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SYNTHETIC STUDIES TOWARDS (-)-CARBA-3'-DEOXY-3'-FLUOROTHYMIDINE.

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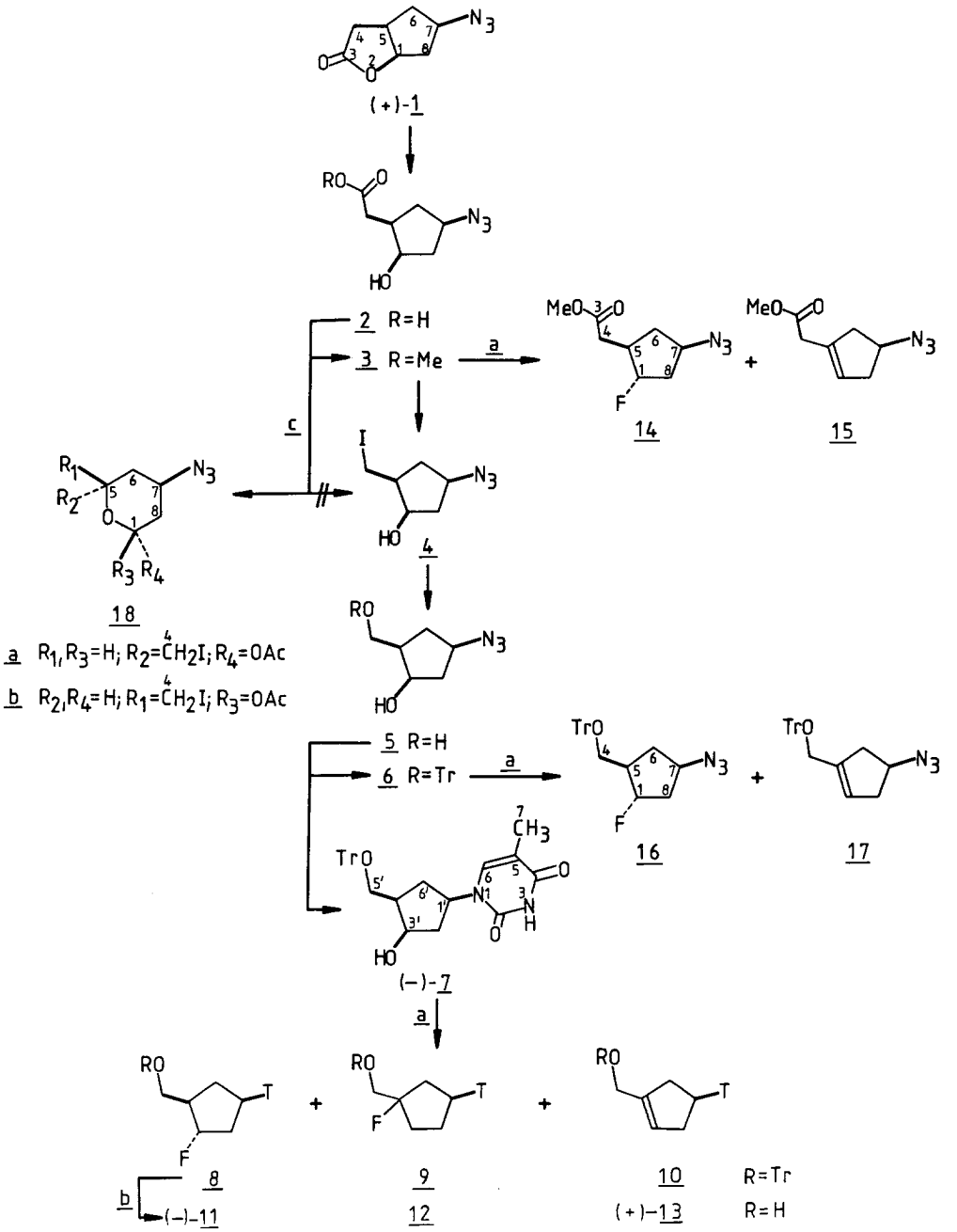
Abstract: Stereospecific synthesis of (-)-carba-3'-deoxy-3'-fluorothymidine (-)-11 is reported from the protected (-)-carbocyclic 3'-epi-thymidine (-)-7 using diethylaminosulfur trifluoride. Under the conditions used, extensive dehydration of the blocked precursor into 10 and formation of the 4'-fluoro analogue (9) were also observed. An attempted simplification of our methodology based on (+)-(1R,5S)-2-oxabicyclo[3.3.0]oct-6-en-3-one failed, but a novel cyclopentane (2) ring expansion to tetrahydropyran (18) was discovered.

