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단 신

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

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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 developing electron density at C9.[3] In our previous study, it was observed that introduction of halides at C3 exerted deactivating effect in the epoxide opening of tricyclic model compound.[4] In this note we report the electronic effect for epoxide opening of tricyclic models with electron-donating or electron-withdrawing group at C2 or C3.

Acid-induced epoxide opening was performed under weak acidic condition. (*Scheme* 1) Each epoxides, **2a-2d** were converted to the corresponding diols, **3a-3d** and allylic alcohols, **4a-4d** in high yields (>95%), respectively. The allylic alcohol was probably generated by dehydration of the diol.[5] To better understand the electronic effects of the substituents on the aromatic ring for epoxide opening the electron densities developing at C1a were calculated. *Table* 1 shows the reaction times and electron densities for epoxides.

Experimental results for epoxide opening of model compounds showed a significant reaction rate difference. The order of reactivity was relatively in accord with that of developing electron density at C1a calculated by MOPAC-93 method. Interestingly, compound **2b** with fluorine at C2 showed much less reactivity and low electron density as compared with compound **2f** with fluorine at C3. This fact implies that fluorine at meta-position to the epoxide exerts a typical inductive effect as an electron-withdrawing group, while fluorine at para-position to the epoxide confers strong resonance effect overriding the inductive effect. Introduction of a methyl group at C3 also gave positive effect to epoxide opening, while existance of

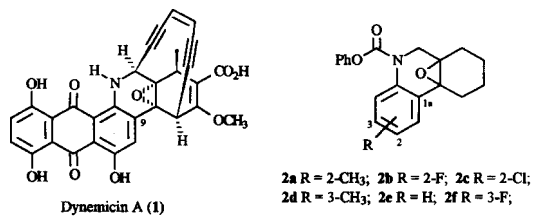
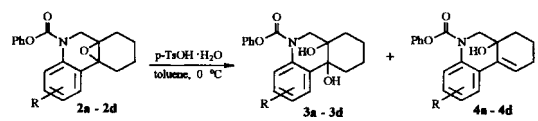


Fig. 1.



Scheme 1.

Table 1. Reaction Times for Acid-Induced Epoxide Opening and Electron Density at C1a of Substituted Compounds[a]

Epoxides	Reaction Times[b] (min)	Products	Electron Densities at C1a of Substrates[c]
2a	12	3a, 4a	4.0866
2b	58	3b, 4b	4.0649
2c	35	3c, 4c	4.0817
2d	3	3d, 4d	4.0981
2e	10	3e, 4e	4.0879
2f	7	3f, 4f	4.1012

[a]Values for **2e** and **2f** were adapted to compare from reported paper, ref. 4. [b]End point of the reaction was checked on TLC. [c]MOPAC-93 calculation method was used for electron density at C1a.

a methyl group at C2 yielded rather negative effect in comparison with unsubstituted compound, **2e**.[6] Unfortunately, introduction of methoxy and nitro group at C3 which are expected to give strong positive and negative effect, respectively were failed because of synthetic problem.[7] But, the large electron density value[8] at C1a and the identification of epoxide-opened products implied that the existence of methoxy group at C3 would strongly activate the epoxide opening.

In conclusion, our experimental result shows that any substituent at C3 can exhibit a significant positive effect on the rate of the epoxide opening of dynemicin A models. Futhermore, the result also indicates that calculation method could be used to find an optimal derivative of **2**, which can serve as a lead compound for potent enediyne anticancer related to dynemicin A.

EXPERIMENTAL SECTION

Genenral Techiques. Melting points were recorded on a Büchi 512 capillary melting point appratus and were not corrected. NMR spectra were recorded on a Varian Unity Plus FT-300, Bruker DPX-300, or Bruker DRX-500 instrument. IR spectra were recorded on a Perkin Elmer 1430 IR spectrophotometer. All reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) under UV lamp. All new compounds were identified by spectroscopic methods.

