Pergamon

Tetrahedron Letters, Vol. 35, No. 34, pp. 6259-6262, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01343-8

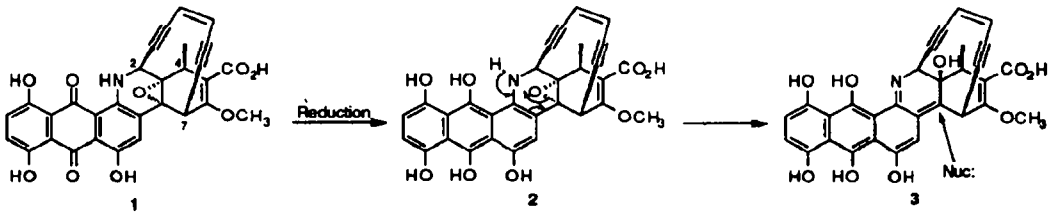
An Advanced Dynemicin A Model: Stabilization of the 3,8-Epoxide by Anthraquinone Functionality in the Absence of the Bridging Enediyne

Taeyoung Yoon,† Matthew D. Shair,[1,†,‡] and Samuel J. Danishefsky,*[,†,‡]

Department of Chemistry, Yale University, New Haven, Connecticut 06511

Abstract: Annulation of a quinone aminal like structure with a lithiated cyanophthalide leads to a quinone stabilized epoxide in the dynemicin series.

Soon after the isolation and identification of dynemicin A (**1**)[2a,b], Semmelhack advanced a proposal dealing with the chemical issues of its bioactivation.[3] An important element of Semmelhack's argument was that the anthraquinone was the key stabilizing element for maintenance of the 3,8-epoxide. The quinone functionality attenuates the internal nucleophilicity[4] of the tetrahydroquinoline type of nitrogen. Reduction of the quinone system to the hydroquinone level would correspondingly destabilize the epoxide (see structure **2** and arrows therein). Another possible feature of dynemicin involved in providing viability to the o-aminobenzyl type of epoxide, could well be the cyclic enediyne linkage. The enediyne shape virtually obliges a "front side" mode for nucleophilic opening of the epoxide. This constraint, in turn, requires a fully developed iminoquinonemethide intermediate (cf **3**) to precede solvolysis of the epoxide. We wondered whether quinonoid stabilization would extend to substrates lacking the enediyne "strap". Below, we report the synthesis of advanced dynemicin model **13** in which such an epoxide type is rendered viable by the "quinone attenuation" effect.

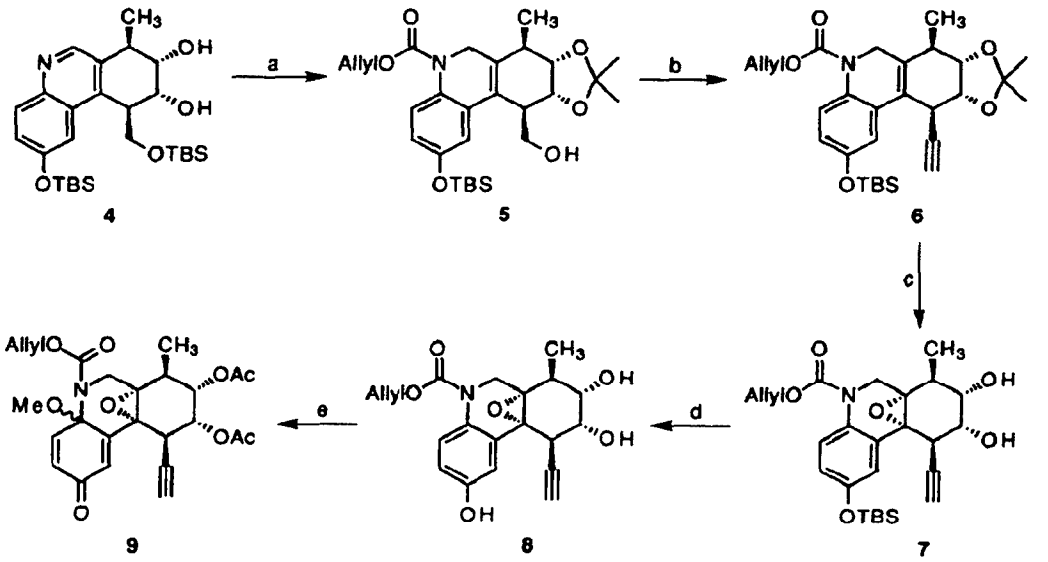


The synthesis commences with the previously described **4**[5] (Scheme I). Reductive carboallyloxylation of this compound was accomplished through the agency of tributyltin hydride and allylchloroformate.[6] Following isopropylidene formation and protecting group manipulation as shown, compound **5** was in hand. The hydroxymethyl group was upgraded to an acetylene (see structure **6**) in the usual way.[7] Hydrolysis of the ketal, followed by directed epoxidation of the resultant diol, afforded diol **7** and after desilylation, compound **8**. Oxidation of the latter with phenyliodosobenzendiaceteate in

† Present Address: Department of Bioorganic Chemistry, Memorial Sloan-Kettering Cancer Center, New York, N.Y. 10021
‡ Present Address: Department of Chemistry, Columbia University, New York, N.Y. 10027

methanol,[8] under the conditions shown, followed by acetylation, afforded the two quinoneaminal diastereomers **9**.

