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Synthesis of an Esperamicin Core Analog with an Epoxide Trigger

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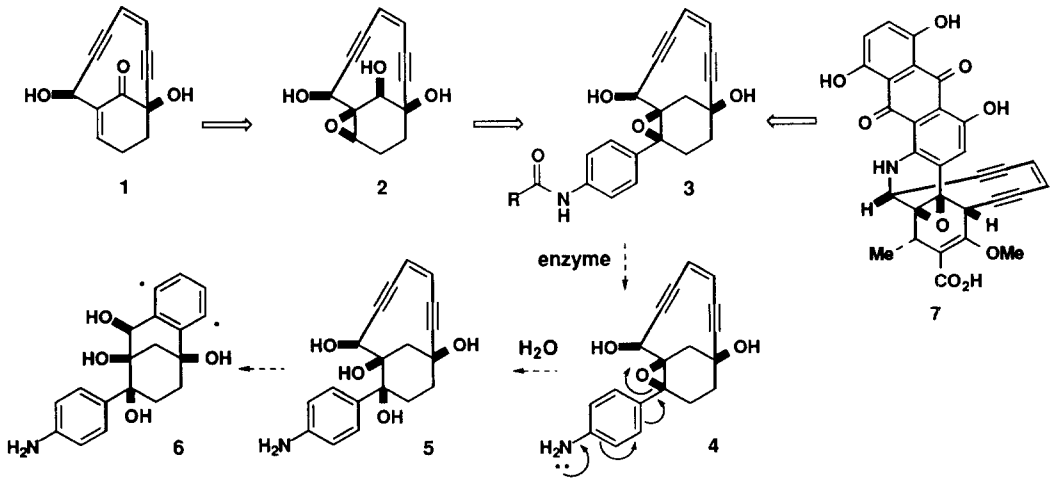
Abstract: An esperamicin core analog **4** with an epoxide trigger like that found in the related enediyne, dynemicin, was prepared. Surprisingly, it was found to be relatively stable; the *p*-aminophenyl substituent did not facilitate epoxide solvolysis to the extent that had been anticipated. A mild acid, pyridinium *p*-toluenesulfonate, was found to induce solvolysis of **4** and led to the formation of the cycloaromatized product **25**. Copyright © 1996 Elsevier Science Ltd

BMY-46108[1] (**1**), a core analog of the enediyne antibiotic, esperamicin, displayed interesting antitumor activity in early preclinical models. For the SAR study of **1**, the epoxide analog **2**[2] was made and found to be stable and biologically inactive. Evidently the epoxide function at the bridgehead position of **2** prevents the enediyne portion of this molecule from undergoing a Bergman[3] cycloaromatization. This led us to consider making an epoxide analog (**3**) which carried an *p*-amidophenyl substituent. It should function as a prodrug[4] and undergo enzymatic cleavage *in vivo* (Scheme 1) to give the aniline **4**. This amino epoxide should then undergo assisted epoxide solvolysis to give **5** which could undergo cycloaromatization to give a diradical intermediate (**6**) that could effect DNA cleavage and lead to cell death. It utilizes a triggering mechanism similar to that found in

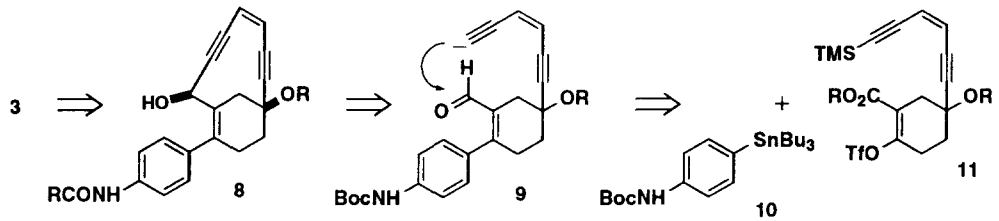
Scheme 1



another member of the enediyne family, dynemicin (**7**).[5] Enediyne **3** should be stable and biologically inactive until the amide group undergoes enzymatic cleavage. This feature would make it an attractive candidate for tumor specific delivery by a drug targeting approach such as Antibody-Directed Enzyme Prodrug Therapy (ADEPT).[6]

The retrosynthesis of **3** is outlined in Scheme 2. It was to be prepared by epoxidation of the bicyclic olefin **8** that was formed by intramolecular addition[1c,e] of the acetylene anion to the aldehyde group of **9**. The latter could be derived from the product of the palladium-catalyzed coupling of the vinyl triflate **11** with the aryl stannane **10**. An attractive feature of this approach is that it would allow for the rapid synthesis of analogs with different aryl triggering elements by the coupling of **11** with other aryl stannanes.

