Total Synthesis of L-Biopterin from L-Tartaric Acid *via* 5-Deoxy-L-arabinose

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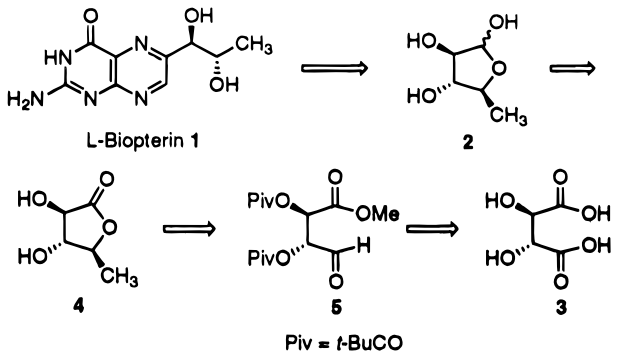
L-Biopterin **(1)**, one of the most ubiquitous compounds in the class of the naturally occurring pterins, was isolated from human urine as a growth factor of *Crithidia fasciculata* by Patterson *et al.*[1] Through its 5,6,7,8-tetrahydro form, **1** functions as an essential enzyme cofactor in the conversion of phenylalanine to tyrosine[2] and tyrosine to DOPA,[3] in melanine synthesis,[4] and in tryptophan hydroxylation.[5] As a consequence, tetrahydrobiopterin has been developed as a remedy for central nervous system diseases such as phenylketonuria, Parkinson's and Alzheimer's diseases, and depression.[6]

Since the first synthesis of L-biopterin **(1)** by Patterson *et al.*,[7] several syntheses have been reported,[8−13] especially by Viscontini's group.[8] In most of those,[8,9] L-rhamnose and L-arabinose are the starting materials to the key intermediate, 5-deoxy-L-arabinose **(2)**.[10] More recently, novel attractive syntheses of L-biopterin were described, employing less expensive ethyl *(S)*-lactate[11] or D-ribose[12] as starting materials; the key intermediate is then 5-deoxy-L-ribose (epimer in C2 of 5-deoxy-L-arabinose **(2)**). L-Biopterin **(1)** was also prepared by condensation of triaminobutoxypyrimidine with 2-formyloxiranes.[13]

In this paper, we describe a new synthetic access to 5-deoxy-L-arabinose **(2)** that employs L-tartaric acid **(3)** as starting material and thus improves both efficiency and economy. We thought that 2,3-dihydroxy-4-methylbutyrolactone **(4)** could be an excellent precursor of **2**. The retrosynthesis is presented in Scheme 1. This strategy relies on the condensation of 2,5,6-triamino-4-pyrimidinol with 5-deoxy-L-arabinose phenylhydrazone, which is directly prepared from 5-deoxy-L-arabinose **(2)**. Compound **2** could be obtained by reduction of the lactone **4** which presents the necessary asymmetric centers. Starting from L-tartaric acid **(3)** in which the configuration of two carbons is already determined we could achieve the stereospecific construction of the third contiguous asymmetric center by a stereoselective Grignard reaction on aldo ester **5**.

Scheme 1



The first phase of our work was the functional transformation of L-tartaric acid **(3)** to give the desired aldo ester **5** (Scheme 2). After simultaneous protection of the 2,3-diol system and transformation into an intermediate anhydride,[14] the acid chloride **6** was directly provided by the action of methanol[15] followed by thionyl chloride.[15] Reduction of **6** with bis(triphenylphosphine)copper(I) borohydride in acetone gave the aldo ester **5** in 90% yield. Compound **5** was then submitted to a Grignard reaction using methylmagnesium bromide and to deprotection under acidic conditions to afford (2*R*,3*S*,4*S*)-2,3-dihydroxy-4-methylbutyrolactone **(4)** in 78% yield. The Grignard addition appears critical because of the possibility of obtaining a mixture of epimeric lactones **7** transformed into **4** in which the newly created asymmetric center could be either (4*R*) or (4*S*). It is noteworthy that under conditions reported in Scheme 2, only the (4*S*)-lactone **4** (de > 98%) is recovered.[16] This high stereoselectivity in the Grignard reaction can be rationalized by steric hindrance due to the pivalate groups and will be discussed elsewhere.[17] Moreover, optical rotations of (2*R*,3*S*,4*S*)-lactone **4** and of its enantiomer (2*S*,3*R*,4*R*) are described in the literature[18,19] and are in total agreement with our own results (Table 1).

