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Communications

Synthesis of Cyclopent[a]anthraquinone Bearing an Aminomethyl Group as DNA-Intercalating Agent

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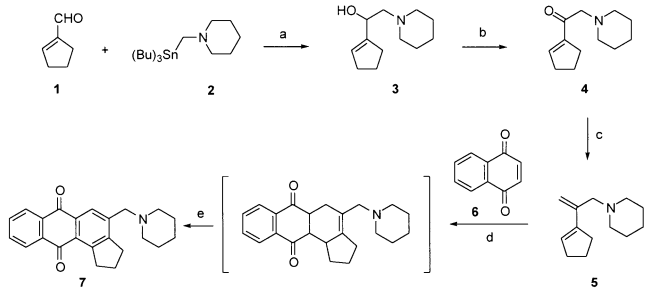
The anthraquinone ring system has formed the basis of a number of clinical and experimental anticancer drugs such as doxorubicin, mitoxantrone, and anthrapyrazoles.[1] The planarity of anthraquinone molecule allows an intercalation between adjacent DNA base pairs, which results in formation of a ternary complex with DNA topoisomerase II producing double-strand breaks in the DNA and cell death.[2] The biological activity of anthraquinone is greatly affected by the different substituents of the planar ring system.[3] It might be, therefore, of interest to design and synthesize the potential intercalating agents. We chose the planar cyclopent[a]anthracene-9,10-dione[4] bearing the aminomethyl substituents, which is anticipated to exhibit DNA intercalating. This report describes the synthesis of cyclopent[a]anthracene-9,10-dione with piperidinomethyl substituent.

We speculated that the cyclopentanthraquinone ring system **7** might be formed by the Diels-Alder reaction of naphthoquinone **6** with the diene **5** and the subsequent dehydrogenation. As shown in the Scheme 1, the initial step was to prepare diene **5** from 1-cyclopentenealdehyde **1**. Treatment



Scheme 1. Reaction conditions: (a) *n*-BuLi, THF, -78 °C, 1 h, 48 %; (b) TFAA, DMSO, THF, -78 °C, Et_3N, rt, 48%; (c) $Ph_3P^+MeI^-$, *s*-BuLi, THF, -78 °C-rt, 62%; (d) toluene, reflux, 20 h; (e) Pd/C, 1-octene, toluene, reflux, 80%.

of **1** with piperidinomethyl lithium generated from piperidinomethyl tributylstannane[5] **2** with *n*-BuLi furnished the alcohol **3**. The ketone **4** was prepared by the Swern oxidation[6] of alcohol **3** using TFAA and DMSO. Wittig reaction[4b] of ketone with methyltriphenylphosphonium iodide and *s*-BuLi in dry THF at -78 °C afforded a diene **5** in a good yield. Preparation of 2-(1-cyclopenten-1-yl)-3-(piperidyl)-1-propene **5** was as follows: To a mixture of methyltriphenylphosphonium iodide (2.1 g, 5.2 mmol, 200 M%) in dry THF (10 mL) was added slowly *s*-BuLi (4.1 mL, 5.2 mmol, 200 M%, 1.3 M cyclohexane) at -78 °C. After the reaction mixture was stirred for 30 min, a solution of **4** (0.5 g, 2.6 mmol, 100 M%) in dry THF (10 mL) was added to the mixture. The mixture was stirred at 0 °C for 1 h and then was stirred at room temperature for an additional 3 h. The mixture was treated with saturated aqueous NH_4Cl solution (20 mL) and extracted with ether. The combined extracts were dried, filtered, evaporated, and purified by flash column chromatography (eluent; ethyl acetate, $R_f = 0.8$) to give **5** (0.29 g, 62% yield). ^1H NMR (300 MHz, $CDCl_3$) 5.96-5.20 (1H, m), 5.12 (1H, s), 5.03 (1H, s), 3.09 (2H, s), 2.51-2.42 (4H, m), 2.37 (4H, bt), 1.93-1.83 (2H, m), 1.60-1.53 (4H, m), 1.46-1.40 (2H, m).

Finally, cycloaddition of naphthoquinone **6** with the diene **5** in refluxing toluene for several hours, which was followed by treatment with 10% Pd/C in refluxing 1-octene provided the requisite cyclopentanthraquinone **7** in good yield. Its intermediate, 1a,2,3,5,5a,11a-hexaydro-*1H*-cyclopent[a]anthracene-6,11-dione was not isolated but directly dehydrogenated to the corresponding **7**. Preparation of cyclopentanthraquinone **7** was as follows: A mixture of **5** (0.5 g, 2.8 mmol, 100 M%) and 1,4-naphtoquinone (0.5 g, 3.1 mmol, 110 M%) in toluene (20 mL) was refluxed for 20 h. To the reaction mixture was then added 10% Pd/C (0.1 g) and 1-octene (1 mL). Then, the mixture was refluxed for an additional 36 h,

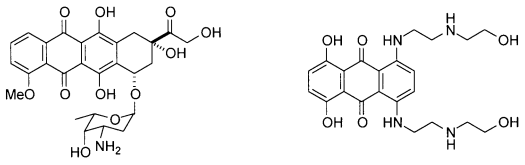


Figure 1. Structure of two clinically used 9,10-anthraquinones.

allowed to cool to room temperature, filtered, and washed with ether. The combined filtrates was dried, filtered, evaporated, and purified by flash column chromatography (eluent; ethyl acetate/hexane=2/8, $R_f = 0.4$) to give **7** (0.96 g, 80% yield). ^{1}H NMR (300 MHz, $CDCl_3$) 8.30-8.25 (2H, m), 8.19 (1H, s), 7.78-7.73 (2H, m), 3.53 (2H, s), 3.52 (2H, t, $J = 7.7$ Hz), 3.02 (2H, t, $J = 7.7$ Hz), 2.42 (4H, bt), 2.25-2.15 (2H, m), 1.62-1.55 (4H, m), 1.48-1.44 (2H, m); HRMS (EI) cacd for $C_{23}H_{23}NO_2$ 345.1729, found 345.1724.

After successful development of the model compound, we are applying the same scheme to the preparation of various cyclopentanthraquinones containing dialkylaminomethyl group to speculate detailed structure and activity relationships of the new cyclopentanthraquinone derivatives.

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5. 1-(*N,N*-Dialkylamino)alkyltributylstannanes from 1-(*N,N*-dialkylamino)alkylbenzotriazoles. See: Katritzky, A. R.; Chang, H. X.; Wu, J. *Synth.* **1994**, 907.
6. To a solution of trifluoroacetic anhydride (0.5 mL, 3.3 mmol, 130 M%) in dry THF (10 mL) was added slowly DMSO (0.5 mL, 7.0 mmol, 270 M%) at -55 °C. After being stirred for 10 min, **3** (0.5 g, 2.6 mmol, 100 M%) in THF (10 mL) was added dropwise into the mixture. The reaction mixture was stirred at the same temperature for additional 1 h and then quenched with triethylamine (2 mL). The mixture was warmed to room temperature, added with ice water, extracted with ether, dried, evaporated, and purified by flash column chromatography (eluent; acetone, $R_f = 0.6$) to give **4** (0.24 g, 48% yield).