Ready Access to Highly Functionalized Quinolines. Useful Intermediates for Synthesis of Enediyne Compounds Related to Dynemicin A

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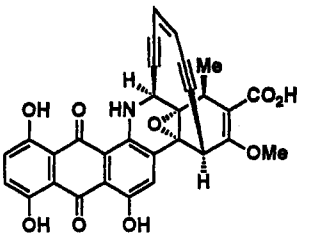
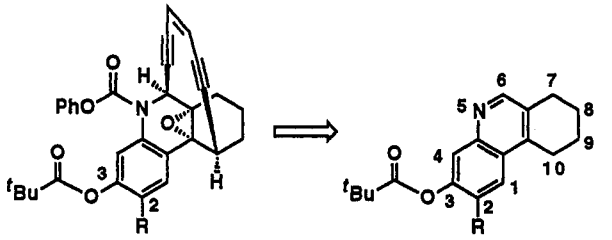
The discovery of enediyne class of antitumor antibiotics,[1-6] such as dynemicin A (1),[1] has sparked excitement in the scientific community due to the complex molecular architectures and the intriguing modes of action.[7] These antibiotics isolated in the forms of prodrugs exhibit biological activity via a bioreduction step. Upon activating, the conjugated enediyne moiety constrained in a 10-/9-membered ring undergoes the Bergman cycloaromatization[8] to form 1,4-benzenoid diradicals. The sp^2 carbon-centered radicals abstract protons from the bound DNA target followed by DNA radical fragmentation and DNA strand cleavage. Research efforts in a number of laboratories[7a,d] have been devoted to the design and syntheses of enediyne analogs to mimic the biological action of the natural products including a recent total synthesis of calicheamicin γ_1^I.[9]

The anthraquinone moiety in dynemicin A (1) is believed to act as an initiator for the activation of this antibiotic. It has been suggested that epoxide opening plays a critical role in the action of the drug; that suggestion is supported by the results of molecular modeling[10] and mechanistic studies.[11] Evidence also comes from studies on synthetic



1: dynemicin A

mimics such as **2a**.[12] The C3 (phenanthridine skeleton numbering) ester group of **2a** was built up for its potential conversion into a hydroxy group under physiological conditions, which then initiated epoxide opening and cycloaromatization of the enediyne moiety.[12d] One can expect that a hydrophilic substituent (hydroxyethoxy) on the C2 position[12c] such as in **2b** may improve the aqueous solubility of the molecule or serve as a tether to form drug conjugates with target-selective binders such as oligosaccharides[13] in calicheamicin γ_1^I and esperamicin A_1 and DNA intercalators found in other antitumor agents.[7a] The C2 substituent may also act as an intramolecular nucleophile to assist in the hydrolysis of the ester functionality through an eight-membered ring transition state.[14] According to the reported synthetic scheme,[12d,15] construction of **2a,b** requires highly functionalized quinoline derivatives such as **3a,b**. This note describes a synthetic route for



2a: R = H **3a: R = H**
2b: R = OCH_2CH_2OH **3b: R = OBn**

ready access to multiply functionalized quinoline systems, which are useful intermediates for the synthesis of biological active enediyne compounds of the dynemicin A type.

Results and Discussion

Formation of the three-fused-ring skeleton, 7,8,9,10-tetrahydrophenanthridine, has been previously achieved by acid-promoted intramolecular cyclization of a 1a,10a-

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(14) A free hydroxy group at the C2 position may assist in releasing the C3 hydroxy group through a five-membered ring transesterification process.

