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Hydroxylated C-branched pyrrolidines, C-branched prolines and C-branched piperidines from a 2-*C*-methyl sugar lactone; efficient azide displacement of a tertiary triflate with inversion of configuration

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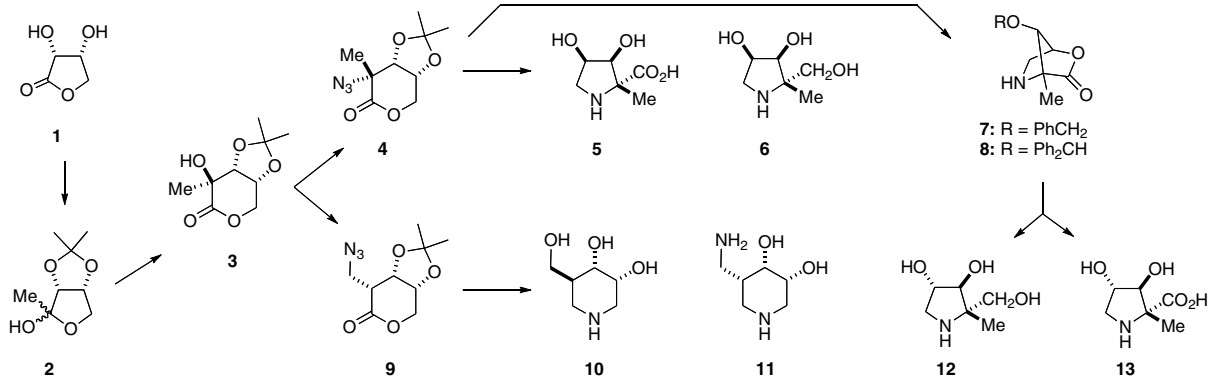
ABSTRACT

The versatility of 3,4-*O*-isopropylidene-2-*C*-methyl-D-arabinonolactone [from D-erythronolactone] as a chiron for complex piperidines and pyrrolidines is illustrated by the synthesis of *(2R,3S,4S)*- and *(2R,3S,4R)*-dihydroxy-2-*C*-methyl prolines, 1,4-dideoxy-1,4-imino-4-*C*-methyl-L-ribitol and 1,4-dideoxy-1,4-imino-4-*C*-methyl-L-arabinitol, and isofagomine derivatives; the enantiomeric series is equally accessible from L-erythronolactone.

Although carbohydrates comprise the most extensive family of chirons,[1] there are only a few examples of the use of *C*-branched sugars as chirons in synthesis.[2] 2-C-Branched carbohydrate lactones are readily available by the Kiliani reaction on ketoses[3] or by an Amadori-calcium oxide sequence.[4] 2-*C*-Methyl-D-ribonolactone has been used in the synthesis of branched 2′-[5] and 4′-[6] C-nucleosides, 4-*C*-methylpentuloses,[7] and of branched imino sugars.[8] The protected 2-*C*-methyl *arabinono*-lactone **3** can be prepared from D-erythronolactone **1** and has been used in syntheses of 2′-*C*-methyl nucleosides[9] and carbon-branched ketoses.[7] This Letter illustrates the potential of carbon-branched lactone **3** as a starting material by short syntheses of hydroxylated pyrrolidines and piperidines containing a *C*-methyl substituent.

The protected 2-*C*-methyl-D-arabinonolactone **3** was prepared in an overall yield of around 60% from D-erythronolactone **1** by acetonation followed by addition of methylmagnesium bromide to afford the lactols **2,** and then a Kiliani reaction with sodium cyanide (Scheme 1).[10] The key transformation of the protected lactone **3** to the azides **4** and/or **9** proceeded efficiently. The tertiary *ribo*-azide **4** may be directly transformed into the *C*-methyl pyrrolidines **5** and **6**. An inversion of configuration at C-4 in **3** allowed conversion to the bicyclic lactones **7** and **8** which can be



Scheme 1. *C*-Methyl branched prolines and imino sugars from 2-*C*-methyl*arabinono*-lactone.

