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단 신

염기조건에서 Dynemicin A에 관련된 모델 화합물들의 에폭시드 열림에 대한 치환체 효과

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Substituent Effect for Epoxide Opening of Model Compounds Related to Dynemicin A under Basic Condition

Yong Pyo Hong* and Jung Hee Kim
Department of Chemistry, Andong National University, Andong 760-749, Korea
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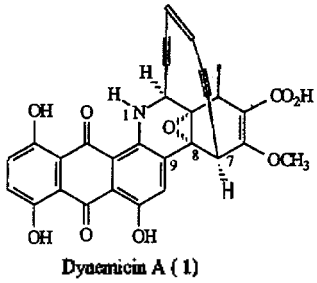
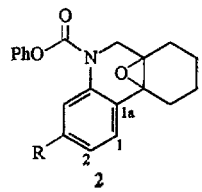
Dynemicin A (**1**) is a potent antitumor antibiotic with unique molecular structure and fascinating mode of action.[1] It has been known that DNA cleaving ability of **1** is attributed to the benzenoid diradical generation of enediyne system via Bergman cycloaromatization reaction.[2] The activation of dynemicin A is triggered by epoxide opening induced by bioreduction of quinone system, followed by developing electron density at C-9.[3] Electron density at C-9 is dependent upon electron releasing power of both nitrogen and oxygen on benzene ring. We reported previously the substituent effect for epoxide opening with tricyclic model compounds under weak acidic condition.[4] For instance, compound **2** with substituent at C-3 on benzene ring and protecting group on nitrogen represented a significant rate difference for the epoxide opening reflecting electron density developing at C-1a. Here, we note the substituent effect for epoxide opening of tricyclic free amines which are dynemicin A mimics under basic condition.

Synthesis of Model Compound. The synthetic method for unsubstituted model compound is representatively shown in *Scheme* 1. Compound **3**[4] was treated with sodium 2-(phenylthio)ethoxide to exchange *N*-protecting group according to a known method[5]. Continuously, oxidation with *m*-chloroperoxybenzoic acid (*m*CPBA) gave the target compound **4** in high yield. Compounds **5-8** were easily prepared by the same synthetic method alternating the starting material.

Reaction of Model Compounds in Weak Basic Condition. Compounds **4-8** were treated with 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) to see the substituent effect for epoxide opening at 0 ℃ and 40 ℃ in wet toluene, respectively. Each compound gave the corresponding diols **4a-8a** and enols **4b-8b** in 87 to 96% yield (*Scheme* 2).

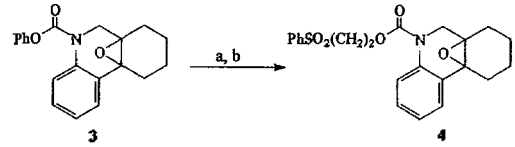


Dynemicin A (1)



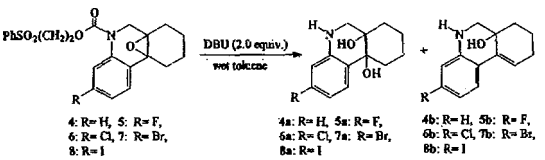
2

Fig. 1.

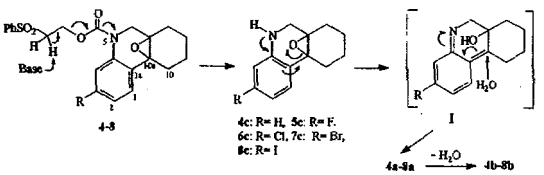


3 4

Scheme 1. (a) $PhSCH_2CH_2OH$ (2.0 equiv.), NaH (2.0 equiv.), THF, 25 ℃, 15 min; (b) mCPBA (2.5 equiv.), CH_2Cl_2/sat. $NaHCO_3$ (1:1), 0 ℃, 10min.



Scheme 2. Base-Catalyzed Epoxide Opening of Model Compounds.



Scheme 3. Mechanism for Product Formation.

The plausible mechanism for product formation is shown in *Scheme* 3. Protection group at *N*-5 is removed to give free amines **4c-8c** by base (DBU). The epoxide opening with the aid of nitrogen gives the intermediate **I**. Continually, attack to C-10a by H_2O will give the diols **4a-8a**. On the other hand, elimination of water from diols will give the enols **4b-8b**. Even though the free amines could not be isolated and identified, the presumable corresponding spots were observed on TLC during the reactions.

