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Synthesis of a Calicheamicin Deoxyaglycone Model by an Intramolecular Acetylide Cyclization

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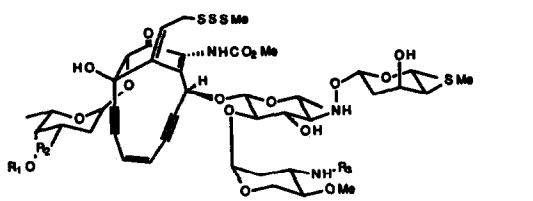
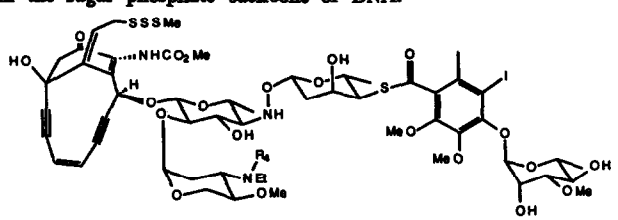
Summary: Reaction of enediyne aldehyde **16** with $LiN(SiMe_3)_2$ leads to intramolecular acetylide cyclization to the epimeric carbinols **17** comprising a deoxyaglycone model for the calicheamicins. NOE studies permit stereochemical assignments for these epimers, which in turn suggest that C-8 stereochemistry (calicheamicin numbering) assigned for the calicheamicins may require revision.

Investigators at Bristol-Myers and at Lederle have recently assigned the structures of two series of potent antitumor agents, the esperamicins (**1**)[1] and the calicheamicins (**2**)[2], respectively. These structurally remarkable natural products are glycosidic derivatives attached to a common aglycone framework, the bicyclo[7.3.1]trideca-4,9-diene-2,6-diyne system. The aglycone core possesses an allylic trisulfide, a methyl carbamate group, and the characteristic bridging 7-carbon enediyne chain believed responsible for the DNA-damaging properties of these substances. The mechanism of DNA strand scission by these agents has been proposed[1,2] which involves the bioreductive conversion of the trisulfide to a thiol, triggering intramolecular Michael addition of the thiol to the enone, and subsequent electrocyclic rearrangement[3] of the enediyne unit to a p-phenylene diradical which can abstract H atoms from the sugar phosphate backbone of DNA.

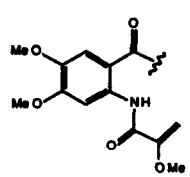


		R_1	R_2	R_3
Esperamicin	A1	H	R	$CH(CH_3)_2$
	A2	R	H	$CH(CH_3)_2$
	A1b	H	R	CH_2CH_3

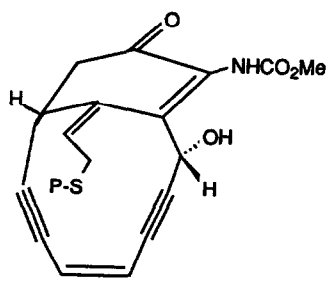


Calicheamicin R_4 = H, MeCO

R-



With the minimum requirements of an enediyne bridge and a suitable nucleophilic trigger thus defined, we selected as a target the deoxyaglycone structure **3** in which P is an appropriate protecting group. Schreiber and Kiessling have recently employed the intramolecular Diels-Alder reaction to construct the ketoester **4**, thus providing the first synthesis of the bicyclic framework of this series.[4] Our strategy on the other hand envisions the key macrocyclization to occur by an intramolecular addition of an acetylide anion to an aldehyde, as elaborated below. The precursor for this approach would be a cyclohexane-1,3-dione such as **5** in which R is a predecessor of an enediyne chain. The symmetry of **5**, in principle, permits the incorporation of the carbamate substituent by nitrosation at C-2,[5] the allylic thioether unit by Torii aldol condensation[6] with $PSCH_2CHO$ at C-4, and introduction of the aldehyde carbon at C-3 as discussed below. *This paper demonstrates the feasibility of the key macrocyclization step within this overall strategy.*



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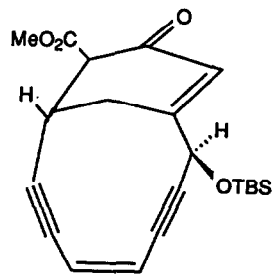

