Synthesis of 7,12-Dimethylbenz[a]anthracene and Its 1,2,3,4-Tetrahydro Derivative

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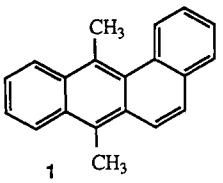
7,12-Dimethylbenz[a]anthracene (1) is a highly potent carcinogen.[1] It is activated by microsomal enzymes to a



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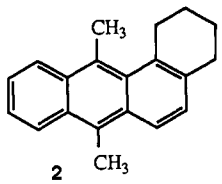

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diol epoxide metabolite that binds covalently to DNA in mammalian cells, leading ultimately to tumor induction.[2,3] Surprisingly, 7,12-dimethyl-1,2,3,4-tetrahydrobenz[a]-anthracene (2), which is saturated in the ring postulated to undergo enzymatic activation, is also highly carcinogenic.[4]

In connection with studies to elucidate the mechanism of carcinogenesis of 2, we attempted to synthesize 2 from 1,2,3,4-tetrahydrobenz[a]anthracene-7,12-dione (**3a**) by utilization of methods previously reported for the preparation of 1 from benz[a]anthracene-7,12-dione (**3**).[5,6] Although 1 was obtained in good yield through addition of methyllithium to 3, followed by reaction of the adduct 4 with anhydrous HCl to yield 5, and reduction of the latter with $SnCl_2$, HCl, or $NaBH_4$, only very low yields (<3%) of 2 were obtainable via an analogous sequence (Scheme I).

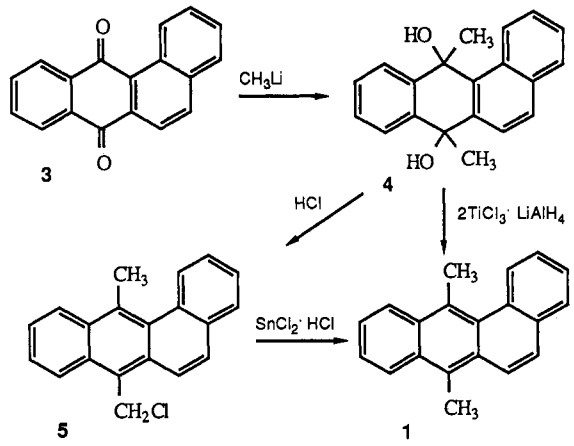
We now report efficient synthesis of 2 via addition of methyllithium to the quinone **3a** followed by treatment of the resulting adduct with $2TiCl_3$·$LiAlH_4$ by the method of Walborsky.[7] This procedure has also been employed to prepare 1 from 3 in two steps. This method constitutes the most convenient synthetic route to both 1 and 2.

The saturated quinone **3a** was prepared from benz[a]-anthracene by reduction with sodium and isoamyl alcohol to 1,2,3,4,7,12-hexahydrobenz[a]anthracene,[8] followed by oxidation with acidic sodium dichromate.

Experimental Section

Materials and Methods. Benz[a]anthracene was prepared by reduction of benz[a]anthracene-7,12-dione with HI in acetic acid[9] and converted to 1,2,3,4,7,12-hexahydrobenz[a]anthracene

Scheme I



by reduction with sodium in isoamyl alcohol.[8] $2TiCl_3$·$LiAlH_4$ was purchased from Aldrich. Proton NMR spectra were obtained on the University of Chicago 500-MHz NMR Spectrometer in $CDCl_3$ with tetramethylsilane as internal standard. The integrated NMR spectra were consistent with the structural assignments and essentially identical with the spectra of authentic standard compounds. All melting points are uncorrected.

1,2,3,4-Tetrahydrobenz[a]anthracene-7,12-dione (3a). A solution of 1,2,3,4,7,12-hexahydrobenz[a]anthracene (600 mg, 2.58 mmol) and sodium dichromate (1.20 g, 4.58 mmol) in acetic acid (60 mL) was heated at reflux for 30 min. The reaction mixture was cooled to room temperature and then poured into 150 mL of 30% sulfuric acid. The precipitate was filtered, washed with water, dried, then dissolved in benzene, and passed through a column of silica gel, eluting with benzene. The crude product (530 mg) was recrystallized from benzene–hexane to yield pure **3a**: 420 mg (62%); mp 153–154.5 °C (lit.[10] mp 152–154 °C).