Scheme 2



The results[7] are outlined in Scheme 3. The known acetylene **12**[8] was coupled[9] with Z-1-chloro-4-trimethylsilylbut-1-en-3-yne[10] to give the enediyne **13**. Protection of the tertiary alcohol was followed by hydrolysis[8] of the ethylene ketal to give the ketone **14**. This was converted to the β-ketoester **15** by using the procedure of Mander.[11] The vinyl triflate **16**[12] was formed and coupled with the aryl stannane **10** using a palladium catalyst and the ligandless reaction conditions of Farina and Roth.[13] The resulting ester **17** was reduced to the alcohol **18** with excess DIBAH. This was oxidized[14] to the aldehyde **19** and the TMS group was removed. We were then ready to examine the cyclization reaction. Treatment of **20** with LiHMSA in THF at rt gave the bicyclic enediyne **21** as a single alcohol isomer.[15] The silyl and Boc protecting groups were simultaneously removed and the amino group of **22** was converted to the base-labile trifluoroacetyl derivative (**23**).[16] Finally, epoxidation of **23** with MCPBA gave **24**, the N-protected derivative of the amino epoxide **4**.

To investigate the cycloaromatization of **4**, the trifluoracetyl group was removed from **24** by treatment with aqueous base. Unlike related amino epoxides, **4** was found to be stable.[17] It could be chromatographed on silica gel, has survived storage at -20 °C for several years without significant decomposition, and was recovered unchanged after 20 hr in methanolic solution at 45 °C. The stability of **4** is likely due to an interaction between the methine and aromatic hydrogen atoms (Figure 1) which raises the energy of the rotational isomer of the aryl group that can stereoelectronically facilitate epoxide opening. It was however found that a mild acid catalyst, pyridinium *p*-toluenesulfonate, will induce **4** to undergo solvolysis and cycloaromatization to give **25**.

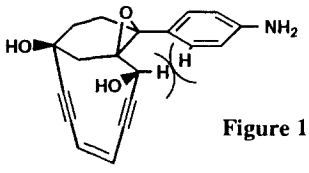
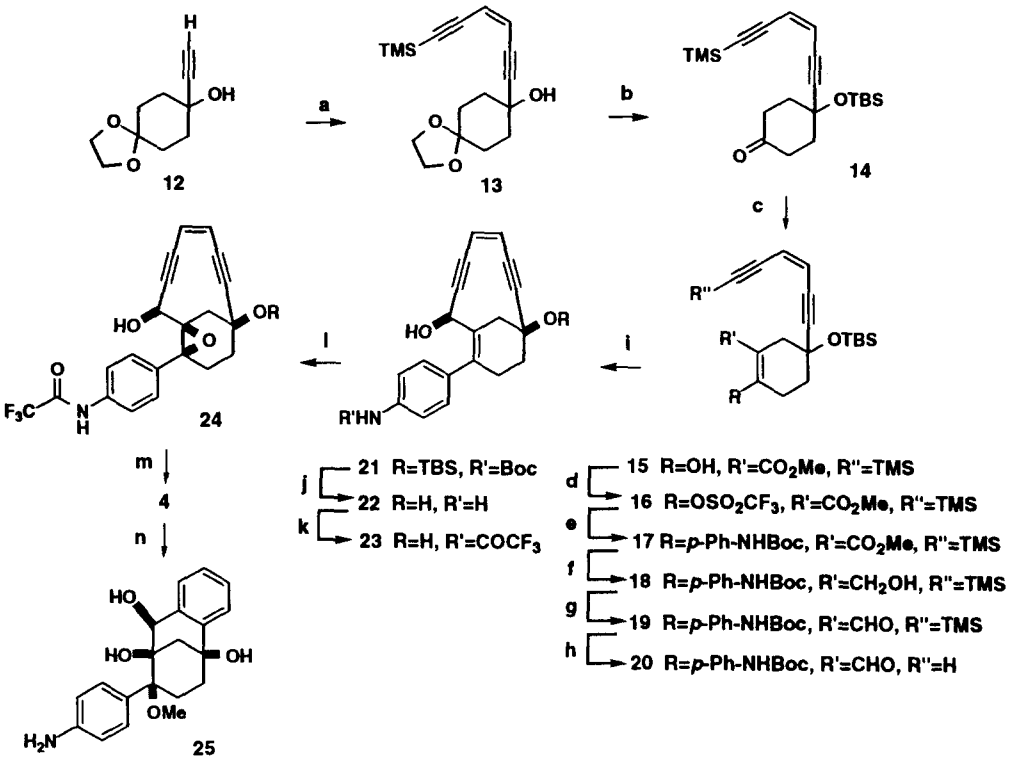