Scheme I

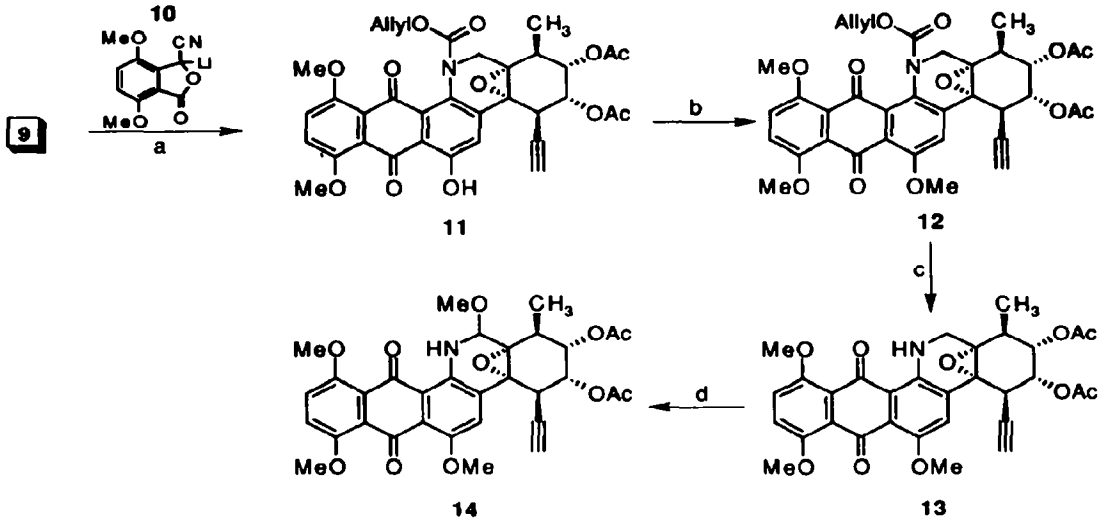


(a) i. $^{n}Bu_3SnH$, $ClCO_2Allyl$, CH_2Cl_2, 0°C, then 2-methoxypropene, pTsOH (cat.) (96%, two steps); ii. TBAF, THF; iii. NaH, TBSCl, THF (79%); (b) i. $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; ii. Ph_3P, CBr_4, CH_2Cl_2, -78°C; iii. $^{n}BuLi$, $PhCH_3$, -78°C to -30°C (74%, three steps); (c) i. 50% aq. TFA, CH_2Cl_2; ii. $VO(acac)_2$, tBuOOH, PhH, rt (83%, two steps); (d) TBAF, THF, 0°C; (e) i. $PhI(OAc)_2$, MeOH, 0°C; ii. Ac_2O, Et_3N, DMAP, CH_2Cl_2 (72%, two steps)

Mixture **9** was treated with cyanophthalide **10** in the presence of lithium tert-butoxide (Scheme II).[9] Apparently, one stereoisomer reacts smoothly and the other poorly, if at all.[10] At the end of the process, there was obtained a 37% yield of **11** and one of the stereoisomers of **9** as a homogenous entity. After conversion of **11** to the permethylated anthraquinone **12**, liberation of the free amine was accomplished through the action of tetrakis(triphenylphosphine)palladium(0)[11] and morpholine, thereby affording compound **13**.

It was of interest to probe, if in a preliminary way, the feasibility of chemistry which might be conducted on such a quinone stabilized 3,8-epoxide. An interesting experiment involved reaction of **13** with DDQ in methanol.[12] There was produced the aminal like structure, **14**. This compound also exhibited reasonable chemical stability and was fully characterized.