Reaction Time. *Table* 1 shows the reaction times to lead to products and the ratios (**a/b**) for diol to enol products at 0 and 40 °C, respectively. The reaction times at 0 °C were very long in comparison with those (7 to 60 min) under acidic condition at the same temperarure.[4a] It is thought that one reason for slow reaction is due to the slow deprotection at *N*-5. But, a significant reaction rate difference appeared for epoxide opening of five compounds. That is, compounds **6-8** with a typical electron withdrawing group at C-3 showed longer reaction times than that of unsubstituted one **4**. On the other hand, introduction of fluorine at C-3 activated the epoxide opening representing a resonance effect by fluorine. For instance, the reaction time of compound **5** was only a half of that of unsubstutited one **4**. The reaction times at 40 °C were dramatically shorter than those of 0 °C. Product formation was completed within 40 min for all compounds. Starting material spots on TLC disappeared in 15 min except compound **8** (20 min). The reactivity for four compounds **4-7** showed a trend according with electronic effect of substituents at C-3.

Table 1. Reaction Times and Product Ratios for model compounds*

Compound	Reaction Time		Product Ratio (a/b)	
	0 °C	40 °C	0 °C	40 °C
4	7 h	20 min	1.3	0.7
5	3.5 h	15 min	4.2	0.8
6	8 h	30 min	3.3	1.0
7	>12 h	40 min	2.4	1.0
8	>12 h	25 min	7.8	8.6

*All reactions were run in duplicate and averaged.

Table 2. Electron density at C-1a of free amines*

Compound	Electron Density
4c	4.118
5c	4.134
6c	4.112
7c	4.105
8c	4.091

*The values were obtained by MOPAC-97 (MNDO) calculation method.

Reaction progress was checked by TLC. The reaction time for epoxide opening is associated with electron density developing at C-1a. Electron densities for free amines **4c-8c** were calculated by MOPAC-97 (*Table* 2). The trend of the calculated values was in relatively accord with that of experimental result. Especially, any trace of **5c** with the highest value was not observed on TLC until the reaction was terminated at 40 °C.

Product Ratio. Experimental results showed a significant difference on the ratio of product formation (*Table* 1). At 0 °C, the formation of diols **4a-8a** was superior to enols **4b-8b**. And, the product formation was competitive at 40 °C. It is thought that the increase of enol product ratios at 40 °C in comparison with 0 °C is due to the activated water elimination. But, the biased values for both reaction time and product ratio of compound **8** at 40 °C were not understood.

In conclusion, our experimental result showed that substituent at C-3 of tricyclic model compound can exhibit a significant effect on the rate of the epoxide opening under basic condition. This means that a new enediyne anticancer related to dynemicin A can be developed by introducing a proper substituent on benzene ring.

EXPERIMENTAL SECTION

Genenral Techniques. NMR spectra were recorded on a Bruker DPX-300 or 500 instrument. All reactions were monitored by thin-layer chromatography carried out on 0.25mm E. Merck silica gel plates (60F-254) under UV light. All new compounds were identified by spectroscopic methods.

