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Concise Synthesis of the Bicyclic Core of the Chromoprotein Antibiotics Kedarcidin and Neocarzinostatin by Transannular Reductive Cyclization of a Tetrayne Precursor.

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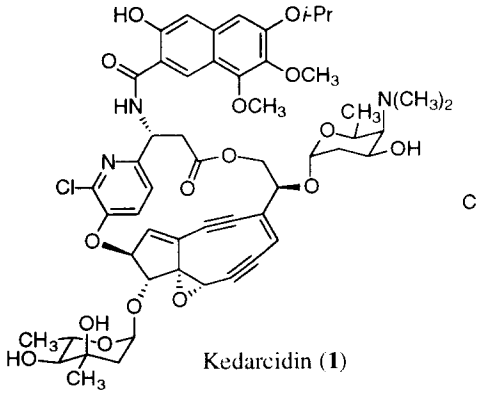
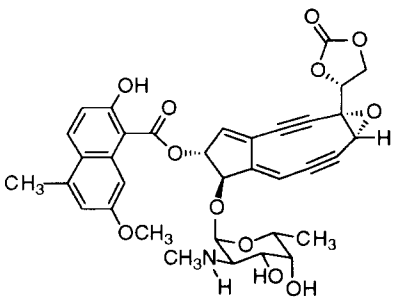
Abstract: The oxygenated [7.3.0]-bicyclododecadienediyne **8** is synthesized in 9 steps from L-dimethyl tartrate. In the key transformation, transannular reductive cyclization of the potassium salt of the tetrayne alcohol **7** with $NaAlH(OCH_2CH_2(NCH_3)_2)_2$, affords the bicyclic product **8** in 50-54% yield. This sequence provides a rapid entry into the strained bicyclic core structures of kedarcidin and neocarzinostatin chromophores (**1** and **2**, respectively).

The chromophore components of the chromoprotein (enediyne) antitumor agents kedarcidin (**1**) and neocarzinostatin (**2**) share a common bicyclic core, but differ in the site of epoxidation within each structure. Acetate incorporation studies suggest that the biosynthetic route to these intriguing structures, in its early stages, may resemble the pathway leading to the naturally occurring linear polyacetylenes, but nothing is known of the steps that form the unsaturated bicyclic framework.[1] In this work we describe a concise synthetic route to the bicyclic core of these agents that utilizes a cyclic polyacetylene precursor and proceeds by a transannular cyclization pathway.

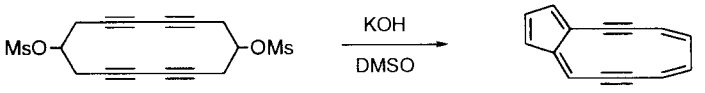


Kedarcidin (**1**)



Neocarzinostatin (**2**)

The inspiration for a transannular cyclization route to the enediyne antibiotics derives from the remarkable transformation shown below, reported by Mayer and Sondheimer in 1966.[2] We have investigated a



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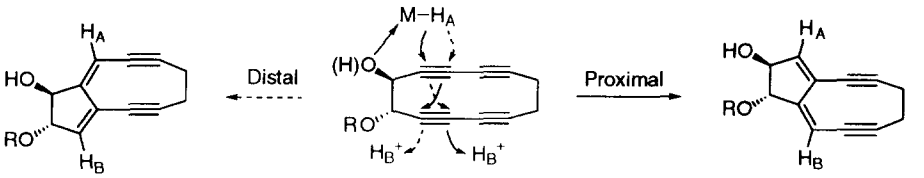
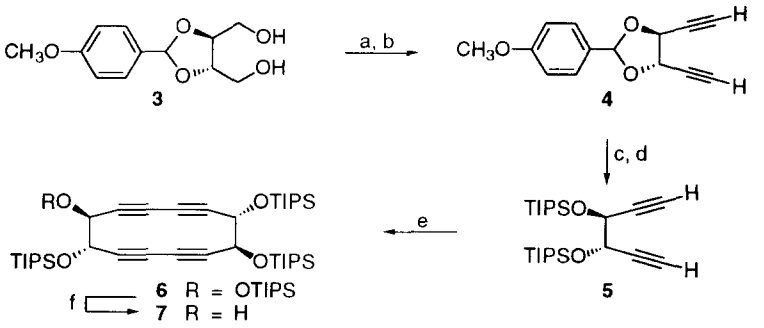
mechanistically distinct transannular cyclization reaction that accommodates the pattern of oxidation within **1** and **2**. This pathway makes use of a hydroxyl group to direct metal hydride addition to an adjacent triple bond in a cyclic tetrayne precursor with concomitant transannular cyclization. As shown below, addition of hydride to either the proximal or the distal carbon of the alkyne could, in principle, produce the kedarcidin/neocarzinostatin ring system. Both modes of addition are precedented in acyclic systems in Corey's pioneering studies of the reduction of propargylic alcohols.[3]



