Pergamon

Tetrahedron Letters, Vol. 36, No. 8, pp. 1213-1216, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00036-4

A RAPID, CONVERGENT, AND REGIOSELECTIVE SYNTHESIS OF 3,7,8-TRIHYDROXY-*TRANS*-7,8-DIHYDROBENZO[A]PYRENE

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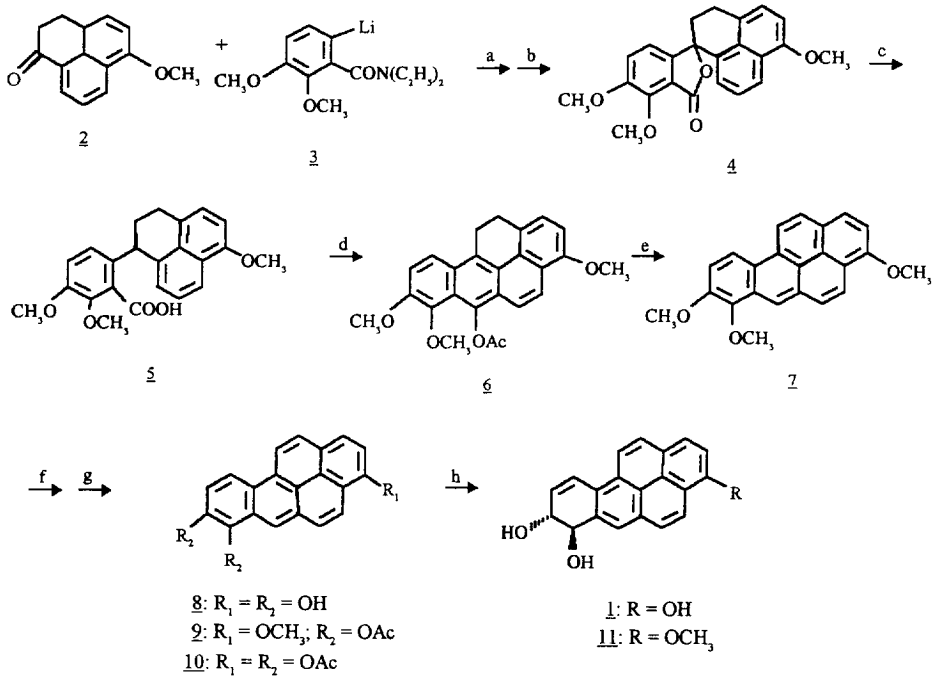
Abstract: A new, highly efficient, and regioselective synthesis of 3,7,8-trihydroxy-*trans*-7,8-dihydrobenzo[a]pyrene and its 3-methoxy analogue is described.

The identification of the phenolic derivatives of dihydrodiol and diol epoxide as metabolites of benzo[a]pyrene (BP) and other polycyclic aromatic hydrocarbons (PAHs)[1] has stimulated considerable research interest in the synthesis of these compounds.[2-5] In an earlier study,[2,3] we reported two multi-steps synthetic procedures, each consisting of 12 to 14 steps, for a total synthesis of 3,7,8-trihydroxy-*trans*-7,8-dihydroBP (1) which is a known metabolite of 3-hydroxyBP[6] (a major metabolite of BP). We have found that the phenolic dihydrodiol 1 which is bioactivated to mutagenic products[7,8] binds to DNA,[9] and undergoes metabolic reactions to produce *trans*-7,8-dihydroxy-9,10-epoxy-7,8,9,10-tetrahydroBP diastereomer(s) [3-hydroxyBPDE(s)].[10] One of the 3-hydroxyBPDE diastereomers, 3,7,8-trihydroxy-9,10-epoxy-7α,8β,9β,10β-tetrahydroBP (3-hydroxy-*anti*-BPDE), has also been identified as a major metabolite of 7,8-dihydroxy-9,10-epoxy-7α,8β,9β,10β-tetrahydroBP (*anti*-BPDE)[11] which is currently being considered the ultimate carcinogen of BP.[12] In view of significant interest generated by these findings, we sought large quantities of 1 because this compound is the most appropriate starting material for the synthesis of the DNA adducts of 3-hydroxyBPDEs *via* 3-hydroxyBPDEs or its 3-acyl analogues.[13] These DNA adducts are needed for investigations of the role of the respective adducts in BP-induced carcinogenesis.

Due to overall low yield (1.5% or less), and the difficulties associated with large scale runs of certain non-regioselective reactions, we found the published procedures[2,3] developed in our laboratory were inadequate for a large scale synthesis of 1 in a timely manner. Later in 1989, Schrode *et al.*[4] reported a regioselective synthesis of 1 in an abstract form, but no experimental details of this synthesis are available in the open literature. Therefore, it was felt that a new and more efficient synthesis of 1 was urgently needed. In the present communication, we wish to report a rapid and regioselective synthesis of 3,7,8-triacetoxyBP (10), and its efficient conversion to 1 (Scheme I). 6-Methoxy-2,3-dihydrophenalenone (2, mp 82 °C), a starting material for the synthesis of 10, was prepared in three convenient steps from commercially available 4-methoxy-1-naphthaldehyde following the analogous procedure published for 5,6-dimethoxy-2,3-dihydrophenalenone.[14]

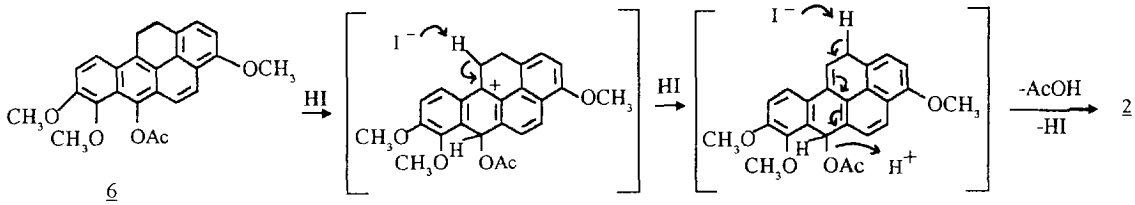
Scheme I[15]