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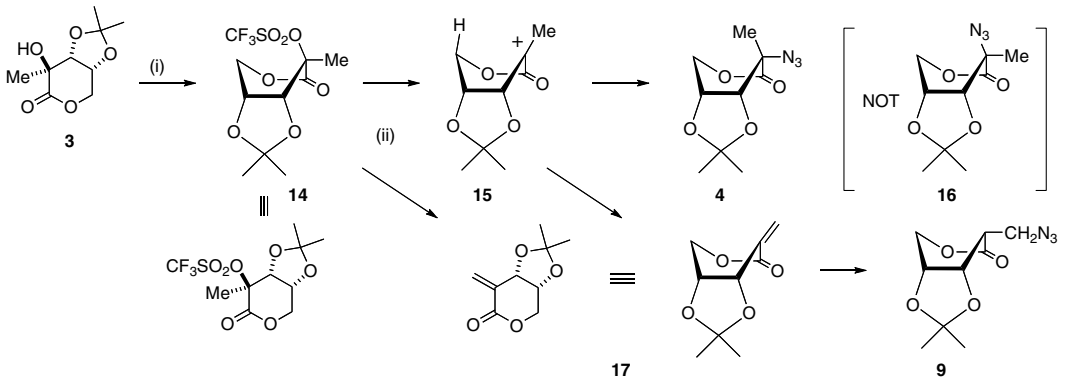


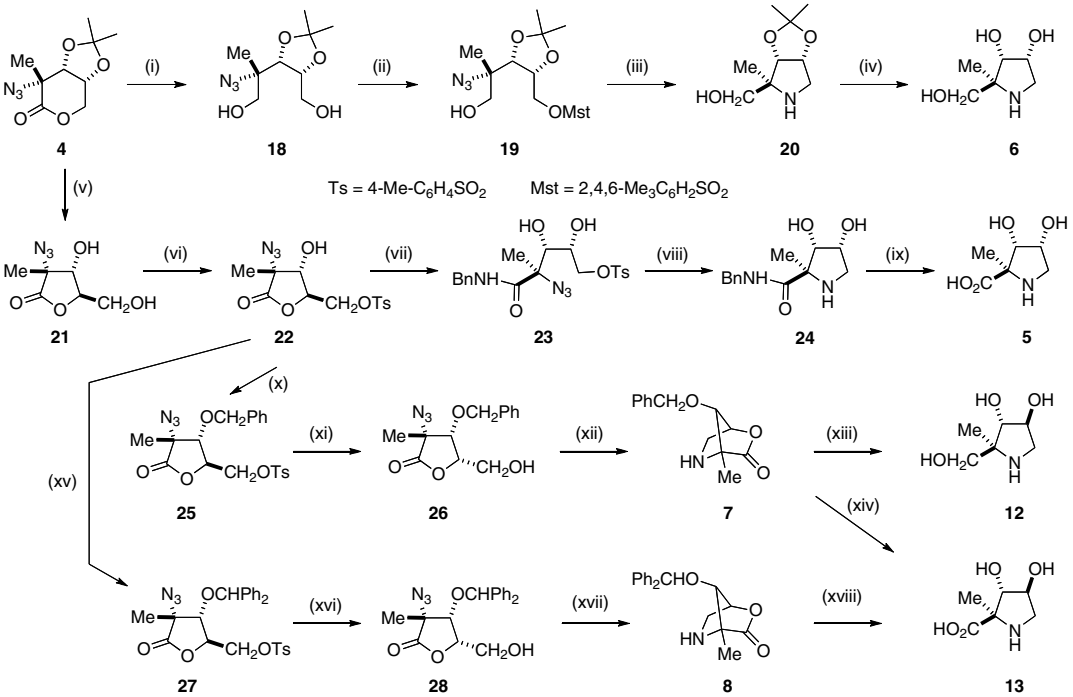
Scheme 2. Preparation of the azides **4** and **9**. Reagents and conditions: (i) $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2; (ii) NaN_3, DMF.

converted to the epimeric pyrrolidines **12** and **13**. The branched azidomethyl lactone **9** provides a short synthesis of the isofagomine analogues **10** and **11**.

