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SYNTHESIS OF 2'(S), 3'(R),5'-TRIHYDROXYPENTYLADENINE[1]

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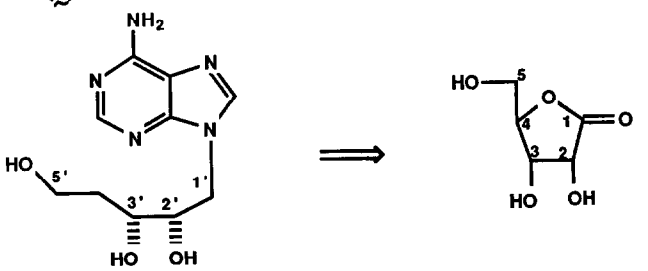
ABSTRACT: A synthesis of 2'(S), 3'(R),5'-trihydroxypentyladenine (1) from D-ribonic acid γ-lactone (2) is described.

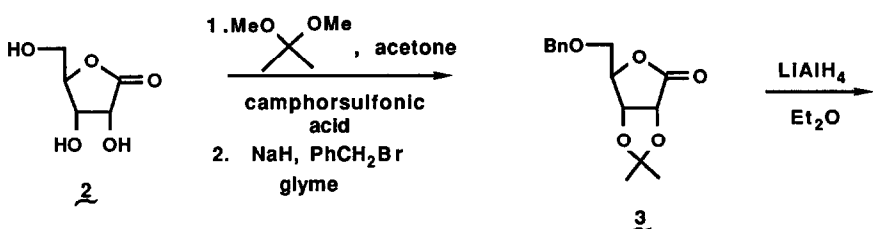
In a project directed towards the synthesis of enzyme inhibitors, we needed 2'(S), 3'(R),5'-trihydroxypentyladenine (1). Surprisingly, literature showed that only 2'(R), 3'(S),5'-trihydroxypentyladenine with the configurations at C-2' and C-3' opposite to those in D-ribose was known.[3] In view of the recent interest in synthesis of open-chain nucleoside and nucleotide analogs as biologically active agents,[4] we wish to report the synthesis of 1 having the same configurations at C-2' and C-3' as those of D-ribose from commercially available D-ribonic acid γ-lactone (2).

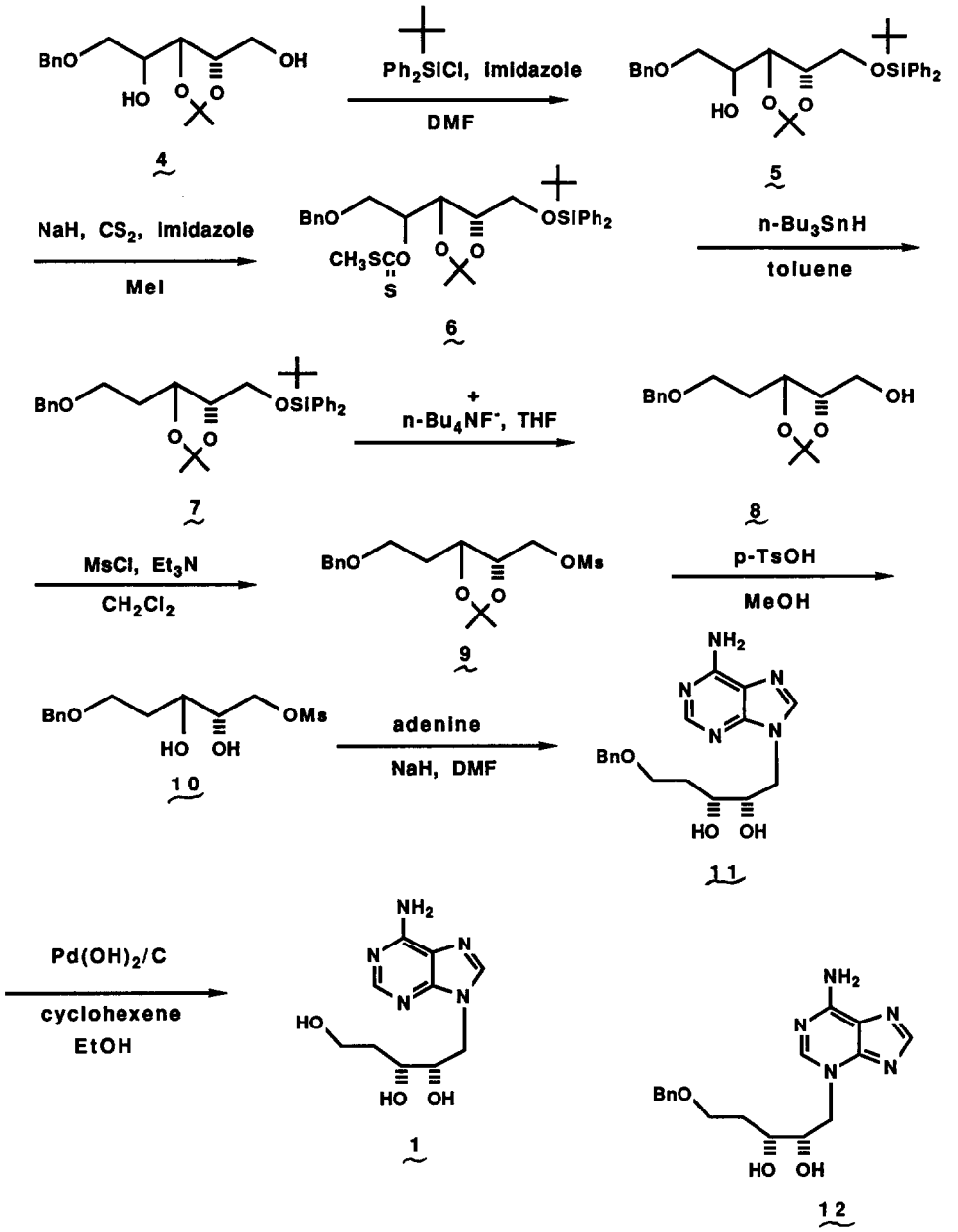


1 2

The strategy shown in Scheme 1 was to remove the oxygen functionality at C-4 in 2, and to convert C-1 of 2 after ring-opening into a mesylate (CH_2OM_s) so that adenine could be attached.

