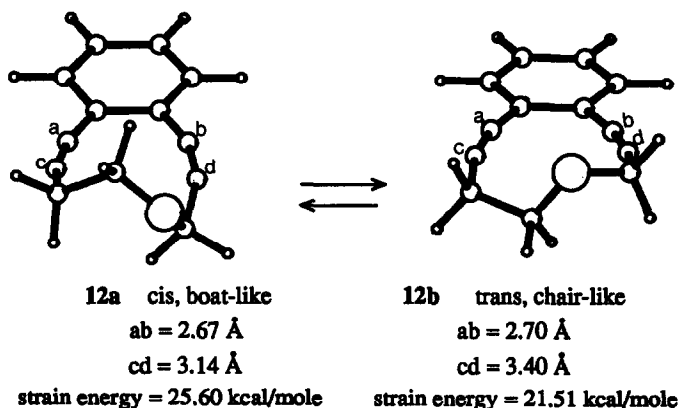
**5** X = H  
**6** X = CH<sub>2</sub>OH

Palladium catalyzed reaction of *o*-dibromobenzene<sup>6</sup> with 3-butynol gave **7** (98%), which upon silylation gave **7a** (98%). Treatment of **7a** with propargyl alcohol<sup>7</sup> / 2 mol% Pd(PPh<sub>3</sub>)<sub>4</sub> / 3 mol% Cu<sub>2</sub>Br<sub>2</sub> / NEt<sub>3</sub> gave bis acetylenic alcohol **8** (75%), which was treated with mesyl chloride / NEt<sub>3</sub> in CH<sub>2</sub>Cl<sub>2</sub> at 0 °C to provide mesylate **10** (78%). Reaction of this mesylate with Bu<sub>4</sub>NF in THF at room temperature gave unexpectedly fluoro allene **13** (40%), presumably via the ten-membered bis acetylene **12**, since treatment of **12**, obtained as described below, gave **13** (45%) as well.

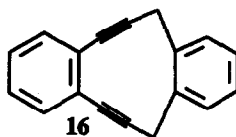
Reaction of alcohol **8** with CBr<sub>4</sub> (2 equiv) / PPh<sub>3</sub> (2 equiv) / CH<sub>3</sub>CN at 0 °C for 15 min gave bromide **9** (95%). Desilylation of **9** with 5 equiv HCl in H<sub>2</sub>O / THF 1:1 gave bromoalcohol **11** (98%). Simultaneous slow addition via a syringe pump of **11** (1 equiv, 4.7 mmol) and KOBu-*t* (1 equiv, 4.7 mmol) into THF (500 mL) over a period of 36 h gave **12** as an oil in 14% yield, in addition to some dimer, **14** m.p. 139-140 °C. The <sup>1</sup>H nmr spectra of **12** and its dimer were indistinguishable, and the identity of the two compounds could be established readily only by mass spectrometry. Much to our surprise, **12** was thermally quite stable, and underwent a Bergman rearrangement<sup>8</sup> to **15**<sup>9</sup> in CH<sub>2</sub>Cl<sub>2</sub> at 37 °C with a half life of 52 h as compared to **5** (t<sub>1/2</sub> = 18 h) and **6** (t<sub>1/2</sub> = 11.8 h). The half life in excess 1,4-cyclohexadiene and benzene was found to be 4 h at 70 °C. Interestingly, the <sup>1</sup>H nmr of the rearrangement product **15** was virtually identical to that of **12**, except for the aromatic region, so that stability analyses had to be carried out using GC / MS<sup>10</sup> as a monitoring device for their conversion.



It had been reported<sup>4</sup> that the cd distance in 5 was 3.25 Å, as established by MM2 calculations. However, inspection of Dreiding models indicated that both 5 and 12 exist in a cis, boat-like conformation 12a, in which the cd distance is relatively short, and a trans, chair-like conformation 12b, in which the cd distance is relatively long. Molecular mechanics calculations using Model, MM2<sup>11</sup> for 5, 6, and 12, indicated that all three exist in a more stable trans conformation with cd  $\cong$  3.4 Å, in equilibrium with a less stable cis, boat-like conformation with cd  $\cong$  3.2 Å.<sup>12</sup> The distances and conformer population of 5, 6 and 12 are presented in Table 1.



Quite interestingly, compound 16<sup>13</sup> undergoes spontaneous cyclization (cd = 3.03 Å)<sup>4</sup>, and Dreiding models show the molecule is locked in the boat-like conformation.



Work is in progress to show if locking the ten-membered ring system into a cis conformation facilitates Bergman cyclization.

**Table 1** Conformer Population At 25 °C From MM2 Calculations

	Half life <sup>a</sup> (t <sub>1/2</sub> ) h	cd for cis conformer (Å)	cd for trans conformer (Å)	Δ(ΔG) kcal/mole	% cis	% trans
 12	52	3.14	3.40	4.09	0.1	99.9
 6	11.8	3.20	3.39	2.90	0.8	99.2
 5	18	3.20	3.47	2.55	1.4	98.6

<sup>a</sup> In CH<sub>2</sub>Cl<sub>2</sub> at 37 °C.

