Experiments Directed toward a Total Synthesis of Dynemicin A: A Solution to the Stereochemical Problem

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Summary: The stereochemical issues required for a total synthesis of dynemicin A (**1**) have been resolved by employing an intramolecular Diels–Alder reaction and a diastereoselective addition of a magnesioacetylide to a quinoline under the influence of methyl chloroformate.

Given the fascinating structure, the potent cytotoxicity, and the novel bioorganic chemistry of dynemicin A (**1**), the interest elicited by this metabolite derivative of *Micromonospora chersina* is not surprising.[2,3] Much of this research has been directed toward the conception, synthesis, and evaluation of structures which, while less complex than dynemicin, still partake of its DNA cleavage capacity.[4] It is presumed[5] that this cutting action involves reduction of the anthraquinone, epoxide solvolysis, enediyne → diyl rearrangement,[6] and intermolecular hydrogen atom transfer, from oligodeoxyribonucleotide targets (**2** → **4**). Impressive strides in dynemicin-inspired biomimetic chemistry have been registered by Nicolaou[4,7] and Wender.[8]

Another facet of the dynemicin problem which has prompted considerable effort has been the challenge of total synthesis. A variety of interesting approaches have been devised in response to this most worthy undertaking.[9] The ranking accomplishment toward this end is the remarkable total synthesis of various O-methylated derivatives of dynemicin methyl ester accomplished by Schreiber and associates.[10] In this paper, we describe a unique solution to the stereochemical issues which must

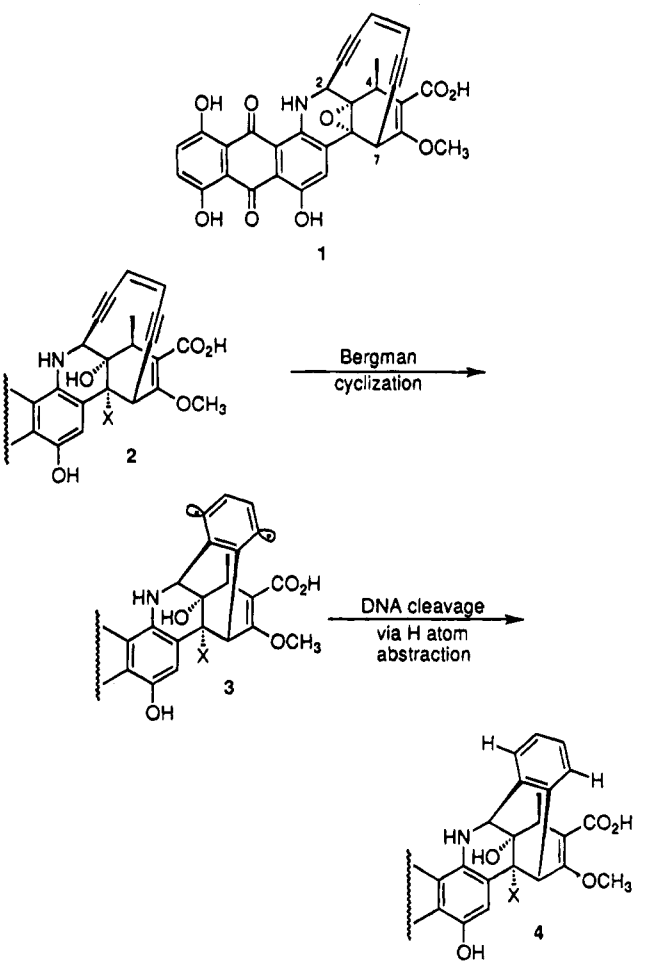

Figure 1.

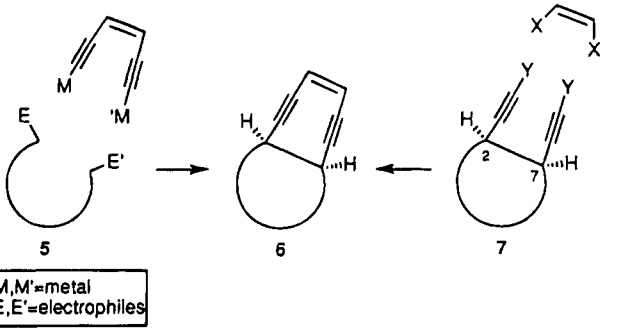

Figure 2.