Synthesis of Compound 2a. Representative Procedure. A solution of 2-methyl-7,8,9,10-tetrahydrophenanthridine[9] (2.00 g, 10.1 mmol) in dichloromethane (30 mL) was cooled to 0 °C and treated with tributyltin hydride (2.66 g, 9.12 mmol) followed by phenyl chloroformate (1.43 g, 9.12 mmol). After 1 h, the reaction mixture was poured into saturated aqueous sodium bicarbonate solution (50 mL) and extracted with dichloromethane (2×50 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4), and evaporated in vacuo. The residue was simply purified by column chromatography to yield 2.75 g of product. The product (1.62 g, 5.07 mmol) in dichloromethane (30 mL) and saturated aqueous sodium bicarbonate (30 mL) was treated with mCPBA (1.48 g of a 71% sample, 6.09 mmol) at 0 °C, and stirred for 1 h. The solution was poured into saturated sodium bicarbonate solution (50 mL) and extracted. The aqueous layer was extracted with further dichloromethane (2×30 mL), and the combined organic layers were dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by flash chromatography (silica gel, 25% ethyl acetate in hexane) to give the epoxide **2a** (1.14 g, 67%) as a white solid: mp 109-111 °C; IR (KBr) ν_{max} 3040, 2970, 1720, 1500, 1380, 1200 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36-7.10 (m, 8H), 4.63 (d, *J*= 13.5 Hz, 1H), 3.14 (br s, 1H), 2.51 (d, *J*=13.5 Hz, 1H), 2.36 (s, 3H), 2.25-2.15 (m, 1H), 2.04-1.93 m, 2H), 1.70-1.58 (m, 3H), 1.35-1.23 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.3, 151.3, 135.0, 134.6, 129.7, 129.2, 128.6, 127.5, 125.9, 125.3, 121.6, 67.4, 57.7, 46.3, 25.4, 24.7, 21.1, 20.6, 19.1.

Physical and Spectroscopic Data for Compound 2b. mp 56-58 °C; IR (KBr) ν_{max} 3030, 2940, 1720, 1500, 1370, 1200 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45 (br s, 1H), 7.37-7.32 (m, 2H), 7.22-7.10 (m, 4H), 7.04-6.97 (m, 1H), 4.65 (d, *J*=14.7 Hz, 1H), 3.11 (br s, 1H), 2.47 (dt, *J*= 14.7, 4.2 Hz, 1H), 2.18-1.90 (m, 3H), 1.70-1.57 m, 3H), 1.35-1.20 (m, 1H); ^{13}C NMR (75 MHz,

$CDCl_3$): 160.4 (J_{CF}=238 Hz), 154.8, 151.6, 133.7, 129.7, 128.7, 128.2, 126.1, 122.0, 115.2 (J_{CCF}=23 Hz), 114.3 (J_{CCF}=23 Hz), 68.0, 57.7, 46.7, 25.7, 25.0, 20.9, 19.5.

Physical and Spectroscopic Data for Compound 2c. mp 63-65 °C; IR (KBr) ν_{max} 3060, 2940, 1720, 1490, 1380, 1200 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.47-7.10 (m, 8H), 4.64 (d, J=14.4 Hz, 1H), 3.14 (br s, 1H), 2.47 (dt, J=14.7, 4.2 Hz, 1H), 2.20-2.09 (m, 1H), 2.06-1.89 m, 2H), 1.73-1.57 (m, 3H), 1.34-1.20 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.0, 151.0, 135.8, 131.8, 130.7, 129.3, 128.0, 127.4, 127.1, 125.5, 121.5, 67.6, 57.3, 46.1, 25.2, 24.6, 20.4, 19.0.

Physical and Spectroscopic Data for Compound 2d. mp 111-113 °C; IR (KBr) ν_{max} 3040, 2940, 1720, 1380, 1200 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.39-7.31 (m, 4H), 7.21-7.12 (m, 3H), 7.01 (d, J=7.5 Hz, 1H), 4.64 (d, J=13.8 Hz, 1H), 3.14 (br s, 1H), 2.49 (br d, J=14.7 Hz, 1H), 2.33 (s, 3H), 2.23-2.12 (m, 1H), 2.07-1.87 m, 2H), 1.70-1.57 (m, 3H), 1.33-1.20 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.3, 151.2, 138.0, 137.0, 129.2, 126.9, 126.7, 126.6, 126.1, 125.3, 121.6, 67.3, 57.6, 46.3, 25.3, 24.7, 21.2, 20.6, 19.1.

Acid-induced Epoxide Opening of Compound 2a.

