# Epoxide Opening and Bergman Cyclization of Tricyclic Enediyne Models Possessing A Methoxy Group

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Dynemicin A (**1**) is a potent antitumor antibiotic containing enediyne and anthraquinone structures.[1] Its biological action to cleave DNA strand has been attributed to the enediyne's ability to form a phenylene diradical.[2] It has been known that the activation of **1** is triggered by epoxide opening induced by developing electron density at C9.[3] Accordingly, use of proper substituent on the benzene ring of a model compound (*i.e.*, **2a**) can accumulate electron density at C1a and then, the epoxide opening and Bergman cyclization to give a diradical will be accelerated. We reported in a previous paper that the existence of electron donating group at C3 activates the epoxide opening.[4] We now communicate the acid-induced epoxide opening and Bergman cyclization for tricyclic dynemicin A models **2a**, **3a**, and **4a** which have methoxy group at C3.


Dynemicin A (**1**)

New Models
2a: n=0, 3a: n=1, 4a: n=2
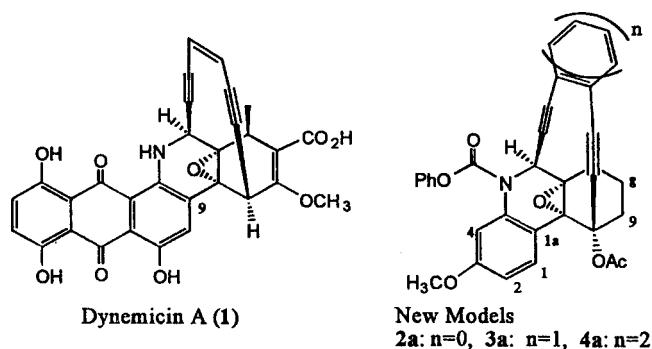
Model compounds were easily prepared by the known synthetic method of tricyclic enediyne compound related to dynemicin A.[5] Scheme 1 shows a synthetic procedure of enediyne model compound **2a** starting from 3-substituted quinoline derivative **5**.[6] The cyclized product **14** was finally acetylated to give the target model **2a** to protect pinacol-pinacolone rearrangement under Bergman cyclization condition. On the other hand, benzenediyne **3a** and naphthalenediyne **4a** were prepared by similar synthetic methods starting from the intermediate **10** using 1-iodo-2-(trimethylsilyl)ethynylbenzene and naphthalene 1,2-ditriflate, respectively instead of vinyl chloride **11**.[7]

The acid-induced epoxide opening followed by Bergman cyclization for compounds **2a**, **3a**, and **4a** were performed with *p*-toluenesulfonic acid in benzene/1,4-cyclohexadiene (3/1) at 40 °C (Scheme 2). Table 1 shows the reaction times for the reaction. Expectedly, conversion to the corresponding diols was very fast in comparison with C3 unsubstituted model which needed 80 min.[8] Enediyne **2a** gave Bergman reaction product **2c** in 8 minutes *via* its epoxide opened product **2b** which was detected only as a trace amount on TLC. The epoxide groups of compounds **3a** and **4a** were opened to give bezenediynediol **3b** and naphthalenedi-
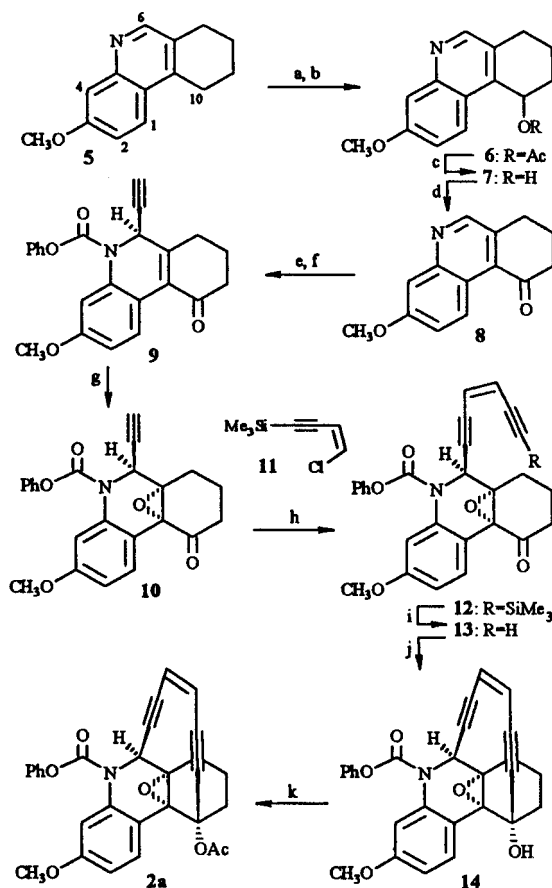
Scheme 1. Synthesis of Model Compound **2a**. Reagents and conditions: (a) 1.2 equiv of *m*CPBA, CH₂Cl₂, 25 °C, 2 h, 89%; (b) Ac₂O, 25 °C, 4 h, 98%; (c) K₂CO₃ (catalytic), MeOH, 25 °C, 7 h, 97%; (d) 1.7 equiv of PCC, 4 Å molecular sieves, CH₂Cl₂, 25 °C, 1 h, 79%; (e) 1.1 equiv of 'BuMe₂SiOSO₂CF₃, 1.5 equiv of 2,6-lutidine, CH₂Cl₂, 0 °C, 30 min, 96%; (f) 1.2 equiv of ethynylmagnesium bromide, 1.1 equiv of PhOCOCl, THF, −78 °C to 25 °C, 30 min and then, dil. HCl, 100%; (g) 1.5 equiv of *m*CPBA, CH₂Cl₂, 25 °C, 25 min, 68%; (h) 1.6 equiv of **11**, 0.06 equiv of Pd(PPh₃)₄, 0.24 equiv of CuI, 2.0 equiv of ⁿBuNH₂, benzene, 25 °C, 2 h, 59%; (i) 4.0 equiv of AgNO₃, 7.0 equiv of KCN, H₂O, EtOH, THF 25 °C, 10 min, 82%; (j) 1.0 equiv of LDA, toluene, −78 °C, 30 min, 61%; (k) 20.0 equiv of Ac₂O, 0.4 equiv of DMAP, pyridine, 25 °C, 2 h, 87%.