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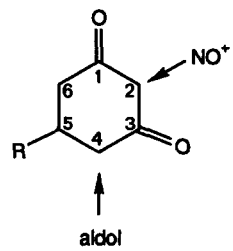
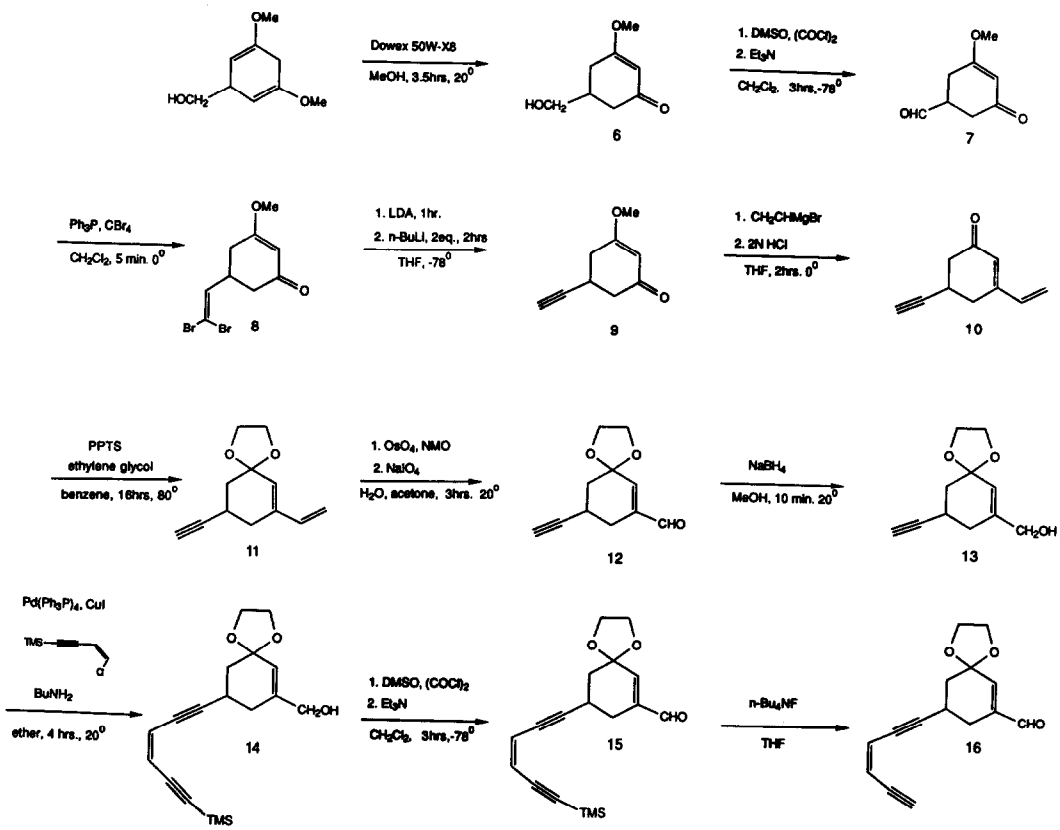


5

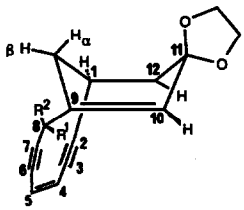
Hydrolysis of the known 3,5-dimethoxy-1,4-dihydrobenzyl alcohol[7] with Dowex 50W-X8 resin gave the β-methoxyenone **6** in 63% yield (Scheme 1).[8] Swern oxidation transformed **6** to the aldehyde **7**, which with CBr_4 and Ph_3P produced the crystalline dibromoolefin **8**, mp 84-85 °C, in 51% overall yield. Reaction of **8** with 1 equiv of LDA protected the ketone as its enolate, and subsequent addition of 2 equiv n-BuLi formed on workup the acetylene **9**, mp 72-73 °C, in 76% yield. Addition of 2.5 equiv. CH_2=CHMgBr at 0° followed by quenching with dilute HCl gave in 91% yield the conjugated dienone **10**.[9]

