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AN EFFICIENT SYNTHETIC ROUTE FOR A VERSATILE CILIAPTERIN DERIVATIVE AND THE FIRST CILIAPTERIN D-MANNOSIDE SYNTHESIS

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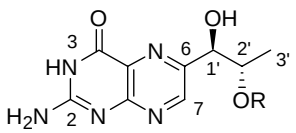
Abstract – The key precursor, N^2-(*N*,*N*-dimethylaminomethylene)-1'-*O*-(4-methoxybenzyl)-3-[2-(4-nitrophenyl)ethyl]ciliapterin (**15**) was efficiently prepared from D-xylose *via* an improved route. The first synthesis of 2'-*O*-(α-D-mannopyranosyl)ciliapterin (**2c**) was achieved by treatment of **15** with 2,3,4,6-tetra-*O*-benzoyl-α-D-mannnopyranosyl bromide in the presence of silver triflate and tetramethylurea, followed by removal of the protecting groups.

INTRODUCTION

Some pterins having a hydroxyalkyl side-chain at C-6, such as biopterin (**1a**) and ciliapterin (L-*threo*-biopterin) (**2a**), have been found as glycosidic forms in certain prokaryotes. As examples of pterin glycosides from green sulfur photosynthetic bacteria, limipterin (**1b**) and tepidopterin (**2b**) were isolated from *Chlorobium limicola f. thiosulfatophilum*[1] and *Chlorobium tepidum*,[2] respectively. Meanwhile, from cyanobacteria have been found 2'-*O*-(α-D-glucopyranosyl)biopterin (**1c**) (from *Anacystis nidulans*,[3] *Synechococcus* sp.,[4] and *Spirulina platensis*)[5] and 2'-*O*-(α-D-mannopyranosyl)ciliapterin (**2c**) (from *Aphanizomenon flos-aquae*).[6,7] Various other glycosides consisting of different pterins and sugar moieties have also been found in nature, although some of them have remained unclear concerning the position and the anomeric structure of the glycosidic linkage.[8]



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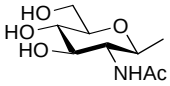
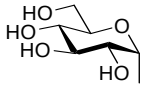
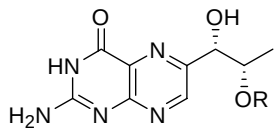
1b R = 

1c R = 



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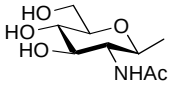
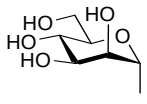
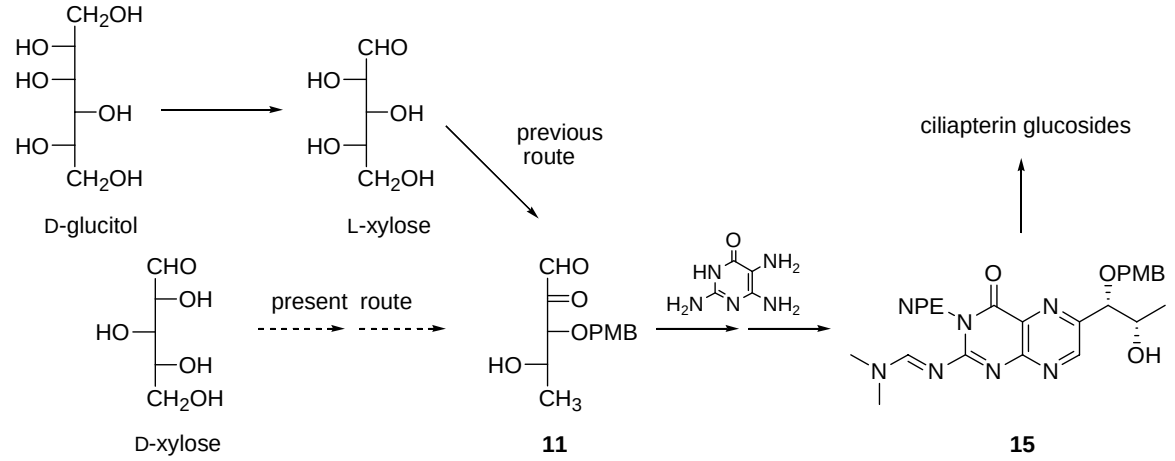
2b R = 

