Synthesis of the Anthraquinone Part of Dynemicin A *via* Diels-Alder Reaction[1]

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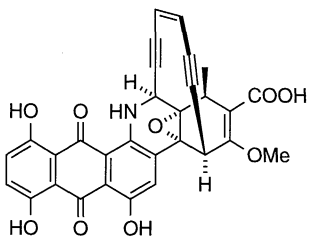
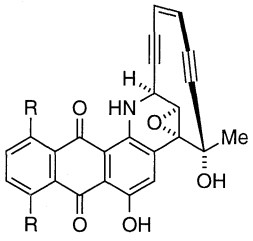
The anthraquinone moiety of dynemicin A was synthesized by Diels-Alder reaction between bromonaphthoquinone and a novel diene having the D ring and aromatization as key steps.

Dynemicin A (**1**),[2] one of potent enediyne antitumor antibiotics,[3] was characterized as the hybrid structure between enediyne and anthraquinone parts, the latter of which was found in many anthracycline antibiotics. The latter part is thought to play an important role not only for association to double stranded DNA as a intercalator but for a triggering device for Bergman reaction *via* reduction of the quinone part. Interestingly, aromatized dynemicins such as dynemicin O, P, and Q exhibited significant biological activities, which indicated that existence of unknown action mechanisms.[4]



dynemicin A (**1**)



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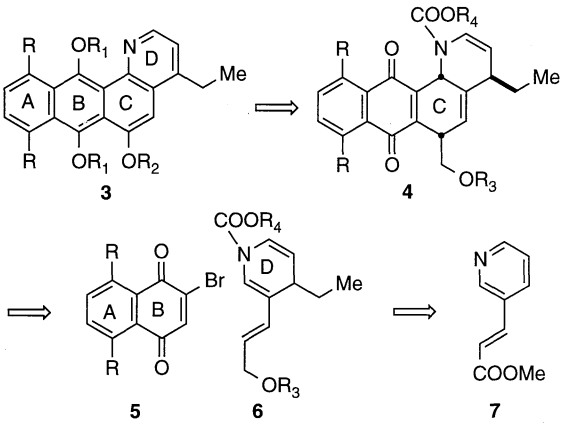
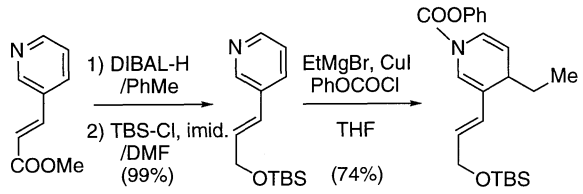
In the course of our studies on dynemicin A, we have synthesized the model compounds having cyclic enediyne, epoxide, and aniline moieties.[5] These compounds showed weaker DNA cleaving activities and cytotoxicities than naturally occurring dynemicin A. These results prompted us to synthesize the advanced model compound as **2** having anthraquinone as a intercalator. This paper deals with the synthesis of simple anthraquinone part (R = H) for **2**.[6, 7]

Our synthetic plan is shown in Scheme 1. Based on our previous synthesis of simple model compounds, we planed to synthesize hydroquinone **3** as a protected form of quinone group, which was compatible with acetylide addition for introduction of the enediyne moiety. The hydroquinone **3** was expected to be synthesized from quinone **4** by aromatization of C and D rings and reduction of the quinone moiety. The quinone **4** was retrosynthesized to naphthoquinone **5** and diene **6** through Diels-Alder reaction.



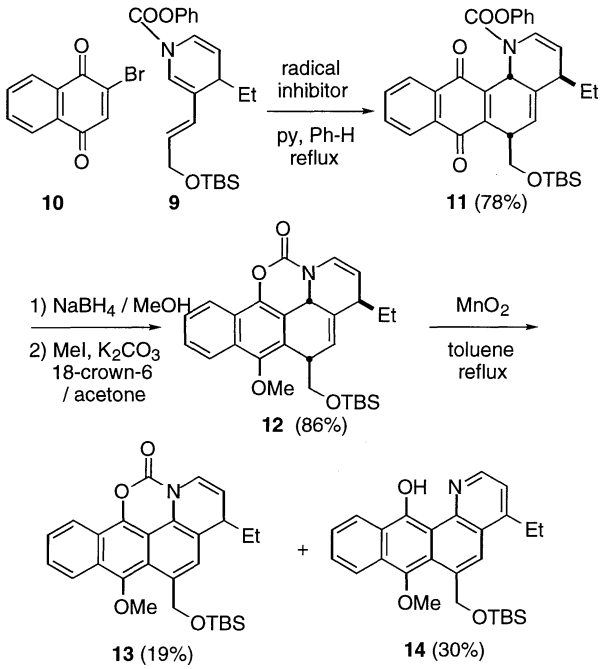
Scheme 1. Synthetic plan.

The synthesis of the diene was started from the reduction of methyl *trans*-3-(3-pyridyl)acrylate (**7**) with DIBAL (Scheme 2). After TBS protection of the resulting alcohol, ethyl magnesium bromide was selectively added to 4 position of the pyridine ring in the presence of CuI and phenyl chloroformate[8] to afford dihydropyridine **9**. Any regioisomeric product was not detected.