7,12-Dimethyl-1,2,3,4-tetrahydrobenz[a]anthracene (2). To a solution of **3a** (524 mg, 2 mmol) in benzene (100 mL) was added methyllithium (20 mmol of a 1.3 M solution in ether), and the solution was stirred at ambient temperature under argon overnight. The product was worked up conventionally and utilized directly in the next step.

The solid $2TiCl_3$·$LiAlH_4$ complex (1.73 g, 5 mmol) was added cautiously to 60 mL of anhydrous THF at 0 °C under an argon atmosphere, stirred for 30 min, and then heated at reflux for 1 h. The black suspension was again cooled to 0 °C; then, the dimethyl diol adduct dissolved in 40 mL of dry THF was added. The reaction mixture was stirred at room temperature until the evolution of hydrogen subsided and then heated at reflux for 3 h. The product was worked up conventionally to afford crude 2, 570 mg. This material was dissolved in ether and adsorbed on silica gel. The ether was removed under vacuum, and the product was added to the top of a column of silica gel. The product that eluted with petroleum ether was recrystallized from ether–petroleum ether to yield pure 2: 380 mg (73%); mp 89.5–90.5 °C (lit.[10] mp 89–90 °C); NMR δ 1.69 (quintet, 2, H_3), 1.92 (quintet, 2, H_2), 2.96 (t, 2, H_4), 3.01 (s, 3, 7-CH_3), 3.11 (s, 3, 12-CH_3), 3.27 (t, 2, H_1), 7.11 (d, 1, H_5, J = 9.0 Hz), 7.44 (m, 2, $H_{9,10}$), 7.99 (d, 1, H_6, J = 9.0 Hz), 8.22 (m, 2, $H_{8,11}$).

7,12-Dimethylbenz[a]anthracene (1). Analogous reaction of 3 (2.58 g, 10 mmol) with methyllithium (50 mmol) in benzene (200 mL) furnished the dimethyl diol adduct that was reacted with $2TiCl_3$·$LiAlH_4$ following the procedure described in the preceding example. The crude product (2.5 g) was dissolved in benzene, adsorbed on silica gel, and chromatographed on a column of silica gel. Elution with hexane gave 1: 1.53 g (60%); mp 121–123 °C (lit.[11] 122–123 °C); NMR spectrum of 1 in good agreement with that reported.[12]

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Registry No. 1, 57-97-6; 2, 67242-54-0; 3, 2498-66-0; 3a, 72648-43-2; 4, 2518-00-5; 4a, 105091-10-9; 1,2,3,4,7,12-tetrahydrobenz[*a*]anthracene, 16434-62-1.

A Convenient Synthesis of Polyoxamic Acid, 5-*O*-Carbamoylpolyoxamic Acid, and Their Unnatural D Isomers

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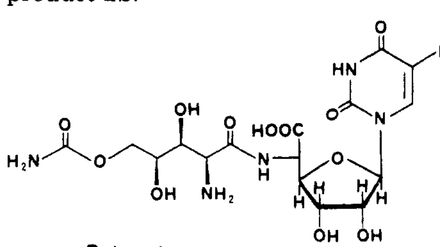
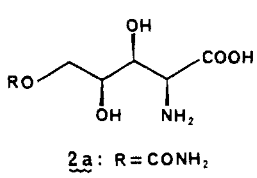
Polyoxins, e.g., **1a–d** are a family of antifungal antibiotics that has been extensively studied for some time.[1] They are widely used in Japan against phytopathogenic fungi,[1d–g] acting as competitive inhibitors of the enzyme chitin synthetase,[1b,2] leading to blockade of the biosynthesis of chitin, an essential component of the fungal cell wall.[3] A common structural feature of the polyoxins is a dipeptide comprised of a unique functionalized polyhydroxynorvaline commonly named 5-*O*- or δ-carbamoylpolyoxamic acid (**2a**) coupled to one of several related nucleoside amino acids. The name polyoxamic acid is given to the decarbamoylated natural product **2b**.[1a]

