Efficient Route to the Nine-Membered Cyclic Diyne System: Tuning of the Extremely Facile Cope Rearrangement of 1,5-Diyne

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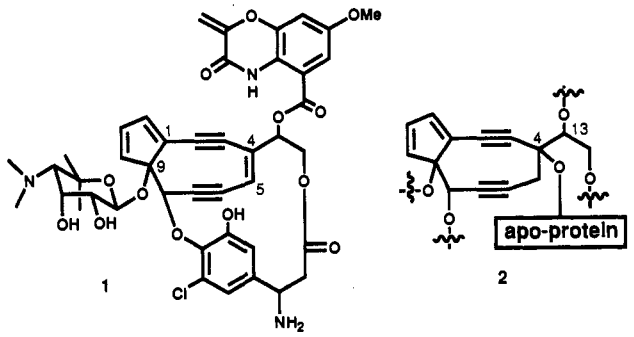
Very recently, a chromophore of both the potent antitumor, antibiotic chromoprotein C-1027 (**1**)[1] and kedarcidin[2] has been shown to possess a highly strained bicyclo[7.3.0]dodecadiyne core structure. Since such nine-membered 3-ene-1,5-diyne systems

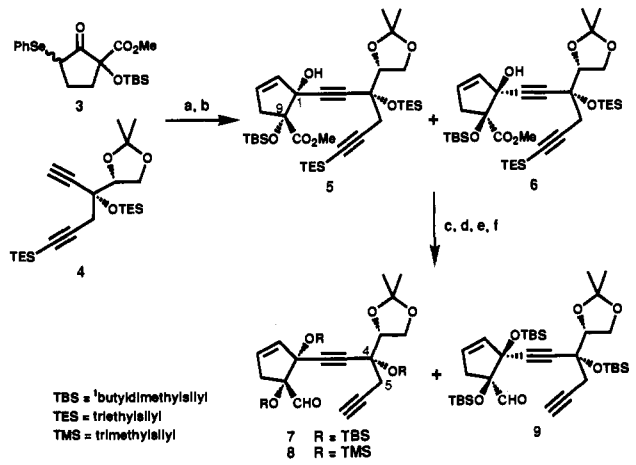


1 2

are highly labile to undergo cycloaromatization at ambient temperature,[1-3] a specific mechanism which prevents spontaneous aromatization of **1** should be identified in the holoprotein. Although some noncovalent stabilization interactions have been suggested between **1** and the apoprotein, they have not been verified.[1b,4] The most simple alternative might be to bond them covalently as a protein conjugate **2**.[5] This strategy, which masks the 3-ene-1,5-diyne system **1** as a 1,5-diyne **2**, is also a fascinating approach from the perspective of design and synthesis of related DNA-cleaving molecules.[3b,6] We describe here a general and efficient route to the highly strained bicyclo[7.3.0]dodecadiyne system and a fine tuning of the extremely facile Cope rearrangement of nine-membered cyclic 1,5-diynes.

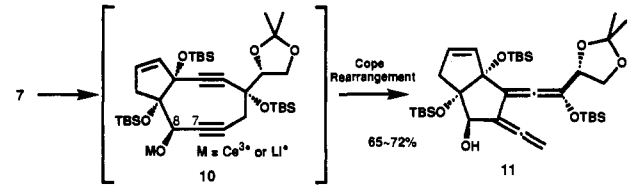
Several groups have recently succeeded in synthesizing the relevant nine-membered diynes. They used techniques to minimize the high enthalpic and entropic barriers, such as ring contraction,[3b,6,7] assembly of either a *cis*-epoxide[8a] or *cis*-olefin between the two acetylenic bonds, and bending of the acetylenic bond as a cobalt complex.[9] These results encouraged us to examine the straightforward construction of the bicyclo[7.3.0]dodecadiyne system through an intramolecular acetylide addition, from a precursor such as **7**, which possesses a conformationally nonrigid C4–C5 single bond.

Scheme 1[a]



[a] (a) EtMgBr, THF, −78 °C to room temperature, 79%; (b) THF, 82%; (c) TBAF, THF, 93%; (d) $^tBuMe_2SiOTf$, 2,6-lutidine, CH_2Cl_2, 85%, or Me_3SiOTf (77%); (e) DIBAL-H, CH_2Cl_2, −60 °C, 83%; (f) Dess–Martin periodinane, CH_2Cl_2, 87–97%.

Scheme 2[a]



[a] $LiN(TMS)_2$ (6–23 molar equiv), anhydrous $CeCl_3$ (7–20 molar equiv), THF (3–6 mM), −30 °C to room temperature, 30 min.