Introduction. Among the nucleoside analogues 3'-deoxy-3'-fluorothymidine is the most potent anti-HIV agent synthesized so far.[1,2] However, its selectivity is somewhat lower than that of the 3'-azido analogue. Consequently, it seemed worth preparing a hopefully less toxic, but chemically and enzymatically more stable structural analogue, the carba-3'-deoxy-3'-fluorothymidine. After completion of this study a paper appeared on chemoenzymatic synthesis of the title compound by H.Griengl et al.[3] This preliminary report also prompted us to summarize our synthetic results, based on our earlier methodology,[4-7] with experimental details.

Results and Discussion. It seems to be plausible that enantiomerically pure carbocyclic 5'-O-trityl-3'-epi-thymidine[7] (-)-7 may serve as a versatile precursor for the preparation of different carba-3'-deoxy-3'-substituted thymidines (Scheme 1). Reactions proceeding either with inversion or retention of C3' configuration would provide a series of analogues. DAST[8] is known to convert chiral secondary alcohols into the corresponding fluoro

SCHEME 1


(+)-1
2 R=H
3 R=Me
a
14
15
c
18
a R1,R3=H; R2=4CH2I; R4=OAc
b R2,R4=H; R1=4CH2I; R3=OAc
4
5 R=H
6 R=Tr
16
17
(−)-7
8
9
10 R=Tr
(+)-13 R=H
11
12
b
a DAST, CH2Cl2, 0°C or -70°C; b HCO2H, Et2O; c IBDA, I2, CCl4, hν, reflux.

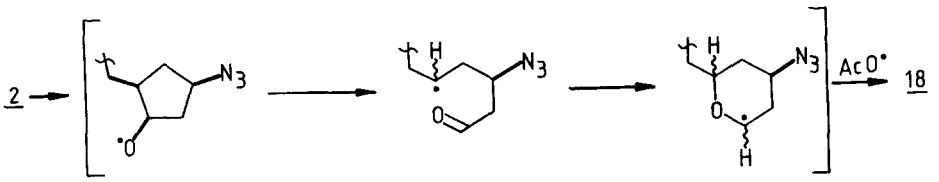
derivatives usually with full inversion of configuration.[9] When protected alcohol (-)-7 was treated with 4 equivalents of DAST in CH_2Cl_2 at 0°C, however, a mixture of products was obtained as evidenced by silica gel TLC and NMR spectroscopy (vide infra). Besides the desired 3'-fluoro analogue 8, cyclopentenylthymine derivative 10 and 4'-fluoro-3'-deoxy compound 9 were also isolated in relatively high portions. Similar result was gained when the reaction was performed at -70 °C. This kind of extensive dehydration with DAST is rare, but not without precedents.[10] HF addition to the previously formed C=C bond of 10, in accord with the Markovnikov's rule, may account for the formation of 9. The mixture [(8+9):10 ~ 2:1 by TLC] was treated with HCO_2H in Et_2O[11] in order to remove the trityl protective group and attain a better resolution by dry column flash chromatography (DCFC).[6,7,12] Contrary to the separation of (+)-13 (ratio of [(-)-11+12]/(+)-13~1.7 by weight), silica gel thin layer and column chromatography proved to be insufficient to separate the mixture of 8 and 9 or (-)-11 and 12. However, ^1H and ^{13}C NMR showed the latter sample to be a two-component mixture (ratio of (-)-11/12 ~ 2.3 by NMR). The regio- and stereochemistry of the fluorine substitution were assigned on the basis of ^1H and ^{13}C NMR data. The proton NMR data of (-)-11 revealed the presence of the fluorine atom at position C3', but gave no information about the stereochemistry at this chiral centre. The S configuration of C3' derives from the carbon chemical shifts in comparison with those of (+)-carba-thymidine[4], a compound of known stereochemistry. The 4'-fluoro substitution for compound 12, formed as a single diastereomer, is evident from both the vicinal fluorine-proton and the geminal and vicinal fluorine-carbon coupling constants (see Experimental), but the NMR data were insufficient for assignment of the relative stereochemistry. In contrast, optical rotation measurement could not reveal the inhomogenity of this sample, as the measured $[\alpha]_D^{23}$-10° for the mixture of (-)-11 and 12 agreed well with that published[3] for (-)-11 ($[\alpha]_D^{20}$-11°). A routine MS analysis of the mixture provided the expected molecular ion and also located the fluorine substi-