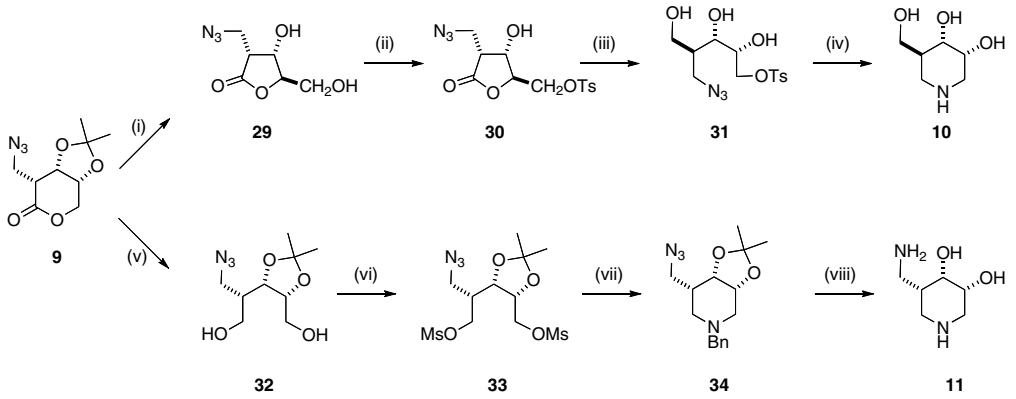
Esterification of the tertiary alcohol **3** with triflic anhydride in dichloromethane in the presence of pyridine gave the triflate **14** (Scheme 2). Reaction of **14** in situ with sodium azide in DMF afforded a separable mixture of the azides **4** [mp 88–90 °C; $[\alpha]_D^{22}$ −129.7 (*c*, 1.05 in $CHCl_3$), 52% yield] and **9** (mp 90–92 °C; $[\alpha]_D^{23}$ −168.2 (*c*, 0.99 in CH_3CN) 28% yield) in a combined yield of 80%.

From X-ray crystallographic analysis, the alcohol **3**[11] and the azides **4**[12] and **9**[13] all exist in a boat conformation in the solid state; the nucleophilic displacement at the tertiary center in **14** presumably proceeded via an S_N1 pathway to give the carbocation **15**. Attack on **15** by the azide from the less hindered side afforded the major product **4**, avoiding an approach of the nucleophile on a pathway past the flagpole hydrogen; none of the *ribo* epimer **16** was isolated. The branched azide **9** plausibly arose by loss of a proton from **15** to the enoate **17** which on Michael addition by azide afforded **9** in which the stereochemistry is determined by protonation to give the less hindered product. The exact ratio of **4**–**9** depended on how long the reaction mixture was allowed to stand in DMF before the addition of azide. If the triflate **14** was left in DMF at room temperature overnight and then azide was added, the azide **9** (with none of **4**) was formed in 47% overall yield from the alcohol **3**; if azide was not added, the intermediate alkene **17**[14] could be isolated in 70% yield from **3**. Addition of sodium azide to a solution of pure **17** in DMF did not give any **9**, so it seems that the triflic acid from decomposition of **14** is necessary for catalysis of the Michael addition.

The use of *ribo*-azide **4** for the synthesis of pyrrolidines containing a carbon branch is shown in Scheme 3. Reduction of the lactone **4** with lithium borohydride in THF gave the open chain diol **18** (oil, $[\alpha]_D^{23}$ +22.7 (*c*, 1.02 in MeOH), 90%). Reaction of **18** with tosyl chloride was unselective; however, reaction of **18** with mesitylsulfonyl chloride in pyridine resulted in selective esterification of the less hindered primary alcohol to form the mesitylate **19** (oil; $[\alpha]_D^{19}$



Scheme 3. Reagents and conditions: (i) $LiBH_4$, THF, 90%; (ii) MstCl, pyridine, 72%; (iii) H_2, Pd, dioxane; (iv) CF_3COOH, H_2O, dioxane, 83% over 2 steps; (v) CF_3COOH, H_2O, dioxane, 89%; (vi) TsCl, pyridine, 68%; (vii) $PhCH_2NH_2$, THF, 82%; (viii) H_2, Pd, dioxane; (ix) concd HCl 83% over two steps; (x) $PhCH_2Br$, NaH, DMF, 65%; (xi) KOH, dioxane; then Dowex, 86%; (xii) $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2; then H_2, Pd/C, dioxane, 72%; (xiii) $NaBH_4$, MeOH; then H_2, Pd/C, H_2O, 89%; (xiv) NaOH, dioxane-H_2O; then H_2, Pd/C, H_2O, 87%; (xv) Ph_2CHN_2, dioxane, heat, 60%; (xvi) KOH, dioxane; then Dowex, 72%; (xvii) $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2; then H_2, Pd/C, dioxane, 42%; (xviii) NaOH, dioxane-H_2O; then H_2, Pd/C, H_2O, 90%.