2c R = 

The physiolosical functions of these pterin glycosides appear to have been little investigated[9] in contrast to the well-documented parent pterin: e.g., **1a** exhibits enzyme cofactor activity in hydroxylation of aromatic amino acid[10] and synthesis of nitric oxide[11] as the form of its tetrahydro derivative. Attempts at preparing natural pterin glycosides have also scarcely been made so far, except for our synthetic studies on limipterin (**1b**) from **1a**[12] and tepidopterin (**2b**) from D-glucitol via an appropriately protected ciliapterin derivative (**15**)[13] (Scheme 1). In this scheme, the L-*threo* configuration of the side chain of **15** was derived from those of C-3 and C-4 of L-xylose prepared from D-glucitol in three steps.[14]

In the present study, we have attempted to improve preparation of the key intermediate (**15**) via an alternative route involving inversions of C-3 and C-4 configurations of D-xylose. We also describe the first synthesis of a natural pterin glycoside, 2'-*O*-(α-D-mannopyranosyl)ciliapterin (**2c**).

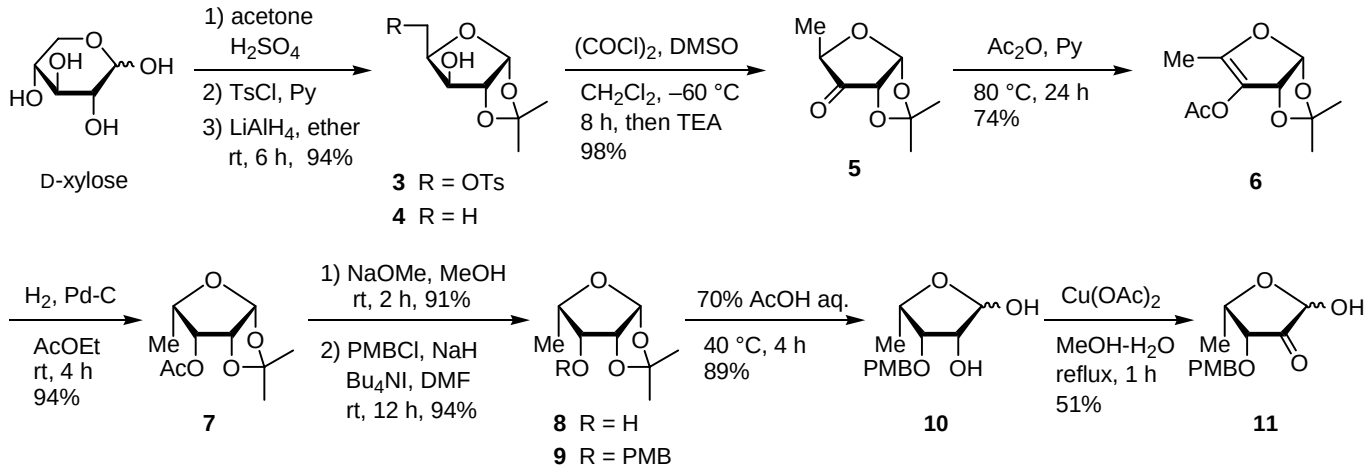


Scheme 1

RESULTS AND DISCUSSION

D-Xylose was converted into 5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose (**4**) via the 5-*O*-tosyl derivative (**3**) according to the reported procedures[15] with a slightly modification (Scheme 2). The transformation of D-*xylo* configuration of **4** into L-*lyxo* form was achieved by way of the 3-enofuranose intermediate.[16] Namely, compound **4** was oxidized with oxalyl chloride-DMSO to give the α-D-*erythro*-pentofuranos-3-ulose derivative (**5**)[17] (in 98% yield), which was treated with acetic anhydride in pyridine at 80 °C to afford the enol acetate (**6**) in 74%. Hydrogenation of **6** in the presence of Pd-C exclusively proceeded from less hindered upper side of the furanose ring, providing the 3-*O*-acetyl-L-lyxofuranose derivative (**7**).

The 3-*O*-acetyl group of **7** was then cleaved with sodium methoxide in methanol to yield 5-deoxy-1,2-*O*-isopropylidene-β-L-lyxofuranose (**8**). Treatment of **8** with *p*-methoxybenzyl chloride and sodium hydride in DMF gave the 3-*O*-PMB derivative (**9**), which afforded 5-deoxy-3-*O*-PMB-L-lyxose (**10**) by hydrolysis in 70% acetic acid. The selective oxidation of 2-hydroxy group of **10** with cupric acetate[18] provided the L-*erythro*-pentos-2-ulose derivative (**11**).