Scheme 2. Synthesis of diene **9**.

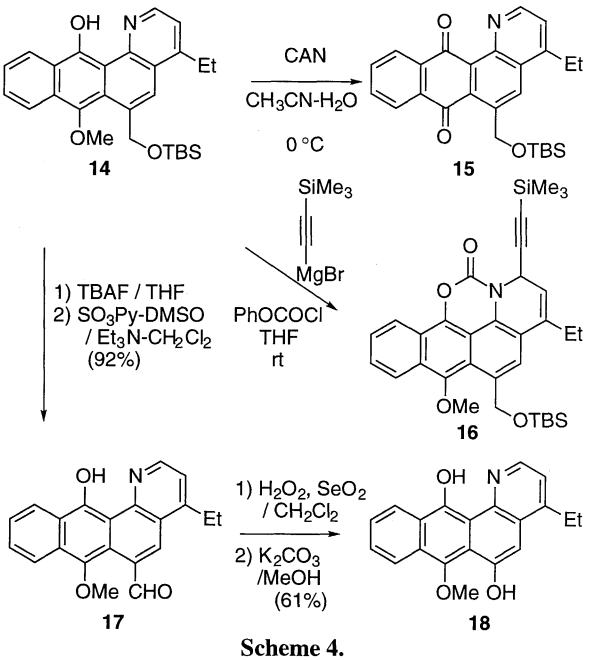
Diels-Alder reaction of the diene **9** with 2-bromonaphthoquinone (**10**)[9] proceeded in the presence of pyridine and radical inhibitor (5-*tert*-butyl-4-hydroxy-2-methylphenyl sulfide)[10] to afford the desired product **11**[11] in good yield (Scheme 3).[12] Addition of pyridine was indispensable for trapping hydrobromic acid liberated from the initial Diels-Alder adduct, which would cause decomposition of the product without pyridine.



Scheme 3.

Unexpectedly, all attempts to aromatize C and D rings in Diels-Alder adduct **11** were unsuccessful. During some experiments to reduce the quinone of **11** for trials to aromatize the hydroquinone, we found that treatment of **11** with $NaBH_4$ gave a hydroquinone having cyclic carbamate, which was converted to the methyl ether **12** with MeI and K_2CO_3 in the presence of 18-crown-6. In contrast with the quinone **11**, the hydroquinone **12** was found to be feasible for aromatization. In fact, the reaction of **12** with activated MnO_2 under toluene reflux gave a mixture of aromatized products **13** and **14**.[13]

Having the desired compound **14** in our hands, we examined some preliminary transformations for the synthesis of advanced model compound **2** (Scheme 4). Firstly, the hydroquinone **14** could be oxidized with CAN to give the corresponding quinone **15** in 51% yield. Secondly, the introduction of acetylene group was examined. The product **14** was set for introduction of the next enediyne by using the acetylide anion. Excess amount of magnesium acetylide was added to the aromatized compounds **14** in the presence of phenyl chloroformate to give **16** in 21% yield.[14] Thirdly, the extra carbon of aromatized product **14** was removed as follows. After desilylation of **16**, the resultant alcohol was oxidized with SO_3·Py-DMSO to give the aldehyde **17**. Baeyer-Villiger oxidation of **17** with H_2O_2 (30%) in the presence of SeO_2 (cat.)[15] followed by hydrolysis furnished **18**[16] in 61% yield.



Scheme 4.

This study should provide a promising route leading to a variety of analogs of **3** and the advanced dynemicin A model compound **2**. Further studies are in progress.

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References and Notes

1 Part of this study was presented at the 35th Symposium on the Chemistry of Natural Products, Symposium Papers, p 519-526, Kyoto, Japan, Oct., 1993.

2 M. Konishi, H. Ohkuma, K. Matsumoto, T. Tsuno, H. Kamei, T. Miyaki, T. Oki, H. Kawaguchi, G. D. VanDuyne, and J. Clardy, *J. Antibiot.*, **42**, 1449 (1989).

3 Review: K. C. Nicolaou and W.-M. Dai, *Angew. Chem., Int. Ed. Engl.*, **30**, 1387 (1991).

4 M. Miyoshi-Saitoh, N. Morisaki, Y. Tokiwa, S. Iwasaki, M. Konishi, K. Saitoh, and T. Oki, *J. Antibiot.*, **44**, 1037 (1991).

5 T. Nishikawa, A. Ino, M. Isobe, and T. Goto, *Chem. Lett.*, **1991**, 1271; T. Nishikawa, A. Ino, and M. Isobe, *Tetrahedron*, **50**, 1449 (1994); T. Nishikawa, M. Yoshikai, K. Obi, and M. Isobe, *Tetrahedron Lett.*, **35**, 7997 (1994); T. Nishikawa, M. Yoshikai, K. Obi, T. Kawai, R. Unno, T. Jomori, and M. Isobe, *Tetrahedron*, **51**, 9339 (1995).

