Experimental Section

To a suspension of zinc (200 mg, 3.06 mmol) in dry THF (10 mL) was added 4-bromo-2-methyl-2-butene (200 mg, 1.34 mmol), and the solution was stirred at room temperature for 1 h. The solution was filtered through a Schlenk filter and kept under argon for the following reaction. To a solution of (1*R*,2*S*,3*R*)-(+)-3-[*N*-benzenesulfonyl-*N*-(3,5-dimethylphenyl)amino]-2-bornanol (116 mg, 0.28 mmol) in dry THF (5 mL) was added the solution of prenylzinc bromide prepared above and the solution was stirred at room temperature for 15 min. The solution was treated with aldehyde **1** (40 mg, 0.19 mmol) and HMPA (0.5 mL, 2.87 mmol) and was heated to reflux for 72 h. A saturated aqueous solution of NH_4Cl (5 mL) was added into the reaction mixture. The solution was diluted with EtOAc (50 mL), washed with brine (30 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography with EtOAc/hexane (5/95) ($R_f = 0.38$ in EtOAc/hexane, 10/90) to give alcohol **2** as a colorless oil (47 mg, 87 % yield). IR (neat): $\tilde{\nu} = 3382$, 2930, 2921, 2847, 1466, 1378, 1254, 1107, 1061, 835, 775 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 5.53$ (t, $J =$ 5.5 Hz, 1H), 5.09 (t, $J = 7.2$ Hz, 1H), 4.21 (d, $J = 6.0$ Hz, 2H), 3.98 (t, $J =$ 5.5 Hz, 1H), 2.20 – 2.27 (m, 2H), 1.70 (d, $J = 1.0$ Hz, 3H), 1.62 (s, 6H), 1.59 – 1.63 (m, 1H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 137.88$ (C), 134.81 (C), 125.97 (CH), 119.91 (CH), 76.59 (CH), 60.01 (CH_2), 34.02 (CH_2), 25.94 ($3 \times CH_3$), 25.82 (CH_3), 18.34 (C), 17.93 (CH_3), 12.03 (CH_3), – 5.13 ($2 \times CH_3$); MS: *m*/*z* (%): 284 (M^+, 1), 215 (48), 157 (23), 83 (100), 75 (92), 73 (62), 70 (25), 69 (28); HRMS calcd for $C_{16}H_{32}O_2Si$ (M^+): 284.2172; found: 284.2177.

Received: August 19, 1997 [Z 10829 IE]
German version: *Angew. Chem.* **1998**, *110*, 482 – 484

Keywords: alkylations · asymmetric synthesis · prenyl anions · rosiridol · total synthesis

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[13] The structure of rosiridol was further confirmed unambiguously by NOESY, COSY, HMQC, DEPT, and HMBC experiments. $[\alpha]_D^{25} = -7.1$ ($c = 0.4$ in acetone); lit.: $[\alpha]_D^{25} = -7.7$ ($c = 1.0$ in acetone).[4]
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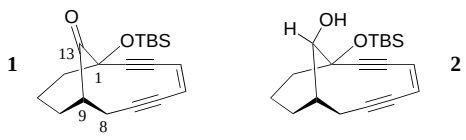
Actuating Cycloaromatization of a Bicyclo[7.3.1]enediyne by Annelation: An Example of Inverse Dependence on Bridge Atom Hybridization**

Michael H. Nantz,* David K. Moss, John D. Spence, and Marilyn M. Olmstead

The calicheamicin and esperamicin enediynes[1] have inspired numerous synthetic and mechanistic studies aimed toward understanding their DNA-cleaving activity.[2] In addition to natural calicheamicin γ_1^I,[3] many structural mimics have been synthesized and shown[4] to undergo the principal transformation responsible for the biological activity, Bergman cycloaromatization[5] of the 1,5-diyn-3-ene unit. We have been especially intrigued by the work of Magnus et al. who first determined the reactivity of bicyclo[7.3.1]enediyne analogues.[6] They showed that the bicyclo[7.3.1] ring of **1** is resistant to enediyne cycloaromatization at ambient temperature and reacts slowly[7] at 71 °C to form the corresponding C(2)–C(7) benzenoid product. In contrast, a change in the hybridization of the one-carbon bridge (C13) from sp^2 to sp^3 (**1** → **2**) was shown to effect a dramatic increase in the rate of cycloaromatization.[8] The tendency toward cycloaromatization was attributed to strain attenuation. These observations point toward the possibility of devising a bicyclo[7.3.1] model system wherein rehybridization of the one-carbon bridge may



