A Remarkable Cross Coupling Reaction to Construct the Enediyne Linkage Relevant to Dynemicin A: Synthesis of the Deprotected ABC System

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Summary: The deprotected phenol–acid ABC ring system of dynemicin A was synthesized featuring a novel palladium-mediated double cross coupling reaction to construct the cyclic enediyne.

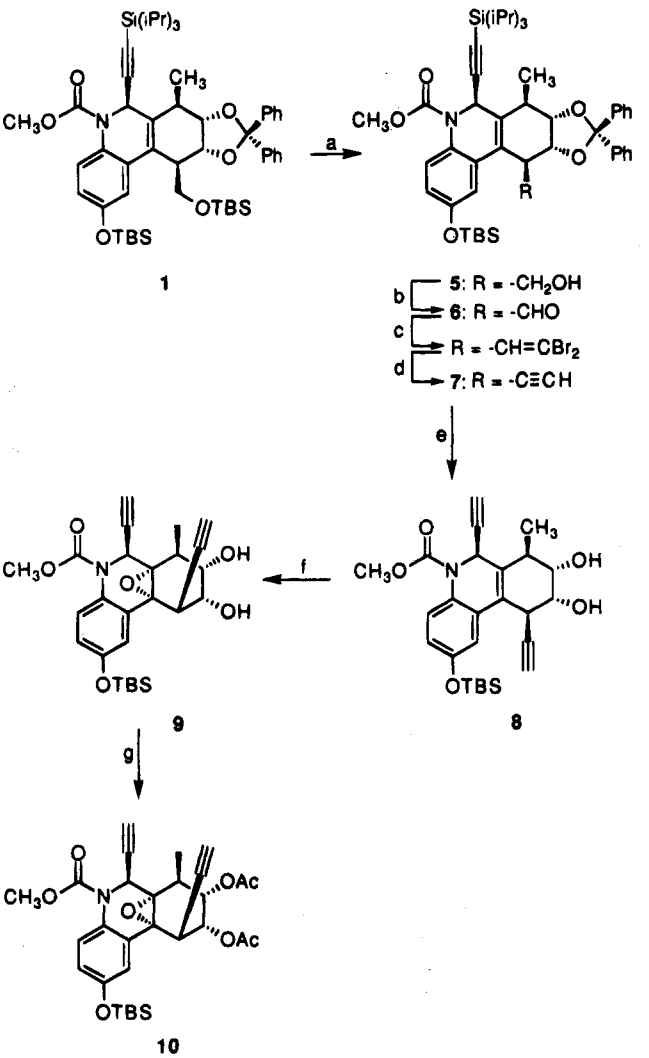
In the previous paper in this issue,[2] in connection with a proposed total synthesis of dynemicin A (**4**) (see Scheme 5),[3] we had described the preparation of compound **1** (Scheme 1). In this compound, the crucial stereochemical issues required in a dynemicin synthesis had been resolved in a favorable way. The central chemical question which was to be addressed in our proposal was that of the feasibility of constructing a cyclic enediyne linkage through cross coupling of an appropriately activated diyne with a complimentary, suitably activated, 1,2-disubstituted (*Z*)-ethylene (**2** → **3**).[4]

Accordingly, we set as an interim goal the conversion of compound **1** to the diyne epoxide **10**, wherein this question could be assessed. We proceeded as shown in Scheme 1.

Treatment of **1** with HF resulted in liberation of the primary alcohol group. Compound **5** thus obtained was oxidized by the method of Swern[5] to afford the labile aldehyde **6**. The latter was converted in a Corey–Fuchs transformation[6] to the acetylide **7**. Per desilylation and cleavage of the acetal linkage followed by selective silylation of the phenolic function gave rise to **8**.

With the array of three β-disposed carbon appendages, as well as the α-disposed (and potentially facially directing) diol, the introduction of the α-epoxide could be anticipated. In the event, treatment of compound **8** with *m*-CPBA gave rise to epoxide **9**. Acetylation of **9** provided **10**, poised for cyclization.

Scheme 1[a]



[a] Key: HF, CH_3CN, $CHCl_3$, rt, 1 h (60%); (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to rt (95%); (c) Ph_3P, CBr_4, 0 °C, then **6**, 0.5 h (86%); (d) ^nBuLi, $PhCH_3$, −78 °C, 4 h (80%); (e) (i) TBAF, THF, 0 °C, 1 h, (ii) HF, CH_3CN, $CHCl_3$, rt, 24 h, (iii) NaH, THF, **8**, then TBSCl, rt (80% over three steps); (f) *m*-CPBA, CH_2Cl_2, rt, 4 h, (90%); (g) Ac_2O, Pyr, DMAP (cat.), rt, 24 h (85%).