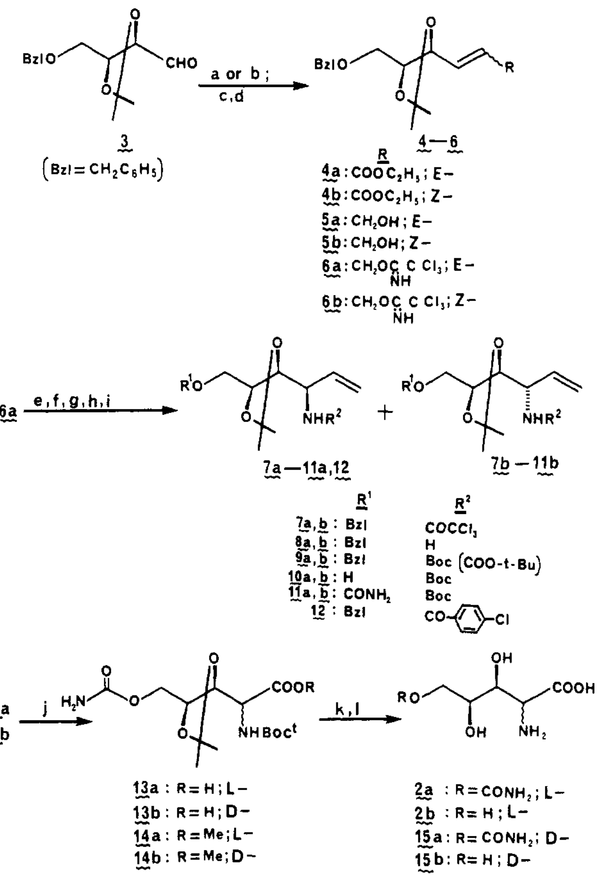


	Polyoxins	R
1a:	B	CH_2OH
1b:	D	COOH
1c:	J	CH_3
1d:	L	H



2a: R = $CONH_2$
2b: R = H

Scheme I[a]



[a] Reagents and conditions: (a) $(EtO)_2P(O)CH_2COOEt$, NaH, THF, rt,[17] (quant.); (b) $Ph_3P{=}CHCOOEt$, MeOH, rt (98%); (c) DIBAL-H, toluene, rt (85%); (d) Cl_3CCN, Et_2O, Et_2O, NaH (cat.); (e) xylene, reflux, 48 h (28% each diastereomer from **5**); (f) NaOH, THF–H_2O, 60 °C (82%); (g) $(BOC)_2O$, Et_3N, Et_2O (quant.); (h) Na, NH_3 (96%); (i) *p*-nitrophenyl chloroformate, Et_3N, Et_2O, 0 °C, 18 h, NH_3–MeOH (75% overall); (j) $NaIO_4$, $RuCl_3$ (cat.), CH_3CN–CCl_4–H_2O (70%); (k) MeOH (5–8 equiv), trifluoroacetic acid, rt, 45 min (73%); (l) 0.6 N NaOH, 60 °C, 2 h (58%).

In seeking a practical route to **2a**, and more usefully still a derivative with suitable protection for peptide coupling, use of L-tartaric acid with its inherent C-2 axis of symmetry appeared to us to be most appropriate. A purported synthesis of **2a** also utilizing L-tartaric acid has been described by Mukaiyama et al.,[4] the crucial step in which was stereoselective addition of a titanium acetylide species to the aldehyde **3**. A lengthy synthesis of **2b** based on higher carbohydrate starting materials has also appeared,[5] as well as an aldol condensation based synthesis[6] from D-erythrose of a protected D-**15a** derivative.

Our own strategy for the introduction of the α-amino acid functionality involved the use of the Overman–Claisen imidate rearrangement[7,8] as a key step, since we needed both the natural L and unnatural D isomers of the title compounds. In the course of our present work we noted some inconsistencies in the earlier report[4] (vide infra). This led us to confirm rigorously the authenticity of our

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