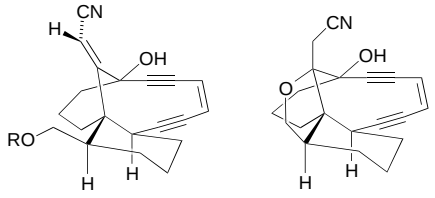
[*] Prof. M. H. Nantz, D. K. Moss, J. D. Spence, Dr. M. M. Olmstead
Department of Chemistry, University of California
Davis, CA 95616 USA
Fax: (+1) 916-752-8995
E-mail: mhnantz@ucdavis.edu

[**] Support of this work by the University of California Cancer Research Coordinating Committee is gratefully acknowledged.

  1433-7851/98/3704-0470 $ 17.50+.50/0

occur through intramolecular reaction, analogous to the activation mode of the natural enediynes.[9]

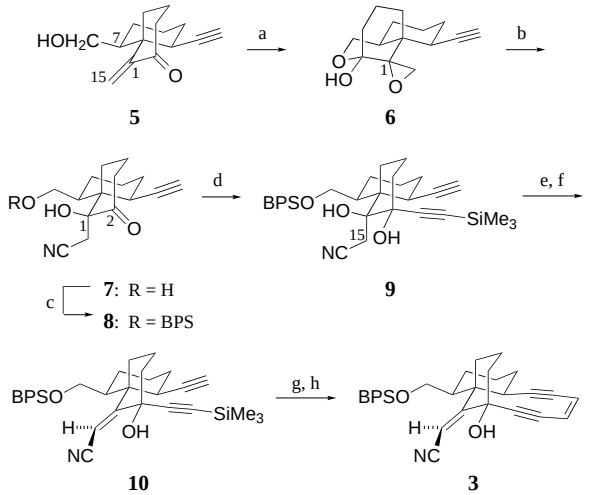
We report here on the synthesis of a system that incorporates these features. We have rigidly positioned a nucleophilic group near the bridging carbon by annelation of a cyclohexane ring to the C(8)–C(9) bond of the ten-membered carbocycle. To closely mimic the natural enediynes, a Michael acceptor group was chosen to replace the bridging carbonyl of **1**. These changes are illustrated in structure **3**. Enediyne **3** (R = Si*t*BuPh$_2$) has been prepared and unmasked to give **4**, the product of an intramolecular Michael addition to the one-carbon bridge of the bicyclo[7.3.1] system. A study of the



3 **4**

cycloaromatization kinetics for enediynes **3** and **4** has revealed that, in contrast to the Magnus system, rehybridization from sp^2 to sp^3 along the ten-membered ring serves to inhibit cycloaromatization.

Scheme 1 depicts a synthesis of **3** from spirocyclic enone **5**, which is available from monoethyl malonate in eight steps and 24% yield.[10] To convert C(1) of **5** into an electrophilic one-carbon bridge, C(1) was transformed into the β-center of a vinyl nitrile. Treatment of **5** with basic *tert*-butyl hydroperoxide in benzene[11] afforded a separable 7:1 mixture of epoxide diastereomers in 84% combined yield. The assigned stereochemistry at C(1) for the major isomer **6** is tentative.[12]

