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THE FIRST STEREOSPECIFIC SYNTHESIS OF (+)-(1R,2S,4R)-4-AMINO-2-HYDROXY-1-CYCLOPENTANEMETHANOL AND (+)-CARBOCYCLIC THYMIDINE.

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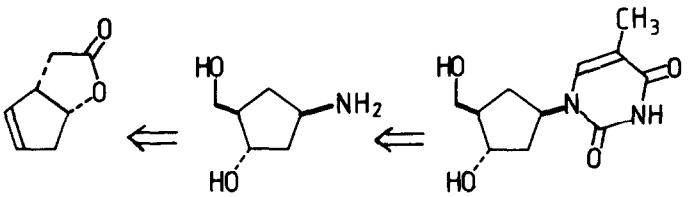
Abstract: The first stereospecific synthesis of the title compounds is described.

During the past two decades much attention has been given to synthetic[1] and biological[2] studies of the carbocyclic analogues of nucleosides. (-)-Aristeromycin and (-)-neplanocin A are natural representatives of these compounds. Yet, only a few enantiomerically pure synthetic carbocyclic nucleoside analogues have been obtained through chemoenzymatic approaches[3], multistep synthesis[4], and by chromatographic[5] or enzymatic[6] resolution of racemic intermediates, nucleosides or nucleotides. The key synthetic precursor, 13 of the carbocyclic analogues of 2'-deoxyribonucleosides has also not yet been prepared in a non-racemic form. A recent paper[7] on the asymmetric synthesis of a close analogue of 13 prompted us to disclose a part of our synthetic efforts in progress in this field. We report herewith on the first stereospecific synthesis of the (+)-(1R,2S,4R)-4-amino-2-hydroxy-1-cyclopentanemethanol, 13 and the (+)-carbocyclic thymidine, 14.

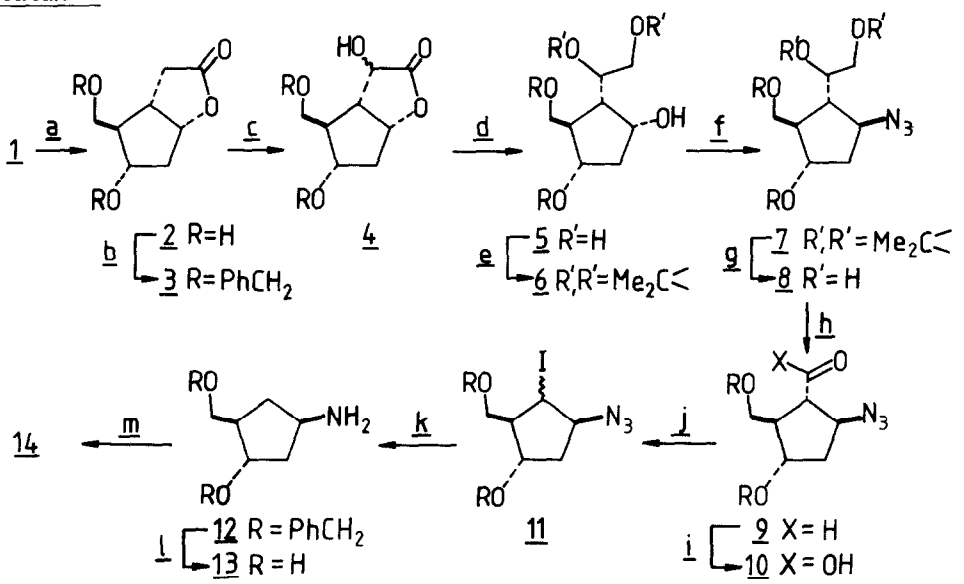


1 13 14

Unsaturated bicyclic lactone 1 has been selected as a commercially available enantiomerically pure starting material known from the prostaglandin chemistry[8].

Apparently three sets of chemistry had to be elaborated in order to obtain 13 from 1 : first, introduction of a hydroxy and a hydroxymethyl group to the C=C double bond with high regio- and stereoselectivity; then conversion of a secondary OH group into an amino group with inversion of configuration, and last but not least, elimination of the acetic acid moiety from the molecule.