Scheme 2

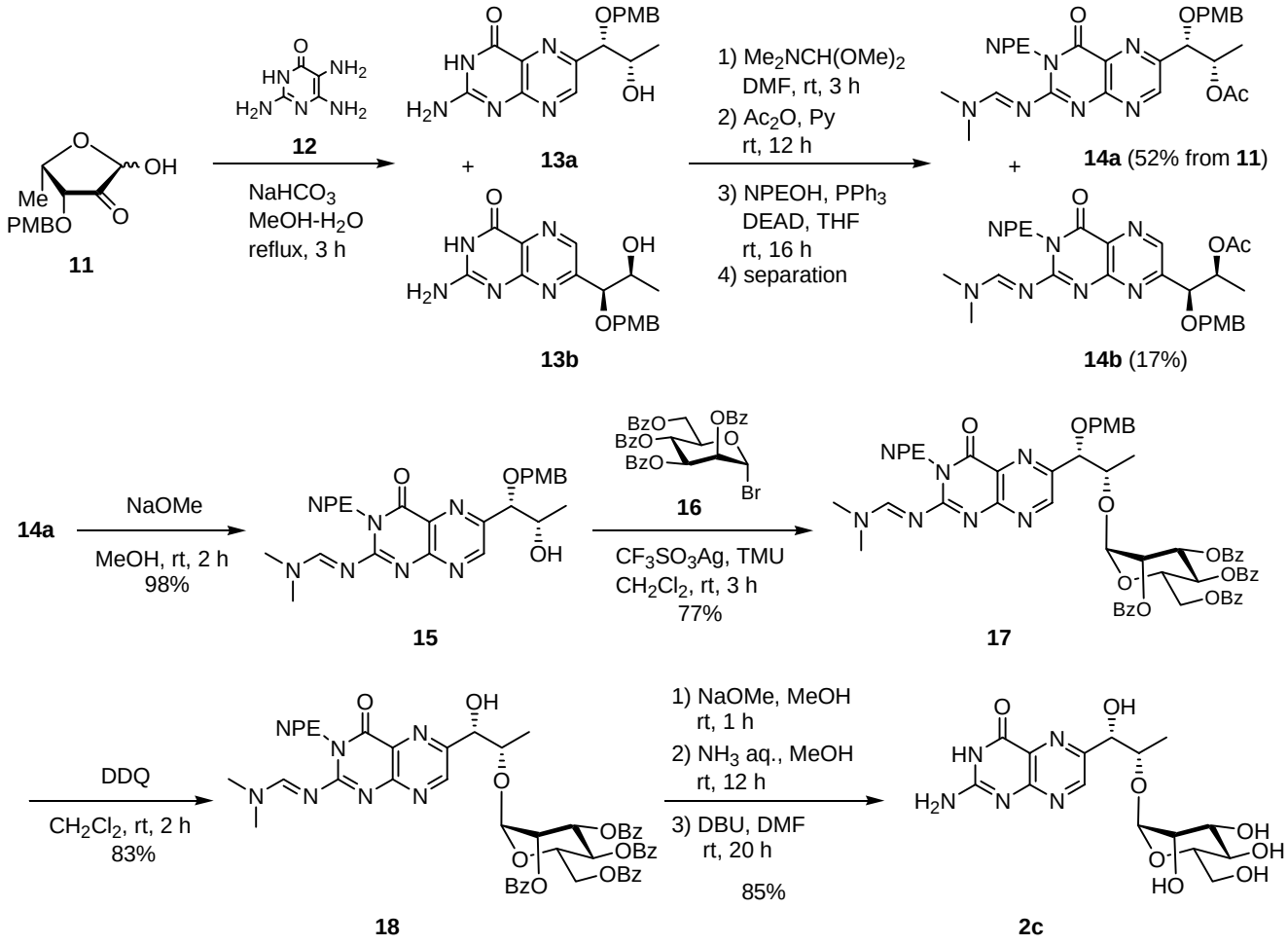
The pteridine ring formation of **11** with 2,5,6-triamino-4-hydroxypyrimidine (**12**) and the subsequent introduction of protecting groups were carried out by employing the reported procedures[13] (Scheme 3). Namely, condensation of **11** and **12** in an aqueous sodium bicarbonate solution afforded an inseparable mixture of the ciliapterin derivative (**13a**) and its C-7 substituted isomer (**13b**) in a ratio of 75:25. These products were separated after the three-step-procedures for introduction of *N*,*N*-dimethylaminomethylene, acetyl, and 2-(4-nitrophenyl)ethyl (NPE) groups, providing 2'-*O*-acetyl-N^2-(*N*,*N*-dimethylamino-methylene)-1'-*O*-PMB-3-NPE-ciliapterin (**14a**) (52% overall yield from **11**) and its C-7 substituted congener (**14b**) (17%). Methanolysis of the isolated **14a** in the presence of sodium methoxide yielded the 1'-*O*-PMB derivative (**15**), a key precursor for the 2'-*O*-glycosylation.