#### Acknowledgments

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#### References and notes

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- General Procedure For Coupling Reaction**

To *o*-dibromobenzene (5.0 mmol, 0.60 mL) in triethylamine (15 mL), under nitrogen at room temperature was added 3-butyne-1-ol (7.5 mmol, 0.57 mL), Pd(0)(PPh<sub>3</sub>)<sub>4</sub> (116 mg, 2 mol%) and Cu<sub>2</sub>Br<sub>2</sub> (43 mg, 3 mol%).

The reaction was heated and stirred for 3 h and then concentrated in vacuo, extracted with ether (2x100 mL) and washings of the ether extracts with aqueous  $\text{NH}_4\text{Cl}$  (3x15 mL), drying over  $\text{MgSO}_4$ , concentrating and purifying by column chromatography gave **7** in 78% yield.

7. All compounds were characterized by  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 200 MHz), LRMS with specific ion monitoring to ascertain purity and HRMS. Significant characterization data includes: **7**:  $\delta$  2.57(t, 1H,  $J=6.0$  Hz, OH), 2.74(t, 2H,  $J=5.8$  Hz,  $\text{CH}_2$ ), 3.83(q, 2H,  $J=6.0$  Hz,  $\text{CH}_2$ ), 7.13-7.61(m, 4H,  $\text{C}_6\text{H}_4$ );  $m/e$  224( $\text{M}^+$ ), 206( $\text{M}^+ - \text{H}_2\text{O}$ ), 155( $\text{M}^+ - \text{C}\equiv\text{CCH}_2\text{CH}_2\text{OH}$ ), 145( $\text{M}^+ - \text{Br}$ ), 224.0131(calcd 224.0121). **7a**:  $\delta$  0.098(s, 6H, 2 $\text{CH}_3$ ), 0.98(s, 9H,  $\text{SiC}(\text{CH}_3)_3$ ), 2.68(t, 2H,  $J=7.3$  Hz,  $\text{CH}_2\text{C}\equiv\text{C}$ ), 3.85(t, 2H,  $J=7.3$  Hz,  $\text{CH}_2\text{OSi}$ ), 7.17-7.39(m, 4H,  $\text{C}_6\text{H}_4$ );  $m/e$  281( $\text{M}^+ - \text{C}(\text{CH}_3)_3$ ), 223( $\text{M}^+ - \text{Si}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$ ), 280.9325(calcd 281.8981). **8**:  $\delta$  0.093(s, 6H, 2 $\text{CH}_3$ ), 0.90(s, 9H,  $\text{C}(\text{CH}_3)_3$ ), 2.67(t, 2H,  $J=7.0$  Hz,  $\text{CH}_2\text{C}\equiv\text{C}$ ), 3.85(t, 2H,  $J=7.0$  Hz,  $\text{CH}_2\text{OSi}$ ), 4.52(s, 2H,  $\text{OCH}_2\text{C}\equiv\text{C}$ ), 7.22(m, 2H,  $\text{C}_6\text{H}_4$ ), 7.38(m, 2H,  $\text{C}_6\text{H}_4$ );  $m/e$  257( $\text{M}^+ - \text{C}(\text{CH}_3)_3$ ), 199( $\text{M}^+ - \text{Si}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$ ), 183( $\text{M}^+ - \text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$ ), 257.1010(calcd 257.0998). **9**:  $\delta$  0.093(s, 6H, 2 $\text{CH}_3$ ), 0.907(s, 9H,  $\text{C}(\text{CH}_3)_3$ ), 2.69(t, 2H,  $J=7.3$  Hz,  $\text{C}\equiv\text{CCH}_2$ ), 3.86(t, 2H,  $J=7.3$  Hz,  $\text{CH}_2\text{OSi}$ ), 4.19(s, 2H,  $\text{CH}_2\text{Br}$ ), 7.22(m, 2H,  $\text{C}_6\text{H}_4$ ), 7.39(m, 2H,  $\text{C}_6\text{H}_4$ ). **10**:  $\delta$  0.085(s, 6H, 2 $\text{CH}_3$ ), 0.89(s, 9H,  $\text{C}(\text{CH}_3)_3$ ), 2.70(t, 2H,  $J=6.0$  Hz,  $\text{CH}_2\text{C}\equiv\text{C}$ ), 3.19(s, 3H,  $\text{CH}_3$ ), 3.88(t, 2H,  $J=6.0$  Hz,  $\text{CH}_2\text{OSi}$ ), 5.15(s, 2H,  $\text{CH}_2\text{OSO}_2$ ), 7.20(m, 2H,  $\text{C}_6\text{H}_4$ ), 7.37(m, 2H,  $\text{C}_6\text{H}_4$ ). **11**:  $\delta$  (bs, 1H, OH), 2.74(t, 