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Synthesis of a Simple Model Compound of Dynemicin and Cycloaromatization with Pinacol-Pinacolone Rearrangement in the Strained Enediyne Medium Ring

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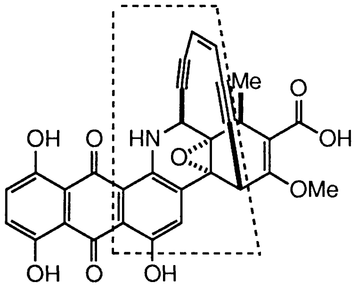
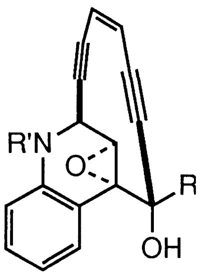
Novel bicyclo[7.3.1]-tridecadiyne system included in dynemicin was synthesized from a quinoline aldehyde in 9 steps. Key step was the cyclization with silyl acetylene to ketone carbonyl group through fluoride activation with CsF. The cyclized compound did aromatize under acidic condition, with opening of the epoxide ring, to give a Bergman product that was further converted with pinacol-pinacolone rearrangement.

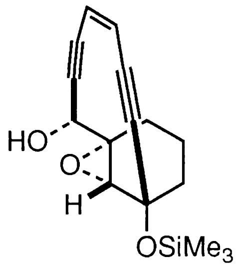
Dynemicin A (**1**) was isolated from *Micromonospora chersina* by Konishi *et al.* at Research Institute of Bristol-Myers in Tokyo.1) This antibiotic is similar to previously reported esperamicin/calicheamicin antibiotics in the strained cyclic enediyne which is responsible for powerful antitumor activity by cleaving DNA chain.2) We started the synthetic studies on Dynemicin A in order to explore active mimics of dynemicin A.3) Recently we described the synthesis of cyclic enediyne compound (**3**) having epoxide as a trigger for Bergman cycloaromatization but no aniline moiety that might help opening the epoxide.4) In this letter, we report the synthesis of a model compound as **2**, which contains the aromatic moiety.5)



Dynemicin A (**1**)



2a R= H, **2b** R= Me



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From our preliminary studies on **2a**, we had found ardent difficulty to obtain the precursor aldehydes (corresponding to **8** or **9** R= H, respectively) in sufficient amount for next cyclization because of unstability of the epoxy aldehyde under the oxidation conditions.5c) Therefore we switched the target molecule into homologous compound **2b** through the ketone **8** and **9** (R= Me). The starting quinoline aldehyde **4**, that was prepared in about 50% yield from commercially available lepidine after SeO_2 oxidation, was reacted with MeMgBr and the resulting alcohol was silylated to provide **5** [^{1}H-NMR ($CDCl_3$) δ 1.55(Me, d, J= 6.5 Hz), 5.53(1H, q, J= 6.5) ppm]. Addition of the magnesium acetylide to **5** with concomitant carbamoylation under Yamaguchi condition6) afforded the adduct **6** [m/z 457 (M^+)] in high yiled as diastereomixture (ca. 1:1), which