As an appropriate glycosyl donor for preparation of **2c**, 2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl bromide (**16**),[19] available from D-mannose in two steps, was utilized. Thus, glycosylation of **15** was attained by the condensation with **16** in the presence of silver triflate and tetramethylurea (TMU) in dichloromethane at room temperature for 3 h, affording the 2'-*O*-(α-D-mannopyranosyl)ciliapterin derivative (**17**) in 77% yield. The α-anomeric structure of **17** was derived from the results of NOE experiments of the ^{1}H-NMR spectrum in addition to the characteristic tendency of the predominant α-glycoside formation of D-mannose. In an NOESY spectrum of **17**, no cross peaks with respect to H-1/H-3 and H-1/H-5 of the D-mannopyranosyl moiety were detected, whereas a strong NOE was observed between the 1,3-*syn*-diaxial H-3 and H-5 protons, indicating an equatorial orientation of H-1, namely an α-anomeric form, of **17**.

Removal of the protecting groups of **17** was carried out as follows: oxidation of **17** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) afforded 1'-*O*-free **18** (in 83% yield), which was treated with sodium methoxide in methanol to cleave benzoyl groups, and then with aqueous ammonia to cleave the *N*,*N*-dimethylaminomethylene group. The NPE group was finally removed by treatment with DBU,[20] thus providing 2'-*O*-(α-D-mannopyranosyl)ciliapterin (**2c**) in 85% (overall yield from **18**). The precise structure of **2c** was established by ^{1}H-NMR spectrum with the aid of decoupling techniques and 2D COSY measurement (Table 1). It is noteworthy that an extraordinary upfield shift was observed for

the H-5 signal (δ 2.51) of the mannopyranosyl moiety compared with that of α-D-mannopyranose (δ 3.49).[21] This suggests that **2c** in a DMSO solution exists in such a conformation as H-5 of the sugar moiety locating above the pterin ring where an appreciable shielding effect is exerted.

Thus the first synthesis of ciliapterin D-mannnoside (**2c**) was achieved utilizing an improved synthesis of the key precursor (**15**) by way of an alternative route from D-xylose in a 1.5 time better overall yield. Extension of this work including applications of these findings in synthesizing other natural pterin glycosides and their analogs is in progress.



Scheme 3

EXPERIMENTAL

All reactions were monitored by TLC (Merck Silica gel 60 F_{254}) with an appropriate solvent system [(*A*) 1:2, (*B*) 1:1 AcOEt-hexane, (*C*) AcOEt, and (*D*) 5:3:1 2-PrOH-AcOEt-H_2O]. Column chromatography was performed with Daiso Silica Gel IR-60/210w. Components were detected by exposing the plates to UV light and/or 20% H_2SO_4-EtOH, with subsequent heating. Optical rotations were measured with a JASCO P-1020 polarimeter in $CHCl_3$. The NMR spectra were measured in $CDCl_3$ with Varian Unity

Table 1. 600 MHz ^{1}H-NMR Spectral Parameters for ciliapterin derivatives (**15**, **17**, **18**, **2c**).[a]

Com-pound	Chemical shifts / δ (coupling constants / Hz)												
	Pterin moiety				Me_2NCH=N-2		NPE-N(3)						
	H-7	H-1' ($J_{1',2'}$)	H-2' ($J_{2',3'}$)	H_3-3'	Me_2N	CH=N	H(*o*) ($J_{o,m}$)	H(*m*)	CH_2CH_2N ($^2J_{H,H}$)	CH_2CH_2N ($^3J_{H,H}$)	CH_2N ($^2J_{H,H}$)		Other signals
15	8.92	4.57 (5.6)	4.04 (6.4)	1.17	3.24, 3.19	8.88	7.40 (8.7)	8.13	3.16	4.61, 4.59 (7.8)	(12.5)		3.78 (MeO of PMB[b]) 2.78 (HO-2')
17	9.03	4.91 (6.6)	4.35 (6.4)	1.16	3.25, 3.19	8.90	7.34 (8.5)	8.09	3.13	(7.8)	4.56		3.67 (MeO of PMB[c])
18	9.12	5.10 (4.4)	4.53 (6.4)	1.31	3.24, 3.17	8.86	7.35 (8.5)	8.11	3.10, 3.08 (13.1)	(7.8)	4.51		4.08 (HO-1')
2c	8.69	4.66 (3.7)	4.07 (6.3)	1.12	7.15 (H_2N-2)[d]		11.30 [H-N(3)][d]						5.62 (HO-1')[d]