Figure 1

Scheme 3[a]



[a] conditions: (a) (Z)-ClCH=CH-C≡CTMS, n-Bu3N, Pd[P(Ph)3]4 (cat), CuI (cat), THF, rt; (b) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, -78 °C to rt, then 35% aq. CF_3CO_2H, $CHCl_3$, rt (81% from **12**); (c) LiHMSA, $NCCO_2Me$, HMPA (cat), THF, -78 °C (73%); (d) Tf_2O, DIPEA, CH_2Cl_2, -78 °C to rt (84%); (e) *p*-BocNHPhSn(Bu)3, Pd2dba3(cat), LiCl, NMP, rt (71%); (f) DIBAH, CH_2Cl_2, -78 °C to rt (92%); (g) (n-Pr)4NRuO4 (cat), N-methylmorpholine N-oxide, 4 A° sieves, CH_2Cl_2 (90%); (h) K_2CO_3 (cat), MeOH, rt; (i) LiHMSA, THF, rt; (j) 25% aq. H_2SO_4, dioxane, rt (63% from **20**); (k) CF_3COSEt, dioxane, 60 °C (58%); (l) MCPBA, THF, 0 °C, (73%); (m) aq. LiOH, THF, rt, 19 h (93%); (n) pyridinium *p*-toluenesulfonate (3 equiv.), MeOH : 1,4-cyclohexadiene = 4 : 1, 45 °C, 4.5 hr (18%).

In conclusion, an esperamicin core analog (**4**) with an epoxide trigger similar to that found in dynemicin was synthesized and found to be unexpectedly stable. A suitably modified analog that undergoes epoxide solvolysis more readily was subsequently prepared. That work is described in the following paper.

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† Present address: Vion Pharmaceuticals, 4 Science Park, New Haven, CT 06511.

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7. Satisfactory combustion and/or HRMS data were obtained for all new compounds. Selected data for **4**: white solid; slow decomposition from about 80 to 100 °C; ^{1}H NMR (DMSO-d_6) δ 1.45-1.66 (m, 2H), 1.82 (d, J = 14.1 Hz, 1H), 1.97 (dd, J = 4.2, 15.3 Hz, 1H), 2.29 (m, 1H), 2.99 (d, J = 14.1 Hz, 1H), 3.51 (d, J = 5.1 Hz, 1H), 5.02 (br s, 2H, exchanges with D_2O), 5.70 (d, J = 5.1 Hz, 1H, exchanges with D_2O), 5.76 (s, 1H, exchanges with D_2O), 6.05 (d, J = 9.7 Hz, 1H), 6.20 (d, J = 9.7 Hz, 1H), 6.43 (d, J = 8.3 Hz, 2H), 6.86 (d, J = 8.3 Hz, 2H); IR (KBr disc) 3372, 2204, 1622 cm^{-1}; MS (DCI) 308 (MH^+). For **25**: oil; ^{1}H NMR (DMSO-d_6) δ 1.68-1.82 (m, 2H), 1.87 (d, J = 11.3 Hz, 1H), 2.19 (d, J = 10.8 Hz, 1H), 2.86 (s, 3H), 3.78 (d, J = 3.7 Hz, 1H, s on addition of D_2O), 4.45 (s, 1H, exchanges with D_2O), 4.68 (d, J = 4 Hz, exchanges with D_2O), 4.96 (br s, 2H, exchanges with D_2O), 5.24 (s, 1H, exchanges with D_2O), 6.46 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.2 Hz, 2H), 7.12 (d, J = 7.7 Hz, 1H), 7.19 (t, J = 7.3 Hz, 1H), 7.28 (t, J = 7.8Hz, 1H), 7.52 (d, J = 7.3 Hz, 1H); IR (KBr disc) 3366, 1621 cm^{-1}; MS (negative ESI) 340 ($M-H^-$).

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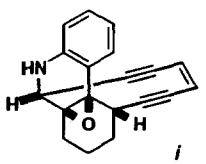
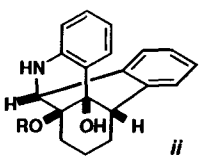


i



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