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An Efficient One-Pot Synthesis of Cyclic Skeletons Related to Dynemicin A Models

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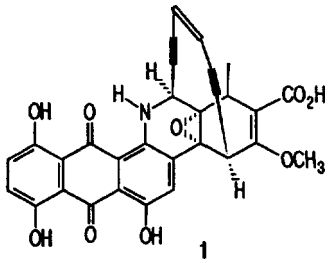
Dynemicin A (**1**) is a potent antitumor antibiotic isolated from the fermentation broth of *Micromonospora chersina*.[1] It has been confirmed that the anthraquinone moiety in **1** initiates the drug to activate *via* intercalation into minor groove of DNA and then, bioreduction of the quinone system.[2] The following internal epoxide ring opening triggers Bergman cycloaromatization[3] of the constrained 10-membered enediyne system to give benzenoid diradical resulting in DNA strand breakage. The suggestion that epoxide opening is a critical step of the drug activation has been supported by the results of molecular modeling and mechanistic studies.[4]



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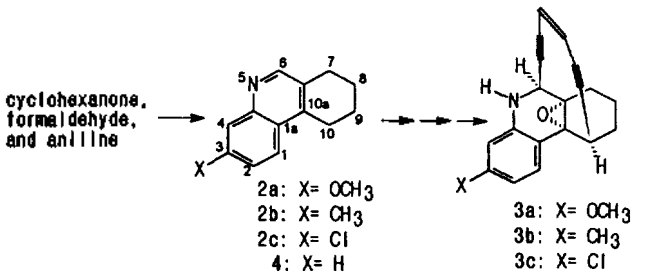
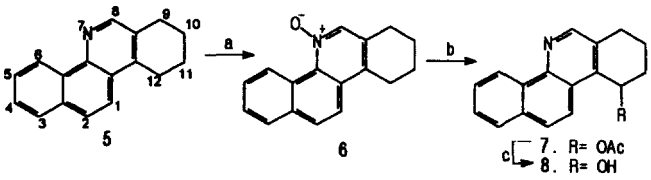
Even though many tricyclic dynemicin A models have been synthesized, most of the models have focused on the biological activity induced by substituent effect on enediyne system or DNA intercalator effect.[5] One can expect that a substituent on benzene ring can also affect epoxide ring opening electronically and then, biological activity of the models. Accordingly, it is thought that tricyclic models (*i.e.*, **3a-c**) with substituent at C3 position can provide a good information on activation and DNA cleavage of dynemicin A type drugs (Scheme 1). This note describes an efficient preparation method of tricyclic skeletons (*i.e.*, **2a-c**) which can be served as a precursor of new C3-substituted enediyne models. According to the recent reports,[6] tricyclic skeletons (e.g. **4**) have been prepared from ethyl 2-cyclohexanonecarboxylate and aniline. However, the use of expensive reagents, poor overall yield (<20%), moreover, complicate and time-consuming synthetic procedure enforced us to search another strategy for a large scale preparation of the requisite materials. For an efficient synthesis of substituted fused ring skeletons, previously reported method[7] was a little modified as follows; Cyclohexanone and aqueous formaldehyde (0.95 eq) were stirred at room temperature in the presence of catalytic amount of soda lime until the solution became clear (2 h). After neutralized by acetic acid, substituted aniline (1.0 equiv) and its hydrochloride (0.5 equiv) were added to the solution. The solution mixture was diluted with ethanol and then, heated overnight at reflux temperature. After purification with column chromatography, the products were obtained in 30%, 29%, and 26% yields for **2a**, **2b**, and **2c**, respectively. Interestingly, the use of meta substituted anilines led to high yield formation of desired compounds compared with ortho and para substituted anilines.[8] This trend is consistent with previously reported suggestion[9] that an electron-donating substituent at C3 position can facilitate the formation of 1a-10a bond under acidic condition. The generation of tetracyclic skeleton **5** by using cyclohexanone, formaldehyde, and 1-aminonaphthalene was also accomplished in much better yield (20%) than conventional method (5%) utilizing ethyl 2-cyclohexanonecarboxylate and 1-aminonaphthalene. Further reactions with **5** were performed to prepare C12-functionalized compound **8** which is the requisite intermediate for the preparation of dynemicin A type tetracyclic enediyne models (Scheme 2).



Scheme 1. Formation of tricyclic compounds.



Reagents and conditions: (a) 1.2 equiv of mCPBA, CH_2Cl_2, 25 °C, 2 h, 80%; (b) Ac_2O, 100 °C, 30 min, 20%; (c) K_2CO_3 (catalytic), MeOH, 25 °C, 7 h, 92%.

Scheme 2. C10-functionalization of tetracyclic compound.