	Gycosyl moiety							
	H-1 ($J_{1,2}$)	H-2 ($J_{2,3}$)	H-3 ($J_{3,4}$)	H-4 ($J_{4,5}$)	H-5 ($J_{5,6a}$)	H^a-6 ($J_{6a,6b}$)	H^b-6 ($J_{5,6b}$)	Other signals
17	5.19 (1.9)	5.63 (3.3)	5.86 (10.1)	6.09 (10.2)	4.53 (2.4)	4.48 (12.5)	4.20 (3.7)	8.09, 8.02, 7.99, 7.80 [Bz(*o*)] 7.41, 7.34, 7.34, 7.23 [Bz(*m*)] 7.56, 7.56, 7.47, 7.40 [Bz(*p*)]
18	5.27 (1.9)	5.65 (3.2)	5.75 (10.2)	6.08 (10.2)	4.23 (2.7)	4.55 (12.4)	4.23 (3.5)	8.06, 8.01, 7.92, 7.80 [Bz(*o*)] 7.37, 7.37, 7.33, 7.24 [Bz(*m*)] 7.57, 7.54, 7.45, 7.40 [Bz(*p*)]
2c	4.65 (1.2)	3.48 (2.9)	3.18 (9.5)	3.30 (9.5)	2.51 (1.6)	3.22 (11.7)	3.18 (3.4)	4.62, 4.44, 4.18, 3.37 (HO-2,3,4,6)[d]

[a] **15, 17, 18** in $CDCl_3$, **2c** in DMSO-d_6. [b] δ 7.21 [H(*o*), $J_{o,m}$ = 8.7 Hz], 6.84 [H(*m*)], 4.47, 4.41 (CH_2, ^2J = 11.2 Hz). [c] δ 7.28 [H(*o*), $J_{o,m}$ = 8.8 Hz], 6.78 [H(*m*)], 4.54, 4.50 (CH_2, ^2J = 11.2 Hz). [d] Confirmed by D_2O exchange.

Inova AS600 (600 MHz for ^{1}H, 151 MHz for ^{13}C) at 23 °C, unless otherwise stated. The solvent peak was used as an internal standard for chemical shifts: in $CDCl_3$, δ 7.26 for ^{1}H, 77.00 for ^{13}C; in DMSO-d_6, δ 2.50 for ^{1}H, 39.70 for ^{13}C. The assignments of ^{13}C signals were made with the aid of 2D C-H COSY measurements.

5-Deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose (4).[15]

The following modification of the literature procedures[15] was made. To a solution of **3** (7.82 g, 22.7 mmol) in dry Et_2O (80 mL) was added lithium aluminum hydride (1.72 g, 45.5 mmol) at 0 °C under argon. The mixture was stirred at rt for 6 h, and then water was added. The precipitates were filtered

off and washed with $CHCl_3$. The filtrate was washed with aqueous NaCl, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography with 1:2 AcOEt-hexane to give **4** (3.72 g, 94%) as colorless needles: mp 67–68 °C (from 1:1 AcOEt-hexane) (lit.,[15a] mp 66–67 °C, 84% yield); R_f = 0.42 (*B*).

5-Deoxy-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranose-3-ulose (5).[17]

To a solution of oxalyl chloride (5.00 mL, 57.3 mmol) in dry CH_2Cl_2 (30 mL) was added a solution of DMSO (6.50 mL, 91.6 mmol) in dry CH_2Cl_2 (10 mL) at –60 °C. After having been stirred for 20 min, a solution of **4** (4.03 g, 23.1 mmol) in dry CH_2Cl_2 (5.0 mL) was slowly added at –60 °C. Stirring was continued at the same temperature for 8 h and then TEA (18.0 mL, 129 mmol) was added. The mixture was stirred at rt for 30 min, diluted with $CHCl_3$, washed with water, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography with 1:2 AcOEt-hexane to give **8** (3.91 g, 98%) [lit., 81%[17a] (by use of RuO_4), 83%[17b] (by use of PCC)] as a colorless syrup: R_f = 0.33 (*B*).

3-*O*-Acetyl-5-deoxy-1,2-*O*-isopropylidene-α-D-*glycero*-pent-3-enofuranose (6).