2H,  $J=7.0$  Hz,  $\text{C}\equiv\text{CCH}_2$ ), 3.84(t, 2H,  $J=7.0$  Hz,  $\text{C}\equiv\text{CCH}_2\text{OSi}$ ), 4.20(s, 2H,  $\text{CH}_2\text{Br}$ ). **12**:  $\delta$  2.68(t, 2H,  $J=7.6$  Hz,  $\text{C}\equiv\text{CCH}_2$ ), 4.07(t, 2H,  $J=7.6$  Hz,  $\text{CH}_2\text{O}$ ), 4.51(s, 2H,  $\text{C}\equiv\text{CCH}_2\text{O}$ ), 7.22(m, 2H,  $\text{C}_6\text{H}_4$ ), 7.39(m, 2H,  $\text{C}_6\text{H}_4$ );  $m/e$  (CI with  $\text{NH}_3$ ): 200( $\text{M} + \text{NH}_3 + \text{H}^+$ ), 183( $\text{M} + \text{H}^+$ ), 182( $\text{M}$ ), 152( $\text{M} - \text{CH}_2\text{O}$ ), 183.0809(calcd 183.0809). **13**:  $\delta$  2.15(bs, 1H, OH), 2.72(t, 2H,  $J=6.5$  Hz,  $\text{C}\equiv\text{CCH}_2$ ), 3.82(t, 2H,  $J=6.5$  Hz,  $\text{CH}_2\text{O}$ ), 4.41(s, 1H,  $\text{CH}=\text{CF}$ ), 5.22(d, 1H,  $J=47.4$  Hz,  $\text{C}=\text{CHF}$ ), 7.27(m, 2H,  $\text{C}_6\text{H}_4$ ), 7.42(m, 2H,  $\text{C}_6\text{H}_4$ );  $^{19}\text{F}$  NMR( $\text{C}_6\text{H}_5\text{CF}_3$ ):  $\delta$  -150.63(d,  $J=47.4$  Hz,  $\text{C}=\text{CHF}$ );  $m/e$  202( $\text{M}^+$ ), 184( $\text{M}^+ - \text{H}_2\text{O}$ ), 183( $\text{M}^+ - \text{F}$ ), 170( $\text{M}^+ - \text{CHF}$ ), 202.0772(calcd 202.0794). **14**:  $\delta$  2.71(t, 4H,  $J=7.6$  Hz, 2 $\text{C}\equiv\text{CCH}_2$ ), 3.91(t, 4H,  $J=7.6$  Hz, 2 $\text{CH}_2\text{O}$ ), 4.51(s, 4H, 2 $\text{C}\equiv\text{CCH}_2\text{O}$ ), 7.22(m, 4H, 2 $\text{C}_6\text{H}_4$ ), 7.39(m, 4H, 2 $\text{C}_6\text{H}_4$ );  $m/e$  (CI with  $\text{NH}_3$ ): 364( $\text{M} + \text{H}^+$ ), 364.1463(calcd 364.1463). **15**:  $\delta$  2.71(t, 2H,  $J=7.6$  Hz,  $\text{CH}_2\text{CH}_2\text{O}$ ), 4.01(t, 2H,  $J=7.6$  Hz,  $\text{CH}_2\text{CH}_2\text{O}$ ), 4.51(s, 2H,  $\text{C}_{10}\text{H}_6\text{-CH}_2\text{O}$ ), 7.23(m, 2H,  $\text{C}_{10}\text{H}_6$ ), 7.48(m, 4H,  $\text{C}_{10}\text{H}_6$ );  $m/e$  (CI with  $\text{NH}_3$ ): 154( $\text{M} - \text{CH}_2\text{O}$ ), 184.0887(calcd 184.0888).
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9. The conversion of **12** to **15** was found to be quantitative by GC/MS.
10. Gas chromatographic analyses were performed isothermally at 150 °C at a rate of 10 °/min, cold injection, on a Hewlett-Packard 5890 operated with a fused silica capillary column (25x0.2), a flame ionization detector and a 3392A HP integrator. GC/MS were performed on a Varian 3500 capillary gas chromatograph with a Finnigan Mat 700 Ion Trap detector. All injections were made after removal of solvent, in acetone.
11. The program used is Model-version KS 2.7. This is a modified version of Model (version 1.1) written by Kosta Steliou, University of Montreal (June 1986), with Professor Clark Stills' (Columbia University) permission. Model is an interactive molecular modeling program using the Allinger MM2 force field and minimization scheme.
12. For the nitrogen, carbon and sulfur 10-membered benzo-cyclics the cd distances for the cis conformer is found to be: 3.16 Å, 3.20 Å and 3.24 Å, respectively.
13. Sondheimer, F.; Wong, H.N.C. *Tetrahedron Lett.* **1980**, *21*, 217.