The oxidation of **5** with m-chloroperoxybenzoic acid gave N-oxide **6** in high yield. The treatment of **6** with acetic anhydride furnished C8 and C12 acetoxylated products in competitive manner.[10] Unfortunately, the formation of unwanted C8-acetoxylated product surpassed the generation of C12-functionalized compound **7**. Finally, the acetate **7** was easily hydrolized to yield alcohol **8** under basic condition.

Further studies are underway for the generation of compounds **3a-c**.

Experimental Section

General Techniques. Melting points were recorded on

a Buchi 512 capillary melting point appratus and were not corrected. NMR spectra were obtained with a varian Unity Plus FT-300 instrument. IR spectra were recorded on a Perkin Elmer 1430 IR spectrophotometer. Elemental analyses were performed by Korea Basic Science Center and Center for Science instrument of Kyungpook National University.

All reactions were monitered by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light.

3-Methoxy-7,8,9,10-tetrahydrophenanthridine (2a). A catalytic amount of soda lime (40 mg) was slowly added to the solution including cyclohexanone (10.0 g, 102 mmol), formaldehyde (38%, 7.65 g, 97 mmol), and water (1.2 mL). The mixture was stirred at room temperature until the solution became clear (2 h). After neutralized by acetic acid, m-anisidine (12.6 g, 102 mmol), m-anisidinehydrochloride (8.13 g, 51 mmol), and ethanol (10.0 mL) were added to the solution and then, the solution mixture was heated at 100 ℃ for 20 h. The reaction mixture were evaporated to remove ethanol *in vacuo*, and the residue was poured into saturated sodium bicarbonate (500 mL) and extracted with ethyl acetate (3×250 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was purified by flash chromatography (silica, 50% ethyl acetate in hexane) to give **2a** (6.60 g, 30%): white solid; mp 73-74 ℃; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.55 (s, 1H, H6), 7.80 (d, J=9.3 Hz, 1H, H1), 7.39 (d, J=2.7 Hz, 1H, H4), 7.17 (d, J=6.6 Hz, 1H, H2), 3.94 (s, 3H, OCH_3), 3.06 (t, J=6.3 Hz, 2H, CH_2), 2.86 (t, J=6.3 Hz, 2H, CH_2), 1.95-1.86 (m, 4H, CH_2CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ=159.5, 152.6, 148.0, 141.4, 127.7, 123.8, 122.6, 118.9, 108.0, 55.5, 27.0, 25.0, 22.6, 22.5; IR (KBr): 2930, 1620, 1420, 1240, 1030 cm^{-1}; Anal. Calcd for $C_{14}H_{15}NO$: C 78.84, H 7.09, N 6.57. Found: C 78.31, H 7.09, N 6.54.

3-Methyl-7,8,9,10-tetrahydrophenanthridine (2b). Prepared in 29% yield in a similar manner as that described for **2a**. **2b**: white crystalline solid; mp 48-49 ℃; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.57 (s, 1H, H6), 7.82 (s, 1H, H4), 7.80 (d, J=8.7 Hz, 1H, H1), 7.35 (d, J=6.9 Hz, 1H, H2), 3.08 (t, J=6.3 Hz, 2H, CH_2), 2.87 (t, J=6.3 Hz, 2H, CH_2), 2.54 (s, 3H, CH_3), 1.96-1.86 (m, 4H, CH_2CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ=152.3, 146.5, 140.9, 137.8, 128.9, 128.6, 128.2, 125.4, 122.2, 26.9, 24.8, 22.4, 22.3, 21.5; IR (KBr): 2930, 1570, 1460 cm^{-1}; Anal. Calcd for $C_{14}H_{15}N$: C 85.24, H 7.66, N 7.10. Found: C 84.53, H 7.58, N 7.09.

3-Chloro-7,8,9,10-tetrahydrophenanthridine (2c). Prepared in 26% yield in a similar manner as that described for **2a**. **2c**: yellow crystalline solid; mp 123-124 ℃; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.59 (s, 1H, H6), 8.01 (d, J=2.1 Hz, 1H, H4), 7.80 (d, J=9.0 Hz, 1H, H1), 7.43 (d, J=6.6 Hz, 1H, H2), 3.04 (t, J=6.3 Hz, 2H, CH_2), 2.86 (t, J=6.3 Hz, 2H, CH_2), 1.99-1.91 (m, 4H, CH_2CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ=153.4, 146.7, 141.3, 133.6, 129.9, 128.6, 127.0, 126.0, 124.0, 27.0, 24.8, 22.2, 22.1; IR (KBr): 3040, 2940, 1680, 1530 cm^{-1}; Anal. Calcd for $C_{13}H_{12}NCl$: C 70.07, H 5.88, N 6.81. Found: C 70.23, H 5.62, N 6.34.