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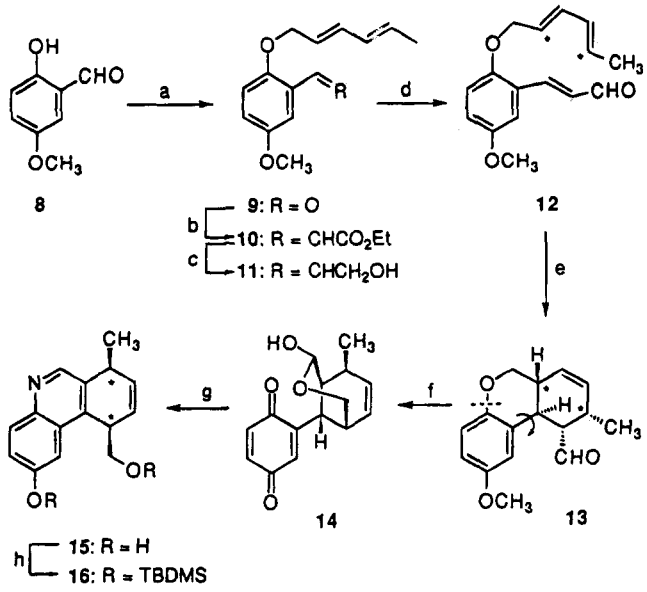
Scheme 1[a]



[a] Key: (a) (*E,E*)-sorbyl bromide, K_2CO_3, acetone, reflux, 0.5 h (96%); (b) NaH, $(EtO)_2P(O)CH_2CO_2Et$, THF, 0 °C to rt, 0.5 h (95%); (c) DIBALH, CH_2Cl_2, −78 °C, 1 h (94%); (d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to rt (92%); (e) $ZnCl_2$, CH_2Cl_2, rt, 72 h (60%); (f) CAN, H_2O, CH_3CN, 0 °C, 0.5 h (62%); (g) NH_4OAc, AcOH, H_2O, 100 °C, 0.5 h; 0 °C, NH_4OH; (h) TBDMSCl, imidazole, CH_2Cl_2, DMF, 0 °C to rt, 2 h (86%) over two steps.

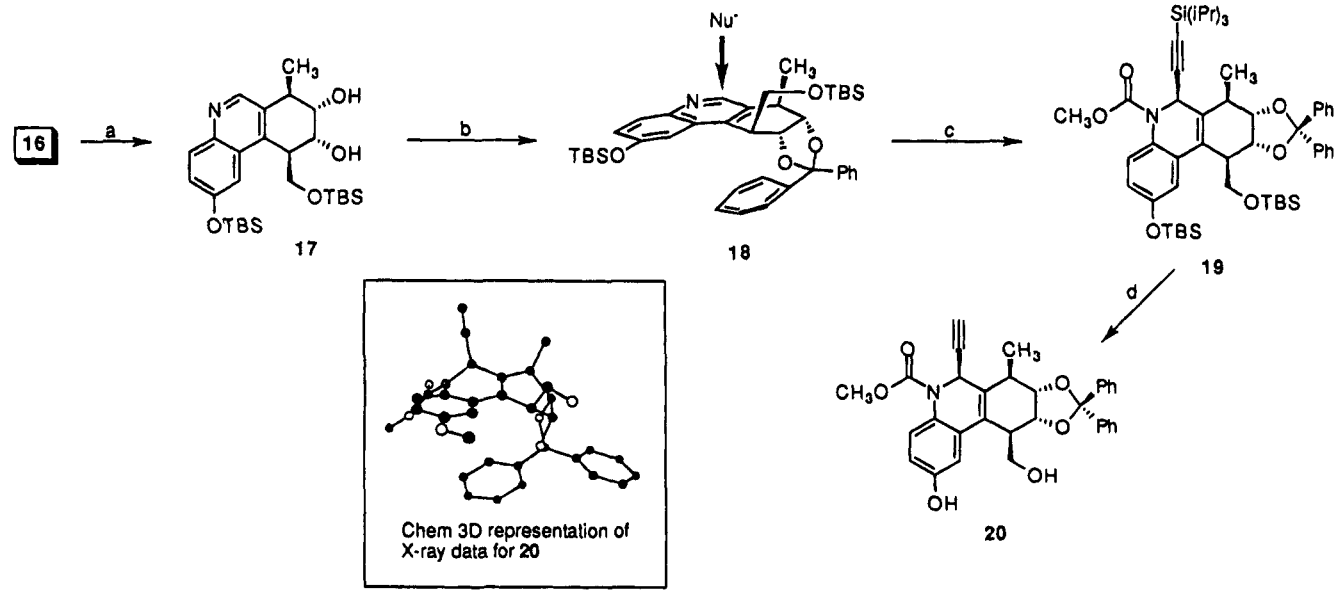
be addressed in any total synthesis undertaking directed toward dynemicin.