The lactone **4** was then reduced to lactol **2** (5-deoxy-L-arabinose) using DIBALH. The lactol **2** was transformed into L-biopterin **(1)** according to known procedures.[8f,12] The treatment of the crude lactol **2**[20] with phenylhydrazine in methanol gave phenylhydrazone **8** (72% yield), which is identical to that derived from

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(20) The product is contaminated by starting material **4** and tetrol (total reduction). These products do not interfere with the next step.

S0022-3263(96)01426-0 CCC: $12.00

Scheme 2

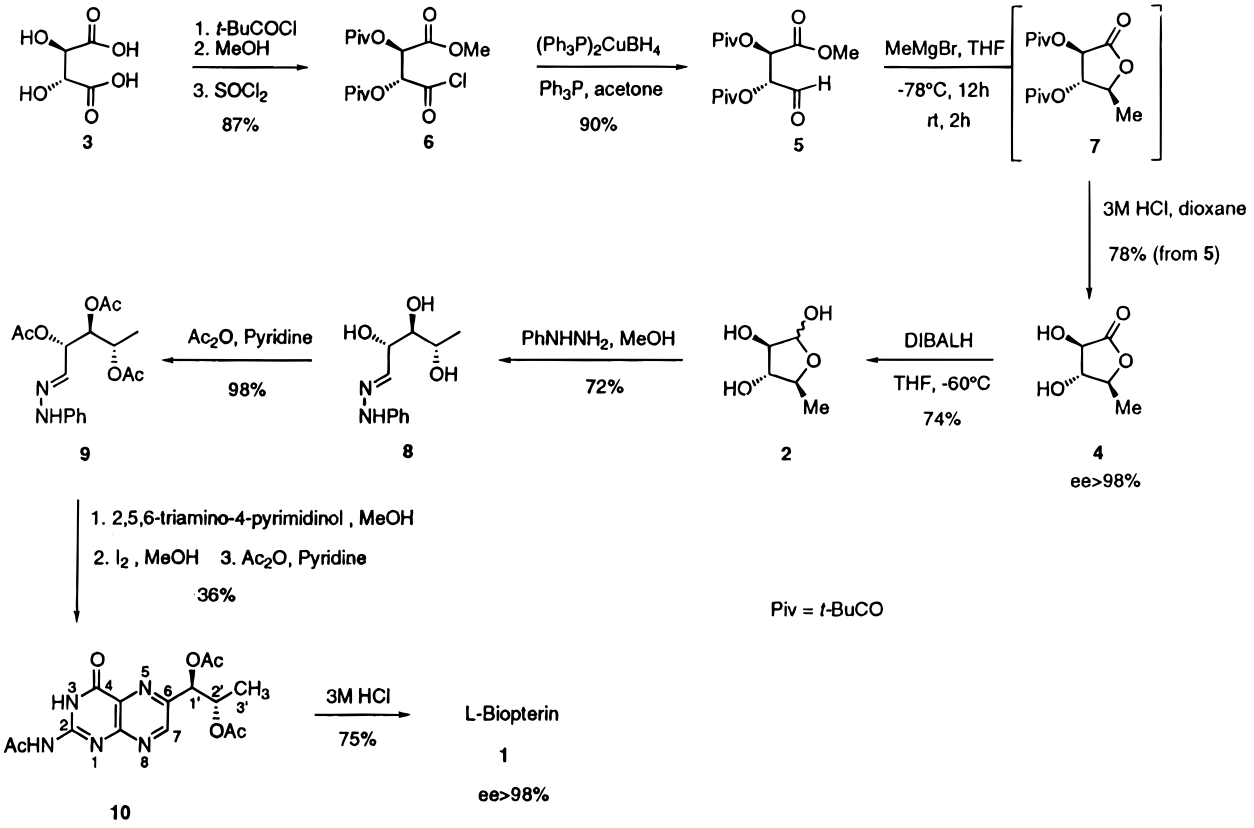

Table 1. Optical Rotations. Comparison to Literature

compd	$[\alpha]^{22}_D$ this work	$[\alpha]^{20}_D$ lit. (ref)
4	$-38^{a,b}$	$+37.3^{b,c}$ (19)
10	-109.8^{d}	-108^{d} (12, 21)
1	-65^{e}	-66^{e} (8f, 12)

