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First Synthesis of a Representative, Natural Pterin Glycoside: 2'-*O*-(α-D-Glucopyranosyl)biopterin

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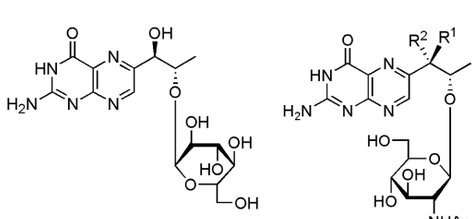
Abstract

Glycosylation of N^2-(N,N-dimethylaminomethylene)-1'-*O*-(4-methoxybenzyl)-3-[2-(4-nitrophenyl)ethyl]biopterin (14) with the novel donor 4,6-di-*O*-acetyl-2,3-di-*O*-(4-methoxybenzyl)-α-D-glucopyranosyl bromide (19) in the presence of silver triflate and tetramethylurea predominantly afforded the corresponding α-D-glucopyranoside (20a), from which 2'-*O*-(α-D-glucopyranosyl)biopterin (1) was obtained by the successive removal of the protecting groups.

Key words: biopterin D-glucoside, pterin glycoside, glycosylation, protecting groups

Introduction

Some pterins having a hydroxyalkyl side-chain at C-6 have been found as glycosidic forms in certain prokaryotes, representative examples being 2'-*O*-(α-D-glucopyranosyl)biopterin (1) isolated from various kinds of cyanobacteria [1−6] and limipterin [2'-*O*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)biopterin] (2) isolated from a green sulfur photosynthetic bacterium [7]. Glycosides (3−5) of other pterins such as ciliapterin (L-*threo*-biopterin), neopterin and 6-hydroxymethylpterin have also been isolated from cyanobacteria, anaerobic photosynthetic bacteria and chemoautotrophic archaebacteria [8−10]. We have undertaken a synthetic exploration of various types of glycosides of biopterin and related pterins owing to a marked interest in their physiological functions and biological activities as well as the structural proof of those natural products [11−17]. We present here the first synthesis of 2'-*O*-(α-D-glucopyranosyl)biopterin (1), which remained unprepared since its first discovery in 1958.



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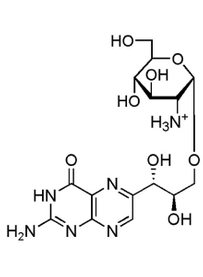
2 R^1 = OH, R^2 = H
3 R^1 = H, R^2 = OH



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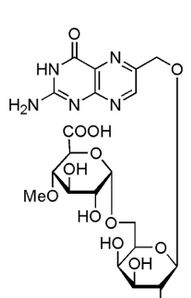

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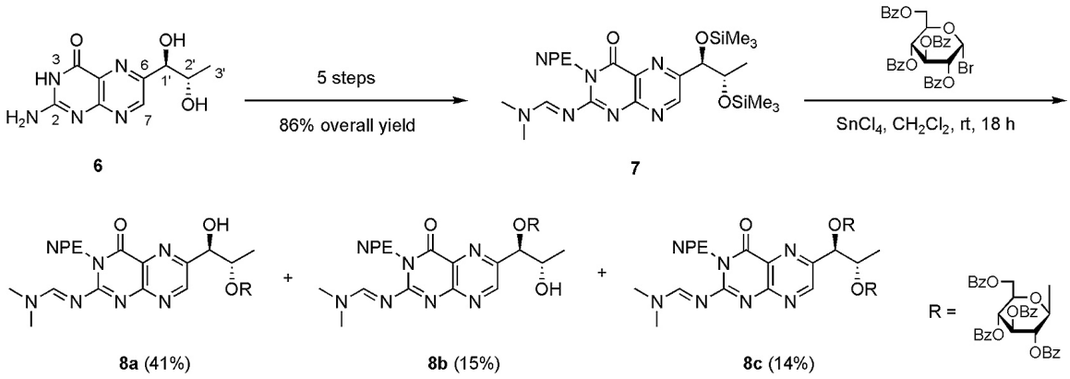
Results and Discussion