Representative Procedure. A solution of epoxide **2a** (20 mg, 0.059 mmol) in toluene (3 mL) was treated with *p*-toluenesulfonic acid monohydrate (5.7 mg, 0.029 mmol) and the mixture was stirred at 0 °C. After 12 min the solution was poured into saturated sodium bicarbonate solution (10 mL) and extracted with ethyl acetate. The aqueous layer was extracted with further ethyl acetate (10 mL), and the combined organic layers were dried (Na_2SO_4) and evaporated in *vacuo*. The residue was purified by flash column chromatography (silica gel, 33% ethyl acetate in hexane) to give the diol **3a** (10.5 mg, 50%) and the allylic alcohol **4a** (9 mg, 45%). **3a**: white solid; mp 107-109 °C; IR (KBr) ν_{max} 3480, 3040, 2940, 1700, 1380, 1950 cm^{-1}; ^1H NMR (300 MHz, DMSO-d^6): δ 7.57 (d, J=8.4 Hz, 1H), 7.44-7.36 (m, 3H), 7.27-7.17 (m, 3H), 7.01 (d, J=8.4 Hz, 1H), 4.67 (s, 1H), 4.63 (s, 1H), 3.98 (ABq, J=13.5 Hz, 1H), 3.87 (ABq, J=13.5 Hz, 1H), 2.28 (s, 3H), 1.87-1.76 (m, 3H), 1.66-1.52 (m, 3H), 1.39-1.23 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d^6): δ 153.5, 151.2, 135.7, 133.3, 133.0, 129.5, 127.4, 127.2, 125.6, 122.9, 122.0, 71.7, 69.9, 51.9, 36.9, 33.3, 22.2, 21.6, 20.8. **4a**: white cryatalline solid; mp 179-181 °C; IR (KBr) ν_{max} 3480, 3030, 2950, 1720, 1380, 1200 cm^{-1}; ^1H NMR (300 MHz, DMSO-d^6): δ 7.52-7.37 (m, 4H), 7.26-7.16 (m, 3H), 7.00 (d, J=8.4 Hz, 1H), 6.45 (t, J=3.6 Hz, 1H), 5.06 (s, 1H), 4.30 (d, J=12.9 Hz, 1H), 3.07 (d, J=12.9 Hz, 1H), 2.34-2.21 (m, 2H), 2.27 (s, 3H), 1.98-1.88 (m, 1H), 1.76-1.64 (m, 2H), 1.39 (t, J=12.0 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d^6): δ 154.2, 151.7, 133.8, 133.5, 133.2, 129.7, 127.7, 126.1, 125.7, 124.6, 123.9, 123.7, 122.3, 64.7, 55.5, 33.6, 26.3, 21.0, 16.9.

Physical and Spectroscopic Data for Compound 3b. mp 58-60 °C; IR (KBr) ν_{max} 3460, 3020, 2940, 1700, 1380, 1200 cm^{-1}; ^1H NMR (300 MHz, DMSO-d^6): δ 7.74-7.69 (m, 1H), 7.45-7.40 (m, 2H), 7.32-7.19 (m, 4H), 7.09-7.02 (m, 1H), 4.91 (s, 1H), 4.78 (s, 1H), 4.02 (ABq, J=13.5 Hz, 1H), 3.90 (ABq, J=13.5 Hz, 1H), 2.08-1.54 (m, 5H), 1.44-1.23 (m, 3H); ^{13}C NMR (75 MHz, DMSO-d^6): δ 159.3 (J_{CF}=238 Hz), 156.0, 151.0, 139.0, 133.1, 130.0, 129.2, 125.1, 125.0, 113.9 (J_{CCF}=23 Hz), 113.4 (J_{CCF}=23 Hz), 72.3, 70.2, 53.6, 37.4, 33.9, 23.0, 21.9.

Physical and Spectroscopic Data for Compound 4b. mp 57-59 °C; IR (KBr) ν_{max} 3450, 3030, 2940, 1710, 1490, 1380, 1195 cm^{-1}; ^1H NMR (300 MHz, DMSO-d^6): δ 7.66-7.52 (m, 2H), 7.44-7.17 (m, 2H), 7.26-7.01 (m, 4H), 6.56 (br s, 1H), 5.17 (s, 1H), 4.32 (d, ϑ=12.8 Hz, 1H), 3.10 (d, J=12.8 Hz, 1H), 2.34-2.26 (m, 2H), 2.03-1.88 (m, 1H), 1.77-1.65 (m, 2H), 1.39 (t, J=12.5 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d^6): δ 159.3 (J_{CF}=238 Hz), 154.0, 151.4, 132.3, 129.5, 128.4, 126.6, 125.7, 125.6, 122.2, 122.0, 113.6 (J_{CCF}=23 Hz), 109.3 (J_{CCF}=23 Hz), 64.2, 55.1, 33.1, 26.1, 16.6.