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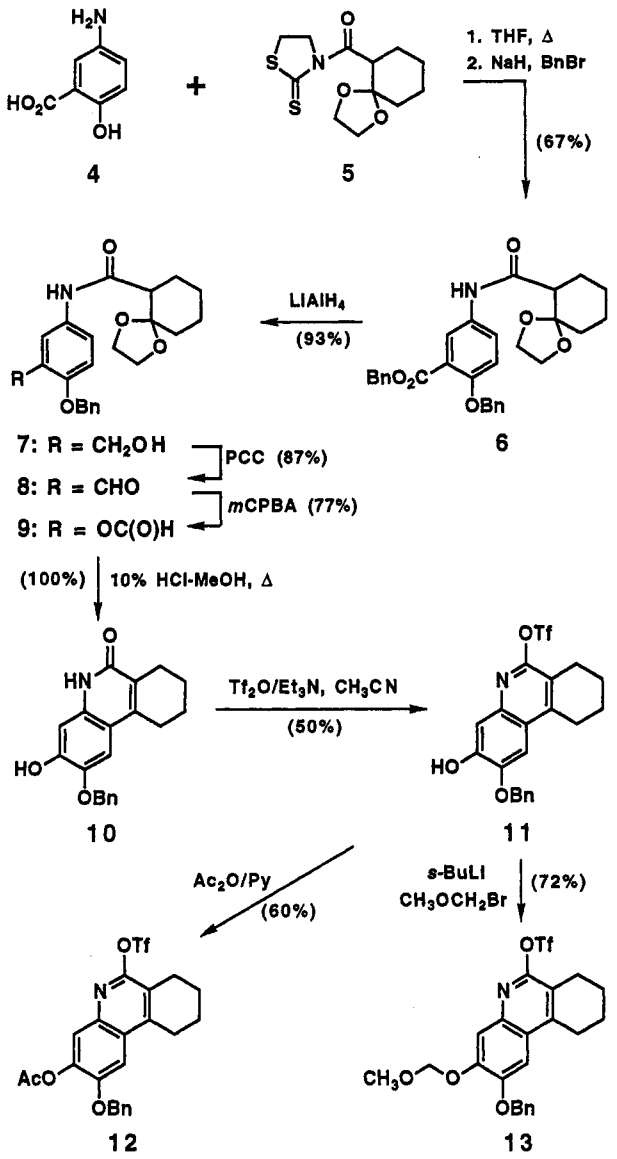
Scheme I.



seco intermediate prepared from aniline and ethyl 2-oxocyclohexanecarboxylate at 200 °C.[16] Concentrated sulfuric acid was used as the catalyst together with heating to force the ring cyclization, which produced the product in poor yield (<40%).[12c,16] Obviously, these conditions are not the choice for advanced precursors possessing polyoxygenated functionality. In the previous work,[10d] it was realized that an electron-donating substituent on the C3 position can facilitate the formation of the 1a–10a bond under much milder acidic conditions (10% HCl in THF–H_2O, reflux) in quantitative yield. For the synthesis of the type of compound **3b**, the unstable 4-amino-1,2-benzenediol[17] or its equivalent, 4-nitro-1,2-benzenediol (4-nitrocatechol, commercially available, but relatively expensive) is required and the potential difficulty in differentiating the two hydroxy groups may complicate the synthetic sequence. Described in Scheme I is a practical synthesis which has the potential to produce multigram quantities of the requisite materials. Starting from inexpensive 5-aminosalicyclic acid (**4**, Scheme I), the 1a,10a-seco (phenanthridine skeleton numbering) intermediate **6** was obtained exclusively via a highly selective amide bond formation reaction between **4** and 3-acyl-1,3-thiazolidine-2-thione (**5**) followed by benzylation.[12d] Preparation of **6** has been carried out on a 100-g scale in good yield. Selective reduction of **6** with $LiAlH_4$ at 0 °C for 30 min gave **7** (93%) which was oxidized back to aldehyde **8** (PCC, 4-Å molecular sieve, 25 °C, 1 h) in excellent yield. Efforts have been directed to the intramolecular cyclization within **6** and **7** aiming at the synthesis of versatile phenanthridine derivatives. However, under acidic conditions (10% HCl/Δ or concentrated H_2SO_4/100 °C), compounds **6** and **7** or their corresponding free ketone derivatives failed to give the desired cyclization products. It is obvious that the substituents at C3 (phenanthridine skeleton numbering) of compounds **6** and **7** are either electron-withdrawing in nature or too weakly electron-donating to promote cyclization. Conversion of the formyl group of **8** into formate **9** (77%) was successful with *m*CPBA in CH_2Cl_2 at room temperature for 14 h. Then, refluxing a mixture of **9** with 10% HCl in aqueous MeOH for 30 min furnished quantitatively **10** as a white solid. This "one-pot" cyclization may be viewed as a cascade reaction of acidic hydrolysis of both the formate and ketal groups in **9** followed by acid-assisted intramolecular cyclization of the phenolic ketone intermediate.[18] Treatment of **10** with trifluoromethanesulfonic anhydride in the presence of Et_3N at 0 °C for 30 min and then at room temperature for another 30 min provided quinoline **11** in 50% yield (not optimized). The hydroxy group in **10** remained intact during this transformation probably due to the intramolecular hydrogen bonding with the C2 oxygen atom. This was also the case of compound **11** as shown by its high TLC R_f value. Acetylation of **11** gave acetate **12** (60%), while protection with methoxymethyl bromide (*s*-BuLi, room temperature, 1 h) yielded **13** (72%). The trifluoromethanesulfonate group in compounds **11–13** is advantageous for further elaboration and can serve as the coupling position with acetylene derivatives under the standard Pd(0)–Cu(I) conditions.[12c,19]