Scheme 4. Reagents and conditions: (i) Dowex 50 H^+, dioxane, H_2O, 85%; (ii) TsCl, DABCO, MeCN, 65%; (iii) $LiBH_4$, THF, 55%; (iv) H_2, Pd/C, dioxane, 85%; (v) DIBALH, CH_2Cl_2; then $LiBH_4$, THF, 75%; (vi) MsCl, pyridine, 81%; (vii) $PhCH_2NH_2$, heat, 72%; (viii) CF_3CO_2H, dioxane; then H_2, Pd/C, dioxane, 72%.

+17.8 (*c*, 0.90 in $CHCl_3$), 72%). Hydrogenation of the protected azide **19** in the presence of palladium on carbon in dioxane gave the corresponding amine which spontaneously cyclized to form the protected imino sugar **20**, which with trifluoroacetic acid in aqueous dioxane (4:1:1) afforded 1,4-dideoxy-4-*C*-methyl-1,4-imino-L-ribitol **6**[15] (83% over two steps; 54% from **4**).

An alternative strategy was investigated where the isopropylidene protecting group was removed at an early stage. Hydrolysis of the protected δ-azido **4** with trifluoroacetic acid in aqueous dioxane (4:1:1) gave the γ-lactone **21**[16] (mp 74–76 °C; $[\alpha]_D^{23}$ −105.5 (*c*, 1.00 in MeOH), 89% yield), the primary alcohol of which was selectively esterified by reaction with tosyl chloride in pyridine to afford the tosylate **22** (mp 108–109 °C; $[\alpha]_D^{22}$ +104.2 (*c*, 0.98 in MeCN, 68%). Treatment of **22** with benzylamine in THF gave the open chain azidoamide **23** (oil; $[\alpha]_D^{21}$ −6.2 (*c*, 1.00 in $CHCl_3$), 82%). Hydrogenation of the azide **23** in the presence of palladium on carbon in dioxane gave the corresponding amine which spontaneously cyclized to form the pyrrolidine amide **24**. The amide **24** was hydrolyzed by concentrated aqueous hydrochloric acid to give *(2R,3S,4R)*-dihydroxy-2-*C*-methyl proline **5**[17] (83% over two steps; 41% from **4**). Only one isopropylidene group is used throughout this sequence.

The epimeric iminosugar **12** and proline **13** required an additional inversion of configuration at C4 of the D-*arabinono*-lactone **21**. The remaining free alcohol in the tosylate **22** was protected by treatment with benzyl bromide and sodium hydride in DMF to give **25**; subsequent treatment with potassium hydroxide in dioxane afforded the L-lyxonate **26** (mp 104–106 °C; $[\alpha]_D^{22}$ +40.6 (*c*, 1.00 in $CHCl_3$)) in 54% yield over the two steps. Esterification of **26** with triflic anhydride in the presence of pyridine followed by catalytic hydrogenation gave the bicyclic lactone **7** [oil; $[\alpha]_D^{21}$ −71.0 (*c*, 1.00 in MeCN)] in 72% yield. Reduction of lactone **7** with sodium borohydride and removal of the benzyl protecting group by hydrogenolysis gave 1,4-dideoxy-4-*C*-methyl-1,4-imino-L-arabinitol **12**[18] in 89% yield.

Treatment of the bicyclic lactone **7** with sodium hydroxide in aqueous dioxane followed by hydrogenation yielded *(2R,3S,4S)*-dihydroxy-2-*C*-methyl proline **13**,[19] epimeric with **5**, in 87% yield. Benzhydryl may be used as an alternative protecting group:[20] treatment of the tosylate **22** with diphenyldiazomethane in dioxane afforded the benzhydryl ether **27** (60%) which with potassium hydroxide in aqueous dioxane gave the epimeric alcohol **28** (mp 121–123 °C; $[\alpha]_D^{21}$ +46.3 (*c*, 0.80 in $CHCl_3$)) in 72% yield. Triflation of **28**, followed by catalytic hydrogenation, gave the benzhydryl protected lactone **8** (mp 116–118 °C; $[\alpha]_D^{21}$ −26.0 (*c*, 1.00 in MeCN)) in 42% yield; the structure of **8** was firmly established by X-ray crystallographic analysis.[21] Reaction of **8** with sodium hydroxide in aqueous dioxane followed by removal of the protecting group by hydrogenation gave the proline **13** (90% yield), identical in all respects to the sample prepared from the benzyl protected lactone **7**.