To stabilize subsequent intermediates, dienone **10** was converted in 61% yield to the dioxolane **11** with $HOCH_2CH_2OH$ and pyridinium p-toluenesulfonate catalysis; use of pTSA as catalyst produced significant amounts of the isomeric Δ 3,4-diene. Catalytic osmylation followed by periodate cleavage produced aldehyde **12** which was reduced by $NaBH_4$ to carbinol **13** in 61% overall yield. At this point, Castro-Stephans coupling[10] of the acetylene with (Z)-1-chloro-4-trimethylsilyl-1-buten-3-yne[11] using $Pd(PPh_3)_4$/CuI/n-$BuNH_2$ gave 59% of the silyl enediyne **14**, which was oxidized under Swern conditions to the aldehyde **15**. Desilylation with n-Bu_4NF gave in 60% overall yield the key cyclization precursor, enediyne aldehyde **16**. The structure **16** was confirmed by detailed analysis and decoupling of its 300 MHz ^{1}H-NMR spectrum, and by IR and high resolution mass spectra.[12]

SCHEME 1

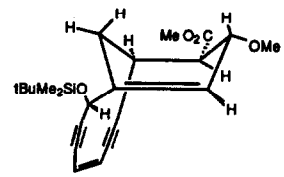


Inverse addition of **16** by syringe pump to a dilute solution of $LiN(SiMe_3)_2$ in THF for 6 hrs at 20°C, followed by aq. NH_4Cl workup, led on SiO_2 gel chromatography to the isolation of a presently inseparable 3:1 mixture of epimeric cyclized carbinols **17a** and **17b** in 42% yield (based on 30% recovered **16**). Structure **17** rests upon IR, MS, HRMS[13] as well as 300 MHz ^{1}H-NMR[14] and ^{13}C-NMR[15] comparison with data for the Schreiber ester **19**. The stereochemistry of the major epimer **17a** has been demonstrated by irradiation of H-8 at δ 5.12 (benzene, degassed) leading to a 25% NOE enhancement of the H-13β signal of δ 2.90 but no effect on the H-10 signal. Reaction of the mixture **17ab** with p-PhC_6H_4COCl (Et_3N, DMAP, CH_2Cl_2, 20°C, 3 h) resulted in selective acylation of **17a** to give predominantly ester **18a**,[16] in which the H-10 is shifted δ 0.21 downfield from **17a**, and for which NOE results closely paralleled those cited for **17a**. It is noteworthy that neither **17a** nor **18a** exhibited long-range coupling >1.0 Hz for $J_{5,8}$, whereas in both the esperamicins and calicheamicins, as well as in the model **19**, $J_{5,8} \propto$ 1.4-2.7 Hz. *These data suggest that the stereochemistries at C-8 for the last 3 systems are identical, but differ from that of our major carbinol epimer* **17a**.[17] Finally, we report that deketalization of mixture **17** (0.2 M HCl, aq. acetone, 20°C, 90 min) gave 90% yield of the epimeric hydroxyenones **20**, fully characterized by IR, NMR, MS and HRMS.[18,19]



17a $R^1 = OH, R^2 = H$

17b $R^1 = H, R^2 = OH$



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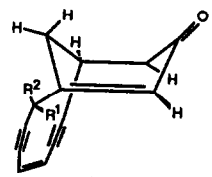

