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Synthesis of a Hybrid Analog of the Esperamicin and Dynemicin Cores

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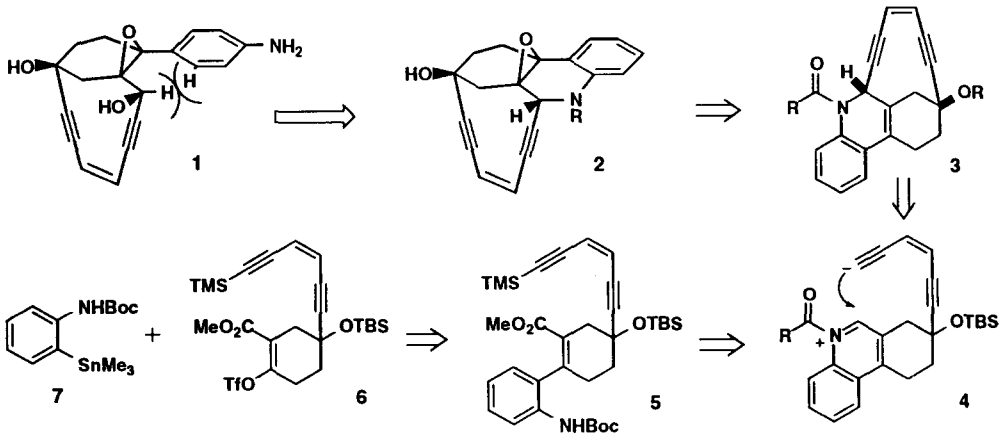
Abstract: An enediyne analog (**2**, R=H) that is a hybrid of the core structures of esperamicin and dynemicin was prepared . The key step in its synthesis was a Reissert-type reaction that involved intramolecular addition of the anion of a Z-1,3-diyn-2-ene to an N-acyl tetrahydrophenathridinium intermediate. It was found that **2** (R=H) readily undergoes epoxide rearrangement to an allylic alcohol (**16**). Both **2** (R=H) and **16** form the same cycloaromatized product **17** when heated in MeOH at 45 °C. Copyright © 1996 Elsevier Science Ltd

We have described the synthesis of an esperamicin core analog (**1**) that possesses an epoxide trigger similar to that found in dynemicin.[1] Its unexpected stability was thought to arise from an interaction between the methine and aromatic hydrogen atoms of **1** which raises the energy of the rotational isomer of the aryl group that can stereoelectronically facilitate epoxide opening. We became interested in modifications of **1** that would result in analogs with more reactive epoxide triggers. This led us to synthesize **2** which has the electron donating aryl residue constrained in a configuration that should facilitate epoxide opening. This analog would be an interesting hybrid of the esperamicin and dynemicin core structures.