Synthesis of Compound 4. Representative procedure. To a suspension of NaH (250 mg of 60% dispersion in mineral oil, 6.23 mmol) in dry THF (12 mL) was added 2-(phenylthio)ethanol (0.84 mL, 6.23 mmol) followed by stirring at 25 °C for 5 min. The resulting solution was added to a solution of **3** (1.00 g, 3.12 mmol) in dry THF (19 mL). After stirring at 25 °C for 10 min, the reaction mixture was diluted with ethyl ether (50 mL), poured into H_2O (100 mL), and extracted with ethyl ether (2 × 100 mL). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by column chromatography (silica, 33% ethyl ether in hexane) to give the product in quantitative yield. To a solution of the above product in dichloromethane (15 mL) and saturated aqueous sodium bicarbonate (15 mL) was added *m*CPBA (70%, 1.35 g, 7.81 mmol) followed by stirring at 0 °C for 10 min. The reaction mixture was poured into saturated aqueous sodium bicarbonate (100 mL) and extracted with dichloromethane (2× 100 mL). The combined organic layers were dryed (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by column chromatography (silica, 67% ethyl ether in hexane) to provide **4** (1.15 g, 88% from **3**). ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.88 (d, *J*=7.6 Hz, 2H, aromatic), 7.70 (t, *J*=7.6 Hz, 1H, aromatic), 7.61 (t, *J*=7.6 Hz, 2H, aromatic), 7.45 (d, *J*=7.6 Hz, 1H, aromatic), 7.24-7.17 (m, 2H, aromatic), 7.14 (t, *J*=7.6 Hz, 1H, aromatic), 4.31 (br s, 1H, OCH_2), 4.22 (br s, 1H, OCH_2), 4.05 (br s, 1H, NCH_2), 3.75-3.68 (m, 2H, SCH_2), 2.92 (d, *J*=14.1 Hz, 1H, NCH_2), 2.32-2.28 (m, 1H, CH_2), 2.14-2.08 (m, 1H, CH_2), 1.85-1.80 (m, 1H, CH_2), 1.74-1.68 (m, 1H, CH_2), 1.51-1.44 (m, 2H, CH_2), 1.42-1.37 (m, 1H, CH_2), 1.22-1.17 (m, 1H, CH_2); ^{13}C NMR (125.8 MHz, DMSO-d_6): δ 154.0, 139.3, 136.7, 134.0, 129.5, 129.4, 127.7, 127.6, 126.8, 125.6, 124.9, 67.4, 59.2, 57.0, 54.1, 45.0, 24.7, 24.2, 20.0, 18.8.

Spectroscopic data for compound 6. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.92 (d, *J*=7.6 Hz, 2H, aromatic), 7.73 (t, *J*=7.6 Hz, 1H, aromatic), 7.64 (t, *J*=7.6 Hz, 2H, aromatic), 7.51 (d, *J*=7.6 Hz, 1H, aromatic), 7.42 (d, *J*= 2.1 Hz, 1H, aromatic), 7.25 (dd, *J*=7.6, 2.1 Hz, 1H, aromatic), 4.41-4.31 (m, 2H, OCH_2), 4.12-4.05 (m, 1H, NCH_2), 3.77 (br s, 2H, SCH_2), 3.00 (d, *J*=14.3 Hz, 1H, NCH_2), 2.35-2.28 (m, 1H, CH_2), 2.17-2.07 (m, 1H, CH_2), 1.90-1.71 (m, 2H, CH_2), 1.53-1.36 (m, 3H, CH_2), 1.30-1.18 (m, 1H, CH_2); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 153.6, 139.2, 137.9, 133.9, 132.1, 129.4, 128.5, 128.4, 127.5, 125.2, 124.7, 67.5, 59.4, 56.7, 54.0, 44.8, 24.6, 24.1, 19.8, 18.8.

Base-Induced Epoxide Opening of Compound 4. Representative procedure. A solution of epoxide **4** (20 mg, 0.048 mmol) in wet toluene (2 mL) was cooled to 0 °C (ice/water bath) and then, DBU (15 mg, 0.097 mmol) was added to the solution. The reaction progress was probed at a proper interval by TLC. When the product formation was completed the solution was concentrated *in vacuo*. The residue was purified by column chromatography (silica, 33% ethyl acetate in hexane) to give diol **4a** (5.5 mg, 52%) and allylic alcohol **4b** (3.9 mg, 40%). **4a**: ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.19 (dd, *J*=7.7, 1.2 Hz, 1H, aromatic), 6.86 (td, *J*=7.7, 1.2 Hz, 1H, aromatic), 6.46-6.40 (m, 2H, aromatic), 5.71 (br s, 1H, N*H*), 4.29 (br s, 1H, O*H*), 3.87 (br s, 1H, O*H*), 3.13 (d, *J*=11.3 Hz, 1H, NCH_2), 2.87 (br d, *J*=11.3 Hz, 1H, NCH_2), 1.95-1.85 (m, 1H, CH_2), 1.77-1.70 (m, 1H, CH_2), 1.60-1.45 (m, 3H, CH_2), 1.35-1.22 (m, 2H, CH_2), 1.10-0.98 (m, 1H, CH_2); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 144.1, 127.4, 127.3, 126.5, 114.8, 113.3, 71.9, 69.7, 48.7, 33.7, 31.6, 23.5, 22.5. **4b**: ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.25 (dd, *J*=7.8, 1.2 Hz, 1H, aromatic), 6.87 (td, *J*=7.8, 1.2 Hz, 1H, aromatic), 6.50-6.42 (m, 2H, aromatic), 6.00 (t, *J*=3.9 Hz, 1H, C*H*CH$_2$), 5.77 (br s, 1H, N*H*), 4.20 (br s, 1H, O*H*), 3.04 (dd, *J*=12.1, 3.1 Hz, 1H, NCH_2), 2.87 (d, *J*=12.1 Hz, 1H, NCH_2), 2.18-2.12 (m, 2H, CH_2), 1.92-1.80 (m, 1H, CH_2), 1.73-1.58 (m, 2H, CH_2), 1.34-1.25 (m, 1H, CH_2); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 143.9, 134.5, 127.2, 124.2, 118.3, 118.1, 115.5, 114.0, 62.9, 52.2, 34.6, 26.0, 17.3.