Cyclization reactions were studied using the cyclic tetrayne **7**, prepared by the route shown. Thus, Swern oxidation of the known L-tartrate-derived diol **3**[4] followed by direct subjection of the resulting dialdehyde to dibromoolefination[5] afforded the corresponding bis-dibromoolefinated product.[6] Treatment of this product with *n*-butyllithium (4.1 equiv) afforded the diyne **4** in 75% yield.[7] After exchange of the hydroxyl protective groups (**4** → **5**), copper-mediated oxidative dimerization of **5** then provided the crystalline, D_2-symmetric cyclic tetrayne **6** in 52% yield.[8] In the solid state, **6** was stable to storage at –20 °C for several months, however, solutions of **6** were found to be sensitive to oxidative decomposition upon standing at 23 °C. X-ray crystallographic analysis



(a) i. $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C; ii. PPh_3, CBr_4, Et_3N, CH_3OH, 0 °C.[6] (b) *n*-BuLi, THF, –78 → 0 °C, 75%. (c) 3N HCl, THF, 98%. (d) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 → 25°C, 94%. (e) $Cu(OAc)_2$, DBU, O_2, pyridine, Et_2O, 60 – 80 °C, 52%. (f) $Et_3N{\cdot}3HF$, THF, 61%.

of **6** showed that the triple bonds are distinctly nonlinear (∠C(2)-C(3)-C(4) = 163.5° and ∠C(3)-C(4)-C(5) = 168.3°) and that the carbocyclic ring is twisted from planarity (C(1)-C(2)-C(7)-C(8) dihedral angle = 54°). Presumably, this twisting relieves transannular non-bonded interactions of the π electrons[9] while simultaneously positioning the bulky triisopropylsilyl ether groups in pseudo-equatorial orientations.

Limited exposure of tetrayne **6** to triethylamine trihydrofluoride afforded the alcohol **7** in 61% yield.[11] Treatment of solutions of **7** in THF at 0 °C with $NaAlH_2(OCH_2CH_2OCH_3)_2$ ("Red-Al", 1 equiv)[12] afforded a

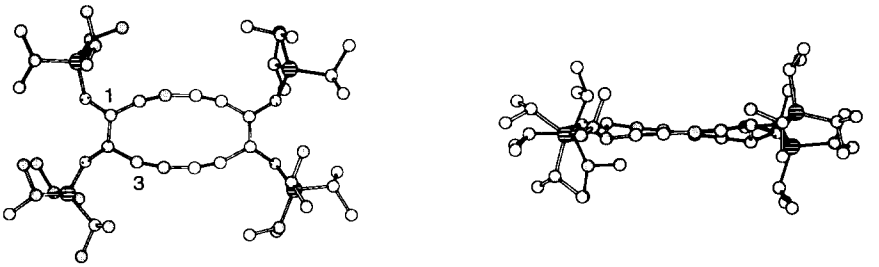
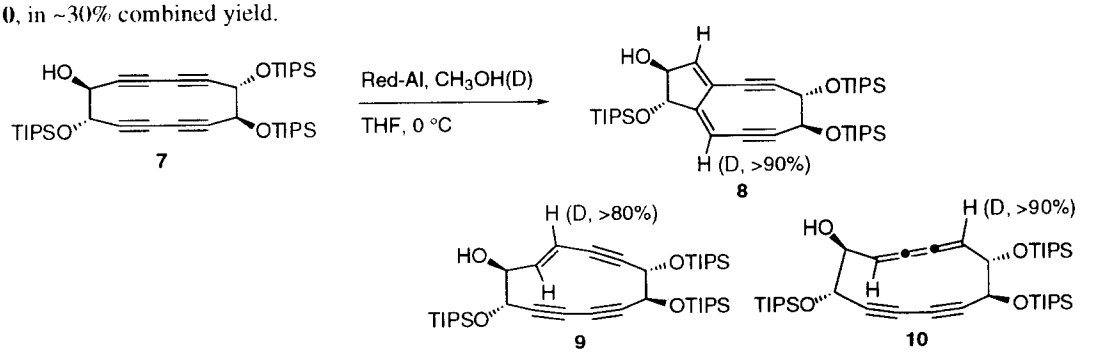


Figure 1. X-ray Crystal Structure of Tetrayne **6**.[10]

mixture of the desired transannular cyclization product **8** and two isomeric, non-cyclized products, *trans*-olefin **9** and *trans*-cumulene **10**, in yields and ratios that varied with the water content of the reaction mixture.[13] Rigorously dried substrate solutions produced only the non-cyclized products **9** (43%) and **10** (8%), whereas protic additives were found to promote the formation of **8**. For example, addition of Red-Al (5.7 equiv) to a solution of **7** in THF containing methanol (10 equiv) at 0 °C afforded approximately equal amounts of **8**, **9**, and **10**, in ~30% combined yield.