[a] (2*R*,3*S*,4*S*). [b] *c* 1.1, EtOH. [c] (2*S*,3*R*,4*R*). [d] *c* 1.08, $CHCl_3$. [e] *c* 0.2, 0.1 N HCl.

L-rhamnose.[8f] Phenylhydrazone **8** was acetylated to **9**, which after a reaction with 2,5,6-triamino-4-pyrimidinol and oxidation with I_2 and acetylation, gave triacetylbiopterin **(10)**.[12] This compound was purified by preparative TLC and obtained in 36% yield. Physical data of triacetylbiopterin **(10)** are in total agreement with the literature[12,21] (Table 1). Compound **10** underwent a deprotection step leading to L-biopterin **(1)** which, without further purification, was exactly the same as the compound previously prepared by Viscontini.[8f]

In conclusion, this work describes the synthesis of L-biopterin **(1)** starting from L-tartaric acid **(3)**. This synthesis improves the preparation of lactone **4** by highly stereoselective addition of Grignard reagent on aldo ester **5**. This excellent result prompted us to condense successfully several Grignard reagents on compound **5**. These studies will be reported in due course.[17]

Experimental Section

Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded on 200 and 50 MHz spectrometers, respectively. Chemical shifts are reported in ppm and, *J* values are quoted in Hz. Preparative TLC were run on silica gel (SDS) 60, 17 μm F254, 1 mm.

(2*R*,3*R*)-Methyl 4-Chloro-4-oxo-2,3-dipivaloxybutanoate (6). Acid chloride **6** was obtained following the literature procedures[14,15] in 87% yield (oil) from **3**: IR (neat) 1812, 1774, 1748 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16 (s, 9H), 1.17 (s, 9H), 3.69 (s, 3H); 5.71 (d, 1H, $J = 2.6$), 5.75 (d, 1H, $J = 2.7$); ^{13}C NMR ($CDCl_3$) δ 26.58, 26.63, 38.65, 52.9, 69.4, 76.6, 165.3, 167.9, 176.3, 176.6; MS (CI/NH_3) *m*/*z* 352 $[M + H]^+$; $[\alpha]^{26}_D$ −35.4 (*c* 1.3, $CHCl_3$). Anal. Calcd for $C_{15}H_{23}O_7Cl$: C, 51.36; H, 6.61. Found: C, 51.42; H, 6.73.

(2*R*,3*R*)-Methyl 4-Oxo-2,3-dipivaloxybutanoate (5). To acid chloride **6**[14,15] (5.0 g, 14.26 mmol) in acetone (80 mL, dried 30 min over 4 Å sieves) was added triphenylphosphine (7.6 g, 29 mmol). To the resulting solution was added bis(triphenylphosphine)copper(I) borohydride (8.8 g, 14.6 mmol) at rt, and the reaction mixture was stirred for 1.5 h. The white precipitate (Ph_3PCuCl) was removed by filtration, and the filtrate was evaporated to dryness. The residue was extracted with ether (the ether insoluble residue was triphenylphosphine−borane). The ether was removed, the residue was dissolved again in $CHCl_3$ (80 mL), and the resulting solution was stirred for 1 h with copper(I) chloride (2.87 g, 29 mmol) to remove the remaining triphenylphosphine. The reaction mixture was filtered, the $CHCl_3$ was evaporated, and the residue was extracted with ether (a 1/1 Ph_3P/CuCl complex was formed which was soluble in $CHCl_3$ but insoluble in ether). After 30 min without stirring, the mixture was filtered, the ether was evaporated, and the residue was chromatographed on silica gel (PE/Et_2O 90/10 to 50/50 to remove the resulting Ph_3P) to give aldehyde **5** (4 g, 90%, oil): IR (neat) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.19 (s, 9H), 1.23 (s, 9H), 3.73 (s, 3H), 5.50 (d, 1H, $J = 2.6$), 5.59 (d, 1H, $J = 2.6$), 9.45 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 26.6, 26.7, 38.6, 52.6, 69.3, 75.9, 166.5, 176.8, 177.1, 194; MS (CI/CH_4) *m*/*z* 317 $[M + H]^+$; $[\alpha]^{21}_D$ −2.8 (*c* 7.83, $CHCl_3$). Anal. Calcd for $C_{15}H_{24}O_7$: C, 56.95; H, 7.65. Found: C, 56.80; H, 7.60.