Spectroscopic data for compound 5a. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.23-7.18 (m, 1H, aromatic), 6.24-6.17 (m, 2H, aromatic), 6.12 (br s, 1H, N*H*), 4.21 (br s, 1H, O*H*), 4.02 (br s, 1H, O*H*), 3.14 (br d, *J*=11.3 Hz, 1H,

NCH_2), 2.90 (br, 1H, NCH_2), 1.95-1.85 (m, 1H, CH_2), 1.76-1.70 (m, 1H, CH_2), 1.60-1.50 (m, 3H, CH_2), 1.42-1.25 (m, 2H, CH_2), 1.11-1.03 (m, 1H, CH_2); ^{13}C NMR (125.8 MHz, DMSO-d_6): δ 163.4 ($^1J_{CF}$=239 Hz), 146.9, 129.4, 119.0, 102.2 ($^2J_{CF}$=22 Hz), 99.6 ($^2J_{CF}$=24 Hz), 71.7, 69.5, 48.5, 33.7, 31.5, 23.5, 22.5.

Spectroscopic data for compound 5b. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.25 (dd, *J*=8.5, 6.8 Hz, 1H, aromatic), 6.27-6.20 (m, 2H, aromatic), 6.18 (br d, *J*=3.7 Hz, 1H, N*H*), 5.97 (t, *J*=3.2 Hz, 1H, C*H*CH$_2$), 4.39 (s, 1H, O*H*), 3.08 (dd, *J*=12.2, 3.7 Hz, 1H, NCH_2), 2.90 (d, *J*=12.2 Hz, 1H, NCH_2), 2.18-2.12 (m, 2H, CH_2), 1.92-1.82 (m, 1H, CH_2), 1.69 (dt, *J*=12.9, 3.2 Hz, 1H, CH_2), 1.63-1.59 (m, 1H, CH_2), 1.30 (td, *J*=13.3, 3.2 Hz, 1H, CH_2); ^{13}C NMR (125.8 MHz, DMSO-d_6): δ 162.1 ($^1J_{CF}$= 240 Hz), 145.3, 129.5, 125.9, 118.0, 114.9, 101.9 ($^2J_{CF}$= 22 Hz), 99.1 ($^2J_{CF}$=24 Hz), 62.7, 51.8, 34.6, 26.0, 17.3.

Spectroscopic data for compound 6a. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.20 (d, *J*=8.0 Hz, 1H, aromatic), 6.46-6.42 (m, 2H, aromatic), 6.14 (br s, 1H, N*H*), 4.48 (br s, 1H, O*H*), 4.08 (br s, 1H, O*H*), 3.15 (br d, *J*=11.1 Hz, 1H, NCH_2), 2.99 (br, 1H, NCH_2), 1.95-1.85 (m, 1H, CH_2), 1.80-1.68 (m, 1H, CH_2), 1.65-1.50 (m, 3H, CH_2), 1.45-1.35 (m, 2H, CH_2), 1.17-1.05 (m, 1H, CH_2); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 145.5, 131.8, 128.3, 123.5, 118.3, 114.1, 70.6, 68.2, 47.2, 33.7, 32.6, 22.2, 21.4.

Spectroscopic data for compound 6b. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.24 (d, *J*=8.3 Hz, 1H, aromatic), 6.53(d, *J*=2.0 Hz, 1H, aromatic), 6.44 (dd, *J*=8.3, 2.0 Hz, 1H, aromatic), 6.23 (d, *J*=3.4 Hz, 1H, N*H*), 6.03 (t, *J*=4.0 Hz, 1H, C*H*CH$_2$), 4.50 (s, 1H, O*H*), 3.11-3.06 (m, 1H, NCH_2), 2.91-2.87 (m, 1H, NCH_2), 2.17-2.12 (m, 2H, CH_2), 1.90-1.82 (m, 1H, CH_2), 1.71-1.58 (m, 2H, CH_2), 1.34-1.24 (m, 1H, CH_2); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 145.1, 133.6, 131.5, 125.9, 119.1, 117.3, 114.9, 112.6, 65.2, 51.8, 34.5, 26.1, 17.3.