tution to the cyclopentyl moiety (Experimental). The fragmentation pattern rendered, however, no information on the inhomogenity of the sample. Along our synthetic line we also tried to introduce fluorine to the cyclopentyl skeleton at two earlier stages. These fluorinations (3 → 14 and 6 → 16) were, however, again accompanied by the dehydration process leading to 15 and 17 (ratio of 14/15 ~ 5.6 and 16/17 ~ 1.0 by NMR). In all of our three cases the elimination is quite favoured probably because the $^{-}OSF_2NEt_2$ nucleofuge and the 4'-H can reach the anti-periplanar conformation in the transition state and the possible most highly substituted (trialkyl) olefin may form (Zaitsev's rule). In spite that the presence of 4'-fluoro derivatives could not be detected by ^1H NMR spectroscopy (100 MHz) in the product mixtures in these latter cases, HF addition can not be precluded. Therefore, our findings warn that one should also consider the formation of potential side-products in the reactions of DAST with certain cyclopentanol derivatives.

Direct conversion of 2 into 4 would considerably simplify our methodology[5,7] for the preparation of different optically active carbocyclic 2'-deoxyribonucleoside analogues. The IBDA-I_2 iododecarboxylation[4-6,13] of hydroxycarboxylic acid 2 provided, however, a mixture of tetrahydropyran derivatives 18a and 18b, as the major TLC-detectable products (ratio ~1:1 by NMR) in low isolated yield, rather than the requisite α-hydroxy iodomethylcyclopentane compound 4. (Approx. 13 % of lactone (+)-1 could be recovered.) NMR spectroscopy and MS served firm basis for the structure elucidation (including stereochemistry) of the chromatographically unresolved reaction mixture. The presence of the acetoxy group at C1 position in both 18a and 18b was determined on the basis of the down-field carbon-13 chemical shift values (90.73 and 92.02 ppm, respectively). The stereochemistry at the chiral centres are reflected by characteristic coupling constant values of the relevant protons. We have found that the proton (H1) at the newly formed chiral centre and also H5 are axial in both compounds, while H7 is axial in 18b and equatorial in 18a. The carbon-13 NMR data are in agreement with these observations. The ring carbon atoms of 18a, due to the differences in α, β and γ substi-

tuent effects of an axial and an equatorial substituent, are all shifted upfield to those of 18b (see also Experimental). Formation of the products can speculatively be explained e.g. through the following mechanism: homolytic cyclopentane ring opening (β-fragmentation) induced by alkoxy radicals (which may likely arise from the corresponding alkyl hypoiodite species), followed by intramolecular trapping of C-radical and final recombination of alkyl and acetoxy radicals to provide trisubstituted tetrahydropyrans 18 (Scheme 2). According to this mechanism uncertain degree of epimerization may have occured only at two carbon stereocentres. The NMR data and the $[\alpha]_D^{24}$ -14° for 18 are in agreement with this premise. Although reactions of alkoxy and acyloxy radicals generated by the same reagents were recently studied extensively, similar ring transformation has not yet been mentioned.[14]

SCHEME 2



Experimental.

Abbreviations. HIV, human immunodeficiency virus; DAST, diethylaminosulfur trifluoride; IBDA, iodobenzene diacetate; DCFC, dry column flash chromatography; H hexane; E ethyl acetate; M methanol; T, thymin-1-yl; b, broad.

Materials. Dichloromethane was distilled from P_2O_5, carbon tetrachloride from CaH_2. DAST was the product of Janssen Chimica, Belgium. IBDA was prepared as described in the literature.[15] Precoated silica gel TLC plates (DC-Alufolien, Kieselgel 60 F_{254}, 0.2 mm) were purchased from Merck, Darmstadt. UV-light, phosphomolybdic acid and sulfuric acid were used to detect compounds on TLC plates.