20a $R^1 = OH, R^2 = H$

20b $R^1 = H, R^2 = OH$

18a $R^1 = O_2CC_6H_4\text{-}p\text{-}C_6H_5, R^2 = H$

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6. Torii, S.; Inokuchi, T.; Ogawa, H., Bull. Chem. Soc. Jpn. 1979, 52, 1233.
7. Chapman, O.L.; Fitton, P., J. Am. Chem. Soc. 1963, 84, 41.
8. All Scheme I compounds gave 300 MHz ^{1}H-NMR, IR, MS and HRMS or combustion analyses in accord with the reported structures. Data for selected compounds are given below.
9. Dienone **10**: IR (film) 1660, 1580 cm^{-1}; 300 MHz ^{1}H-NMR ($CDCl_3$): δ 6.50 (1 H, dd, J = 10.8, 17.5 Hz), 5.97 (1 H, s), 5.62 (1 H, d, J = 17.5 Hz), 5.51 (1 H, d, J = 10.8 Hz), 3.08 (1 H, m), 2.83 (1 H, dd, J = 4.60, 17.52 Hz), 2.70 (1 H, dd, J = 4.60, 17.52 Hz), 2.60-2.46 (2 H, m), 2.16 (1 H, d, J = 2.28 Hz). HRMS: Calcd for $C_{10}H_{10}O$: 146.0732; Found 146.0730.
10. a) Stephana, R.D.; Castro, C.E., J. Org. Chem. 1963, 28, 3313; b) Ratovelomanana, V.; Linstrumelle, G., Tetrahedron Lett. 1981, 22, 315; c) Guillerm, D.; Linstrumelle, G. Tetrahedron Lett. 1985, 26, 3811.
11. The chloroenyne **14** was prepared by coupling of $Me_3SiC{\equiv}CH$ and Z-ClCH=CHCl according to the procedure of reference 10c. Calcd for $C_7H_{11}SiCl$: C, 52.98; H, 6.99; C, 22.34. Found: C, 53.09; H, 7.07; Cl, 22.08.
12. Aldehyde **16**: IR (film): 1685 cm^{-1}; 300 MHz ^{1}H-NMR ($CDCl_3$): δ 6.42 (1 H, s), 9.51 (1 H, s), 5.90 (1 H, d, J = 11.1 Hz), 5.77 (1 H, dd, J = 2.0, 11.1 Hz), 4.15-3.95 (4 H, m), 3.33 (1 H, d, J = 2.0 Hz), 3.01 (1 H, m), 2.77 (1 H, dd, J = 4.8, 18.1 Hz), 2.21 (1 H, dt, J = 1.3, 13.2 Hz), 2.13 (1 H, ddd, J = 2.3, 11.4, 13.7 Hz), 1.92 (1 H, t, J = 13.2 Hz). HRMS: Calcd for $C_{15}H_{14}O_3$: 242.0943. Found 242.0917.
13. Mixture of **17a** and **17b**: IR ($CHCl_3$): 3400, 1260, 1100 cm^{-1}. HRMS (m/e): Calcd for $C_{15}H_{14}O_3$, 242.0943; Found 242.0920.
14. Major epimer **17a**: 300 MHz ^{1}H-NMR ($CDCl_3$): δ 5.86 (H-4, dd, J = 9.6, 1.0 Hz); 5.76 (H-5, d, J = 9.6); 5.62 (H-10, d, J = 2.6); 5.12 (H-8, s); 4.07-3.91 (4H, m); 3.27(H-1, m); 2.90 (H-13β, d, J = 14.8); 2.49-2.05 (4H, m). Key signals for Schreiber ester **19**: δ 5.83 (H-5?, dd, J = 9.9, 2.4 Hz); δ 5.74 (H-4?, dd, J = 9.9, 1.2); 5.55 (H-10, br s); 5.22 (H-8, s).
15. Major epimer **17a**: ^{13}C-NMR ($CDCl_3$, partial): δ 143.3 (C-10), 122.4 and 121.5 (C-4/C-5), 67.7 (C-8). Schreiber ester **19**: δ 142.5 (C-10), 121.9 and 121.6 (C-4/C-5), 69.2 (C-8).
16. Ester **18a**: HRMS: Calcd for $C_{28}H_{22}O_4$: 422.1518; Found: 422.1527.
17. Although most of the ^{1}H-NMR signals of epimer **17b** were visible in spectra of **17**, they were too weak and overlapping with those of **17a** to interpret long-range J or NOE data on this minor component.
18. Hydroxyenones **20**: IR ($CHCl_3$) 2200, 1675 cm^{-1}. 300 MHz ^{1}H-NMR ($CDCl_3$): δ 6.02 (1 H, d, J = 4.4 Hz), 5.89-5.79 (2 H, m), 5.23 (1 H, s), 3.60 (1 H, m), 3.17 (1 H, d, J = 13.3 Hz), 2.80-2.50 (4 H, m). MS (m/e) 198 (M^+). HRMS (m/e) Calcd. for $C_{13}H_{10}O_2$: 198.0681; Found: 198.0677.
19. Partial support of this research by a grant from the American Cyanamid Co. is gratefully acknowledged. We thank Drs. G.A. Ellestad, M.D. Lee, D.B. Borders, and C. Ziegler (Lederle Div., American Cyanamid Co.) for valuable discussions regarding the spectra of **2** and its derivatives.

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