Described above is a practical synthesis of highly functionalized quinoline systems by a short sequence (seven to eight steps from **4**). Each reaction was performed selectively and in good chemical yield. The described procedures will allow a rapid preparation of the requisite compounds such as **11–13** for the synthesis of designed enediyne compounds related to dynemicin A.

Experimental Section

General. Melting points are uncorrected. Elemental analyses were performed by Shanghai Institute of Organic Chemistry,

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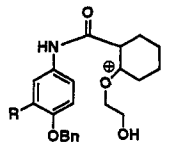
(18) It is possible for **9** to undergo the intramolecular cyclization under the acidic conditions via an alternative mechanism, which consists of the formation of carbocation **I** from **9** followed by Friedel–Crafts alkylation and β-elimination to provide **10**. In order to facilitate the intramolecular Friedel–Crafts alkylation, hydrolysis of the formate to hydroxy group is critical because the carbocation **I** with electron-withdrawing (R = CO_2Bn) and weakly electron-donating (R = CH_2OH) groups at the *para* position of the reaction center failed to initiate the cyclization in the cases of compounds **6** and **7**. The author thanks the reviewer and the journal editor for pointing out this possibility.



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Chinese Academy of Sciences, Shanghai, China. Other experimental details can be found in the previous report.[12d]

***N*-[4-(Benzyloxy)-3-(hydroxymethyl)phenyl]-1,4-dioxaspiro[4.5]decane-6-carboxamide (7).** To a solution of 6[12d] (5.00 g, 9.97 mmol) in dry THF (100 mL) cooled in an ice–water bath (ca. 0 °C) was added in portions $LiAlH_4$ (0.38 g, 9.97 mmol) followed by stirring for 30 min at the same temperature. The reaction mixture was quenched by dropwise addition of saturated aqueous Na_2SO_4 solution, diluted with ether (200 mL), and dried over anhydrous Na_2SO_4. The solid materials were filtered off and washed with ether (2 × 30 mL). The combined organic solution was evaporated under reduced pressure and the residue was purified by flash column chromatography (silica gel, 50% ethyl acetate in petroleum ether) to provide the product 7 (3.70 g, 93%): colorless crystalline solid, mp 114.5–115.0 °C (from ethyl acetate–ether); R_f = 0.30 (silica gel, 50% ethyl acetate in petroleum ether); IR (KBr) 3450 (shoulder), 3363, 2933, 1664, 1535, 1503, 1230, 1044 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.24 (br s, 1 H), 7.53 (dd, J = 8.8, 2.7 Hz, 1 H), 7.45–7.32 (m, 6 H), 6.88 (d, J = 8.8 Hz, 1 H), 5.09 (s, 2 H), 4.70 (br s, 2 H), 4.07–3.90 (m, 4 H), 2.63 (dd, J = 11.1, 4.5 Hz, 1 H), 2.41 (br s, 1 H), 2.01–1.25 (m, 8 H); MS (EI^+) m/z (rel inten) 397 (M^+, 7), 169 (100). Anal. Calcd for $C_{23}H_{27}NO_5$: C, 69.50; H, 6.85; N, 3.52. Found: C, 69.61; H, 6.66; N, 3.49.

