Pergamon

Tetrahedron Letters, Vol. 35, No. 48, pp. 8989-8990, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01993-2

Total Synthesis of 2'-Deoxycadeguomycin, a New Pyrrolo[2,3-*d*]pyrimidine Nucleotide Analogue

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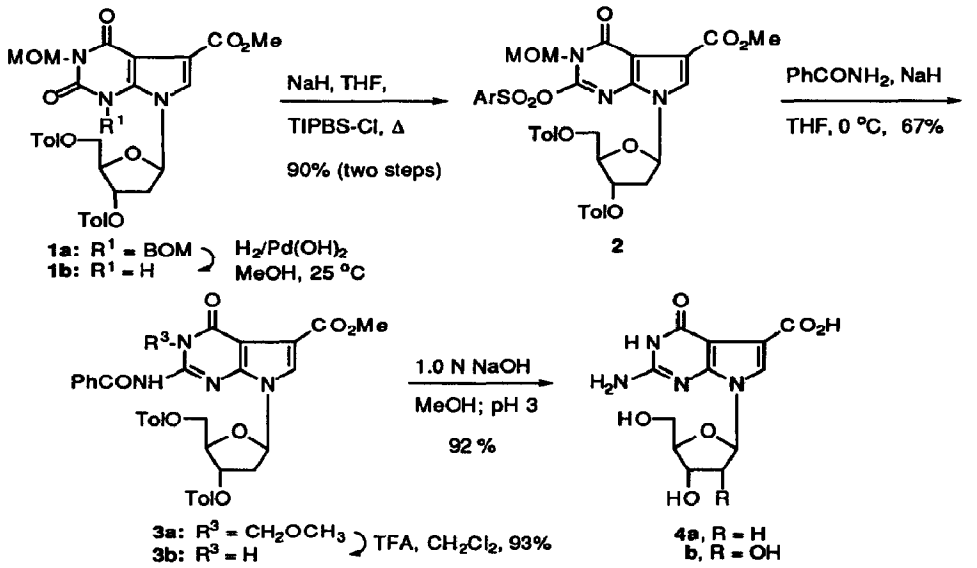
Abstract: This paper describes an efficient synthetic route to a novel pyrrolo[2,3-*d*]pyrimidine nucleotide analogue, 2'-deoxycadeguomycin **4a**. The key transformation involves the conversion of the differentially protected pyrrolo[2,3-*d*]pyrimidin-2,4-dione base portion in **1a** into a protected 2-amino-pyrrolo[2,3-*d*]pyrimidin-4-one **3a**.

As part of our interest in developing a general new approach for the synthesis of pyrrolo[2,3-*d*]pyrimidine (7-deazapurine) nucleotide analogues, we now report the synthesis of 2'-deoxycadeguomycin **4a**, an analogue of the antitumor compound, cadeguomycin **4b**, a naturally occurring 7-carboxy-7-deazaguanosine isolated from a strain of the soil actinomycete *Streptomyces hygroscopicus*.[1] Our strategy incorporates a versatile synthetic intermediate which contains a differentially protected pyrimidin-2,4-dione ring portion and a C-5 triflate functional handle.[2] In this way, a flexible array of ring substitution patterns and sugar units can be introduced from a common precursor. In this communication we highlight the conversion of pyrrolo[2,3-*d*]pyrimidin-2,4-dione **1a** (a 7-deazaxanthine) into the 2-amino-pyrrolo[2,3-*d*]pyrimidin-4-one nucleus represented in **4a** (a 7-deazaguanosine).

Our synthetic route starts with the β-2'-deoxyribosyl-5-methoxycarbonyl-pyrrolo[2,3-*d*]pyrimidin-2,4-dione **1a**, which has been efficiently prepared via palladium-catalyzed methoxycarbonylation of a C-5 triflate intermediate.[2] Differential protection of the *N*-1 and *N*-3 positions allowed us to selectively remove the *N*-1 benzyloxymethyl (BOM) group using Pearlman's catalyst.[3] The resulting free amide **1b**[4] was converted into its 2-O-sulfonyl derivative **2**[4] by treatment with sodium hydride and triisopropylbenzenesulfonyl chloride (TIPBS-Cl). The amination at C-2 presented difficulties due to completing side reactions. For example, the reaction of **2** with various nitrogen nucleophiles (NH_3, $CH_3CONHNa$), afforded significant amounts of compound **1b** resulting from cleavage of the sulfonyl ester bond.[5] This problem was circumvented by using a sterically larger nucleophile derived from benzamide. As a result, the desired compound **3a**,[4] was afforded in 67% yield with the 2-amino group conveniently introduced as its protected benzamide derivative. At this stage, the

methoxymethyl group at *N*-3 was removed by treatment with TFA to afford **3b** in high yield.[4] The final step involved simple base hydrolysis of the toluoyl esters from the 3′ and 5′ hydroxyl groups, the benzamide group at the 2-amino position, and the methyl ester at C-5. The final product, **4a**,[4] was conveniently isolated by precipitation from the reaction solution following acidification to pH 3.



This paper demonstrates the utility of a new approach for the synthesis of 7-deazapurine nucleotides as revealed by the synthesis of 2-deoxycadeguomycin, a 7-deazaguanosine derivative. Further work in progress is aimed at the conversion of key intermediates related to compounds **1a** and **2** into 4-amino- and 4-oxopyrrolo[2,3-*d*]pyrimidine nucleotide analogues (7-deazaadenosines and 7-deazainosines, respectively) and will be reported in due course.

Acknowledgements: This research was supported, in part, by the donors of the Petroleum Research Fund, administered by the American Chemical Society. E.D.E. is grateful for support provided by the American Cancer Society Junior Faculty Research Award.

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(*Received in USA* 6 *September* 1994; *revised* 3 *October* 1994; *accepted* 7 *October* 1994)