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STEREOSPECIFIC SYNTHESIS OF (-)-CARBOCYCLIC 2',3'-DIDEOXYTHYMIDINE, A POTENTIAL ANTI-AIDS AGENT.

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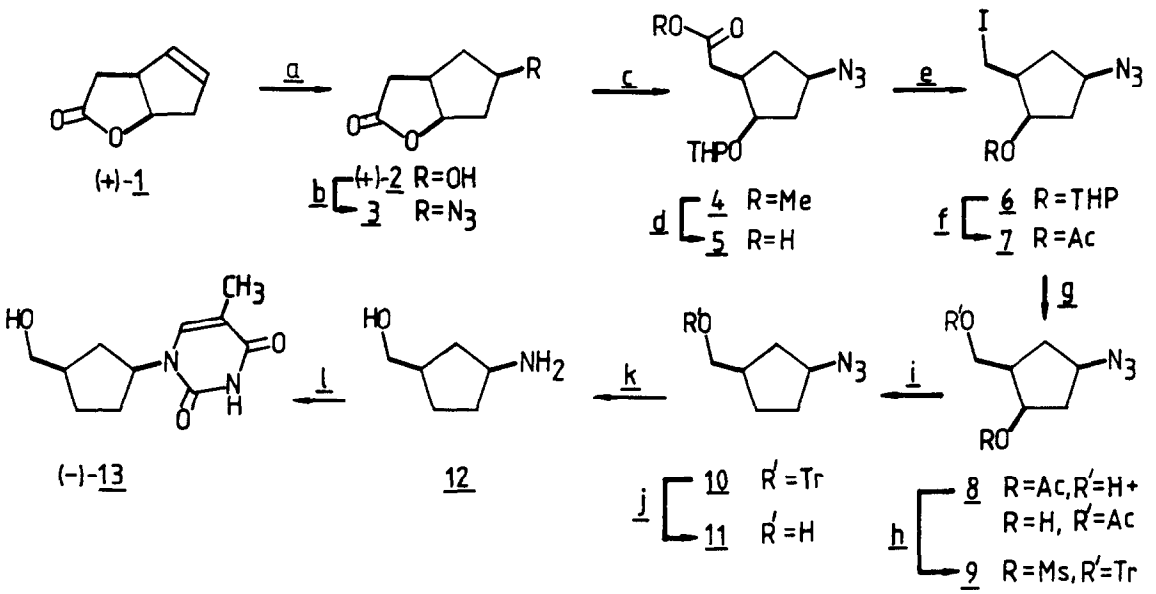
Abstract: The stereospecific synthesis of the title compound (-)-13 is described from the unsaturated bicyclic lactone (+)-1 via a versatile synthetic precursor (12) of carba-2',3'-dideoxynucleosides. The key step of the procedure is the regio- and stereoselective hydroxylation of (+)-1.

Current interest in anti-HIV (human immunodeficiency virus) nucleoside analogues (e.g. 2',3'-dideoxythymidine[1], which proved to be less toxic than the corresponding cytidine analogue) and a recent report [2] on the synthesis of enantiomerically pure carbocyclic analogue of 3'-azido-2',3'-dideoxythymidine prompted us to publish herewith the first stereospecific way to (-)-13. Racemic 13 has been synthesized by Shealy et al.[3] using a different strategy. To our knowledge, no data for the anti-HIV activity of (±)-13 are available at present. The racemic mixture has only been tested against carcinoma and leukemia cells but displayed no detectable activity either in vitro or in vivo[3].