yenediol **4b** in 10 and 35 minutes, respectively. Their intermediates were identified on TLC. Moreover, the naphthalene derivative **4b** was thermodynamically very stable under the reaction condition. It is thought that the rate difference for the epoxide opening is related to other factors such as steric effect as well as electronic effect. On the other hand, compound **3a** and **4a** aromatized to yield Bergman

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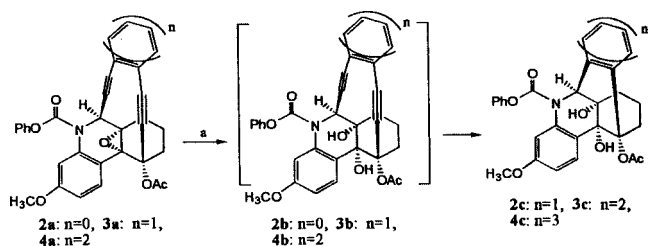
Scheme 2. Epoxide Opening and Bergman Cyclization for Model compounds. Reagent and condition: (a) 1.2 equiv of *p*-TsOH·H$_2$O, benzene/1,4-cyclohexadiene (3/1), 40 °C.

Table 1*. Reaction Times for Model Compounds[9]

Substrate	Reaction time (min)	Product	Yield (%)
2a	–	2b	–
	8	2c	77
3a	10	3b	–
	30	3c	77
4a	35	4b	–
	90	4c	51

*Reaction progress was monitered by TLC. All reactions were run in duplicate and the reaction time was averaged. R$_f$ values for each compound in ethyl acetate/hexane (1/2) are as follows; 2a 0.57, 2c 0.31, 3a 0.56, 3b 0.16, 3c 0.29, 4a 0.59, 4b 0.12, 4c 0.26.

cyclization products 3c and 4c in 30 minutes and in 90 minutes, respectively. Especially, naphthalenediyne 4a was about 50% converted to 4c during this time, and remained unchanged for a prolonged reaction time. Our experimental result confirmed that the epoxide opening is a triggering step of dynemicin A activation and enediyne system affects both epoxide opening and Bergman cyclization.

In summary, the introduction of methoxy group at C3 of tricyclic dynemicin A model compounds activated the epoxide opening and Bergman cyclization under acidic conditions. This fact suggests that tricyclic model compounds with methoxy group at C3 can be developed as new anticancer drugs. For further study, we are now preparing dynemicin A mimics which have a methoxy group at C3, a base-labile protecting group at N5, and an H at C10. Finally, biological activity test such as DNA cleavage or cytotoxicity will be performed for all the model compounds.