After a variety of failed attempts to achieve cyclization by utilizing the Sonogashira variant of the Castro–Stevens coupling method,[7] a novel departure was undertaken. The acetylenic functions were iodinated through the agency of *N*-iodosuccinimide and silver nitrate as shown (Scheme 2).[8] The resulting bis-iodo acetylide **12** was treated with (*Z*)-bis(trimethylstannyl)ethylene (**11**)[9]

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(1) Recipient of a predoctoral fellowship from Memorial Sloan-Kettering Cancer Center.

(2) See the previous paper in this issue.

(3) For approaches to a total synthesis of Dynemicin A, see: (a) Porco, J. A., Jr.; Schoenen, F. J.; Stout, T. J.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 7410. (b) Chikashita, H.; Porco, J. A., Jr.; Stout, T. J.; Clardy, J.; Schreiber, S. L. *J. Org. Chem.* **1991**, *56*, 1692. (c) Wood, J. L.; Porco, J. A., Jr.; Taunton, J.; Lee, A. Y.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 5898. (d) Taunton, J.; Wood, J. L.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 10378. (e) Nicolaou, K. C.; Hwang, C.-K.; Smith, A. L.; Hwang, S. V. *J. Am. Chem. Soc.* **1991**, *113*, 3106. (f) Wender, P. A.; Zercher, C. K. *J. Am. Chem. Soc.* **1991**, *113*, 2311. (g) Magnus, P.; Fortt, S. M. *J. Chem. Soc., Chem. Commun.* **1991**, 544. (h) Nishikawa, T.; Isobe, M.; Goto, T. *Synlett* **1991**, 393. (i) Nicolaou, K. C.; Gross, J. L.; Kerr, M. A.; Lemus, R. H.; Ikeda, K.; Ohe, K. *Angew. Chem.* **1994**, *106*, 790.

(4) For a demonstration that a 1,2-diiodo-(*Z*)-ethylene does undergo a double cross coupling to form a cyclic enediyne, see: Huynh, C.; Linstrumelle, G. *Tetrahedron* **1988**, *44*, 6337.

(5) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1979**, *44*, 4148.

(6) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769.

(7) Sonogashira, K.; Tohda, Y.; Nagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467.

(8) Hofmeister, H.; Annen, K.; Laurent, H.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 727.

0022-3263/94/1959-3755$04.50/0

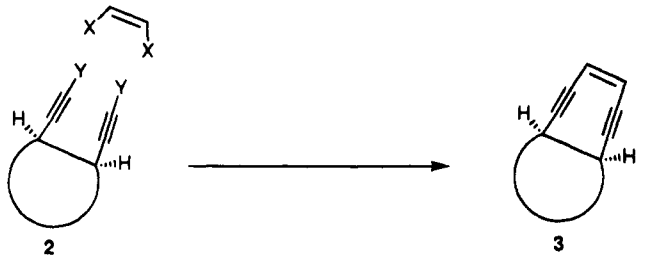
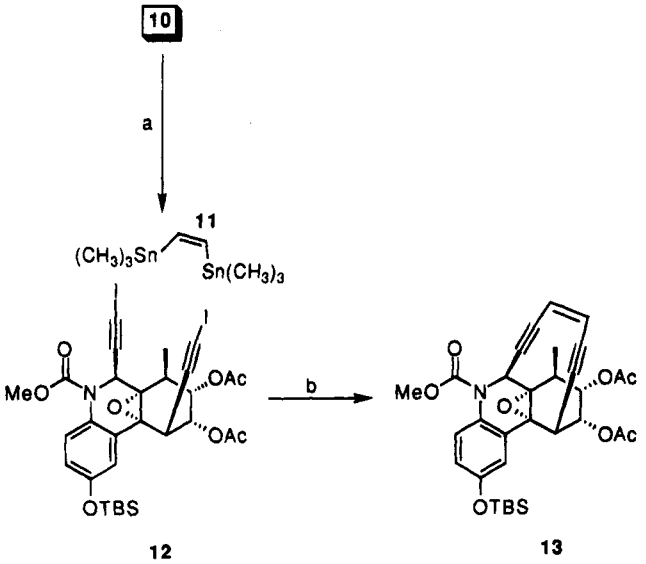


Figure 1.