(2*R*,3*S*,4*S*)-2,3-Dihydroxy-4-methylbutyrolactone (4) *via* Protected Lactone 7. Methylmagnesium bromide (9.5 mmol, 3.2 mL, 3 M in Et_2O) was added, at −70 °C, to a solution of aldehyde **5** (2.0 g, 6.3 mmol) in THF (45 mL). After the mixture was stirred at −70 °C for 12 h, the mixture was warmed to rt during 2 h for lactonization step (TLC control). The mixture was cooled to 0 °C and hydrolyzed with a saturated NH_4Cl solution. THF was removed, and the residue was extracted with

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ether. The organic layer was dried ($MgSO_4$) and evaporated. The lactone **7** could be isolated by chromatography on silica gel (PE/Et_2O 90/10) (90% yield, oil): IR (neat) 1804, 1742 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (s, 9H), 1.21 (s, 9H), 1.49 (d, 3H, J = 6.4), 4.42 (qd, 1H, J = 6.5, 6.5), 5.18 (dd, 1H, J = 7.1, 7.1), 5.48 (d, 1H, J = 7.3); irradiation of the protons of the methyl on C4 led to the unambigous observation of a selective Overhauser effect (5%) on H2 (Scheme 2); ^{13}C NMR ($CDCl_3$) δ 18.6, 26.8, 38.6, 72.4, 76.3, 77.1, 168.8, 176.9, 177.3; MS (CI/tBuH) m/z 301 $[M + H]^+$; $[\alpha]^{23}_D$ −21.9 (*c* 1.22, $CHCl_3$). Anal. Calcd for $C_{15}H_{24}O_6$: C, 59.98; H, 8.05. Found: C, 60.08; H, 7.97.

A solution of crude protected lactone **7** (6.3 mmol) in dioxane (60 mL) and 3 M HCl (120 mL) was stirred at reflux during 18 h. After being cooled, the reaction mixture was concentrated. The remaining solids were washed twice with hot AcOEt, and the washings were filtered, dried, and concentrated by azeotropic distillation with toluene. Purification on silica gel (PE/AcOEt 70/30) gave lactone **4** (0.65 g, 78% from **5**): mp 124−125 °C (lit.[18] 125 °C); IR (neat) 3366, 1748 cm^{-1}; ^1H NMR (CD_3OD) δ 1.41 (d, 3H, J = 6.2), 3.78 (dd, 1H, J = 8.8, 8.7), 4.17 (qd, 1H, J = 6.2, 8.3), 4.32 (d, 1H, J = 9.0), 4.82 (s, 2H); ^{13}C NMR (CD_3OD) δ 18.1, 75.4, 78.4, 80.5, 176.4; MS (CI/tBuH) m/z 115 $[M + H - H_2O]^+$, 133 $[M + H]^+$; $[\alpha]^{21}_D$ −37.0 (*c* 1.1, EtOH) (lit.[19] enantiomer (2*S*,3*R*,4*R*) $[\alpha]^{13}_D$ +37.3 (*c* 1.01, EtOH). Anal. Calcd for $C_5H_8O_4$: C, 45.46; H, 6.10. Found: C, 45.64; H, 6.26.