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9. All isolable compounds were confirmed by spectroscopic methods. For example, compound 2a, ^{1}H NMR (CDCl$_3$): δ=7.85 (d, J=8.9 Hz, 1H, aromatic), 7.42-7.36 (m, 2H, aromatic), 7.31-7.15 (m, 3H, aromatic), 7.06 (br s, 1H, aromatic), 6.78 (dd, J=8.9, 2.7 Hz, 1H, aromatic), 5.91 (d, J=10.0 Hz, 1H, olefinic), 5.73 (dd, J=10.0, 1.7 Hz, 1H, olefinic), 5.55 (br s, 1H, NC*H*C≡C), 3.82 (s, 3H, OC*H*$_3$), 2.55-2.50 (m, 1H, C*H*$_2$CH$_2$), 2.39-2.00 (m, 4H, C*H*$_2$C*H*$_2$), 2.23 (s, 3H, C(=O)C*H*$_3$), 1.79-1.72 (m, 1H, C*H*$_2$CH$_2$); ^{13}C NMR (CDCl$_3$): δ=169.6, 159.4, 151.4, 137.5, 131.2, 129.8, 128.7, 126.2, 124.7, 123.3, 121.9, 120.0, 112.9, 111.7, 98.1, 95.8, 94.3, 89.1, 78.2, 73.8, 63.5, 55.7, 51.0, 29.9, 23.3, 22.3, 18.9. Compound 3c, ^{1}H NMR (DMSO-d$_6$): δ= 8.07 (br s, 1H, aromatic), 8.00-7.97 (m, 1H, aromatic), 7.86-7.82 (m, 1H, aromatic), 7.83 (s, 1H, aromatic), 7.54-7.47 (m, 3H, aromatic), 7.37-7.28 (m, 5H, aromatic), 6.98 (br s, 1H, aromatic), 6.66 (dd, J=8.8, 2.4 Hz, 1H, aromatic), 5.90 (br s, 1H, NC*H*C≡C), 5.63 (s, 1H, O*H*), 5.33 (s, 1H, O*H*), 3.57 (s, 3H, OC*H*$_3$), 3.17-3.07 (m, 1H, C*H*$_2$CH$_2$), 2.25-2.16 (m, 2H, C*H*$_2$C*H*$_2$), 2.24 (s, 3H, C(=O)C*H*$_3$), 2.10-2.02 (m, 1H, C*H*$_2$CH$_2$), 1.81-1.74 (m, 1H, C*H*$_2$CH$_2$), 1.52-1.46 (m, 1H, C*H*$_2$CH$_2$); ^{13}C NMR (DMSO-d$_6$): δ=170.7, 157.8, 151.1, 137.9, 136.1, 133.0, 132.7, 132.3, 130.8, 129.3, 128.3, 127.7, 127.5, 126.9, 126.4, 126.3, 125.5, 124.2, 123.2, 121.9, 109.1, 107.5, 91.7, 75.0, 69.3, 63.7, 54.8, 32.4, 32.3, 22.7, 19.4. Compound 4b, ^{1}H NMR (DMSO-d$_6$): δ=8.12 (d, J=9.1 Hz, 1H, aromatic), 8.05 (s, 1H, aromatic), 7.91 (s, 1H, aromatic), 7.89-7.85 (m, 2H, aromatic), 7.56-7.52 (m, 2H, aromatic), 7.44-7.39 (m, 2H, aromatic), 7.27-7.20 (m, 3H, aromatic), 6.98 (br s, 1H, aromatic), 6.78 (dd, J=9.1, 2.7 Hz, 1H, aromatic), 6.31 (br s, 1H, O*H*), 5.61 (br s, 1H, O*H*), 5.50 (s, 1H, NC*H*C C), 3.63 (s, 3H, OC*H*$_3$), 2.85-2.80 (m, 1H, C*H*$_2$CH$_2$), 2.25 (s, 3H, C(=O)C*H*$_3$), 2.24-2.20 (m, 1H, C*H*$_2$CH$_2$), 2.10-1.83 (m, 3H, C*H*$_2$C*H*$_2$), 1.72-1.65 (m, 1H, C*H*$_2$CH$_2$); ^{13}C NMR (CDCl$_3$): δ=168.0, 158.0, 153.1, 151.0, 136.1, 132.0, 131.7, 130.6, 129.4, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 125.6, 125.1, 124.0, 123.0, 121.8, 111.1, 110.0, 97.3, 97.0, 88.8, 85.8, 81.8, 75.3, 74.6, 56.8, 55.0, 34.5, 32.2, 22.2, 18.1.