Since the absolute stereochemistry of **1** has not been determined, except for that of the amino sugar moiety,[1,10] we started our synthesis with racemic functionalized cyclopentanone **3**[11] and optically pure **4**,[12] assuming that the configurations at C4 and C13 of the putative conjugate **2** are identical to those of the neocarzinostatin chromophore.[13] Stereospecific addition of **4** to **3** gave the 1,9-*cis*-diol derivatives **5** and **6**, which were converted to the diastereomeric aldehydes **7** and **9**, respectively, as shown in Scheme 1. When cyclization of **7** was attempted by addition of a large excess of lithium hexamethyldisilazide [$LiN(TMS)_2$, 20-30 equiv in THF at −50 °C, only the C_2 symmetrical dimer was produced at a 20–40% yield, even under high-dilution conditions (2 mM). In the presence of anhydrous cerium chloride,[8,14] however, a monomeric product was formed at a higher temperature (−30 °C to room temperature). Surprisingly, a bis-allene **11**[15] was isolated as a single stereoisomer at a yield of up to 72%. Formation of the C7–C8 bond clearly indicated that the nine-membered cyclic diyne **10** acted as an intermediate and was followed by Cope rearrangement (Scheme 2). A similar dimerization and allene formation were also observed in the reactions of diastereomer **9**. The $LiN(TMS)_2/CeCl_3$-mediated slow

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(7) Wender, P. A.; Harmata, M.; Jeffrey, D.; Mukai, C.; Suffert, J. *Tetrahedron Lett.* **1988,** *29,* 909.

(8) (a) Myers, A. G.; Harrington, P. M.; Kuo, E. Y. *J. Am. Chem. Soc.* **1991,** *113,* 694. (b) Nishikawa, T.; Isobe, M.; Goto, T. *Synlett* **1991,** 393.

(9) Magnus, P. *Tetrahedron, Symposia-in-Print* **1994,** *50,* 1397.

(10) Iida, K.; Ishii, T.; Hirama, M.; Otani, T.; Yoshida, K.; Minami, Y. *Tetrahedron Lett.* **1993,** *34,* 4079.

(11) Prepared from 1-(methoxycarbonyl)-2-[(trimethylsilyl)oxy]cyclopentene (three steps).

(12) Prepared from 1,2:5,6-di-*O*-isopropylidene-D-mannitol (six steps).

(13) (a) Edo, K.; Mizugaki, M.; Koide, Y.; Seto, H.; Furihata, K.; Otake, N.; Ishida, N. *Tetrahedron Lett.* **1985,** *26,* 331. (b) Myers, A. G.; Proteau, P. J.; Handel, T. M. *J. Am. Chem. Soc.* **1988,** *110,* 7212.

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(15) The configuration of the newly formed secondary alcohol was determined by an advanced Mosher method: Kusumi, T.; Ohtani, I.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991,** *113,* 4093.

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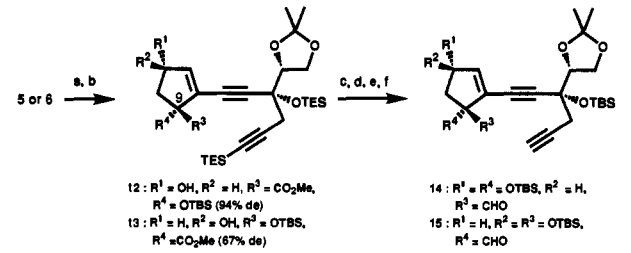
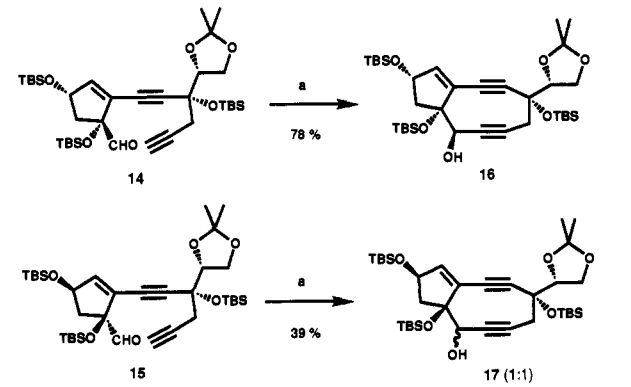
Scheme 3[a]



[a] (a) PCC, 3 Å molecular sieves, CH_2Cl_2; (b) Darvon alcohol, $LiAlH_4$, Et_2O, –30 °C; (c) TBAF, THF; (d) $^tBuMe_2SiOTf$, 2,6-lutidine, CH_2Cl_2; (e) DIBAL-H, CH_2Cl_2, –60 °C; (f) Dess–Martin periodinane, CH_2Cl_2; **14**, 54% from **5**; **15**, 38% from **6**.