Scheme 1

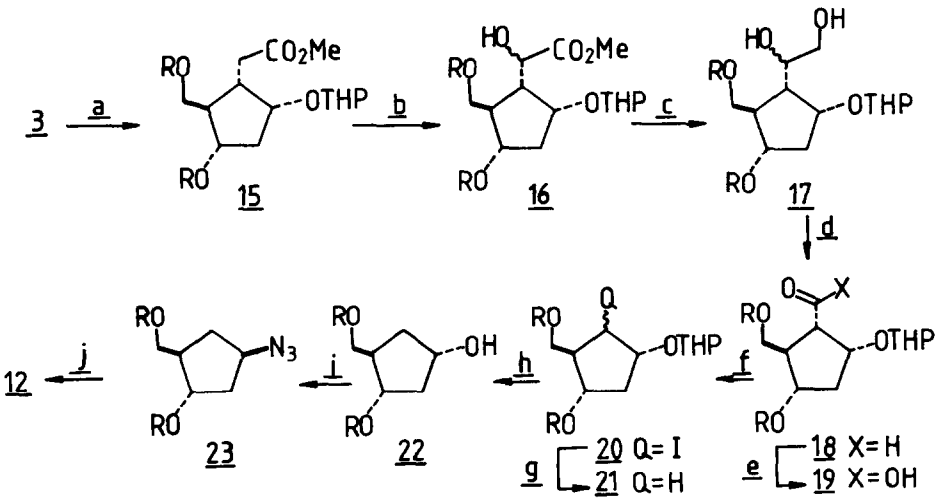


a:i,$(CH_2O)_n$,H_2SO_4,AcOH,60°C,1 day,ii,Amberlite IR-120(H^+),70°C, 15 h ,55% (overall); b:$PhCH_2Br$,NaH,DMF,60%; c:LDA,MoOPH,THF,-78°C(1 h),rt(8 h),58%; d:i,chrom.(SiO_2 column,CH_2Cl_2:acetone14:1 then hexane:EtOAc 1:1),ii,$LiAlH_4$, Et_2O,reflux,91%; e:2,2-dimethoxypropane,p-TsOH,PhH,rt,80%; f:$(PhO)_2P(O)N_3$, DEAD,TPP,THF,rt,10 min,86%; g:80% aq AcOH,rt,7 h ,89%; h:$NaIO_4$,H_2O-dioxane (1:2),rt,10 min,92%; i:H_2CrO_4-acetone,0°C,10 min,93%; j:IBDA,I_2,hν,CCl_4,reflux,15 min,54%; k:n-Bu_3SnH,PhH,reflux,1.5 h,19%; l:80% aq $NH_2NH_2.H_2O$,10% Pd-C,MeOH,reflux,45 min,80%; m:i,MeOCH=C(Me)C(O)NCO,DMF, Et_2O,PhH,-15°C,3 h,60%, ii,25% aq NH_4OH,reflux,2 h,95%

Acid catalysed addition of formaldehyde[9] (Prins reaction) to 1 afforded, after deacetylation, dihydroxy lactone 2 which was protected as dibenzyl ether 3 (Scheme 1). Hydroxylation of 3 with MoOPH[10] yielded diastereomeric α-hydroxy lactones 4 (exo:endo=5:1,by weight). $LiAlH_4$ reduction of the chromatographically separated exo isomer led to the formation of triol 5. Dioxolanation of the vicinal glycol moiety (6) allowed smooth conversion of the unblocked secondary OH group into an azido one [7, $(PhO)_2P(O)N_3$,Ph_3P,$(NCO_2Et)_2$] with complete inversion of configuration[11] securely verified by NMR spectroscopy. After removal of the isopropylidene group from 7 (aq. AcOH), the vicinal diol 8 was cleaved ($NaIO_4$) to aldehyde 9 which was then oxidized (Jones) to carboxylic acid 10. Decarboxylation of 10 into diastereomeric iodo azides 11 [isomer ratio=3:1(TLC)] was accomplished by iodobenzene diacetate (IBDA), I_2

reagents[12]. Azido iodide 11 was then reduced to the cyclopentylamine derivative 12 with n-Bu_3SnH. Debenzylation of 12 to aminocyclopentane diol derivative 13 [α_D^{26} +34°(c 1.0,DMF)] was performed with catalytic transfer hydrogenation (aq. $NH_2NH_2.H_2O$,Pd-C)[13]. Synthesis of the heterocycle (thymine) in 14 was completed according to published procedures[14].