Scheme 2[a]



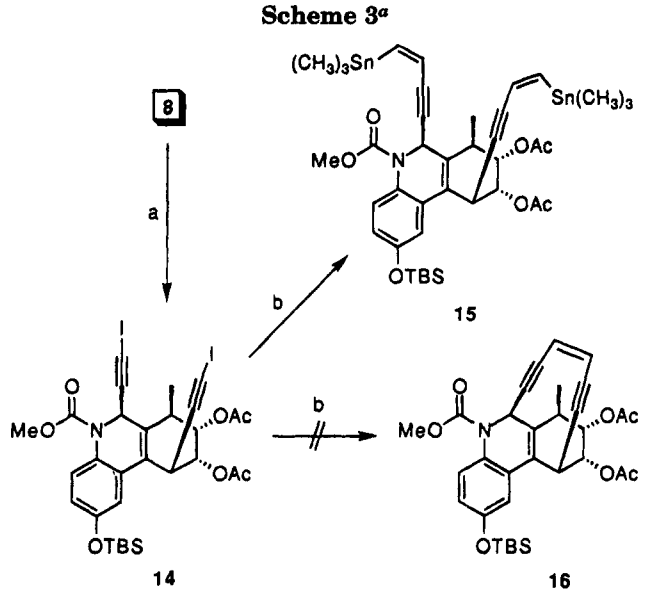
[a] Key: $AgNO_3$ (cat.), *N*-iodosuccinimide, THF, rt, 3 h (100%); (b) **12**, DMF, 60 °C, 10% $Pd(PPh_3)_4$, syringe pump addition of 0.023 M solution of **11** in DMF, 1 h (80%).

in the presence of tetrakis(triphenylphosphine)palladium-(0) under the conditions shown. Gratifyingly, there was obtained an 80% yield of the enediyne **13**. *To our knowledge this is the first such construction of a cyclic enediyne array.*[10]

It is interesting to note that the bis-iodide **14**, prepared as shown in Scheme 3, did not provide cyclic enediyne upon reaction under the conditions which had succeeded for epoxy bis-iodide **12**.[11] Only the inhomogeneous bis-stannyl enyne **15** was detected. The differing performances of the bis(iodoalkynes) **12** and **14** with respect to cyclization to provide enediyne may reflect the increased distance between the acetylene termini in the latter. Alternatively, hybridization differences may predispose **12** for cyclization.

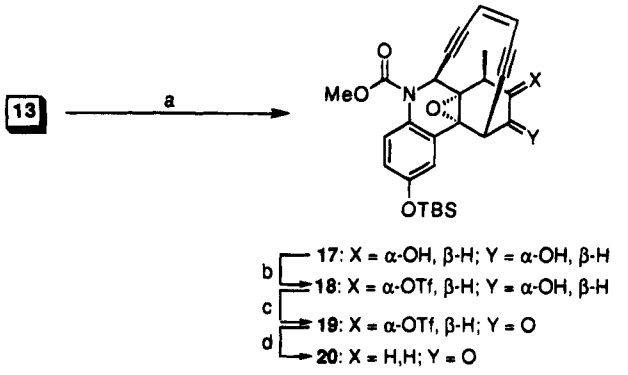
We next turned our attention to the introduction of the elusive enol ether acid functionality mounted at C_5 and C_6 (dynemicin numbering). Toward this end, both acetate linkages of **13** were cleaved through the action of KCN in methanol (Scheme 4). The quasiequatorially disposed

Scheme 3[a]



[a] Key: $AgNO_3$ (1.1 equiv), *N*-iodosuccinimide, THF, rt, 3 h (70%); (b) **14**, DMF, 60 °C, 10% $Pd(PPh_3)_4$, syringe pump addition of 0.023 M solution of **11** in DMF, 1 h.

Scheme 4[a]



[a] Key: KCN, CH_3OH,CH_2Cl_2 0 °C, 20 h (83%); (b) Tf_2O, CH_2Cl_2, Pyr, −20 °C, 1 h (92%); (c) Dess–Martin periodinate, CH_2Cl_2, rt, 3 h (90%); (d) $CrCl_2$, THF, rt, 2 h (94%).

hydroxyl group at C_5 of diol **17** could be selectively triflated to produce compound **18**. The latter, upon oxidation (Dess–Martin)[12] gave rise to keto triflate **19**. Exposure of **19** to the action of chromous chloride provided ketone **20**.[13] Many attempts to carboxylate various site-specific enolates generated by reduction of **19** or by stoichiometric deprotonation of **20** were unsuccessful.

Carboxylation was accomplished by utilizing conditions previously registered by Rathke.[14,15] The rather unstable β-keto acid **21** was converted to its SEM ester **22** as shown. The resultant enol was methylated upon reaction of **19** with (trimethylsilyl)diazomethane in methanol. The properly protected vinylogous carbonate **23** was thus in hand. Reaction of the latter with magnesium bromide[16]

(9) Mitchell, T. N.; Amamria, A.; Killing, H.; Rutschow, D. *J. Organomet. Chem.* **1986**, *304*, 257.

(10) For a conceptually related cyclization approach, applied to a total synthesis of rapamycin, via double coupling of a bis-stannylethylene unit to form an (*E*,*E*,*E*)-triene, see: Nicolaou, K. C.; Chakraborty, T. K.; Piscopio, A. D.; Minowa, N.; Bertinato, P. *J. Am. Chem. Soc.* **1993**, *115*, 4419.