Spectroscopy. ^{1}H and ^{13}C NMR spectra were recorded on Varian XL-100 and XL-400 instruments. Mass spectrometric measurements were carried out on an AEI MS-902 double focusing instrument with ionizing energy of 70 eV. All samples were introduced by direct probe. Optical rotation measurements were performed on a Polamat A (Carl Zeiss, Jena, GDR) polarimeter.

Typical Procedure for DAST Fluorination (step a).

Compounds 8,9 and 10.

A mixture of (-)-7 (0.410 g, 0.85 mM) in 10 mL of CH_2Cl_2 was treated with 0.23 mL (1.72 mM) of DAST at -70°C. After 0.5 h (complete dissolution) TLC showed approx. 50 % conversion. Then the addition of the reagent (0.23 mL) was repeated. After 30 min the temperature was allowed to rise 0 °C and 20 mL of 1 M/L aqueous $NaHCO_3$ solution (0°C) was slowly added (pH = 9). After separation the aqueous layer was further extracted with Et_2O (3x20 mL). The combined organic phase was washed with brine (5 mL), dried over $MgSO_4$ and evaporated to dryness (0.410 g). DCFC (15 g silica gel, H:E = 2:1) yielded a pure mixture of 8,9 and 10 (0.289 g). R_f (H:E = 1:1) = 0.17 (compound 10) and 0.21 (unresolvable mixture of 8 and 9).

Compounds 14 and 15.

Isolated was a pure unresolvable mixture of 14 and 15 (1.13 g, ~50 %).

R_f(H:E=10:1)=0.27.

14: ^{1}H NMR (100 MHz, $CDCl_3$)[16]: δ1.25-2.7(overlapped multiplets, 5-H, 6-H_2 and 8-H_2), 2.48(m, 4-H_2), 3.69(s, CO_2Me), 4.11(m, J=8+7.0+7.0+7.0 Hz, 7-H), 4.87 (m, J=52*+6+3+2.5 Hz, 1-H).[17] (Couplings with fluorine are marked with asterisk. Data for the minor olefin component 15 are not shown.)

Compounds 16 and 17.

DCFC afforded 2.00 g (~64 %) of 16 and 17 as a pure unresolvable mixture.

R_f(H:E=20:1)=0.27.

16: ^{1}H NMR (100 MHz, $CDCl_3$)[16]: δ1.3-2.8(overlapped multiplets, 5-H, 6-H_2 and

8-H_2), 3.09(dd, J=11+6.5 Hz, 4-H_A), 3.17(dd, J=11+5.5 Hz, 4-H_B), 4.06 (overlapped multiplet, 7-H), 4.96(m, J=52*+5.5+2.5+2 Hz, 1-H), 7.2-7.5 (m, aromatics).

17: ^{1}H NMR (100 MHz, $CDCl_3$)[16]: δ1.3-2.8(overlapped multiplets, 6-H_2 and 8-H_2), 3.69(b s, 4-H_2), 4.06(overlapped multiplet, 7-H), 5.88(m,J=2+2+1.5+1.5 Hz, 1-H), 7.2-7.5(m, aromatics).

Detritylation (step b).

A mixture of 8,9 and 10 (0.289 g) was treated with a solution of 99.7 % HCO_2H (2 mL) and Et_2O (2 mL) for 5 min at ambient temperature. As TLC indicated full detritylation, 0.5 mL of H_2O was added to the reaction mixture and it was evaporated to dryness (0.278 g). DCFC (15 g silica gel, EtOAc) provided 0.052 g (25 %, based on (-)-7) of(-)-11 and 12 as a pure mixture, 0.029 g (15 %, based on (-)-7) of (+)-13 and 0.029 g (~10 %) unresolved mixture of (-)-11,12,(+)-13.

Fluoro Derivatives, (-)-11 and 12: R_f (E:M=10:1)=0.52. $[\alpha]_D^{23}$-10° (c 2.0, MeOH). EI-MS (direct inlet, 150 °C), m/e (rel.intensity %): 242(12) M^+, 191(3)M^+-CH_2OH-HF, 127(39) B^++2H, 126(100)B^++H.