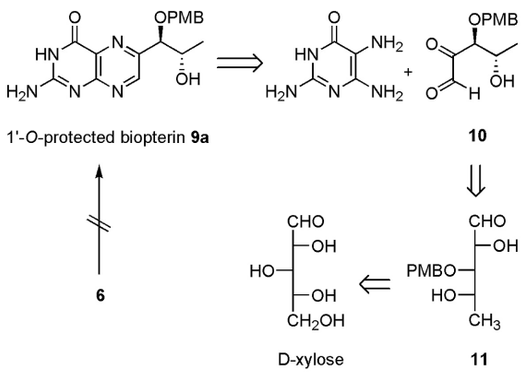
In our initial studies on glycosylation of a side-chain hydroxy group, we had to device suitable protecting and at the same time solubilizing groups for the pyrimidine ring and the side-chain hydroxy groups of the starting material biopterin (6). This was because pterin derivatives are little soluble, owing to the effectively stabilized intramolecular hydrogen bondings in the solid state [18], in such a nonpolar aprotic solvent as dichloromethane in which glycosylation reactions normally proceed smoothly. Thus, 6 was converted in a five-step procedure via intermediate 1',2'-di-*O*-acetyl-N^2-(*N*,*N*-dimethylaminomethylene)-3-[2-(4-nitrophenyl)-ethyl]biopterin into the sufficiently solubilized 1',2'-di-*O*-trimethylsilyl derivative (7) in 86% overall yield (Scheme 1) [12, 19]. Glycosylation of 7 with 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl bromide resulted in the formation of a mixture of 2'-*O*-(β-D-glucopyranosyl) 8a (41%), 1'-*O*-glycosyl isomer 8b (15%) and the 1',2'-di-*O*-glycosyl 8c (14%).

These results prompted us to pursue preparations of a suitably 1'-*O*-protected biopterin derivative in order to achieve complete 2'-*O*-glycosylation as shown in a retrosynthetic analysis for 9a outlined in Scheme 2. This compound was obviously not derived directly from biopterin but it appeared to be best prepared by the condensation of 2,5,6-triamino-4-hydroxypyrimidine with 3-*O*-protected pentos-2-ulose 10, which would be derived from 3-*O*-protected 5-deoxy-L-arabinose 11. As these compounds were both unknown, we explored a synthetic route starting with D-xylose involving C4 inversion and C5 deoxygenation [15]. Moreover, a rational consideration of the available conditions to remove the protecting groups of the glycoside derived from 1'-*O*-protected biopterin 9a led us to employ *p*-methoxybenzyl (PMB) group for protection of 1'-hydroxy, *N*,*N*-dimethylaminomethylene for 2-amino, and 2-(4-nitrophenyl)ethyl (NPE) for N-3 of the ring.

A 9-step synthetic sequence for the 5-deoxy-L-*erythro*-pentos-2-ulose (10) from D-xylose via a known compound 12 [20] and 3-*O*-PMB-5-