6 Synthetic studies on the anthraquinone moiety by other groups: H. Chikashita, J. A. Porco, T. J. Staut, J. Clardy, and S. L. Schreiber, *J. Org. Chem.*, **56**, 1962 (1991); J. Taunton, J. L. Wood, and S. L. Schreiber, *J. Am. Chem. Soc.*, **115**, 10378 (1993); K. C. Nicolaou, J. L. Gross, M. A. Kerr, R. H. Lemus, K. Ikeda, and K. Ohe, *Angew. Chem., Int. Ed. Engl.*, **33**, 781 (1994); T. Yoon, M. D. Shair, S. J. Danishefsky, and G. K. Shulte, *Tetrahedron Lett.*, **35**, 6259 (1994); M. D. Shair, T. Yoon, T.-C. Chou, and S. J. Danishefsky, *Angew. Chem., Int. Ed. Engl.*, **33**, 2477 (1994); M. D. Shair, T.-Y. Yoon, S. J. Danishefsky, *Angew. Chem., Int. Ed. Engl.*, **34**, 1721 (1995); P. Magnus, S. A. Eisenbeis, and N. A. Magnus, *Chem. Commun.*, **1994**, 1545; R. Shimazawa, R. Shirai, Y. Hashimoto, and S. Iwasaki, *BioMed. Chem. Lett.*, **4**, 2377 (1994); A. G. Myers, M. E. Fraley, N. J. Tom, S. B. Cohen, and D. J. Madar, *Chem. Biol.*, **2**, 33 (1995).

7 Another approach from our laboratory: T. Okita and M. Isobe, *Tetrahedron*, **50**, 11143 (1994).

8 D. L. Comins and A. H. Abdullah, *J. Org. Chem.*, **47**, 4315 (1982).

9 J. R. Grunwell, A. Karipides, C. T. Wigel, S. W. Heinzman, J. Parlow, J. A. Surso, L. Clayton, F. J. Fleitz, M. Daffner, and J. E. Stevens, *J. Org. Chem.*, **56**, 91 (1991).

10 Y. Kishi, M. Aratani, H. Tanino, T. Fukuyama, T. Goto, S. Inoue, S. Sugiura, and H. Kakoi, *Chem. Commun.*, **1972**, 64.

11 The *endo* stereochemistry of **11** was determined by NOE experiments.

12 Diels-Alder reactions using more hydroxylated bromonaphthoquinones will be reported in elsewhere.

13 This structure was confirmed by full assignments of ^1H and ^{13}C NMR signals using NOESY and COLOC experiments. **14**: ^1H NMR ($CDCl_3$, 400 MHz) δ 0.25 (6H, s), 1.10 (9H, s), 1.43 (3H, t, J = 7.2 Hz), 3.14 (2H, q, J = 7.2 Hz), 3.93 (3H, s), 5.53 (2H, d, J = 1.8 Hz), 7.33 (1H, d, J = 4.8 Hz), 7.60 (1H, br t, J = 7.2 Hz), 7.68 (1H, br t, J = 7.2 Hz), 8.21 (1H, t, J = 1.8 Hz), 8.25 (1H, br d, J = 8.4 Hz), 8.58 (1H, d, J = 4.8 Hz), 8.73 (1H, br d, J = 8.4 Hz), and 17.5 (1H, s). ^{13}C NMR ($CDCl_3$, 100 MHz) δ -5.21, 14.56, 18.42, 25.80, 26.03, 63.36, 64.52, 109.66, 116.75, 120.45, 121.64, 121.89, 123.88, 123.92, 124.13, 124.65, 127.41, 127.97, 137.77, 142.64, 143.65, 149.45, 149.83, and 155.23.

14 Effort to improve the yield of **16** is underway. **16:** ^1H NMR ($CDCl_3$, 270 MHz) δ 0.10 (9H, s), 0.21 (6H, s), 1.04 (9H, s), 1.22 (3H, t, J = 7.5 Hz), 2.54 (2H, br q, J = 7.5 Hz), 3.93 (3H, s), 5.38 (1H, dd, J = 16, 1.5 Hz), 5.45 (1H, dd, J = 16, 1.5 Hz), 5.58 (1H, dt, J = 5.5, 1.5 Hz), 5.97 (1H, br d, J = 5.5 Hz), 7.45-7.58 (2H, m), 7.78 (1H, t, J = 1.5 Hz), 8.15 (1H, m), and 8.32 (1H, m).

15 L. Syper, *Synthesis*, **1989**, 167.

16 **18**: ^1H NMR ($CDCl_3$, 270 MHz) δ 1.41 (3H, t, J = 7.5 Hz), 3.06 (2H, q, J = 7.5 Hz), 4.13 (3H, s), 7.05 (1H, s), 7.34 (1H, d, J = 5 Hz), 7.59-7.75 (2H, m), 8.21 (1H, br d, J = 8.5 Hz), 8.51 (1H, d, J = 5 Hz), 8.73 (1H, br d, J = 8 Hz), 10.36 (1H, s), and 17.56 (1H, s).