Deuterium incorporation experiments under the latter conditions (using methanol-*d*) showed that all three products were formed by hydride addition to the proximal carbon of the acetylene followed by deuteriation with the position selectivity indicated in the scheme above. The proximal mode of hydride addition is well precedented in both cyclic and acyclic systems.[3,14] Reagents that favor a distal mode of hydride addition in acyclic systems (LAH/$AlCl_3$, *n*-BuLi/DIBAL)[3] are also known, but lead to decomposition when combined with **7**. To date, we have no evidence for the formation of any products from **7** by a distal hydride addition pathway.

The fact that protic additives were required to form **8** suggested that a modified reducing reagent was involved in the pathway leading to this product, perhaps a trialkoxyaluminum hydride reagent formed in situ. Consistent with this analysis, addition of the preformed trialkoxyaluminum hydride reagent $NaAlH(OCH_2CH_2OCH_3)_3$ (1 equiv)[15] to a solution of **7** in THF at 0 °C afforded greater amounts of **8** (16%) relative to **9** (13%) and **10** (10%). Products **9** and **10** were believed to arise from the quenching of a vinyl aluminate intermediate by the hydroxyl group of **7** before cyclization could occur. In support of this idea, it was found that deprotonation of the hydroxyl group of **7** prior to reduction led to a pronounced improvement in the yield of **8**. Optimum results were obtained using potassium bis(trimethylsilyl)amide (KHMDS) as base in combination with the reductant formulated as $NaAlH(OCH_2CH_2N(CH_3)_2)_3$.[16] Thus, addition of KHMDS (1

equiv) to a solution of **7** in THF at –78 °C followed by 1.0 equiv of $NaAlH(OCH_2CH_2N(CH_3)_2)_3$ afforded **8** in 50-54% yield and **9** in 16% yield.[17] It should be noted that implicit in the mechanistic speculations which guided these studies is the premise that the transannular reductive cyclization occurs by a stepwise rather than a concerted process and that **8**, **9** and **10** arise from a common intermediate. If this premise is correct, it is clear, in retrospect, that the putative vinyl aluminate intermediates formed from the reaction of **7** and Red-Al, and **7**, KHMDS, and $NaAlH(OCH_2CH_2N(CH_3)_2)_3$ have very different reactivities. The failure of the former intermediate to cyclize may reflect its stability; a cyclic alkoxy vinyl aluminate intermediate is frequently invoked in these reactions.[3,14]

The methodology described provides a rapid entry into the neocarzinostatin-kedarcidin core structures and demonstrates the viability of a transannular cyclization pathway for such an application. Studies are underway to determine if this chemistry is compatible with functionally more complex structures that might lead to **1** and **2**.

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References and Notes

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2. Mayer, J.; Sondheimer, F. *J. Am. Chem. Soc.* **1966**, *88*, 602, 603. This work is remarkable not only for the transformation depicted, but also for the fact that, to the best of our knowledge, it describes the earliest example of a biradical-forming electrocyclization reaction.
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6. It was crucial to the success of these transformations that the temperature of the Swern oxidation be maintained at –78 °C and that methanol be added to the dibromoolefination reaction in order to consume triphenylphosphine dibromide generated in situ. On scales <10 g, the bis-dibromoolefinated product was isolated in 65-79% yield; using 32 g of diol **3** the yield was 38%.
7. All new compounds afforded satisfactory spectroscopic and analytical data.
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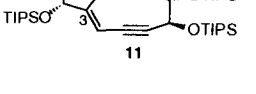
10. The structure shown is actually the enantiomer of **6**, which was synthesized by an identical procedure, albeit starting with D-dimethyl tartrate.
11. By-products arising from over-desilylation were recovered and transformed to **6** by treatment with TIPSOTf and 2,6-lutidine in dichloromethane at 23 °C (mass recovery ~ 96%).
12. (a) Chan, K.; Cohen, N.; De Noble, J. P.; Specian, A. C., Jr.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3497.
13. Triisopropylsilylation of **8** and **10** afforded a non-C_2-symmetric and a C_2-symmetric product respectively, thereby excluding [8.2.0]- and [6.4.0]-bicyclododecadienediyne structures from consideration in the assignment of **8**, and establishing that the cumulene **10** possessed trans stereochemistry. The structure **8** was distinguished from the isomeric structure that would arise from distal hydride addition (vide supra) by ^1H-^{13}C HETCOR NMR spectroscopy. In addition, epoxidation of **8** with *m*-CPBA, a process assumed to be hydroxyl directed, afforded an epoxide (**11**) whose ^{13}C NMR spectrum established that epoxidation of the olefin endocyclic to the 5-membered ring (rather than the 9-membered ring) had occurred.



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17. The small amount of residual olefin **9** is believed to result from the quenching of a vinyl aluminate intermediate by hexamethyldisilazane.