Isofagomines, with a carbon branch in a piperidine ring, are a class of imino sugar glycosidase inhibitors.[22] The 2-*C*-azidomethyl lactone **9** can be used to synthesize isofagomine analogues containing either epimeric carbon branch (Scheme 4). Hydrolysis of the azidomethyl lactone **9** with Dowex 50 H^+ in aqueous dioxane gave the unprotected lactone **29** (mp 98–100 °C; $[\alpha]_D^{18}$ −1.6 (*c*, 0.80 in MeCN)) in 85% yield. Selective esterification of primary alcohol **29** by reaction with tosyl chloride in acetonitrile in the presence of DABCO afforded the primary tosylate **30** (colorless oil; $[\alpha]_D^{18}$ +24 (*c*, 1.00 in MeCN), 65%). Reduction of the lactone **30** with lithium borohydride in THF gave the triol **31** (oil; $[\alpha]_D^{22}$ +4.1 (*c*, 0.85 in MeCN), 55%); hydrogenation of the azido-tosylate **31** yielded *(3R,4S,5S)* 5-hydroxymethyl-3,4-dihydroxypiperidine (4,5-diepi-isofagomine) **10**[23] (85% yield; 26% overall yield from **9**). The aminomethyl substituent in **11** is epimeric with the hydroxymethyl group in **10**. Reduction of the lactone **9** by initial reaction with DIBALH in dichloromethane followed by treatment with lithium borohydride in THF afforded the diol **32** (75%). Esterification of both primary hydroxyl groups in **32** with mesyl chloride gave dimesylate **35** (81%) which on heating in benzylamine at 100 °C formed the protected azido-piperidine **34** (oil, $[\alpha]_D^{22}$ −18.4 (*c*, 0.95 in $CHCl_3$)) in 72% yield. Removal of the acetonide in **34** by trifluoroacetic acid in dioxane, followed by hydrogenation, gave (3*R*,4*S*,5*R*) 5-aminomethyl-3,4-dihydroxypiperidine **11**[24] in 72% yield.

The enantiomers of all the target compounds may be made from L-erythronolactone. Both D-erythronolactone and L-erythronolactone are available from the Humphlett oxygenation of an alkaline solution of D- or L-arabinose, respectively;[25] D-erythronolactone acetonide can also be prepared by hydrogen peroxide oxidation of erythrobic acid, followed by acetonation.[26] In summary, the value of an easily available 2-*C*-methyl lactone **3** (or its enantiomer) as a divergent intermediate for access to highly functionalized pyrrolidines and piperidines containing a carbon branch is demonstrated; for the majority of the syntheses, only a single isopropylidene group is used.