To a solution of **5** (2.00 g, 11.6 mmol) in dry pyridine (15.0 mL) was added acetic anhydride (6.0 mL, 63 mmol). The mixture was stirred at 80 °C for 24 h and then concentrated in vacuo. The residue was diluted with AcOEt and the precipitate was filtered off. The filtrate was evaporated in vacuo and the residue was purified by column chromatography with 1:4 AcOEt-hexane to give **6** (1.84 g, 74%) as a pale yellow syrup: R_f = 0.68 (*A*); ^{1}H-NMR δ 1.46, 1.50 (3H each, 2s, CMe_2), 1.77 (3H, d, $^5J_{2,5}$ = 1.3 Hz, H-5), 2.21 (3H, s, AcO-3), 5.38 (1H, dq, $J_{1,2}$ = 5.4 Hz, H-2), 5.98 (1H, d, H-1). Anal. Calcd for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 55.88; H, 6.80.

3-*O*-Acetyl-5-deoxy-1,2-*O*-isopropylidene-β-L-lyxofuranose (7).

To a solution of **6** (1.80 g, 8.41 mmol) in AcOEt (25 mL) was added 10% Pd-C (1.50 g, 1.41 mmol). The mixture was stirred at rt for 4 h under atmospheric pressure of hydrogen. The catalyst was filtered off and the filtrate was evaporated in vacuo. The residue was purified by short-path column chromatography with 1:2 AcOEt-hexane to give **7** (1.71 g, 94%) as a colorless syrup: R_f = 0.46 (*A*); $[\alpha]_D^{24}$ +65.4° (*c* 3.33); ^{1}H-NMR δ 1.35 (3H, d, $J_{4,5}$ = 6.6 Hz, H-5), 1.36, 1.57 (3H each, 2s, CMe_2), 2.15 (3H, s, AcO-3), 4.27 (1H, quint, $J_{3,4}$ = 6.1 Hz, H-4), 4.78 (1H, dt, $J_{2,3}$ = 5.6, $J_{1,2}$ = 4.4 Hz, H-2), 4.96 (1H, dd, H-3), 5.72 (1H, d, H-1); ^{13}C-NMR δ 15.71 (CO*C*H3), 20.69 (C-5), 26.70, 26.83 (*Me*$_2$C), 72.53 (C-4), 75.71 (C-3), 79.57 (C-2), 104.50 (C-1), 114.37 (Me$_2$*C*), 170.38 (*C*OCH$_3$). Anal. Calcd for $C_{10}H_{16}O_5$: C, 55.55; H, 7.46. Found: C, 55.41; H, 7.62.

5-Deoxy-1,2-*O*-isopropylidene-β-L-lyxofuranose (8).

Compound **7** (975 mg, 4.51 mmol) was dissolved in dry MeOH (10 mL) and then NaOMe (28% in MeOH, 0.30 mL, 1.5 mmol) was added at 0 °C. The mixture was stirred at rt for 2 h and neutralized with Amberlite IR-120(H^+). The resin was filtered off and the filtrate was evaporated in vacuo. The residue was purified by column chromatography with 1:2 AcOEt-hexane to give **8** (715 mg, 91%) as

colorless needles: mp 86–88 °C (from AcOEt-hexane); R_f = 0.25 (*A*); $[\alpha]_D^{24}$ +9.16° (*c* 2.21); ^{1}H-NMR δ 1.35 (3H, d, $J_{4,5}$ = 6.4 Hz, H-5), 1.38, 1.60 (3H each, 2s, CMe_2), 2.60 (1H, d, $J_{3,OH}$ = 8.1 Hz, HO-3), 4.11 (1H, quint, $J_{3,4}$ = 6.1 Hz, H-4), 4.13 (1H, dt, $J_{2,3}$ = 5.9 Hz, H-3), 4.63 (1H, dd, $J_{1,2}$ = 4.4 Hz, H-2), 5.71 (1H, d, H-1); ^{13}C-NMR δ 15.18 (C-5), 26.69, 26.83 (Me_2C), 70.59 (C-4), 78.36 (C-3), 80.09 (C-2), 104.58 (C-1), 114.09 (Me_2C). Anal. Calcd for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 54.99; H, 8.21.

5-Deoxy-1,2-*O*-isopropylidene-3-*O*-(4-methoxybenzyl)-β-L-lyxofuranose (9).