Scheme 1

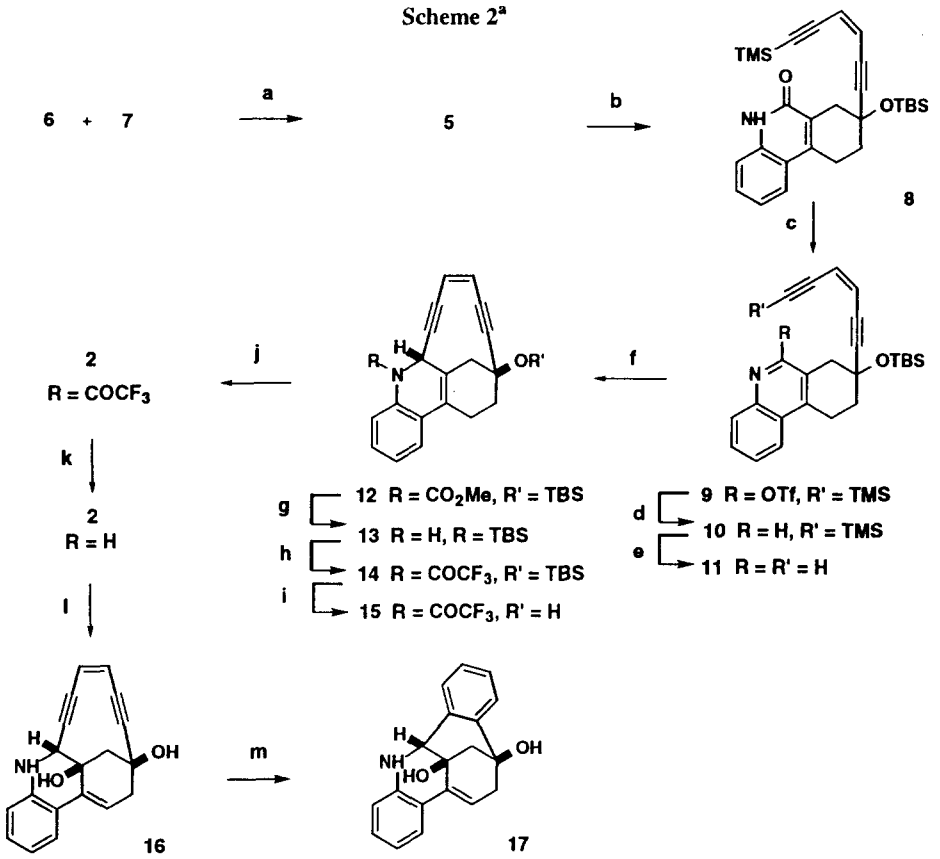


The retrosynthesis of **2** is outlined in Scheme 1. It utilizes the flexible nature of the synthetic route that

was developed to synthesize **1**.[1] The epoxide function was to be introduced at the end of the synthesis. Its olefin precursor **3** was to be formed by intramolecular addition of an acetylene anion to a N-acyl tetrahydrophenanthridinium intermediate **4**.[2] The tetrahydrophenanthridine precursor of **4** was to be constructed using the amino and ester groups of **5**.[3] The latter was to be obtained by the palladium-catalyzed coupling of the *ortho*-substituted aryl stannane **7** with our vinyl triflate intermediate **6**.[1]

The results[4] are outlined in Scheme 2. The palladium-catalyzed coupling of the triflate **6** with the *ortho*-substituted aryl stannane **7** occurred in the presence of the triphenylarsine ligand.[5] The resulting product **5** was converted to the tertrahydrophenanthridinone **8** by treatment with $Al(Me)_3$[6] to simultaneously affect

Scheme 2[a]



[a] conditions: (a) Pd_2dba_3 (0.05 equiv), $As(Ph)_3$ (0.2 equiv), NMP, rt, 1 hr (80%); (b) $Al(Me)_3$ (2.0 M in MePh, 4 equiv.), PhH, rt, (74%); (c) Tf_2O, DIPEA, CH_2Cl_2, -78 °C to rt (89%); (d) $Pd(OAc)_2$ (0.1 equiv), 1,1'-bis(diphenylphosphino)ferrocene (0.2 equiv), HCO_2H (4 equiv), NBu_3 (5 equiv), DMF, 85 °C, 6 min; (e) K_2CO_3 (1 equiv), MeOH, rt (55% from **9**); (f) EtMgBr (1.0 M in THF, 1.2 equiv), THF (12 mM in **11**), 1 hr, rt, then $ClCO_2Me$ (1.1 equiv), 2.5 hr, rt, (57%); (g) DIBAH (1.5 M in CH_3Ph, 4 equiv), CH_2Cl_2, -78 °C to rt; (h) $(CF_3CO)_2O$ (1.2 equiv), pyridine (4.6 equiv), CH_2Cl_2, 0 °C, (83% from **12**); (i) aq. HF (50%), CH_3CN; (j) MCPBA, CH_2Cl_2, 0 °C, (89% from **14**); (k) aq. LiOH (1.0 M, 6 equiv), THF, 0 °C, 5 min (92%); (l) silica gel, EtOAc : hexane = 1:1, 1hr, 84%; (m) MeOH : 1,4-cyclohexadiene = 4 : 1, 45 °C, 6 hr (51%).

condensation and the removal of the Boc group. Conversion of **8** to the triflate **9** was followed by the palladium-catalyzed hydrogenolysis of the triflate group[7] to give the tetrahydrophenathridine **10**. The TMS group was removed from the terminal acetylene group of **10** and we were ready to examine the proposed Reissert-type cyclization reaction. This was conducted at relatively high dilution in THF. Metallation of **12** was affected by treatment with EtMgBr at rt for 1 hr. Methyl chloroformate was then added[8] and the desired cyclization occured within 3 hr at rt. Treatment of the resulting carbamate **12** with excess DIBAH[9] gave the N-deprotected intermediate **13**.[10] This was converted to the trifluoracetamide derivative **14** and the silyl protecting group was removed. Peracid epoxidization of the olefin function in **15** gave **2** (R = $COCF_3$) and completed the synthesis of our analog.