In our total synthesis of calicheamicinone[11] we had introduced the entire enediyne unit through exploitation of the bis nucleophilic potential of a *cis*-diethynylethylene moiety (see Figure 2) (**5** → **6**).[11,12] Happily, other workers in the dynemicin area have applied this central paradigm in one form or another toward the assembly of various analog constructs.[9d,e,g] Of course, if such a scheme could be realized, the required cis configurational relationship between C_2 and C_7 (dynemicin numbering) is, perforce, solved. While we have directed some effort toward application of this procedure to the dynemicin area,[13] our focus of late has centered on a conceptually different idea. We wondered whether cis-related appendages at C_2 and C_7 could be mobilized for cyclization to produce the enediyne. Implemenation of such a plan (see Figure 2) (**7** → **6**) is contingent on prearrangement of the cis relationship of these rather remote loci. Moreover, these stereogenic centers must be coordinated with the C_4 site (dynemicin numbering) bearing the secondary methyl group. We set as an interim goal the synthesis of compound **19** (Scheme 2) in which these questions are addressed.

Alkylation of 5-methoxysalicylaldehyde (**8**)[14] with (*E,E*)-sorbyl bromide[15] afforded a 96% yield of **9**. Emmons condensation of aldehyde **9** with ethyl diethylphosphonoacetate set the stage for the synthesis of enal **12** as shown. The action of the latter with zinc chloride in methylene chloride afforded a 59% yield of **13** with only trace quantities of exo isomer.[16] The suprafaciality of the Diels–Alder reaction was thus used to produce the cis C_4–C_7 connectivity for dynemicin as encoded in the appropriate centers in **13**. The relationship is more readily recognized in **15** which was obtained in two steps from **13**. In the first step, CAN oxidation of **13** leads to **14**. Reaction of the latter with ammonium acetate produced **15** which was then directly converted to the corresponding TBS ether **16** in 86% overall yield.

We next dealt with installation of the required stereochemistry at C_2. Toward this end, compound **16** was treated with catalytic osmium tetraoxide,[17] thereby affording **17** as the only isolated diol. The vicinal hydroxyl groups were engaged as a benzhydrylidene acetal (see **18**). We hoped that the α-face of the molecule would now be sufficiently hindered so as to encourage ethynylation of the azomethine linkage from the β-face. In the event, treatment of **18** with bromomagnesium (triisopropylsilyl)acetylide and methyl chloroformate[18] afforded **19**, whose structure was proven by crystallographic analysis of its tris-desilylated product **20**. In addition to confirming the configurations of **20** as well as showing that the chirality has been properly arranged

Scheme 2[a]



[a] Key: (a) OsO_4, NMO, THF, t-BuOH, 4 h, rt (90%); (b) $Ph_2(OMe)_2$, CH_2Cl_2, 1.1 equiv of H_2SO_4, 40 °C, 2 h (90%); (c) (triisopropylsilyl)acetylene, EtMgBr, THF, rt, 2 h; then −78 °C, add **18**, $ClCO_2CH_3$, −20 °C, 20 h (75% β-diastereomer; 12% α-diastereomer).

for reaching dynemicin A, the crystal structure suggests why the nucleophilic addition of the magnesio (triisopropylsilyl)acetylide had occurred from the β-face. The conversion of **19** to a des DE congener of dynemicin A is described in the following paper in this issue.

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Supplementary Material Available: ^{1}H NMR spectra, IR, and MS data are available for compounds **8**–**19** (13 pages). This material is contained in 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 for ordering information.

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