Compound **8** (292 mg, 1.68 mmol), *p*-methoxybenzyl chloride (0.450 mL, 3.30 mmol), and tetrabutylammonium iodide (180 mg, 0.49 mmol) were dissolved in DMF (10 mL) and, with stirring, sodium hydride (60% in mineral oil, 130 mg, 3.25 mmol) was added at 0 °C under argon. The mixture was stirred at rt for 12 h, diluted with saturated NH_4Cl (5 mL), and evaporated in vacuo. The residue was dissolved in $CHCl_3$, washed with water, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography with 1:3 AcOEt-hexane to give **15** (465 mg, 94%) as a colorless syrup: $[\alpha]_D^{24}$ +36.2° (*c* 2.91); R_f = 0.50 (*A*); ^{1}H-NMR δ 1.33, 1.61 (3H each, 2s, CMe_2), 1.41 (3H, d, $J_{4,5}$ = 6.8 Hz, H-5), 3.81 (3H, s, MeO), 3.92 (1H, dd, $J_{3,4}$ = 7.1, $J_{2,3}$ = 5.1 Hz, H-3), 4.11 (1H, quint, H-4), 4.55, 4.64 (1H each, 2d, ^2J = 11.8 Hz, CH_2O-3), 4.58 (1H, dd, $J_{1,2}$ = 4.2 Hz, H-2), 5.68 (1H, d, H-1), 6.88, 7.29 (2H each, 2d, $J_{o,m}$ = 8.8 Hz, C_6H_4); ^{13}C-NMR δ 16.91 (C-5), 26.01, 26.64 (Me_2C), 55.24 (MeO), 72.04 (CH_2O), 76.97 (C-4), 77.04 (C-3), 78.97 (C-2), 104.42 (C-1), 113.41 (Me_2C), 113.79 [C(*m*) of PMB], 129.51 [C(*o*) of PMB], 129.69 [C(*ipso*) of PMB], 159.38 [C(*p*) of PMB]. Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.18; H, 7.64.

5-Deoxy-3-*O*-(4-methoxybenzyl)-α,β-L-lyxofuranoses (10).

A solution of **9** (200 mg, 0.679 mmol) in 70% AcOH (10 mL) was heated at 40 °C for 4 h. After addition of pyridine (0.20 mL), the mixture was evaporated in vacuo. The residue was purified by column chromatography to give an inseparable anomeric mixture (α:β = 33:67) of **10** (154 mg, 89%) as a colorless syrup: R_f = 0.08 (*A*), 0.15 (*B*); ^{1}H-NMR for α-anomer δ 1.27 (3H, d, $J_{4,5}$ = 6.6 Hz, H_3-5), 2.87 (1H, d, $J_{2,OH}$ = 5.6 Hz, HO-2), 3.07 (1H, d, $J_{1,OH}$ = 2.9 Hz, HO-1), 3.81 (3H, s, MeO), 4.09 (1H, td, $J_{2,3}$ = 5.4, $J_{1,2}$ = 1.5 Hz, H-2), 4.11 (1H, d, $J_{3,4}$ = 4.9 Hz, H-3), 4.38 (1H, qd, H-4), 4.54, 4.56 (1H each, 2d, ^2J = 11.2 Hz, CH_2O-3), 5.28 (1H, dd, H-1), 6.89, 7.27 (2H each, 2d, $J_{o,m}$ = 8.8 Hz, C_6H_4); ^{1}H-NMR for β-anomer δ 1.33 (3H, d, $J_{4,5}$ = 6.6 Hz, H_3-5), 2.89 (1H, d, $J_{2,OH}$ = 9.5 Hz, HO-2), 3.46 (1H, d, $J_{1,OH}$ = 11.2 Hz, HO-1), 3.81 (3H, s, MeO), 3.86 (1H, d, $J_{2,3}$ = 4.6, $J_{3,4}$ = 3.9 Hz, H-3), 4.06 (1H, qd, H-4), 4.10 (1H, dt, $J_{1,2}$ = 4.4 Hz, H-2), 4.62, 4.64 (1H each, 2d, ^2J = 11.2 Hz, CH_2O-3), 5.05 (1H, dd, H-1), 6.89, 7.27 (2H each, 2d, $J_{o,m}$ = 8.8 Hz, C_6H_4). Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.41; H, 7.13. Found: C, 61.20; H, 7.29.