5-Deoxy-L-arabinose (2). To a solution of lactone **4** (0.65 g, 4.9 mmol) in THF (250 mL) at −60 °C was added, in 1 h, a solution of DIBALH (12.25 mmol, 7.7 mL, 1.6 M in toluene). After being stirred vigorously during 30 min, the mixture was hydrolyzed with water (7.5 mL) at −60 °C. A saturated $NaHCO_3$ solution was added until pH = 9−10, then the reaction mixture was warmed up to 32−35 °C (to precipitate aluminum salts) and filtered through Celite 545. Solids were washed with methanol (30 mL) and then ether (75 mL). Solvents were removed by evaporation. A mixture of starting material (0.13 g, 20%), lactol **2** (0.4 g, 60%), and tetrol (0.13 g, 20%, total reduction) was obtained. Lactol **2** was obtained in 74% yield taking into account recovered starting material **4**. This was used as such for the next step. **Lactol 2:** ^1H NMR (CD_3OD) δ 1.27 (d, 3H, J = 6.2), 3.54 (dd, 1H, J = 4.7, 7.7), 3.90 (dd, 1 H, J = 4.7, 2.6), 3.99−4.10 (m, 1H), 4.85 (large s, 3H), 5.08 (d, 0.7H, J = 2.2), 5.13 (d, 0.3H, J = 4.4). **Tetrol:** ^1H NMR (CD_3OD) δ 1.23 (d, 3H, J = 6), 3.61 (d, 2H, J = 7.0), 3.71−3.87 (m, 2H), 4.85 (large s, 4H); MS (CI/tBuH) m/z 117 [M(lactol **2**) + H − $H_2O]^+$, 137 [M(tetrol) + $H]^+$.

5-Deoxy-L-arabinose Phenylhydrazone (8).[8f] To the crude lactol **2** (0.3 g, 2.24 mmol) dissolved in methanol (55 mL) were added, under N_2, phenylhydrazine (242 mg, 2.24 mmol) and then one drop of glacial AcOH. After 1 h at rt, the yellow solution was evaporated under vacuum. The viscous residue was washed with Et_2O (2 × 15 mL), which was discarded. The remaining substance was dissolved in AcOEt (7 mL), the obtained solution was washed twice with H_2O (10 mL), and the organic layer was dried (Na_2SO_4) and evaporated under vacuum to give the hydrazone **8** (0.36 g, 72%): mp 78−80 °C; IR (neat) 3325, 1603 cm^{-1}; ^1H NMR (CD_3OD) δ 1.25 (d, 3H, J = 6.3), 3.43 (dd, 1H, J = 3.6, 7), 3.83 (qd, 1H, J = 6.6, 6.6), 4.42 (dd, 1H, J = 3.6, 5.8), 4.87 (s, 4H), 6.71−7.21 (m, 6H); ^{13}C NMR (CD_3OD) δ 19.6, 68.4, 72.3, 78.4; 113.1, 119.9, 129.9, 176.4, 150.0; MS (CI/tBuH) m/z 207 $[M + H - H_2O]^+$, 225 $[M + H]^+$; $[\alpha]^{23}_D$ +2.8 (*c* 1.1, EtOH). Anal. Calcd for $C_{11}H_{16}N_2O_3$: C, 58.91; H, 7.19; N, 12.49. Found: C, 58.61; H, 6.82; N, 12.25.

5-Deoxy-2,3,4-*O*-triacetyl-L-arabinose Phenylhydrazone (9).[8f] To hydrazone **8** (0.3 g, 1.34 mmol) dissolved in Ac_2O (3 mL) was added, under N_2, pyridine (3 mL). After 4 h at rt, the solution was evaporated under vacuum and the residue dried to give protected hydrazone **9** (0.46 g, 98%, oil): IR (neat) 3300, 1741, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (d, 3H, J = 6.5), 2.01 (s, 3H), 2.07 (s, 3H), 2.08 (s, 3H), 5.07 (qd, 1H, J = 6.2, 5.8), 5.43 (dd, 1H, J = 5.8, 5.7), 5.65 (dd, 1H, J = 5.7, 5.5), 6.80−7.26 (m, 6H), 8.62 (s, 1H); MS (EI) m/z 290 $[M - CH_3CO_2H]^{+\bullet}$, 321 [M − N_2H], 350 $[M]^{+\bullet}$.