Scheme 1

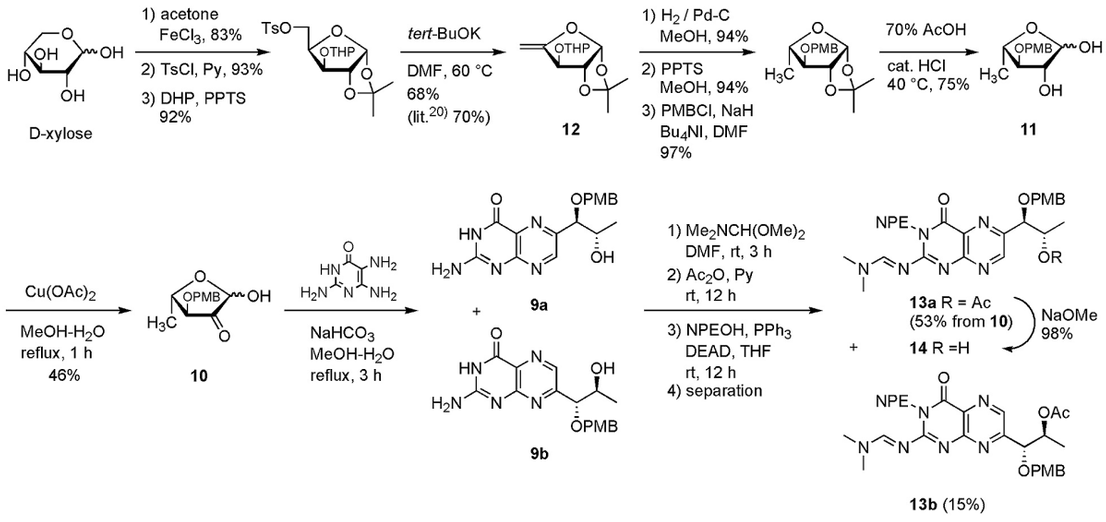


Scheme 2

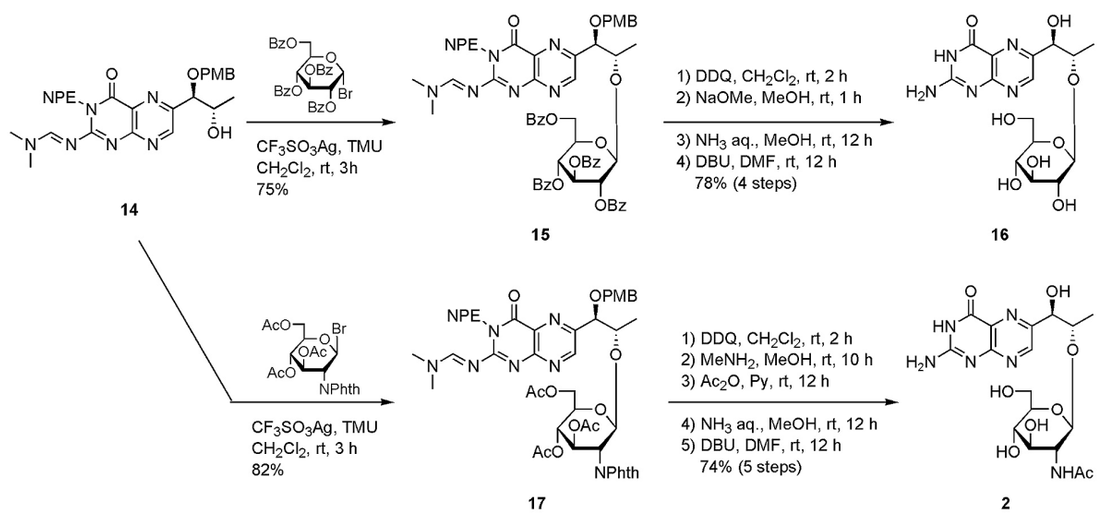
deoxy-L-arabinose (11) is shown in Scheme 3.

Condensation of 10 with 2,5,6-triamino-4-hydroxypyrimidine sulfate in an aqueous sodium bicarbonate solution afforded nearly an 8:2 mixture of the L-biopterin derivative 9a and its 7-substituted isomer (L-primapterin) 9b. Successive treatment of the mixture with *N*,*N*-dimethylformamide dimethyl acetal in DMF, with acetic anhydride in pyridine, and then with NPE alcohol (Mitsunobu reaction), gave the versatile L-biopterin derivative 13a (53% overall yield from 10) and L-primapterin derivative 13b (15%). Methanolysis of 13a in the presence of sodium methoxide quantitatively provided the 1'-*O*-PMB derivative 14, an ideal precursor for 2'-*O*-monoglycosylation [13].

An efficient glycosylation was exemplified by the condensation of 14 with tetra-*O*-benzoyl-α-D-glucopyranosyl bromide in the presence of silver triflate and tetramethylurea (TMU) in dichloromethane, affording 2'-*O*-β-D-glucopyranosyl derivative 15 as a sole product in 75% yield (Scheme 4). Deprotection of 15 efficiently afforded 2'-*O*-(β-D-glucopyranosyl) biopterin (16). Similarly, glycosylation of 14 with 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl bromide provided the 2'-*O*-glucopyranosyl derivative (17) in 82% yield, from which natural product limipterin (2) was