The behavior of the amino epoxide **2** (R = H) was then examined. The trifluoroacetyl group of **2** (R = $COCF_3$) was cleanly removed with aqueous LiOH in THF to give **2** (R = H) as a solid after aqueous workup. This compound was significantly less stable than the previously prepared amino epoxide **1** but could still be characterized. It rapidly underwent rearrangment to the allylic alcohol **16** in the presence of silica gel or a trace of acid, e.g., that found in older samples of halogenated solvents such as $CDCl_3$. The allylic alcohol **16** undergoes cycloaromatization to give **17** when heated in MeOH at 45 °C for 6 hr. The same cycloaromatized product **17** is obtained directly from the amino epoxide **2** (R = H) when it is heated in MeOH at 45 °C for 9 hr. Evidently **2** prefers to react by epoxide rearrangement rather than the epoxide solvolysis that is observed with dynemicin and its analogs.[11]

In conclusion, a unique hybrid analog (**2**, R = H) of the esperamicin and dynamicin core structures was synthesized. This utilized a novel intramolecular Reissert-type reaction to construct the enediyne core structure. As expected, the analog **2** (R = H) possessed a more reactive epoxide trigger than the unconstrained analog **1**. When heated in MeOH, it undergoes epoxide rearrangement to give an allylic alcohol (**16**) which then cycloaromatizes. It was found that both **2** (R = H) and the more stable analog **1** exhibited efficacy in a preliminary *in vivo* mouse tumor screen. These results will be reported in the future.

References and Notes:

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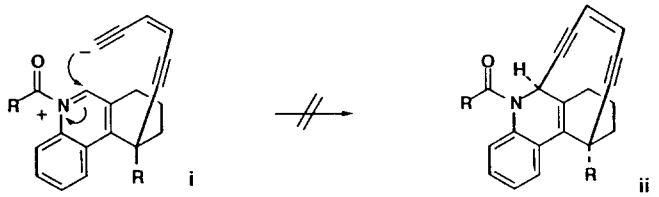
1. Mastalerz, H.; Doyle, T.; Kadow, J.; Vyas, D. preceding paper.

2. This would be an intramolecular version of a type of Reissert reaction that has been explored by Fraenkel and Yamaguchi: (a) Fraenkel, G.; Cooper, J.W.; Fink, C.M. *Angew. Chem. internat. Edit.* **1970**, *9*, 523; (b) Yamaguchi, R.; Nakazono, Y.; Kawanisi, M. *Tetrahedron Lett.* **1983**, *24*, 1801. Interestingly, it had been considered as a way of constructing the dynemicin core (*i* to *ii*), see: (c) Nicolaou, K. C.; Smith, A. L.; Wendeborn, S. V.; Hwang, C.-K. *J. Amer. Chem. Soc.* **1991**, *113*, 3106; (d) Danishefsky, S.; Shair, M. *J. Org. Chem.* **1996**, *61*, 16. However, that cyclization apparently does not proceed because the product *ii* is too strained. In our case, it was felt that the cyclization would occur because **3** would not be as strained, i.e., inspection of the 10-membered ring that incorporates the enediyne functionality in *ii* and **3** reveals that the former compound has a double bond which is trans-substituted (w.r.t. this 10-membered ring) while the analogous double bond is in a less strained exocyclic arrangement in **3**.



3. Similar strategies for the construction of substituted tetrahydrophenathridines for the synthesis of the dynemicin core were reported during and after the completion of this work: (a) Dai, W.-M. *J. Org.Chem.*, **1993**, *58*, 7581; (b) Nishikawa, T.; Isobe, M. *Tetrahedron* **1994**, *50*, 5621; (c) Myers, A.; Farley, M.; Tom, N. *J. Amer. Chem. Soc.* **1994**, *116*, 11556.