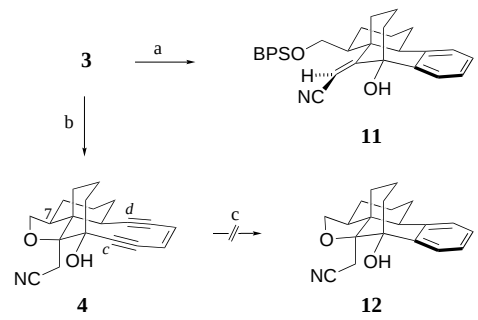


5 **6** **9** **10** **3**

Schema 1. a)*t*BuOOH, Triton-B, C_6H_6, room temperature (RT), 74%; b) Et_2AlCN (5 equiv), toluene, RT, 71%; c) BPSCl, *i*Pr$_2$NEt, DMAP, pyridine, reflux, 75%; d) LiCCTMS (10 equiv), $CeCl_3$ (15 equiv), THF, $-78\,^{\circ}C$, 88%; e) (imid)$_2$C=O, C_6H_6, reflux; f) DBU, C_6H_6, RT, 57% over two steps; g) NIS (2.2 equiv), $AgNO_3$ (0.5 equiv), acetone, $0\,^{\circ}C$, 94%; h) (*Z*)-Me$_3$SnCHCHSnMe$_3$ (2 equiv), [Pd(PPh$_3$)$_4$] (0.1 equiv), LiCl (2 equiv), DMF, $50\,^{\circ}C$, 57%. DMAP = 4-dimethylaminopyridine, imid = imidazol-1-yl, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, NIS = *N*-iodosuccinimide.

Spectroscopic analysis indicates that **6** resides exclusively in its hemiacetal form. Hydrocyanation of **6** using Et_2AlCN according to the method of Nagata[13] gives adduct **7**, which was monosilylated under forcing conditions to afford the *tert*-butyldiphenylsilyl (BPS) derivative **8**. Examination of molecular models suggested that the 1,2-addition of an acetylide anion to C(2) of **8** might proceed stereoselectively to give the axial alkyne required for enediyne installation. Indeed, treatment of **8** with cerium trimethylsilylacetylide[14] generated in situ gave a single 1,2-addition product, assigned diyne **9**, in 88% yield. To differentiate the vicinal tertiary hydroxyl groups in **9** for selective elimination of the C(1) hydroxyl group, a cyclic carbonate was formed to exploit the acidity of the adjacent C(15) methylene position. Reaction of **9** with 1,1′-carbonyldiimidazole in benzene followed by treatment with DBU effected β-elimination of the carbonate to give a single vinyl nitrile stereoisomer in 57% yield. The least sterically encumbered transition state for carbonate elimination favors formation of the (*Z*) isomer, and, consequently, the elimination product has been assigned structure **10**. Completion of the enediyne carbocycle followed an approach developed by Danishefsky et al.[15] Treatment of diyne **10** with *N*-iodosuccinimide in the presence of catalytic silver nitrate converted each alkynyl group into an iodoalkynyl group.[16] Subsequent palladium-mediated cross coupling of the diiodide with (*Z*)-1,2-bis(trimethylstannyl)ethene[17] gave **3** in 57% yield. Enediyne **3** was readily purified and stored without notable change.[18]

Cycloaromatization studies were conducted in 1,4-cyclohexadiene. Enediyne **3** was heated to $37\,^{\circ}C$ to promote cycloaromatization (Scheme 2). At this temperature complete



4 **11** **12**

Schema 2. a) 1,4-Cyclohexadiene, $37\,^{\circ}C$, 2.5 d, 76%; b) *n*Bu$_4$NF (2.5 equiv), THF, RT, 46%; c) 1,4-cyclohexadiene, $60\,^{\circ}C$, 7 d.

consumption of starting enediyne requires roughly 2.5 days and gives benzenoid product **11** in 76% yield. The reactivity of **3** was assessed further by ^{1}H NMR analysis at temperatures ranging from 55 to $85\,^{\circ}C$. Analysis of the data provided the first-order rate constants shown in Table 1. Extrapolated to $37\,^{\circ}C$, the cycloaromatization rate of **3**, $k = 4.52 \times 10^{-5}\ s^{-1}$, is an order of magnitude faster than the extrapolated rate reported for **1**.[7] Molecular modeling of **3** predicts the transannular distance between the remote acetylenic carbons of the enediyne unit ($c-d$ distance[19]) to be identical to that measured in **1**.[20] Thus, the enhancement in reactivity is principally a function of cyclohexane annelation.[21] Presum-

  1433-7851/98/3704-0471 $ 17.50+.50/0

Table 1. Kinetic parameters for the thermal cyclization of **3**.