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14. *Selected data for enoate* **17**: Mp 96–98 °C; $[\alpha]_D^{21}$ −212 (*c*, 0.70 in $CHCl_3$); ν_{max} (KBr disc) 1734 (C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.36, 1.48 (6H, 2 × s, 2 × CH_3), 4.05 (1H, dd, $J_{5,5'}$ 12.8 Hz, $J_{5,4}$ 2.2 Hz, H-5), 4.38 (1H, dd, $J_{5',5}$ 12.8 Hz, $J_{5',4}$ 1.9 Hz, H-5′), 4.57 (1H, d t, *J* 2.0 Hz, $J_{4,3}$ 7.5 Hz, H-4), 4.97 (1H, d, $J_{3,4}$ 7.5 Hz, H-3), 5.85, 6.28 (2H, 2 × s, H-2′a, H-2′b); δ_C (100.6 MHz, $CHCl_3$) 24.5, 26.3 (2 × CH_3), 67.7 (C-5), 72.6 (C-4), 74.9 (C-3), 110.6 (CMe_2), 130.1 (C-2′), 135.1 (C-2), 166.7 (C-1).
15. *Selected data for 4-C-methyl imino-L-ribitol* **6**: Oil, $[\alpha]_D^{21}$ −12.5 (*c*, 1.00 in H_2O); δ_H (400 MHz, D_2O) 1.29 (3H, s, CH_3), 3.21 (1H, dd, $J_{1,2}$ 3.0 Hz, $J_{1,1'}$ 12.7 Hz, H-1), 3.35 (1H, dd, $J_{1',2}$ 4.8 Hz, $J_{1',1}$ 12.7 Hz, H-1′), 3.56 (2H, s, H-5, H-5′), 4.40 (1H, d, $J_{3,2}$ 4.7 Hz, H-3), 4.37–4.40 (1H, m, H-2); δ_C (100.6 MHz, D_2O) 16.2 (CH_3), 48.7 (C-1), 64.2 (C-5), 68.5 (C-4), 70.3 (C-2), 72.7 (C-3).
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17. *Selected data for (2R,3S,4R)-dihydroxy-2-C-methyl proline* **5**: Glass, $[\alpha]_D^{18}$ +11.2 (*c*, 0.50 in H_2O); δ_H (400 MHz, D_2O) 1.40 (3H, s, CH_3), 3.03 (1H, dd, $J_{5,5'}$ 12.0 Hz, $J_{5,4}$ 7.1 Hz, H-5), 3.41 (1H, dd, $J_{5',5}$ 12.0 Hz, $J_{5',4}$ 7.1 Hz, H-5′), 4.14 (1H, d, $J_{3,4}$ 4.1 Hz, H-3), 4.20–4.25 (1H, m, H-4); δ_C (100.6 MHz, D_2O) 17.2 (CH_3), 47.4 (C-5), 70.0 (C-4), 72.7 (C-2), 74.6 (C-3), 175.8 (C=O).
18. *Selected data for 4-C-methyl imino-L-arabinitol* **12**: Oil, $[\alpha]_D^{21}$ + 4.1 (*c*, 1.00 in H_2O); δ_H (400 MHz, D_2O) 1.20 (3H, s, CH_3), 3.07 (1H, dd, $J_{1,1'}$ 12.7 Hz, $J_{1,2}$ 5.0 Hz, H-1), 3.51–3.57 (2H, m, H-1′, H-5), 3.67 (1H, part of an AB system, J_{AB} 12.3 Hz, H-5′), 3.88 (1H, d, $J_{3,2}$ 5.1 Hz, H-3), 4.25–4.29 (1H, m, H-2); δ_C (100.6 MHz, D_2O) 15.2 (CH_3), 47.8 (C-1), 63.8 (C-5), 69.5 (C-4), 74.2 (C-2), 77.3 (C-3).
19. *Selected data for (2R,3S,4S)-dihydroxy-2-C-methyl proline* **13**: Mp 200 °C (dec); $[\alpha]_D^{25}$ + 6.6 (*c*, 1.00 in H_2O); δ_H (400 MHz, D_2O) 1.50 (3H, s, CH_3), 3.33 (1H, d, $J_{5,5'}$ 12.8 Hz, H-5), 3.54 (1H, dd, $J_{5',5}$ 12.8 Hz, $J_{5',4}$ 4.5 Hz, H-5′), 4.28–4.29 (1H, m, H-4), 4.38 (1H, br s, H-3); δ_C (100.6 MHz, D_2O) 17.5 (CH_3), 50.8 (C-5), 73.8 (C-2), 75.2 (C-4), 79.4 (C-3), 176.4 (C-1).
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23. *Selected data for (3R,4S,5S) 5-hydroxymethyl-3,4-dihydroxypiperidine* **10**: Oil, $[\alpha]_D^{22}$ −64.5 (*c*, 1.0 in H_2O); δ_H (400 MHz, D_2O) 2.11 (1H, m, H-5), 2.81 (1H, at, *J* 12.7 Hz, H-6), 3.06 (1H, br d, *J* 12.7 Hz, H-2), 3.30–3.38 (2H, m, H-6′, H-2′), 3.58–3.70 (3H, m, H-4, H-5′a, H-5′b), 4.07 (1H, br s, H-3); δ_C (100.6 MHz, D_2O) 36.9 (C-5), 45.1 (C-6), 48.5 (C-2), 59.9 (C-5′), 65.7 (C-3), 68.0 (C-4).
24. *Selected data for (3R,4S,5R) 5-aminomethyl-3,4-dihydroxypiperidine* **11**: Oil, $[\alpha]_D^{22}$ -4.5 (*c*, 1.1 in H_2O); δ_H (400 MHz, D_2O) 1.97–2.05 (1H, m, H-5), 2.65 (1H, t, *J* 12.3 Hz, H-6′), 2.74 (1H, t, *J* 11.6 Hz, H-2′), 2.85–2.95 (3H, m, H-2, H-6, H-5′a), 3.00 (1H, dd, $J_{5'b,5'a}$ 13.3 Hz, $J_{5'b,5}$ 6.7 Hz, H-5′b), 3.68 (1H, ddd, *J* 11.0 Hz, *J* 4.7 Hz, *J* 2.7 Hz, H-3), 3.95 (1H, br s, H-4); δ_C (100.6 MHz, D_2O) 37.1 (C-5), 39.4 (C-5′), 40.7 (C-6), 43.3 (C-2), 67.3, 67.6 (C-3, C-4).
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