***N*-[4-(Benzyloxy)-3-formylphenyl]-1,4-dioxaspiro[4.5]decane-6-carboxamide (8).** To a solution of 7 (3.70 g, 9.31 mmol) in dry CH_2Cl_2 (50 mL) cooled in an ice–water bath was added molecular sieves (4 Å, 3.00 g of activated powder) and PCC (3.00 g, 13.96 mmol) followed by stirring at rt for 1 h. The reaction mixture was diluted with ethyl acetate (50 mL) followed by passing through a short silica gel column to remove the solid materials. The silica gel was rinsed with ethyl acetate, and the combined collections were evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 50% ethyl acetate in petroleum ether) to furnish 8 (3.20 g, 87%): colorless crystalline solid, mp 97.5–97.8 °C (from ethyl acetate–petroleum ether); R_f = 0.53 (silica gel, 50% ethyl acetate in petroleum ether); IR (KBr) 3373, 2934, 1701 (shoulder), 1670, 1531, 1499 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.51 (s, 1 H), 8.43 (br s, 1 H), 8.17 (dd, J = 9.1, 2.9 Hz, 1 H), 7.55 (d, J = 2.7 Hz, 1 H), 7.45–7.34 (m, 5 H), 7.08 (d, J = 9.1 Hz, 1 H), 5.18 (s, 2 H), 4.05–3.92 (m, 4 H), 2.66 (dd, J = 11.0, 5.5 Hz, 1 H), 2.04–1.25 (m, 8 H); MS (EI^+) m/z (rel inten) 395 (M^+, 20), 91 (100). Anal. Calcd for $C_{23}H_{25}NO_5$: C, 69.86; H, 6.37; N, 3.54. Found: C, 69.49; H, 6.29; N, 3.46.

***N*-[4-(Benzyloxy)-3-(formyloxy)phenyl]-1,4-dioxaspiro[4.5]decane-6-carboxamide (9).** A mixture of 8 (3.08 g, 7.79 mmol) and *m*CPBA (50%, 4.03 g, 11.68 mmol) in CH_2Cl_2 (50 mL) was stirred at rt for 14 h. The solvent of the reaction mixture was evaporated to give a solid residue to which ethyl acetate (50 mL) was added. The resulting solution was washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 33% ethyl acetate in petroleum ether) to give 9 (2.47 g, 77%): colorless crystalline solid, mp 123.5–124.0 °C (from ether); R_f = 0.49 (silica gel, 50% ethyl acetate in petroleum ether); IR (KBr) 3370, 2933, 1769, 1745, 1670, 1517, 1269, 1089 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.31 (br s, 1 H), 8.25 (s, 1 H), 7.49 (d, J = 2.5 Hz, 1 H), 7.43–7.30 (m, 5 H), 7.27 (dd, J = 8.9, 2.5 Hz, 1 H), 6.95 (d, J = 8.9 Hz, 1 H), 5.07 (s, 2 H), 4.10–3.90 (m, 4 H), 2.64 (dd, J = 11.2, 4.3 Hz, 1 H), 2.10–1.25 (m, 8 H); MS (EI^+) m/z (rel inten) 383 (M^+ – 28, 10), 169 (100). Anal. Calcd for $C_{23}H_{25}NO_6$: C, 67.14; H, 6.12; N, 3.40. Found: C, 67.05; H, 5.90; N, 3.32.

2-(Benzyloxy)-3-hydroxy-7,8,9,10-tetrahydrophenanthridone (10). A mixture of 9 (1.89 g, 4.59 mmol) in MeOH (40 mL) and aqueous HCl (37%, 15 mL) was refluxed for 15 min. The reaction mixture was then cooled to rt and concentrated to 20 mL under reduced pressure. The precipitate was collected by filtration and dried over P_2O_5 under vacuum to produce 10 (1.47 g, 100%): white powder, mp 246.0–250.5 °C (dec, from MeOH–H_2O); R_f = 0.23 (silica gel, 3.2% methanol in CH_2Cl_2); IR (KBr) 3500–2500 (br), 1641, 1617, 1542, 1265, 1193 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.80 (s, 1 H), 7.51 (d, J = 7.0 Hz, 2 H), 7.43–7.32 (m, 3 H), 7.29 (s, 1 H), 7.06 (s, 1 H), 5.31 (s, 2 H), 2.98 (t, J = 5.7 Hz, 2 H), 2.66 (t, J = 5.4 Hz, 2 H), 1.99–1.83 (m 4 H); MS (EI^+) m/z (rel inten) 321 (M^+, 18), 230 (100); HRMS (EI^+) for $C_{20}H_{19}NO_3$ (M^+) calcd 321.1365, found m/z 321.1352.