T[°C]	k[s^{-1}]	$t_{1/2}$[min]
55	1.72×10^{-4}	67
62	4.13×10^{-4}	28
71	7.22×10^{-4}	16
78	1.20×10^{-3}	9.6
85	1.56×10^{-3}	7.4

ably the added cyclohexane ring serves to lower the transition state energy for 1,4-diyl formation.[22] Calculation of the differential strain energy (ΔSE) for the **3**→**11** transition according to the method of Maier et al.[23] suggests that the activation energy for the cyclization of **3** is 37% less than that for the cyclization of **1**. Although this approximation supports the postulated effect of the annulation, other factors may contribute and remain to be fully understood.

Compound **3** was treated with nBu$_4$NF to effect desilylation of the C(7) silyloxymethyl group. The liberated hydroxyl group spontaneously adds to the resident vinyl nitrile to give enediyne **4** (Scheme 2) as an isolable crystalline compound. X-ray crystallographic analysis of **4** (Figure 1) yielded a $c-d$ distance of 3.24 Å, a distance smaller than that calculated in **3**

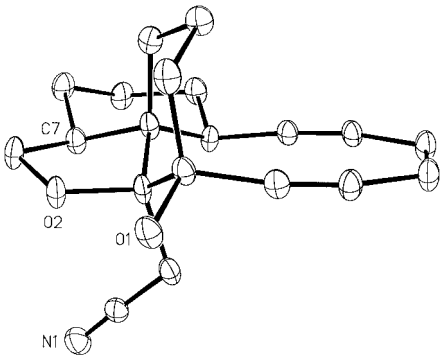


Abb. 1. X-ray crystal structure of enediyne **4**; for clarity 30% probability ellipsoids are depicted and H atoms are removed.

and well within the range for cycloaromatization.[24] However, and in stark contrast to the reactive enediyne **2**,[8] enediyne **4** is resistant to cycloaromatization at ambient temperature. Furthermore, when a solution of **4** in 1,4-cyclohexadiene was heated at 60°C for one week the enediyne was completely recovered. The stability of **4** constitutes an unusual reversal in the behavior of ten-membered enediynes that have undergone rehybridization. Prior to this example, a change in the hybridization of carbon along the enediyne core from sp^2 to sp^3 was known to facilitate cycloaromatization.[2]

Comparison of the calculated ΔSE[23] values for the **3**→**11** and **4**→**12** transformations suggests that enediyne **3** should undergo a more facile transition to its aromatized product; however, the unusual resistance of **4** to cyclization is not readily rationalized by this method.[25] The extraannular strain imparted by tetrahydrofuran annelation presumably is sufficient to deter cycloaromatization, a postulate that may be tested by expanding the heterocycle. Heating **4** at 90°C also failed to effect cycloaromatization; however, unlike the experiment at 60°C, **4** was gradually degraded to multiple products at this temperature. The cyclized product **12** was not detected in the product mixture.

Annelation of a bicyclo[7.3.1]enediyne core has been shown to alter the cycloaromatization reactivity typically controlled by the one-carbon bridge. Unlike prior systems, the enediyne containing an sp^3-hybridized bridging carbon atom is resistant to cycloaromatization whereas the immediate sp^2-hybridized precursor enediyne readily undergoes transformation to its benzenoid counterpart. Given the magnitude of the annulation effect on both actuating and deterring cycloaromatization, this controlling feature may prove to be useful for tuning enediyne systems for physiological applications.

Received: August 26, 1997 [Z10858IE]
German version: *Angew. Chem.* **1998**, *110*, 476–479

Keywords: annulation · cycloaromatizations · enediynes · kinetics · spiro compounds

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[18] A sample of **3** was stored at $-20\,^{\circ}C$ for one week and analyzed. The ^1H NMR spectrum of this material was identical to the spectrum that was obtained from freshly purifed **3**.
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[24] Crystal structure analysis: colorless, monoclinic, $P2_1/n$, $a=7.784(2)$, $b=20.371(6)$, $c=9.891(2)$ Å, $\beta=95.10(2)^{\circ}$, $V=1562.2(7)$ Å^3, $Z=4$, $\rho_{calcd}=1.307$ Mg m^{-3}, $T=130(2)$ K, full matrix refinement on F^2 (Siemens P4, SHELXTL 5, 2077 independent reflections, 1407 with $I>2\sigma(I)$), $R_1(F)=7.46$, $R_2(wF^2)=21.8\,\%$, GOF(F^2) = 1.066. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallogrphic Data Centre as supplementary publication no. CCDC-100780. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; E-mail: deposit@chemcrys.cam.ac.uk).
[25] The difference in the ΔSE values for the cyclization of **4** and **3** was calculated to be 2.79 kcal mol^{-1}. Full theoretical calculations will be reported in a forthcoming account of this work.