Compound 5. Prepared in 20% yield in a similar manner as that described for **2a**. **5**: white crystalline solid; mp 117-118 ℃ (lit.[7] 117 ℃); ^{1}H NMR (300 MHz, $CDCl_3$): δ=9.26 (d, J=7.5 Hz, 1H, H6), 8.65 (s, 1H, H8), 7.84 (d, J=5.7 Hz, 1H, H3), 7.73 (s, 2H, H1 and H2), 7.71-7.59 (m, 2H, H4 and H5), 3.06 (t, J=6.3 Hz, 2H, H12), 2.88 (t, J=6.3 Hz, 2H, H9), 1.96-1.80 (m, 4H, H10 and H11); ^{13}C NMR (75 MHz, $CDCl_3$): δ=150.3, 144.1, 141.5, 132.8, 132.0, 130.6, 127.6, 127.4, 127.2, 126.8, 125.0, 124.4, 120.6, 27.2, 25.3, 22.6, 22.3; IR (KBr): 2930, 1600, 1500 cm^{-1}.

Compound 6. A solution of **5** (2.54 g, 10.9 mmol) in dichloromethane (50 mL) was treated with *m*CPBA (55%, 4.10 g, 13.1 mmol) and stirred at room temperature for 2 h. The reaction mixture was poured into saturated sodium bicarbonate (200 mL) and extracted with dichloromethane (3×100 mL). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography (silica, 5% methanol in ethyl acetate) to give the *N*-oxide **6** (2.18 g, 80%): white crystalline solid; mp 134-135 ℃; ^{1}H NMR (300 MHz, $CDCl_3$): δ=10.89 (d, J=7.2 Hz, 1H, aromatic), 8.46 (s, 1H, aromatic), 7.92-7.71 (m, 5H, aromatic), 3.09 (t, J=6.3 Hz, 2H, CH_2), 2.85 (t, J=6.3 Hz, 2H, CH_2), 2.03-1.95 (m, 2H, CH_2CH$_2$), 1.92-1.84 (m, 2H, CH$_2$CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ=138.9, 135.9, 133.2, 132.5, 131.3, 130.0, 129.2, 128.5, 128.2, 127.7, 127.4, 126.4, 120.0, 26.7, 25.5, 22.4, 21.7; IR (KBr): 2940, 1430, 1122 cm^{-1}.

Compound 7. A solution of **6** (7.00 g, 28.1 mmol) in acetic anhydride (45 mL) was heated at 100 ℃ for 30 min, evaporated to dryness, dissolved in dichloromethane (250 mL), and washed with saturated sodium bicarbonate (500 mL). The organic layer was dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography (silica, 20% ethyl acetate in hexane) to give the acetate **7** (1.64 g, 20%): white crystalline solid; mp 138-139 ℃; ^{1}H NMR (300 MHz, $CDCl_3$): δ=9.27 (d, J=7.5 Hz, 1H, aromatic), 8.82 (s, 1H, aromatic), 7.91-7.85 (m, 2H, aromatic), 7.75-7.64 (m, 3H, aromatic), 6.64 (br s, 1H, C*H*OAc), 3.11 (br d, J=17.1 Hz, 1H, CH_2), 2.97-2.86 (m, 1H, CH_2), 2.32 (br d, J=12.6 Hz, 1H, CH_2), 2.08 (s, 3H, O*Ac*), 2.06-1.98 (m, 3H, CH_2CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ=170.2, 150.4, 144.8, 137.1, 132.7, 131.8, 131.6, 128.4, 127.7, 127.6, 127.0, 124.5, 124.3, 120.1, 64.7, 28.9, 26.7, 21.3, 17.3; IR (KBr): 2940, 1730, 1230 cm^{-1}; Anal. Calcd for $C_{19}H_{17}NO_2$: C 78.33, H 5.88, N 4.81. Found: C 77.44, H 5.73, N 4.82.

Compound 8. To a solution of **7** (200 mg, 0.69 mmol) in methanol (8 mL) was added potassium carbonate (40 mg, 0.29 mmol), and the resulting mixture was stirred at 25 ℃ for 7 h. The reaction mixture was concentrated to 2 mL *in vacuo*, poured into saturated sodium bicarbonate (30 mL), and extracted with dichloromethane (2×30 mL). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo*, and the residue was purified by recrystallization (ether) to yield the alcohol **8** (158 mg, 92%): white solid; mp 207-208 ℃; ^{1}H NMR (300 MHz, DMSO): δ=9.25 (d, J=8.7 Hz, 1H, aromatic), 8.76 (s, 1H, aromatic), 8.21 (d, J=9.0 Hz, 1H, aromatic), 8.02-7.92 (m, 2H, aromatic), 7.74-7.67 (m, 2H, aromatic), 5.28 (br s, 1H, C*H*OH), 2.99 (br d, J=15.3 Hz, 1H, H9), 2.85-2.80 (m, 1H, H9), 2.51-2.50 (br s, 1H, O*H*), 2.10 (br d, J=11.4 Hz, 1H, H11), 2.08-1.79 (m, 3H, H10 and H11); ^{13}C NMR (75 MHz, DMSO): δ=150.7, 144.0, 142.3, 132.6, 131.4, 130.8, 127.8, 127.7, 127.1, 126.9, 125.0, 123.9, 122.6, 61.2, 31.9, 26.7, 16.8; IR (KBr): 3610, 3015, 2940, 1520 cm^{-1}.