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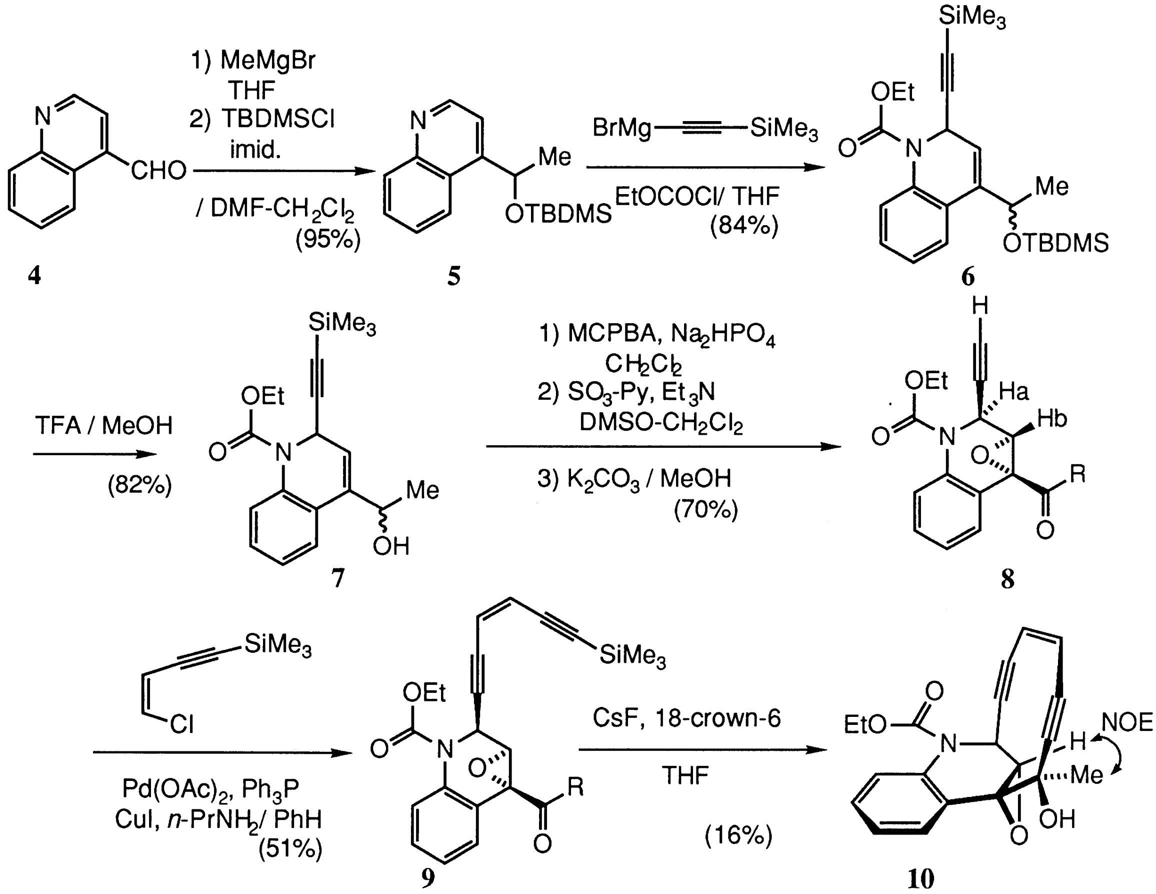
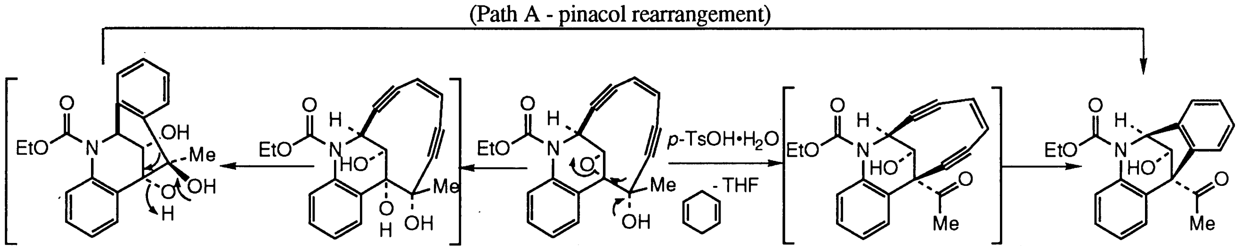
† Deceased August 29, 1990.

was not separated. Selective removal of *O*-silyl group from **6** under acidic condition (TFA/ MeOH) yielded the allylic alcohol **7** [m/z 343 (M^+)]. Epoxidation of **7** with MCPBA was followed by SO_3-Py/DMSO oxidation7) and subsequent desilylation to give single product **8** as crystals [mp 116 °C; ^{1}H-NMR ($CDCl_3$) δ 2.00($C{\equiv}C$-H, d, J= 2.4 Hz), 2.30(Me, s), 3.96(Ha, d, J= 2.9 Hz), 5.86(Hb, m) ppm]. High stereoselectivity in the epoxidation might be due to the steric hindrance of the acetylenic substituent. Stereochemistry of **8** was temporarily assigned from the small coupling constant between Ha and Hb.8) Its terminal acetylene was coupled with (Z)-vinylchloride9) under Sonogashira's condition10) to give the enediyne **9** [^{1}H-NMR ($CDCl_3$) δ 0.20(9H, s), 1.27(3H, t, J= 7.0 Hz), 2.31(3H, s), 3.96(1H, d, J= 2.9 Hz), 4.22(2H, m), 5.64(1H, dd, J= 1.8, 11.1 Hz), 5.78(1H, d, J=11.1 Hz), 6.11(1H, m), 7.12-7.40(2H, m), 7.44(1H, brd, J= 8.0 Hz), 7.61(1H, d, J= 8.0 Hz)].11) The attempted cyclization of **9** with LiF, KF or CsF12) did not give the cyclized product **10**. *In situ* generation of the acetylide anion from the silylacetylene **9** with CsF and 18-crown-6 fortunately gave **10** (**2b** R'= COOEt) [^{1}H-NMR ($CDCl_3$) δ 1.27(3H, t, J= 7.0 Hz), 1.69(Me, s), 4.00(1H, d, J=2.9 Hz), 4.22(2H, m), 5.63(1H, dd, J= 1.8, 9.8 Hz), 5.78(1H, d, J= 9.8 Hz), 5.80(1H, m), 7.12-7.44(3H, m), 8.73(1H, m) ppm]13) in 16% yield. The stereochemistry of newly generated asymmetric center in **10** was almost homogeneous (>95%), and was determined from NOE data (23% enhancement) between the methyl group and epoxyde proton. The synthesis of the bicyclo[7.3.1]-tridecadiyne system with an epoxide ring in it was concluded.