Scheme 4[a]

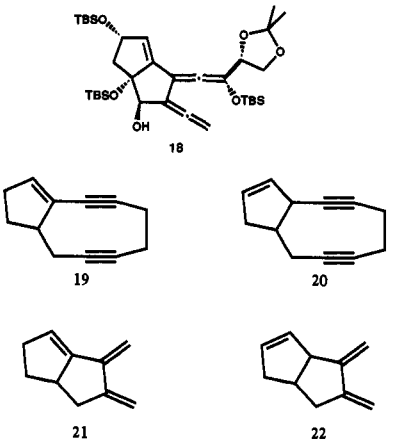


[a] (a) $LiN(TMS)_2$ (10–23 equiv), anhydrous $CeCl_3$ (11–25 molar equiv), THF (1–2 mM), –40 °C to room temperature 1 h.

cyclization of TMS ether **8** and subsequent rapid rearrangement to the corresponding bis-allene occurred even at –78 °C. Cope rearrangement of acyclic 1,5-diynes has been shown to occur above 200 °C.[16] Thus, we found that the bicyclo[7.3.0]-dodecenediyne system, such as in **10**, undergoes an extremely facile Cope rearrangement.

We next examined how we could suppress this rearrangement. Review of the relevant isolated systems[3b,6,8a] suggested that a common structural feature among them is that they contain a cyclopentene double bond exo to the nine-membered ring. Therefore, we synthesized **14** and **15** from **5** and **6**, respectively, as shown in Scheme 3.[15,17] Addition of **14** to the $LiN(TMS)_2$/$CeCl_3$ mixture at –40 °C followed by stirring at room temperature for 1 h yielded a cyclic diyne **16**[15] as a single stereoisomer at a yield of 78% without contamination of the corresponding bis-allene (Scheme 4). Cyclization of the diastereomer **15** also occurred under the same reaction conditions, but nonstereoselectively to give a 1:1 mixture **17** in a moderate yield. ^{13}C-NMR data for **16** and **17**, which are not stable at room temperature but can be stored in solution at –20 °C without deterioration, are consistent with the nine-membered strained acetylenic bonds.[7,8a,13a]

Cope rearrangement of **16** to the bis-allene **18** took place in deoxygenated toluene-d_8 at a higher temperature. The half-life for rearrangement of **16** at 50 °C is 6.4 h (^1H NMR analysis), which indicates that the rate of the Cope rearrangement can be modified by a small structural change, such as the shift of a double bond. Molecular mechanics calculations (CAChe, MM2) for the model compounds **19**–**22** showed that the total energy of **20** is 0.72 kcal/mol higher than that of **19**, and that of **22** is 3.33 kcal/mol less than that of **21**, in which the internal exo double bond substantially destabilizes the bicyclo[7.3.0] system. This calculation suggests that the transformation **10** → **11** is more exothermic, so that **10** would more readily undergo rearrangement than **16** or **17**.



Previous syntheses of both cyclononadiyne and cyclodecadiyne rings related to enediyne antibiotics[18] via intramolecular acetylide additions were ensured by the presence of at least two structural elements which reduced the degree of conformational freedom of the substrate, i.e., *cis*-olefin (or *cis*-epoxide) and an additional five- or six-membered carbocyclic fused ring. In this study, we have demonstrated that $LiN(TMS)_2/CeCl_3$-mediated cyclization procedures[8] can be used to construct the highly strained cyclononadiyne system when the former principal element is absent. The diynes **16** and **17** possess the appropriate functionality to synthesize the chromophores of C-1027[1] and kedarcidin.[2] Efforts to extend the present research are now underway.

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Supplementary Material Available: ^1H-NMR, ^{13}C-NMR, FTIR, and MS or HRMS for **7**, **9**, **11**-**18**, the procedures for the synthesis of **11**, **16**, and **17**, and the synthetic schemes for **3** and **4** (11 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(17) The stereoselectivity of the Darvon alcohol-modified LAH reduction of the intermediate ketones was governed by the C9 stereochemistry; ratio of **12** and its diastereomer = 31:1, **13**:isomer = 5:1. The configuration was determined by NOE experiments.

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