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8. Yields for tricyclic compounds prepared from para and ortho substituted anilines are as follow; *p*-OCH_3: 18%, *o*-OCH_3: trace, *p*-CH_3: 20%, *o*-CH_3: 12%, *p*-Cl: 19%, *o*-Cl: 8%.
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10. Acetoxylation products for C8 and C12 position were identified by ^1H and ^{13}C NMR assignment. For instance, acetyl proton peak of **7** appeared at 2.08 ppm, while that of C8-acetoxylated adult was observed at 2.45 ppm implying aromatic ring substitution.

A Concise Process of Terbinafine Synthesis

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Among relatively few known therapeutic agents against fungal infections, terbinafine **1** has been developed as an extremly effective and almost non-toxic antimycotic agent even with oral administration[1] through intensive studies on structural-activity relationships since the accidental discovery of naftifine.[2]

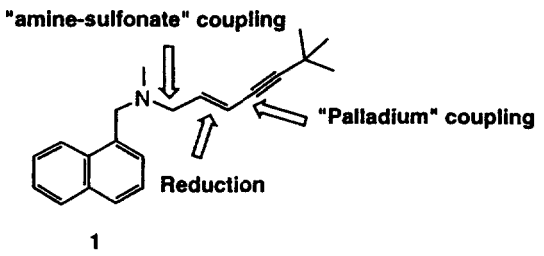
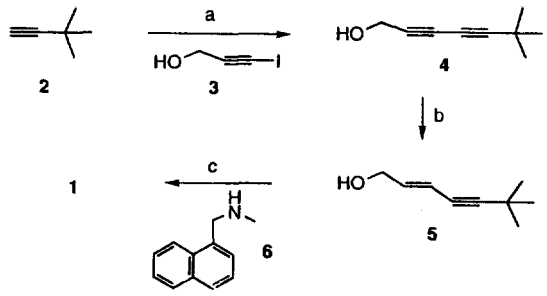


Figure 1.



Regents : (a) **3**, $Pd(PPh_3)_4$, CuI, iPr_2NH (b) Sodium bis(2-methoxyethoxy) aluminium hydride , THF (c) MsCl, Et_3N, DMAP, CH_2Cl_2 ; **6**, K_2CO_3, DMF

Scheme 1.

Terbinafine is an allylamine derivative with an (*E*)-1,3-enyne functionality. Several attempts to synthesize **1**, e.g. condensation of an allylic bromide with the secondary amine, elimination of hydroxyl group, and DIBAL reduction of **1**, 3-diyne, suffered from a lack of stereoselectivity at the olefin.[1,3] Only Stille's vinyl iodide-stannane coupling could furnish the desired stereochemistry stereoselectively, although the notorious toxicity of stannane compound should remain problematic.[4]

In this note we describe a concise, efficient route to the the synthesis of **1** from readily available materials. We envision that palladium coupling for the 1,3-diyne synthesis, stereospecific aluminium hydride reduction to the (*E*)-1,3-enyne functional group, and sulfonate-secondary amine coupling would provide the desired compound (Figure 1).

Commercially available *t*-butyl acetylene **2** was coupled with iodopropargyl alcohol **3**[5] in the presence of $Pd(PPh_3)_4$, CuI, and diisopropylamine to produce a 38% yield of **4**.[6] In order to prepare the desired (*E*)-olefinic alcohol **5**, compound **4** was reduced regio and stereospecifically by sodium bis(2-methoxyethoxy)aluminium hydride[7] in THF solution in a quantitative yield. For the final coupling reaction, compound **5** was first converted to the corresponding methanesulfonate by reaction with methanesulfonyl chloride at 0° within 5 mins., and the crude sulfonate was readily reacted with N-methyl-1-naphthalene-methylamine in DMF solution with K_2CO_3 to afford **1**. Prolonged stirring at the mesylation step yielded allylic chloride as a by-product, which provided a much less yield of **1** in the following coupling reaction with the amine. More practically, terbinafine hydrochloride was obtained as a white solid in 77% yield by HCl-salt formation