Scheme 1





D-Ribonic acid γ-lactone was converted into its acetonide[5] and the primary hydroxy group was protected as benzyl ether to give compound 3. The crude lactone 3 was reduced with lithium aluminum hydride in ether at 0°C to afford 4 as a white solid in ca 30% overall yield

from 2 after HPLC purification [mp 33°C; ^{1}H-NMR ($CDCl_3$) δ: 7.32 (s,5H), 4.57 (s,2H), 4.50-3.50 (m,7H), 3.20 (bs,2H,-OH), 1.33 (2s,6H)]. The primary hydroxy group in 4 was protected with tert-butyldiphenylsilyl chloride to yield silyl ether 5 in 98% yield [^{1}H-NMR ($CDCl_3$) δ: 7.75-7.33 (m,15H), 4.64 (s,2H), 4.50-3.50 (m,7H), 1.33 (s,6H), 1.11 (s,9H)].

In order to remove the C-4 hydroxy group, we used Barton's procedure.[6] Thus, treatment of 5 with sodium hydride and carbon disulfide in the presence of imidazole followed by methyl iodide gave dithiocarbonate 6 in 87% yield after HPLC purification [^{1}H-NMR ($CDCl_3$) δ: 7.75-7.15 (m,15H), 5.80 (m,1H), 4.60-3.50 (m,6H), 4.50 (s,2H), 2.43 (s,3H), 1.43 (s,3H), 1.37 (s,3H), 1.07 (s,9H)]. Compound 6 was then treated with tributyltin hydride in refluxing toluene to afford the C-4 deoxygenated product 7 which was contaminated with tin side-product even after purification by flash column chromatography. This side product, however, could be easily removed by extraction in next step. The silyl ether protecting group in 7 was removed by tetrabutylammonium fluoride in THF. The crude product was dissolved in acetonitrile and washed with hexane to get rid of the tin side-product from the previous reaction. Then purification by flash column chromatography gave pure product 8 as an oil in 46% yield from 6[^{1}H-NMR ($CDCl_3$) δ: 7.33 (s,5H), 4.52 (s,2H), 4.30-4.00 (m,2H), 3.60 (t,4H), 2.18 (t,1H,-OH), 1.86 (dt,2H), 1.43 (s,3H), 1.33 (s,3H)].

At this stage we were ready to attach the adenine molecule. Thus, the hydroxy group in 8 was converted into mesylate 9. Displacement of the mesylate in 9 with adenine anion gave only a low yield of the desired product. Therefore, the acetonide was removed with p-toluenesulfonic acid in methanol to afford the mesylate 10 which was directly reacted with adenine in DMF at 90°C in the presence of sodium hydride. Purification by flash column chromatography gave the desired N_9-alkylation product 11 as a solid in 70% yield from 8 [mp 117-123°C; ^{1}H-NMR (d_6-DMSO) δ: 8.13 (s,1H), 8.01 (s,1H), 7.30 (m,5H), 7.22 (s,2H), 5.15 (d,J=6.6H_z,1H), 5.02 (d, J=6.6 H_z, 1H), 4.43 (s,2H), 4.40 (bs, 1H), 4.03 (dd,1H), 3.57 (t,3H), 3.43 (m,1H), 2.00 (m,1H), 1.55 (m,1H); MS: m/$_z$ 344 (M^+ + 1); $[\alpha]_D$ = -9.8° (c=1, MeOH)]. A side-product was isolated in ca. 16% yield and it was assigned as N_3-alkylation product 12. Structural assignments were based on the C-2, C-8 purine proton signal differences ($\Delta\delta_{2,8}$), which were 0.12 ppm for 11 and 0.4 ppm for 12. In addition, the chemical shifts of N-CH_2 in 11 were at higher field compared with those of 12. These observations were consistent with the results reported in the literature.[7] Finally, removal of the benzyl group by $Pd(OH)_2/C$ in refluxing ethanol in the presence of cyclohexene gave 1 as a white solid in 45% yield from 11 [mp >200°C (dec); ^{1}H-NMR (d_6-DMSO) δ: 8.11 (s,1H), 8.03 (s,1H), 7.20 (s,2H), 5.17 (d, J=6.6 H_z,1H), 4.95 (d,J=6.6H_z,1H), 4.39 (m,2H), 4.00 (dd,1H), 3.53 (m,3H), 3.37 (m,1H), 1.78 (m,1H), 1.43 (m,1H); HRMS: m/$_z$ 253.1179 (M^+), calcd for $C_{10}H_{15}N_5O_3$, 253.1175; $[\alpha]_D$=-3° (c=0.1,DMF)].

In conclusion, we have synthesized 2'(S), 3'(R), 5'-trihydroxypentyladenine (1) with the same configurations at C-2' and C-3' as those of D-ribose from D-ribonic acid γ-lactone (2) in eleven steps in 4% overall yield.

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