Physical and Spectroscopic Data for Compound 3c. mp 73-75 °C; IR (KBr) ν_{max} 3480, 3040, 2940, 1700, 1480, 1380, 1200 cm^{-1}; ^1H NMR (300 MHz, DMSO-d^6): δ 7.76 (d, J=9.3 Hz, 1H), 7.54 (d, J=2.7 Hz, 1H), 7.45-7.40 (m, 2H), 7.30-7.20

(m, 4H), 4.92 (s, 1H), 4.79 (s, 1H), 4.04 (ABq, J= 13.8 Hz, 1H), 3.92 (ABq, J=13.8 Hz, 1H), 2.02-1.54 (m, 5H), 1.45-1.30 (m, 3H); ^{13}C NMR (75 MHz, DMSO-d^6): δ 153.4, 151.1, 138.8, 134.7, 129.7, 129.5, 128.1, 126.5, 125.8, 124.6, 122.1, 71.8, 69.6, 52.0, 37.3, 33.3, 22.4, 21.2.

Physical and Spectroscopic Data for Compound 4c. mp 165-167 °C; IR (KBr) ν_{max} 3460, 3040, 2950, 1710, 1480, 1380, 1200 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d^6): δ 7.74 (s, 1H), 7.66 (d, J= 8.7 Hz, 1H), 7.44-7.39 (m, 2H), 7.29-7.18 (m, 4H), 6.57 (br s, 1H), 5.16 (s, 1H), 4.32 (d, J=12.8 Hz, 1H), 3.11 (d, J=12.8 Hz, 1H), 2.34-2.08 (m, 2H), 2.01-1.87 (m, 1H), 1.82-1.52 (m, 2H), 1.40 (t, J= 12.6 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d^6): δ 153.8, 151.3, 134.8, 132.0, 129.6, 129.5, 128.8, 128.2, 126.3, 125.6, 123.0, 122.1, 122.0, 64.1, 55.0, 33.2, 26.1, 16.6.

Physical and Spectroscopic Data for Compound 3d. mp 66-68 °C; IR (KBr) ν_{max} 3460, 3040, 2940, 1700, 1380, 1200 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d^6): δ 7.53 (s, 1H), 7.46-7.40 (m, 3H), 7.28-7.19 (m, 3H), 6.95 (d, J= 8.4 Hz, 1H), 4.68 (s, 1H), 4.64 (s, 1H), 3.98 (ABq, J=13.8 Hz, 1H), 3.89 (ABq, J=13.8 Hz, 1H), 2.25 (s, 3H), 1.87-1.77 (m, 3H), 1.65-1.50 (m, 3H), 1.42-1.34 (m, 1H), 1.27-1.17 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d^6): δ 153.5, 151.2, 135.8, 135.7, 132.8, 129.5, 126.9, 125.7, 125.1, 123.3, 122.1, 71.6, 69.8, 51.8, 36.8, 33.2, 22.1, 21.7, 21.1.

Physical and Spectroscopic Data for Compound 4d. mp 177-179 °C; IR (KBr) ν_{max} 3470, 3060, 2950, 1720, 1375, 1200 cm^{-1}; ^{1}H NMR (300 MHz, pyridine-d^5): δ 7.83 (s, 1H), 7.63-7.57 (m, 2H), 7.43-7.29 (m, 3H), 7.15 (t, J=8.4 Hz, 1H), 6.92 (d, J=8.4 Hz, 1H), 6.36 (br s, 1H), 4.84 (d, J= 13.8 Hz, 1H), 3.26 (d, J=13.8 Hz, 1H), 2.35-2.18 (m, 2H), 2.21 (s, 3H), 2.04-1.96 (m, 1H), 1.75-1.65 (m, 2H), 1.45 (br t, J=12.6 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d^6): δ 154.9, 152.5, 136.9, 136.6, 134.0, 129.6, 125.7, 125.6, 125.5, 124.2, 123.7, 122.7, 122.5, 65.4, 56.3, 34.1, 26.5, 21.1, 17.5.

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7. The model compound with methoxy group at C3 was ring-opened as soon as the epoxide was introduced, and diol and allylic alcohol were only isolated. The synthesis of compound with nitro group at C3 was failed because of the difficulty of starting material, 3-nitro-7,8,9,10- tetrahydrophenanthridine preparation.
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