Scheme 2



a: i, aq NaOH, MeOH, rt, 40 min, ii, aq $NaHSO_4$, iii, CH_2N_2-Et_2O, iv, DHP, p-TsOH,CH_2Cl_2,rt,40 min,75% (overall); b:LDA,MoOPH,THF,-78°C(1 h),rt(overnight)73%; c:$LiAlH_4$,Et_2O,rt,3 h,69%; d: $NaIO_4$,H_2O-acetone (1:2),rt, 15 min, 83 %; e: PDC,DMF,rt,19 h, 76%; f: IBDA,I_2,hν,CCl_4,reflux,15 min,67%; g: n-Bu_3SnH,Et_2O,reflux,10 h, 99%; h:MeOH,p-TsOH,rt,40 min,74%;i:$(PhO)_2P(O)N_3$, DEAD,TPP,THF,rt,10 min,71%; j: n-Bu_3SnH,PhH,reflux,1.5 h,43%

In an alternative strategy (Scheme 2) we introduced the azido group when degradation of the acetic acid side chain had been completed. The dibenzyl lactone diol 3 was converted to protected trihydroxy ester 15 followed by hydroxylation [16,(MoOPH,isomer ratio=1.8:1(GC)] and subsequent $LiAlH_4$ reduction to diol derivative 17. Cleavage ($NaIO_4$) followed by oxidation (Jones) of 18 led to carboxylic acid 19. Diastereomeric iodo compounds 20 [isomer ratio=2:1(TLC)] formed by decarboxylation (IBDA,I_2,hν) were converted to fully protected triol 21 (n-Bu_3SnH). Cyclopentanol derivative 22 obtained on deblocking (MeOH/p-TsOH) of 21 was transformed into cyclopentylazide derivative 23 [$(PhO)_2P(O)N_3$ and Mitsunobu's reagent] which in turn furnished intermediate 12 with n-Bu_3SnH.

(+)-Carba-thymidine 14 [α_D^{25}+9° (c 1.0,MeOH)] was characterized by CD and ^1H, ^{13}C NMR spectroscopy, MS spectrometry and elemental analysis[15]. All these data are consistent with and corroborate the expected structure 14.

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15. CD(H_2O, 3.44 mmol/L, .05 cm):λ(Δε)282.4(-.526), 276.8(-.660), 270.4 (-.628), 268.4(-.614), 263.8(-.419) nm.
^{1}H NMR (100.1 MHz, Me_2SO-d_6/$CDCl_3$): δ 10.3 (broad s,1H, H-3), 7.24 (q, J=1.5 Hz, 1H, H-6), 5.06 (m, ΣJ=35 Hz, 1H, H-1'), 4.22 (q,ΣJ=16.5 Hz, 1H, H-3'), 3.63 (m, 2H, H-5'), 1.86 (d, J=1.5 Hz, 3H, H-7), 1.40--2.35 (m, 5H, H-2', H-4', H-6').
^{13}C NMR (25.2 MHz, Me_2SO-d_6/$CDCl_3$): δ 163.88(C-4), 151,02(C-2), 137.59(C-6), 109.34(C-5), 71.58(C-3'), 62.69 (C-5'), 53.34 (C-1'), 48.81(C-4'), 39.00(C-2'), 32.26(C-6'), 12.09(C-7).
EI-MS(direct inlet, 140°C), m/e (rel.intensity %): 240(39)M^+, 212(17) M^+-CO, 203(6), 191(4), 183(8), 181(8), 168(5), 153(10) Th+C_2H_4, 127 (100) Th+2H, 126(87) Th+H, 110(15), 96(65).

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