Spectroscopic data for compound 7a. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.13 (d, *J*=8.2 Hz, 1H, aromatic), 6.60 (d, *J*=1.9 Hz, 1H, aromatic), 6.56 (dd, *J*=8.2, 1.9 Hz, 1H, aromatic), 6.14 (br s, 1H, N*H*), 4.49 (br s, 1H, O*H*), 4.09 (br s, 1H, O*H*), 3.13 (br s, 1H, NCH_2), 2.98 (br, 1H, NCH_2), 1.95-1.84 (m, 1H, CH_2), 1.78-1.70 (m, 1H, CH_2), 1.63-1.50 (m, 3H, CH_2), 1.42-1.38 (m, 1H, CH_2), 1.35-1.29 (m, 1H, CH_2), 1.15-1.05 (m, 1H, CH_2); ^{13}C NMR (125.8 MHz, DMSO-d_6): δ 145.8, 128.6, 126.3, 120.5, 117.7, 116.9, 70.6, 68.2, 47.2, 34.5, 32.6, 22.2, 21.5.

Spectroscopic data for compound 7b. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.18 (d, *J*=8.4 Hz, 1H, aromatic), 6.67 (d, *J*=1.9 Hz, 1H, aromatic), 6.55 (dd, *J*=8.4, 1.9 Hz, 1H, aromatic), 6.21 (br s, 1H, N*H*), 6.04 (t, *J*=4.0 Hz, 1H, C*H*CH$_2$), 4.49 (s, 1H, O*H*), 3.08 (dd, *J*=12.3, 3.1 Hz, 1H, NCH_2), 2.88 (d, *J*=12.3 Hz, 1H, NCH_2), 2.20-2.11 (m, 2H, CH_2), 1.90-1.81 (m, 1H, CH_2), 1.71-1.66 (m, 1H, CH_2), 1.64-1.59 (m, 1H, CH_2), 1.33-1.27 (m, 1H, CH_2); ^{13}C NMR (125.8 MHz, DMSO-d_6): δ 145.4, 133.7, 126.3, 120.2, 119.2, 117.7, 117.6, 115.5, 62.6, 51.7, 34.5, 26.1, 17.3.

Spectroscopic data for compound 8a. ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.99 (d, *J*=8.1 Hz, 1H, aromatic), 6.81 (br s, 1H, aromatic), 6.75 (br d, *J*=8.1 Hz, 1H, aromatic), 6.09 (br s, 1H, N*H*), 4.49 (br s, 1H, O*H*), 4.08 (br s, 1H, O*H*), 3.17-3.08 (m, 1H, NCH_2), 3.00-2.90 (br, 1H, NCH_2), 1.95-1.83 (m, 1H, CH_2), 1.78-1.68 (m, 1H, CH_2), 1.65-1.48 (m, 3H, CH_2), 1.45-1.28 (m, 2H, CH_2), 1.15-1.05 (m, 1H, CH_2); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 145.9, 128.7, 125.4, 123.0, 120.8, 97.0, 70.7, 68.1, 47.2, 34.5, 32.5, 22.2, 21.5.

Spectroscopic data for compound 8b. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.03 (d, *J*=8.1 Hz, 1H, aromatic), 6.88 (br s, 1H, aromatic), 6.70 (br d, *J*=8.1 Hz, 1H, aromatic), 6.15 (br s, 1H, N*H*), 6.04 (br s, 1H, C*H*CH$_2$), 4.49 (br s, 1H, O*H*), 3.10-3.05 (m, 1H, NCH_2), 2.95-2.85 (m, 1H, NCH_2), 2.20-2.10 (m, 2H, CH_2), 1.90-1.80 (m, 1H, CH_2), 1.75-1.55 (m, 2H, CH_2), 1.35-1.25 (m, 1H, CH_2); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 146.2, 127.6, 126.3, 125.4, 123.6, 119.2, 116.1, 94.9, 65.2, 51.7, 34.5, 26.0, 17.2.

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