4. Where possible, satisfactory combustion and/or HRMS data were obtained for all new compounds. Selected data for **12**: ^{1}H NMR ($CDCl_3$) δ 0.19 (s, 6H), 0.88 (s, 9H), 1.91 - 2.20 (m, 2H), 2.63 - 2.77 (m, 4H), 3.80 (s, 3H), 5.58 (d, J = 9.6 Hz, 1H), 5.64 (s, 1H), 5.73 (d, J = 9.6 Hz, 1H), 7.09 - 7.57 (m, 4H); ^{13}C NMR ($CDCl_3$) δ -2.80, -2.92, 17.95, 25.30, 25.70, 35.87, 48.28, 50.33, 53.36, 70.19, 85.44, 87.26, 97.17, 102.16, 122.34, 122.57, 123.06, 123.96, 124.42, 126.24, 127.03, 127.59, 132.49, 133.88, 153.98; IR (KBr disk) 1712 cm^{-1}; MS (DCI) 446 (MH^+). For **2** (R = H): ^{1}H NMR ($CDCl_3$) δ 1.91 - 1.96 (m, 2H), 2.39 (d, J = 13.6 Hz, 1H), 2.51 - 2.76 (m, 2H), 2.96 (d, J = 13.6 Hz, 1H), 3.97 (s, 1H, exchanges with D_2O), 4.40 (s, 1H), 5.73 (d, J = 9.6 Hz, 1H), 5.81 (d, J = 9.6 Hz), 6.58 (d, J = 8.0 Hz, 1H), 6.82 (t, J = 7.6 Hz, 1H), 7.13 (t, J = 7.7 Hz, 1H), 7.38 (d, J = 7.7 Hz, 1H); IR (KBr disk) 3340 cm^{-1}; MS (DCI) 290 (MH^+). For **16**: ^{1}H NMR ($CDCl_3$) δ 2.57 (d, J = 14.1, 1H), 2.67 - 2.81 (m, 2H), 2.85 (d, J = 14.5 Hz, 1H), 3.59 (s, 1H, exchanges with D_2O), 4.14 (d, 1H), 4.2 (br s, 1H, exchanges with D_2O), 5.75 (d, J = 9.4 Hz, 1H), 5.82 (d, J = 9.4 Hz, 1H), 6.45 (dd, J = 3.0, 6.2 Hz, 1H), 6.49 (d, J = 7.9 Hz, 1H), 6.82 (t, J = 7.8 Hz, 1H), 7.09 (t, J = 7.8 Hz, 1H), 7.58 (d, J = 7.9 Hz, 1H). For **17**: ^{1}H NMR (DMSO-D_6) δ 2.14-2.20 (m, 3H), 2.57 (d, J = 15.4 Hz, 1H), 4.25 (s, 1H), 5.02 (s, 1H, exchanges with D_2O), 5.31 (d, J = 6.7 Hz, 1H), 5.37 (s, 1H, exchanges with D_2O), 6.33 (t, J = 7.3 Hz), 6.37 (d, J = 6.9 Hz, 1H), 6.78 (s, 1H, exchanges with D_2O), 6.83 (t, J = 7.3 Hz, 1H), 6.90 (d, J = 7.1 Hz, 1H), 7.13 (m, 2H), 7.35 (m, 1H), 7.48 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 43.7, 46.1, 62.1, 68.1, 74.0, 113.4, 117.9, 120.2, 122.5, 125.3, 125.6, 127.1, 127.6, 128.0, 128.6, 136.5, 140.2, 141.1, 142.0; IR (KBr disk) 3411 cm^{-1}; MS (ESI) 273 (MH^+).

5. The coupling of **6** and **7** did not occur under the ligandless reaction conditions that were previously used (reference 1) to couple a *para*-substituted aryl stannane with **6**. Others have reported difficulties with the palladium catalyzed coupling of *ortho*-substituted aryl stannanes with vinyl or aryl triflates and have developed different solutions to overcome the problem, see: Gomez-Bengoa, E.; Echavarren, A. *J. Org. Chem.* **1991**, *56*, 3497 and reference 2 b.

6. For a related condensation reaction that employed refluxing TFA to give phenanthridinones, see: Siddiqui, M.A.; Sneickus, V. *Tetrahedron Lett.* **1988**, *29*, 5463. It was thought that the functionality that is present in **8** would not tolerate these conditions and therefore milder ones were sought. The use of $Al(Me)_3$ was based on the Weinreb transamidation reaction: Levin, J.; Turos, E.; Weinreb, S. *Syn. Commun.* **1982**, *12*, 989.

7. Cacchi, S.; Ciattini, P.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1986**, *27*, 5541. The hydrogenolysis was accompanied by partial reduction of the enediyne part of **10**. Fortunately this could be minimized by using a short reaction time.

8. Metallation of acetylenes by EtMgBr is relatively slow: Brandsma, L. *Preparative Acetylenic Chemistry*, second edition, Elsevier, Amsterdam, 1988, p 31. If $ClCO_2Me$ were added before metallation was complete, significant amounts of other products (relatively unstable and not identified) were also formed.

9. For the deprotection of a related amine by reductive cleavage of a carbamate with $LiAlH_4$, see: reference 2c.

10. This amine exhibited a tendency to revert back to the uncyclized tetrahydrophenanthridine **11**. For example, if a sample of **13** were applied onto a preparative silica gel tlc plate and then developed after standing for 4 hr, a 48% yield of **11** was obtained.

11. Rearrangement of the epoxide group to an allylic alcohol does not occur in the dynemicin system since this would result in the formation of a highly strained compound.

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