(11) A related cyclic enediyne has been synthesized via a transannular Diels–Alder reaction followed by cationic isomerization of the double bond into conjugation by Schreiber and associates; see: ref 2a,c.

(12) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

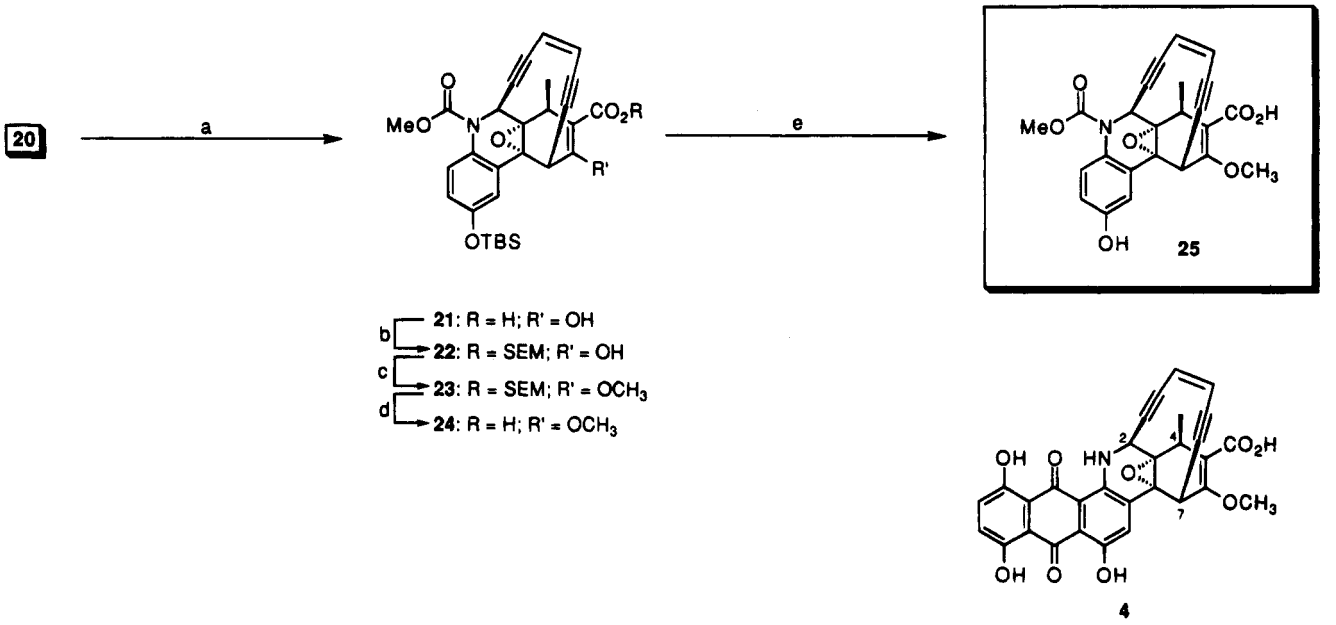
(13) For a review of dehalogenation of α-halo ketones by $CrCl_2$, see: Hanson, J. R. *Synthesis* **1974**, 1.

(14) Tirpak, R. E.; Olsen, R. S.; Rathke, M. W. *J. Org. Chem.* **1985**, *50*, 4877.

(15) While exploring the feasability of the Rathke carboxylation, it had come to our attention that Myers and associates (California Institute of Technology) had used this procedure to install the β-keto acid in a dynemicin model.

(16) Kim, S.; Park, Y. H.; Kee, I. S. *Tetrahedron Lett.* **1991**, *32*, 3099.

Scheme 5[a]



[a] Key: $MgBr_2$, CO_2, Et_3N, CH_3CN, rt, 2 h; (b) SEMCl, $(iPr)_2NEt$, THF, 0.5 h (30% isolated, 75% based on recovered **20** over two steps); (c) $TMSCHN_2$, CH_3OH, rt, 2 h (85%); (d) $MgBr_2$, Et_2O, rt, 3 h (92%); (e) TBAF, THF, 0 °C, 0.5 h (84%).

in ether cleanly generated the free acid **24**.[17] Finally, cleavage of the silyl ether produced the free phenolic acid **25**.

These experiments open up new possibilities for the synthesis of dynemicin-like effectors or other enediyne mimics. They also lend themselves to further progress toward a total synthesis of dynemicin A (**4**) itself. Experiments in this direction are currently in progress.

(17) Attempted deprotection of the methyl ester (**23**, R = Me), prepared by treatment of **21** with TMS diazomethane, with KOH–THF–H_2O led only to decomposition of the starting material.

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Supplementary Material Available: ^1H NMR, IR, and MS data are available for compounds **1**, **5**–**10**, **12**, **13**, and **17**–**25** (21 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.