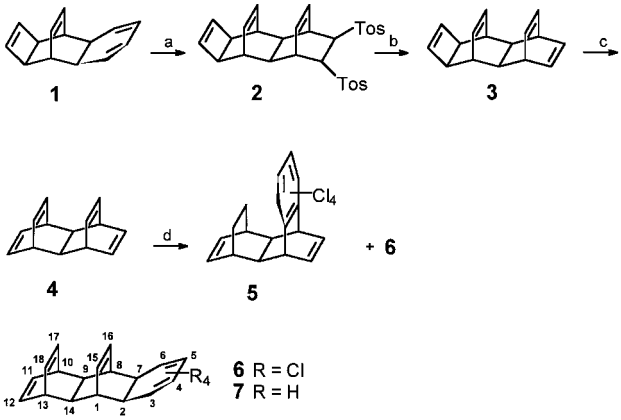
Tetrachloro-*p*-(*o*,*p*)-*o*-tribenzene: A Building Block for Diels–Alder Oligomers of Benzene and for a Laticyclic Conjugated Hexaene**

Wolfram Grimme,* Joachim Gossel, and Johann Lex

Dedicated to Professor Emanuel Vogel on the occasion of his 70th birthday

Some time ago we reported on *p*-(*o*,*p*)-*o*-tribenzene (**7**), the *endo*,*endo*-Diels–Alder trimer of benzene, and anticipated higher oligomers of this type.[1] However, experiments designed to dimerize the tribenzene by a Diels–Alder reaction failed up to 100 °C and 7.5 kbar, the limits of the compound's stability; dimerization apparently requires an activated tribenzene. We report here on tetrachloro-*p*-(*o*,*p*)-*o*-tribenzene (**6**), which undergoes a Diels–Alder reaction with itself under reverse electron demand.[2]

Cycloaddition of (*E*)-1,2-ditosylethene[3] to the tetracycle **1**[1] yields adduct **2**, which can be detosylated with sodium amalgam to pentacycle **3** (Scheme 1). In the next step the



Scheme 1. a) (*E*)-Ditosylethene, EtOAc, reflux, 24 h, 96 %; b) Na(Hg) 2 %, NaH_2PO_4, MeOH, 25 °C, 16 h, 85 %; c) 1. 2,5-dimethyl-3,4-diphenylcyclopentadienone dimer, benzene, 70 °C, 16 h, 95 %; 2. diethyl ether, low-pressure Hg burner, 2 h, 49 %; d) TCTD, benzene, 25 °C, 16 h, 95 %.

cyclobutene ring is degraded by the Dauben method,[4] which entails cycloaddition of 2,5-dimethyl-3,4-diphenylcyclopentadienone followed by photoextrusion of CO and 1,4-dimethyl-2,3-diphenylbenzene. The resulting sesquibicyclo[2.2.2]octadiene (**4**), synthesized previously by another route,[5] undergoes cycloaddition of tetrachlorothiophene dioxide (TCTD)[6] preferentially at one of the laticyclic conjugated double bonds. Through SO_2 extrusion and a dyotropic hydrogen transfer[7] at room temperature the arene **5** is formed. The desired tetrachlorotribenzene **6** is obtained from addition to one of the terminal double bonds (**6**:**5** = **1**:**3**).

Compound **6** cycloreverts to benzene and tetrachlorobenzene at 110.8 °C with a half life of $t_{1/2}=52$ min, a reaction rate

[*] Prof. Dr. W. Grimme, Dr. J. Gossel, Dr. J. Lex
Institut für Organische Chemie der Universität
Greinstrasse 4, D-50939 Köln (Germany)
Fax: (+49) 221-470-5057
E-mail: grimme@uni-koeln.de

[**] This work was supported by the Deutsche Forschungsgemeinschaft.