2-*N*-Acetyl-1′,2′-di-*O*-acetyl-L-biopterin (10).[12,21] Acetylated hydrazone **9** (120 mg, 0.34 mmol) was dissolved in a methanol (2.5 mL)/pyridine (0.5 mL) mixture, and then a solution of sodium dithionite (9 mg, 0.051 mmol) and sodium acetate (64 mg, 0.782 mmol) in water (2.4 mL) and a suspension of 2,5,6-triamino-4-pyrimidinol sulfate (96 mg, 0.374 mmol) in water (3.2 mL) were successively added. The mixture was heated at 40−45 °C under argon for 24 h. To the resulting clear brown solution was added, at rt, iodine (203 mg, 0.8 mmol) in methanol (2.4 mL) within 15 min. The reaction mixture was then concentrated *in vacuo* to *ca*. 3 mL, and the brown suspension was cooled at 0 °C for 1 h. Then the precipitate was collected on a filter and washed with cold water, cold ethanol, and ether. The brown solid was dissolved in hot water (50 °C, 10 mL) and treated with active charcoal to give diacetylbiopterin. Without further purification, the crude diacetate was treated with Ac_2O (0.2 mL) in pyridine (0.3 mL) at 100 °C for 4 h. After concentration *in vacuo*, the residue was extracted with AcOEt. The extract was washed with saturated copper(II) sulfate solution, water, and brine and was dried ($MgSO_4$) and concentrated *in vacuo*. Preparative TLC using AcOEt as eluant gave triacetylbiopterin **10** (45 mg, 36%, pale yellow foam); IR (neat) 3161, 1742, 1677, 1627 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (d, 3H, J = 6.6), 1.99 (s, 3H), 2.16 (s, 3H), 2.46 (s, 3H), 5.46 (qd, 1H, J = 6.7, 4.4), 6.04 (d, 1H, J = 4.4), 8.94 (s, 1H), 11.21 (large s, 1H), 12.77 (large s, 1H); ^{13}C NMR ($CDCl_3$) δ 15.6, 20.8, 20.9, 24.9, 70.4, 75.7, 130.1, 149.1, 149.9, 150.3, 154.3, 159.6, 169.6, 169.8, 173.7; MS (CI/tBuH) m/z 364 $[M + H]^+$; $[\alpha]^{23}_D$ −109.8 (*c* 1.09, $CHCl_3$) (lit.[12] $[\alpha]^{24}_D$ −108 (*c* 1.08, $CHCl_3$)).

L-Biopterin (1).[12] A solution of triacetylbiopterin **10** (40 mg, 0.11 mmol) in 3 M HCl (0.7 mL) was heated at 100 °C for 30 min. The resulting pale yellow solution was concentrated *in vacuo* to give a yellow foam. The residue was then extracted with 3% aqueous NH_4OH solution and the extract was concentrated at *ca*. 1 mL and cooled in an ice bath. After obtention of a precipitate, the liquid was pumped off and the solid was dried under P_2O_5 to give L-biopterin **(1)** as a yellow amorphous solid (19 mg, 75%): mp > 300 °C (lit.[12] mp > 300 °C); ^1H NMR (3 N DCl) δ 1.68 (d, 3H, J = 6.4), 4.62 (qd, 1H, J = 6.5, 5), 5.40 (d, 1H, J = 5.0), 6.10 (large s, 5H), 9.46 (s, 1H); ^{13}C NMR (3 N NaOD + dioxane) δ 19.4, 71.6, 79.0, 127.5, 148.5, 154.0, 155.4, 163.8, 173.5; MS (FAB + Xe, 6 kV, 10 mA, glycerol + 0.1% TFA) m/z 138 $[M + H]^+$; $[\alpha]^{22}_D$ −65.0 (*c* 0.2, 0.1 N HCl) (lit.[12] $[\alpha]^{24}_D$ −66.8 (*c* 0.2, 0.1 N HCl)).

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