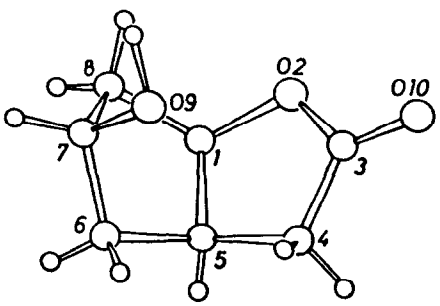
The key step of our approach is the highly regio- and stereoselective hydroxylation of the C=C double bond in (1R,5S)-2-oxabicyclo[3.3.0]-oct-6-en-3-one[4], (+)-1, to cyclopentanol derivative[5] (+)-2 [m.p. 69-70 °C (EtOAc-hexane), α_D^{25}+35° (c 1.25, MeOH)] using $Hg(OAc)_2$ in aqueous THF (Scheme). This finding, which parallels with the regio- and stereoselectivity of the Prins reaction[6], is in remarkable contrast to the low selectivity of other electrophilic additions (e.g. bromination[7,8], phenylselenylation[8]) on the same substrate. The relative stereochemistry of the OH group in (+)-2 was firmly established by an X-ray study[9] (Figure). Conversion of the OH group into azido one was achieved with retention (i.e. double inversion) of configuration through the corresponding iodo derivative[10]. This configurational assignment was anticipated on the basis of the facts that both the reaction of alcohols with triphenylphosphine dihalides[11] and the displacement of halides by azide anion[12] are known to follow essentially true S_{N2} mechanism. This expectation was supported by TLC analyses of the reaction mixtures and the ^1H NMR data of 3[13]. The acetic acid side chain was transformed to iodomethyl group via iododecarboxylation[14]. Acetyl group migration was observed when iodomethyl compound 7 was converted into hydroxymethyl derivative 8

Scheme



a $Hg(OAc)_2$,$NaBH_4$,THF:H_2O (1:1),64%; b i, Ph_3PI_2,Py,CH_2Cl_2,93%; ii, NaN_3,DMF, 72%; c i, aq LiOH, ii, aq $NaHSO_4$, iii, CH_2N_2, iv, DHP,p-TsOH,75%(overall); d i,aq LiOH, ii, aq $NaHSO_4$ 97%; e IBDA,I_2,hν,CCl_4,reflux,10 min,80%; f i, MeOH,p-TsOH,88%; ii, Ac_2O,Py,DMAP,CH_2Cl_2,98%; g m-CPBA,CH_2Cl_2,83%; h i, K_2CO_3,MeOH, 78%; ii, TrCl,Py,81%; iii, MsCl,TEA,CH_2Cl_2,89%; i NaI,Zn,mono-glyme, 74%; j MeOH, p-TsOH, 82%; k H_2/10% Pd-C, MeOH, 78%; l i, MeOCH = C(Me)C(O)NCO,DMF,Et_2O,PhH,-15 °C,3h,71%; ii, 25% aq NH_4OH,reflux, 3h,92%

Figure



Perspective view of the molecule (+)-2. The γ-lactone ring and the 7-OH group are on the same side of the cyclopentane ring. Both O(2) and O(9) atoms are in axial position, O(2)-C(1)-C(8)-C(7)=-94.4(5)° and O(9)-C(7)-C(8)-C(1)=77.3(5)°.

employing m-CPBA[15]. (To overcome side reactions, acid-labile THP groups were in advance displaced by acetyl ones.) Secondary mesyloxy function in 9 was removed with NaI/Zn[16] without any significant amount of elimination products. Synthesis of the heterocycle in (-)-13 was completed according to the literature[3]. ^{1}H NMR[17] and IR data of (-)-13 [m.p. 168 °C, α_D^{22} -13±1° (c 1.0,EtOH)] were in full agreement with those reported in ref.3. and ^{13}C MNR data[18] also corroborate the expected structure.

Further synthetic details and antiviral test results will be communicated in forthcoming papers.

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References and Notes:

1. M. Baba, R.Pauwels, P. Herdewijn, E. De Clercq, J. Desmyter, and M. Vandeputte Biochem. Biophys. Res. Commun. 1987, 142, 128
2. M. Bodenteich and H. Griengl Tetrahedron Lett. 1987, 5311
3. Y.F. Shealy, C.A. O'Dell, and M.C. Thorpe J. Heterocyclic Chem. 1981, 18, 383
4. E.J. Corey and J. Mann J. Am. Chem. Soc. 1973, 95,6832 (Available from Fluka AG.)
5. C.T. Hsu, N.Y. Wang, L.H. Latimer, and C.J. Sih J. Am. Chem. Soc. 1983, 105, 593
(+)-2, ^{1}H NMR (400 MHz, $CDCl_3$)[19]: δ 1.86(m,1H, H-6β), 1.9(m,1H, H-8α), 1.99(m, 1H, H-6α), 2.23(m, 1H, H-8β), 2.57(dd, 1H, J=18.5+3.2 Hz, H-4β), 2.87(dd, 1H, J=18.5+11 Hz, H-4α), 3.05(m, 1H, H-5) 4.47(m, 1H, J=4+3.5 +2.5+2 Hz, H-7), 5.11(dd, 1H, J=6+7.5 Hz, H-1).
6. I. Tömösközi, L. Gruber, G. Kovács, I. Székely, and V. Simonidesz Tetrahedron Lett. 1976, 4639
7. S.M. Ali, N.M. Crossland, T.V. Lee, and S.M. Roberts J. Chem. Soc., Perkin I. 1979, 122
8. J. Béres, I. Tömösközi, unpublished results.
9. A. Kálmán, V. Fülöp, unpublished result.
10. ^{1}H NMR (400 MHz, $CDCl_3$)[19]: δ 2.07(m, 1H, H-6β), 2.35(dd, 1H, J=18.5 +2.5 Hz, H-4β), 2.4(m, 1H, H-6α), 2.43(m, 1H, H-8α), 2.62(m, 1H, H-8β), 2.87(dd, 1H, J=18.5+10 Hz, H-4α), 3.13(m, 1H, H-5), 4.26(m, 1H, J=8+8+ 6+5.5 Hz, H-7), 4.98(m, 1H, J=7+6+2 Hz, H-1).
11. L. Horner, H. Oediger, and H. Hoffmann Liebigs Ann.Chem. 1959, 626, 26; G.A. Wiley, R.L. Hershkowitz, B.M. Rein, and B.C. Chung J. Am. Chem. Soc. 1964, 86, 964

12. M.E.C. Biffin, J. Miller, and D.B. Paul in Patai " The Chemistry of the Azido Group", pp. 57-119, Interscience, New York, 1971.
13. ^{1}H NMR (400 MHz, $CDCl_3$)[19]: δ 1.79(m, 1H, H-6β), 2.05(m, 1H, H-8α), 2.11(m, 1H, H-6α), 2.30(m, 1H, H-8β), 2.47(dd, 1H, J=18.5+3 Hz, H-4β), 2.86(dd, 1H, J=18.5+11 Hz, H-4α), 3.05(m, 1H, H-5), 4.14(m, 1H, J=6+5+2.5+2.5 Hz, H-7), 5.07(m, 1H, J=7.5+6+0.5 Hz, H-1).
14. L. Ötvös, J. Béres, Gy. Sági, I. Tömösközi, and L. Gruber Tetrahedron Lett. 1987, 28, 6381
15. R.C. Cambie, B.G. Lindsay, P.S. Rutledge, and P.D. Woodgate J. Chem. Soc., Chem. Commun. 1978, 919
16. Y. Fujimoto and T. Tatsuno Tetrahedron Lett. 1976, 3325
17. ^{1}H NMR (100.1 MHz, Me_2SO-d_6/$CDCl_3$)[20]: δ~10.3(s, 1H, H-3), 7.26(q, 1H, H-6), 4.7-5.1(m, 1H, H-1'), 3.56(m, 2H, H-5'), 1.88(d, 3H, H-7), 1.4-2.3(m, 7H, H-2', H-3', H-4', H-6').
18. ^{13}C NMR (25.2 MHz, Me_2SO-d_6/$CDCl_3$)[20]: δ 164.17(C-4), 151.31(C-2), 137.03(C-6), 109.89(C-5), 65.06(C-5'), 55.59(C-1'), 39.55(C-4'), 33.98, 29.92, 26.33(C-2',C-3',C-6'), 12.34(C-7).
19. Recorded on a Varian XL-400 instrument. Atomic numbering and α,β spatial assignment refer to the Figure.
20. Recorded on a Varian XL-100 instrument. Atomic numbering corresponds to that of the natural nucleosides.

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