2-(Benzyloxy)-3-hydroxy-6-[[(trifluoromethyl)sulfonyl]oxy]-7,8,9,10-tetrahydrophenanthridine (11). To a suspension of 10 (240 mg, 0.747 mmol) in dry CH_3CN (30 mL) cooled in an ice–water bath (ca. 0 °C) was added Et_3N (0.16 mL, 1.12 mmol) and triflic anhydride (0.19 mL, 1.12 mmol). The resulting mixture was stirred at 0 °C for 30 min and then at rt for another 30 min. The reaction mixture was diluted with ethyl acetate (30 mL) and washed with saturated $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure to give a crude product which was purified by flash column chromatography (silica gel, 50% ether in petroleum ether) to yield 11 (170 mg, 50%, not optimized): colorless crystalline solid, mp 163–165 °C (from ether–petroleum ether); R_f = 0.65 (silica gel, 50% ether in petroleum ether); IR (KBr) 3527, 2954, 1513, 1408, 1213, 1138, 1009 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48–7.36 (m, 5 H), 7.34 (s, 1 H), 7.10 (s, 1 H), 6.18 (br s, 1 H), 5.21 (s, 2 H), 2.93 (t, J = 5.8 Hz, 2 H), 2.76 (t, J = 5.8 Hz, 2 H), 1.98–1.80 (m, 4 H); MS (EI^+) m/z (rel inten) 355 ($M^+ - C_6H_6$ – HF, 9), 199 (100); MS (FAB^+) m/z (rel inten) 454 (M^+ + 1, 63).

3-Acetoxy-2-(benzyloxy)-6-[[(trifluoromethyl)sulfonyl]oxy]-7,8,9,10-tetrahydrophenanthridine (12). A mixture of 11 (20 mg, 0.044 mmol), acetic anhydride (0.5 mL), and pyridine (three drops) was stirred at rt for 30 min. The reaction mixture was diluted with ethyl acetate (10 mL) and washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$ and evaporated to give a crude product which was purified by flash column chromatography (silica gel, 50% ether in petroleum ether) to provide 12 (13 mg, 60%): colorless crystalline solid, mp 194.5–195.2 °C (from ether–petroleum ether); R_f = 0.42 (silica gel, 25% ether in petroleum ether); IR (KBr) 2950, 1769, 1507, 1416, 1237, 1141 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (s, 1 H), 7.50–7.32 (m, 5 H), 7.25 (s, 1 H), 5.21 (s, 2 H), 2.99 (t, J = 5.7 Hz, 2 H), 2.83 (t, J = 5.6 Hz, 2 H), 2.33 (s, 3 H), 2.00–1.84 (m, 4 H); MS (EI^+) m/z (rel inten) 495 (M^+, 8), 91 (100).

2-(Benzyloxy)-3-(methoxymethoxy)-6-[[(trifluoromethyl)sulfonyl]oxy]-7,8,9,10-tetrahydrophenanthridine (13). To a solution of 11 (230 mg, 0.51 mmol) in dry THF (10 mL) cooled in a dry ice–acetone bath (−78 °C) was added *s*-BuLi (1.3 M in cyclohexane, 0.43 mL, 0.56 mmol) followed by stirring for 10 min. Methoxymethyl bromide (46 μL, 0.56 mmol) was injected into the reaction flask at −78 °C. The cooling bath was removed and the reaction mixture was allowed to warm to rt and stirred for 1 h. The reaction was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate (10 mL × 2). The combined organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 25% ether in petroleum ether) to furnish 13 (181 mg, 72%): colorless crystalline solid, mp 107.7–108.6 °C (from ether–petroleum ether); R_f = 0.44 (silica gel, 25% ether in petroleum ether); IR (KBr) 2950, 1506, 1407, 1240, 1219, 1141 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55 (s, 1 H), 7.47 (d, J = 6.9 Hz, 2 H), 7.41–7.30 (m, 3 H), 7.14 (s, 1 H), 5.37 (s, 2 H), 5.27 (s, 2 H), 3.54 (s, 3 H), 2.91 (t, J = 5.9 Hz, 2 H), 2.78 (t, J = 5.8 Hz, 2 H), 1.96–1.80 (m, 4 H); MS (EI^+) m/z (rel inten) 497 (M^+, 1), 83 (100); HRMS (EI^+) for $C_{23}H_{22}F_3NO_6S$ (M^+) calcd 497.1120, found m/z 497.1091.

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Supplementary Material Available: ^1H NMR spectra for the compounds 7–13 (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.