Scheme 1.

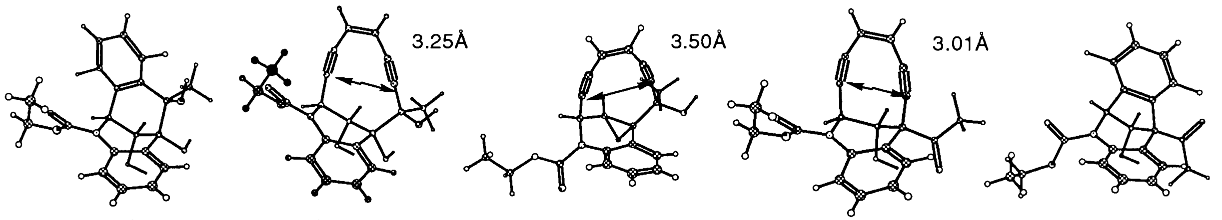
The cycloaromatization of **10** was achieved under acidic condition to cleave the epoxide ring and to diminish the strain to the macro ring system. We first expected that the epoxide opening of **10** might afford **12** *via* **11** through Bergman cycloaromatization. But the product which was obtained, in fact, from **10** with *p*-toluene sulfonic acid in the presence of cyclohexa-1,4-diene in THF solvent was the methyl ketone **14** [^{1}H-NMR (CDCl$_3$) δ 1.45(3H, t, J= 7.0 Hz), 2.51(3H, s), 2.60(1H, d, J=9.5 Hz), 4.36(2H, q, J=7.0 Hz), 4.52(1H, dd, J= 9.5, 4.5 Hz), 5.75(1H, d, 4.5 Hz), 6.97-7.10(2H, m), 7.17-7.32(3H, m), 7.40(1H, dd, J= 6.5, 1.5 Hz), 7.58(1H, d, J= 6.5 Hz), 8.23(1H, d, J= 8.0 Hz); m/z 337 (M$^+$)], in stead.



12 **11** **10** (Path B - pinacol rearrangement) **13** **14**

Scheme 2.

The possible conformations of the above molecules with calculated distances of the 1,6-acetylenic carbons



12a **11a** **10a** **13a** **14a**

This aromatized compound **14** may come from the 1,2-glycol **12** via pinacol-pinacolone rearrangement of the hypothetical intermediate **11** (path A).14) The same product **14** could alternatively be considered as another Bergman cycloaromatization through **13**, a pinacol-pinacolone type rearrangement product with concomitant epoxide opening as shown below (path B). The rearrangement in the latter case, however, has to be associated with ring-shrinking process against the strained 10-membered enediyne system into 9-membered one in **13**. To assist solving the mechanistic questions, some molecular mechanics calculations were considered and the results are indicated above in the form to clarify their conformation (**10a** - **14a**). Molecular mechanics calculation15) of the epoxide**10** concluded its conformation as shown in **10a**, which showed the distance between the 1,6-acetylenic carbons to be 3.50Å. The values on the other enediynes **11a** and **13a** were 3.25Å and 3.01Å, respectively. These products have shorter distances than the original **10a** to allow the cycloaromatization at ordinal temperature.16) The cycloaromatization of **11a** should give **12a**, which could rearrange with phenyl group migration into **14**. On the other hand, if the acetylenic bond with low migratory aptitude could undergo the migration directly from **10a**, the even shorter distance 3.01Å15) between the 1,6-diacetylenic carbons in **13** (indicated by the arrows) would give **14** at an ordinal temperature. The authors conclude, however, the former path A is likely judging from the migratory aptitude.

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11) **9** (R= Me) ^{13}C-NMR(CDCl3) δ -0.2, 14.3, 26.6, 43.6, 60.0, 62.9, 64.9, 82.9, 89.4, 101.4, 103.7, 119.1, 120.9, 121.7, 125.2, 127.1, 128.6, 129.0, 135.0, 202.7 ppm.

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13) **10** (R=Me) ^{13}C-NMR(CDCl3) δ 14.4, 25.4, 45.3, 61.9, 62.8, 66.2, 72.4, 89.0, 90.3, 93.0, 102.1, 122.3, 124.5, 125.1, 126.6, 126.8, 128.2, 131.7, 135.7 ppm.

14) Similar model studies were recently reported in Ref. 5c and in K. C. Nicolaou, A. L. Smith, S. V. Wendeborn, and C.-K. Hwang, *J. Am. Chem. Soc.*, **113**, 3106 (1991).

15) Molecular mechanics calculations were carried out with the Dreiding force field of the BIOGRAF (version 2.20) software package implimented on graphics workstation Iris 4-D/220GTXB (Silicon Graphics). About the force field: S. L Mayo, B. D. Olafson, and W. A. Gooard III, *J. Phys. Chem.*, **94**, 8897 (1990). Details of the result on the other compounds will be repored in the full account of this work.

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