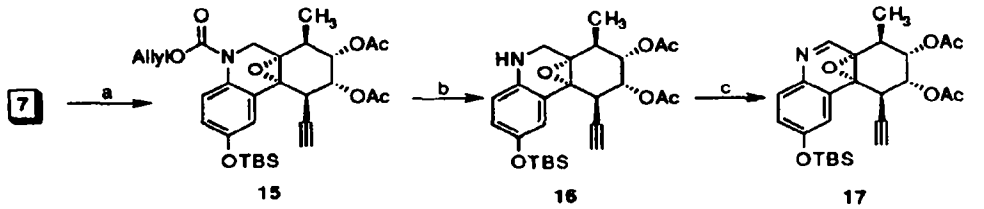
Scheme II



(a) tBuOLi, LiCl, THF, 0°C to reflux (37%); (b) Me_2SO_4, K_2CO_3, acetone, rt to reflux (84%); (c) $Pd(Ph_3P)_4$ (5 mol %), morpholine, THF, rt (96%); (d) DDQ, MeOH, CH_2Cl_2, 0°C (87%)

Given these findings, we were emboldened to explore the possibility of a transiently generated tetrahydroquinoline 3,8 type of epoxide, lacking quinonodial stabilization.[13] For this purpose, we took recourse to compound **15**, the diacetate of **7** (scheme III). Deprotection of the allyl carbamate with tetrakis(triphenylphsophine)palladium(0),[11] in the presence of tributyltin hydride gave rise to the marginally viable **16**. This substance was quickly treated with DDQ to afford the imine **17**. This compound is stable presumably because the lone pair on the nitrogen is stereoelectronically poorly disposed to participate in the opening of the epoxide.

Scheme III



(a) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt; (b) $Pd(Ph_3P)_4$ (5 mol %), ^nBuSnH, wet CH_2Cl_2, 0°C; (c) DDQ, CH_2Cl_2, 0°C (52%, three steps)

Conceivably, the synthetic chemistry practiced here could be of value in a synthesis program directed at dynemicin itself.[14] Moreover, the possibility of a new class of drugs based on a napthaquinone recognition element which could be bioreductivley activated to unleash a vulnerable

epoxide with alkylating potential, is being explored. A formal similarity to the bioreducitivley activated mitomycins [15] presents itself.

Acknowledgements. This work was supported by NIH grant CA 28824.

References and Notes

1. Recipient of a predoctoral fellowship from Memorial Sloan-Kettering Cancer Center.
2. (a) Konishi, M.; Ohkuma, H.; Matsumoto, K.; Tsuno, T.; Kamei, H.; Miyaki, T.; Oki, T.; Kawaguchi, H.; VanDuyne, G. D.; Clardy, J. *J. Antibiot.* **1989**, *42*, 1449. Konishi, M.; Ohkuma, H.; Tsuno, T.; Oki, T.; VanDuyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1990**, *112*, 3715. (b) For an excellent review of the chemistry and biology related to the enediyne antibiotics see: Nicolaou, K. C.; Dai, W. -M. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1387.
3. Semmelhack, M. F.; Gallagher, J.; Cohen, D. *Tetrahedron Lett.* **1990**, *31*, 1521.
4. An analogy can be drawn to the mitomycins in which the quinone stabilizes the indolic nitrogen via delocalization. See ref 15 and references therein.
5. Yoon, T.; Shair, M. D.; Danishefsky, S. J.; and Schulte, G. K. *J. Org. Chem.* **1994**. In Press.
6. Yoon, T. Ph.D. Thesis, Yale University, 1994.
7. (a) Mancuso, A. J.; Huang, S. -L.; Swern, D. *J. Org. Chem.* **1979**, *44*, 4148. (b) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769.
8. Fleck, A. E.; Hobart, S. A.; Morrow, G. W. *Synth. Commun.* **1992**, *22*, 179.
9. For a review, see: Swenton, J. S. in *The Chemistry of the Quinoid Compounds* eds. Patai, S.; Rappoport, Z. John Wiley and Sons, U. K. **1988**, p. 899.
10. It is our belief that the productive diastereomer which leads to an anthraquinone product is the β-methoxy isomer at the aminal center. For a more detailed explanation, see: ref 6.
11. Dangles, O.; Guibe, F.; Balavoine, G.; Leville, S.; Marquet, A. *J. Org. Chem.* **1987**, *52*, 4984.
12. Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885.
13. For an example of a dynemicin model system with marginal stability which lacks urethane stabilization, see: Nicolaou, K. C., Dai, W. -M.; Tsay, S. -C.; Estevez, V. A.; Wrasildo, W. *Science* **1992**, *256*, 1172.
14. For the closest approach to the total synthesis of dynemicin A, see: Taunton, J.; Wood, J. L.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 10378.
15. Danishefsky, S. J.; Egbertson, M. *J. Am. Chem. Soc.* **1986**, *108*, 4648 and references therein. The possibility that the active trigger is a semiquinone rather than a fully reduced hydroquinone is being considered by analogy with the mitomycin case.

(*Received in USA* 2 *June* 1994; *accepted* 8 *July* 1994)