5-Deoxy-3-*O*-(4-methoxybenzyl)-α,β-L-*threro*-pentos-2-uloses (11).[13]

Compound **10** (250 mg, 0.983 mmol) was dissolved in MeOH (6 mL) and water (3 mL). The solution was refluxed and then cupric acetate hydrate (1.00 g, 5.01 mmol) was added. The mixture was refluxed for 1 h and then precipitates were filtered off and washed with AcOEt. The filtrate was concentrated in vacuo and the residue was separated by column chromatography with 1:2 AcOEt-hexane to give **17** (126

mg, 51% yield) as a colorless syrup; R_f = 0.33–0.24 (*B*). From the slower-eluting fraction, compound **10** (51.0 mg, 20%) was recovered.

N^2-(*N*,*N*-Dimethylaminomethylene)-1'-*O*-(4-methoxybenzyl)-3-[2-(4-nitrophenyl)ethyl]ciliapterin (15).[13]

By use of the same procedures described in the literature,[13] compound **11** was converted into **15** in five steps: R_f = 0.06 (*C*); ^{1}H-NMR, see Table 1.

N^2-(*N*,*N*-Dimethylaminomethylene)-1'-*O*-(4-methoxybenzyl)-3-[2-(4-nitrophenyl)ethyl]-2'-*O*-(2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl)ciliapterin (17).

To a solution of **15** (35.0 mg, 0.0623 mmol), 2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl bromide (**16**) (123 mg, 0.187 mmol) and TMU (0.008 mL, 0.066 mmol) in dry CH_2Cl_2 (1.0 mL) was added silver triflate (32.0 mg, 0.125 mmol). The mixture was stirred at rt for 3 h in the dark, diluted with $CHCl_3$, and filtered through Celite. The filtrate was washed with aqueous $NaHCO_3$, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography with 2:1 AcOEt-hexane to give **17** (54.7 mg, 77%) as a pale yellow foam: R_f = 0.48 (*C*); ^{1}H-NMR, see Table 1. Anal. Calcd for $C_{62}H_{57}N_7O_{15}$: C, 65.31; H, 5.04. Found: C, 65.09; H, 5.19.

N^2-(*N*,*N*-Dimethylaminomethylene)-3-[2-(4-nitrophenyl)ethyl]-2'-*O*-(2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl)ciliapterin (18).

To a solution of **17** (74.9 mg, 0.0657 mmol) in CH_2Cl_2 (2.0 mL) containing water (0.10 mL) was added DDQ (89.5 mg, 0.394 mmol). The mixture was stirred at rt for 2 h and then diluted with $CHCl_3$. The mixture was washe with aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated in vacuo. The residue was purified by column chromatography with 1:99 MeOH-$CHCl_3$ to give **18** (55.9 mg, 83%) as pale yellow syrup: R_f = 0.12 (*C*); ^{1}H-NMR, see Table 1. Anal. Calcd for $C_{54}H_{49}N_7O_{14}$: C, 63.59; H, 4.84. Found: C, 63.70; H, 5.01.

2'-*O*-(α-D-Mannnopyranosyl)ciliapterin (2c).

Compound **18** (55.9 mg, 0.0548 mmol) was dissolved in dry MeOH (2.0 mL) and then NaOMe (28% in MeOH, 0.030 mL, 0.15 mmol) was added at 0 °C. The mixture was stirred at rt for 1 h and neutralized with Amberlite IR-120(H^+). The resin was filtered off and the filtrate was evaporated in vacuo. The residue was dissolved in MeOH (4.0 mL) and 28% aqueous ammonia solution (4.0 mL) was added. The mixture was stirred at rt for 12 h and evaporated in vacuo. The residue was dissolved in DMF (1.0 mL) and DBU (0.050 mL, 0.33 mmol) was added. The mixture was stirred at rt for 20 h, diluted with water (4.0 mL), and neutralized with Amberlite FPC3500(H^+). The resin was filtered off and the filtrate was evaporated in vacuo. The residue was washed with $CHCl_3$ and dried under reduced pressure to give **2c** (18.6 mg, 85%) as pale yellow solid: R_f = 0.25 (*D*); ^{1}H-NMR, see Table 1; ^{13}C-NMR (DMSO-d_6) δ 14.90 (C-3'), 60.66 (C-6*), 66.34 (C-4*), 70.93 (C-2*), 70.98 (C-3*), 72.82 (C-2'), 73.73 (C-5*), 75.09 (C-1'), 96.98 (C-1*), 127.45 (C-4a), 148.35 (C-7), 151.40 (C-6), 155.20 (C-8a), 156.51 (C-2), 163.15 (C-4), *for

glycosyl moiety. Anal. Calcd for $C_{15}H_{21}N_5O_8$: C, 45.11; H, 5.30. Found: C, 44.85; H, 5.51.

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