Reagents: (a) TMEDA/THF/-78 °C; (b) p-TsOH/C_6H_6/Reflux; (c) Zn-C_5H_5N/10% KOH/reflux; (d) $ZnCl_2$/Ac_2O-AcOH; (e) HI/50% H_3PO_2; (f) BBr_3/CH_2Cl_2 or C_5H_5N.HCl/Reflux; (g) Ac_2O-C_5H_5N/p-DMAP; (h) $NaBH_4$/O_2/EtOH

The condensation of 2 with N,N-diethyl-2,3-dimethoxy-6-lithiobenzamide (3)[16] at -78 °C in dry THF gave an intermediate which was treated with p-toluenesulfonic acid in refluxing benzene to produce the lactone 4 [mp 206-208 °C (EtOAc)] in overall 66% yield. The reduction of the lactone 4 with Zn/KOH-pyridine[17,18] gave a nearly quantitative yield of the acid 5, mp 90-92 °C. Acid 5 was refluxed with Ac_2O-AcOH (1:1) in the presence of anhydrous $ZnCl_2$[19,20] for 4 hr to produce >90% yield of 6-acetoxy-11,12-dihydro-3,7,8-trimethoxyBP (6), mp 206-208 °C (EtOAc/hexane). A brief treatment (2-3 min) of 6 with HI/50% H_3PO_2[19,20] at 100 °C effected not only the elimination of the 6-OAc group but also the dehydrogenation of the 11,12-double bond, thereby, producing 3,7,8-trimethoxyBP (7) [199-201 °C (EtOAc)] as the sole product in 95% yield. Presumably, the polarization across the para-positions (C_7-C_{10a}) of 6 under acidic conditions results in the formation of a carbonium ion at the C_{10a} position due to the stabilization of this carbonium ion by electron releasing methoxy substituents at the 3 and 8 positions of the molecule. Subsequent elimination of H_{11} and H_{12} protons in two consequtive steps with the aid of I^- results in the formation of 7 (see Scheme II). Demethylation of 2 to form 3,7,8-trihydroxyBP (8) was found to be a challenging part of this synthesis. As reported[5] earlier with the chrysene analogue, the treatment of 7 with BBr_3 in CH_2Cl_2 at room temperature for 3 hr followed by acetylation (Ac_2O-

Scheme II



pyridine/4-diethylaminopyridine) resulted in >95% yield of a product characterized as 3-methoxy-7,8-diacetoxyBP (9), mp 262-263 °C. Longer reaction times did not provide any better results. The UV spectrum of 9 was identical to that of 3-methoxyBP prepared by the methylation (CH_3I-NaOH/HMPA)[21] of authentic 3-hydroxyBP. A partial demethylation of 7 with BBr_3/CH_2Cl_2 was also observed by Seidel and his co-workers.[22] Treatment of 7 with BBr_3/CH_2Cl_2 at refluxing temperature produced 3,7,8-triacetoxyBP (10) in low and variable yields after exhaustive purification.

The resistence of the 3-methoxy substituent of 7 to demethylation by BBr_3 prompted us to investigate other reagents known for the demethylation of methoxy aromatics. After studying several reagents, we found that a complete demethylation of 7 to the relatively unstable 3,7,8-trihydroxyBP (8) can be achieved in 10-15 min with freshly prepared anhydrous pyridinium chloride at 212 °C under argon atmosphere. Acetylation of 8 (Ac_2O-pyridine/4-diethylaminopyridine) immediately after its isolation gave light yellow 3,7,8-triacetoxyBP (10), mp 325-327 °C (THF) in 99% yield based on 7. The triacetate 10 which was found to be highly insoluble in EtOH, CH_2Cl_2, $CHCl_3$, THF, and EtOAc exhibited a UV spectrum (5% THF-EtOH), as expected, identical to that of BP. Treatment of 10 with 3.5-fold (by weight) excess of $NaBH_4$ in absolute ethanol, while bubbling oxygen[23] for 72 hr at ambient temperature, resulted in the formation of 80-90% yield of 3,7,8-trihydroxy-7,8-dihydroBP (1). The phenolic dihydrodiol 1 obtained in this study and in the previous study,[2,3] respectively, has identical ^1H NMR, UV and tlc profiles. A similar treatment of 9 with $NaBH_4$-O_2/EtOH for 48 hr produced 3-methoxy-7,8-dihydro-*trans*-7,8-dihydroxyBP (11), mp 212-214 °C, in 70-80% yield. When 3,7,8-trihydroxyBP (8) was treated with $NaBH_4$-O_2/EtOH, it produced a significant amount of byproduct(s) from which the isolation of 1 in a pure form was difficult to achieve.

The above described convergent approach for the abbreviated synthesis of 1 from conveniently available synthetic intermediate 2 in overall 45-50% yield is a big improvement over the published procedures. The synthetic steps appear to be general and can be run on a scale of several grams. This approach should have general applicability for the synthesis of various biologically important nuclear substituted dihydrodiols and other derivatives of BP and various higher condensed aromatic ring systems that are urgently needed for studying the mechanism of PAH-induced carcinogenesis.

Acknowledgement. This investigation was supported by a grant # 1RO1 ESO4130-04 awarded to SK by the National Institute of Environmental Health Sciences, DHHS.

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(*Received in USA* 17 *October* 1994; *revised* 13 *December* 1994; *accepted* 19 *December* 1994)