Scheme 3

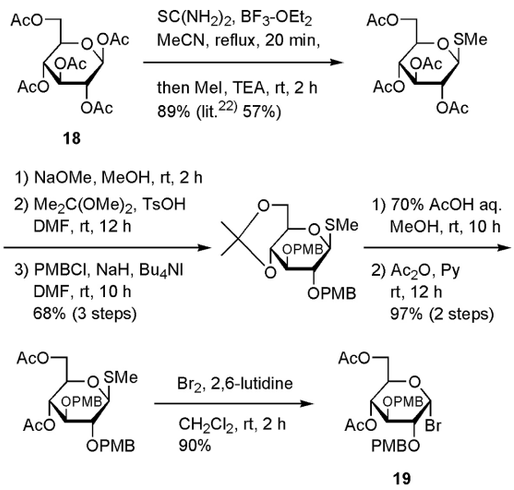


Scheme 4

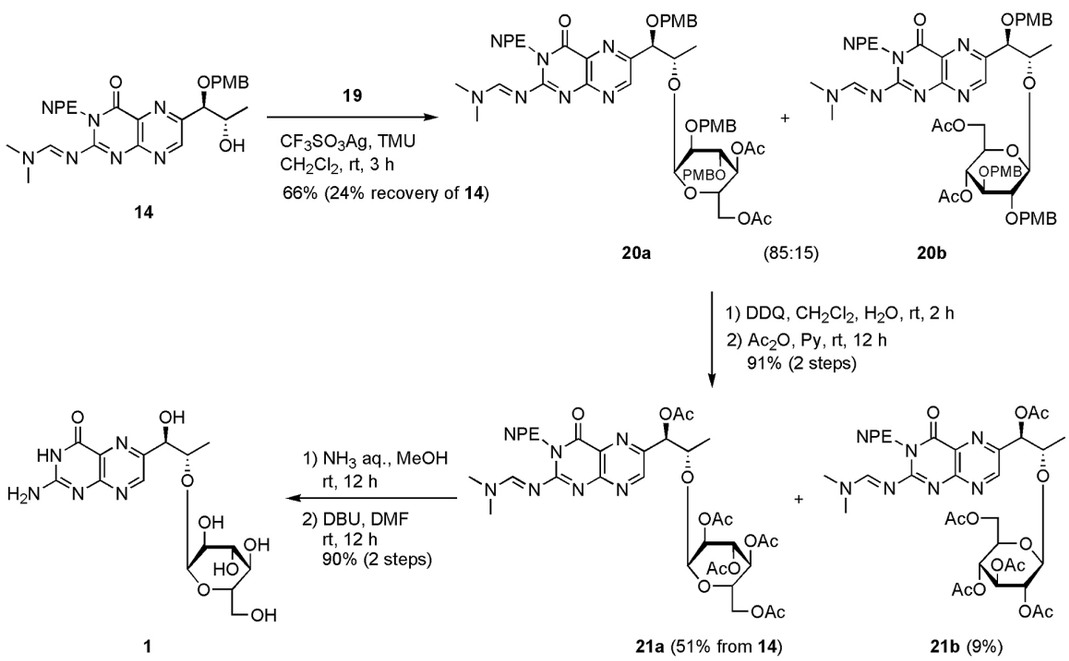
obtained smoothly after deprotection [15].

The stereoselective formation of the β-glycoside (15) from 14 was mainly caused by participation of the 2-*O*-benzoyl group of the glycosyl donor through the formation of an acyloxonium ion intermediate [21]. Accordingly, in order to avoid such a neighboring group participation in synthesis of biopterin α-D-glucoside (1), we sought to introduce an ether substituent for protection of 2-OH of a glycosyl donor; thus PMB and acetyl groups were respectively chosen for protection of 2,3-OH and 4,6-OH of the glycosyl moiety. A synthetic route is shown in Scheme 5 for such an appropriately protected α-D-glucopyranosyl bromide derivative (19) starting with penta-*O*-acetyl-β-D-glucopyranose (18) via methyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside [22].

Then, glycosylation of 14 was found to give the best result when it was treated with 4.0 mol equiv. of the glycosyl bromide (19) in dichloromethane in the presence of silver triflate (2.0 mol equiv.)



Scheme 5



Scheme 6

and tetramethylurea (1.0 mol equiv.), affording an inseparable anomeric mixture (85:15) of the 2'-*O*-(α-D-glucopyranosyl)biopterin derivative (20a) and its β-anomer (20b) in 66% yield, along with the recovery of 15 (24%) (Scheme 6). Separation of these isomers was achieved by removal of PMB groups and the subsequent acetylation, affording the 21a in 51% (total yield from 15) and its β-anomer (21b) in 9%. Removal of the protecting groups of 21a was accomplished as usual, furnishing the desired 2'-*O*-(α-D-glucopyranosyl)biopterin (1). The α-anomeric structure of 21a was derived from its $J_{1,2}$ value (3.9 Hz) of ^{1}H-NMR, while the larger $J_{1,2}$ value (8.1 Hz) confirmed the β-form of 21b [23].

We have developed an effective way for selective preparation of both pterin 2'-*O*-β- and 2'-*O*-α-glycosides. By use of the key intermediate 1'-*O*-PMB-biopterin derivative (14) and the novel glycosyl donor (19) the first synthesis of biopterin α-D-glucoside (1) was achieved.

Acknowledgements

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