(-)-11 (major component): ^{1}H NMR (400 MHz, $CDCl_3$/DMSO-d_6)[18]: δ1.68-2.35 (overlapped multiplets, 2′-H_2, 6′-H_2 and 4′-H), 1.91(d, J=1.2 Hz, 7-H_3), 3.64(dd, J=11+5 Hz, 5′-H_A), 3.80(dd, J=11+4 Hz, 5′-H_B), 4.26(b s, OH), 5.12 (m, J=11+10+8+8 Hz, 1′-H), 5.13(m, J=53*+5.5+2+1.5 Hz, 3′-H), 7.27(q, J= 1.2 Hz, 6-H), 10.4(b s, NH).

^{13}C NMR (100 MHz, $CDCl_3$/DMSO-d_6)[18]: δ12.53(C7), 30.98(C6′), 37.71(J = 21.8 Hz*, C2′), 46.52(J=20.5 Hz*, C4′), 54.71(C1′), 62.54(J=8.5 Hz*, C5′), 96.11 (J=173.6 Hz*, C3′), 110.79(C5), 137.28(C6), 151.32(C2), 164.24(C4).

12 (minor component): ^{1}H NMR (400 MHz, $CDCl_3$/DMSO-d_6)[18]: δ1.8-2.5 (overlapped multiplets, 2′-H_2, 3′-H_2 and 6′-H_2), 1.91(d, J=1.2 Hz, 7-H_3), 3.74

(dd, J=18*+12 Hz, 5'-H_A), 3.77(dd, J=16.5*+12 Hz, 5'-H_B), 4.42(b s,OH), 5.07 (overlapped multiplet, 1'-H), 7.15(q,J=1.2 Hz, 6-H), 10.4(b s,NH).
^{13}C NMR (100 MHz, $CDCl_3$/DMSO-d_6)[18]: δ12.51(C7), 29.26(C2'), 32.71(J=23.3 Hz*, C3'), 38.94(J=23.4 Hz*, C6'), 55.94(C1'), 65.55(J=28.8 Hz*, C5'), 104.6 (J=174.6 Hz*, C4'), 110.73(C5), 137.50(C6), 151.20(C2), 164.28(C4).

Unsaturated Derivative (+)-13: R_f(E:M=10:1)=0.45. $[\alpha]_D^{23}$+18° (c 1.45, MeOH).
^{1}H NMR (100 MHz, $CDCl_3$/DMSO-d_6)[18]: δ1.88(d, J=1.2 Hz, 7-H_3), 2.3-3.05 (overlapped multiplets, 2'-H_2 and 6'-H_2), 4.18(b s, 5'-H_2), 5.36(m, J=9+8.5 +4+4 Hz, 1'-H), 5.68(m, J=2+1.5+1.5+1.5 Hz, 3'-H), 7.09(q, J=1.2 Hz, 6-H), 10.26(b s, NH).

Ring Expansion (step c). A mixture of 2 (0.900 g, 4.86 mM), 4.19 g (13.0 mM) IBDA and I_2 (3.30 g, 13.0 mM) in 150 mL of CCl_4 was refluxed over a 250-W tungsten-filament lamp for 10 min. The addition of the reagents and the reflux was repeated. Then the cooled reaction mixture was successively washed with 70 mL of 5 % aqueous $Na_2S_2O_3$ solution, H_2O (10 mL), saturated aqueous $NaHCO_3$ (10 mL, pH=9), H_2O (10 mL) and dried over $MgSO_4$. The residue (5.47 g) obtained on evaporation was purified by DCFC (15 g silica gel, H:E=1:1 and then 15 g SiO_2, H:E=10:1). Isolated was 0.192 g (9.1 %) of 18. R_f (H:E = 5:1)=0.20 and 0.27. $[\alpha]_D^{24}$-14° (c 2.88, MeOH).
EI-MS (direct inlet, 100 °C), m/e (rel. intensity %): 325(1.7)M^+, 266(5.2) M^+-OAc, 222(1.7)M^+-(OAc+C_2H_4O), 195(2.2)M^+-(OAc+N_2+C_2H_3O), 184(1.5)M^+-CH_2I, 138(12.5)M^+-(OAc+HI), 128(9.5)HI, 127(1.9)I, 110(4.6)M^+-(OAc+HI+N_2), 95(1.9) M^+-(OAc+HI+HN_3).

18a: ^{1}H NMR (400 MHz, $CDCl_3$)[16]: δ1.70(m,J=13.5+10+3.5 Hz, 6-H_α), 1.79(m,J= 13.5+9+3.5 Hz, 8-H_α), 1.93(m,J=13.5+4+2.6+2 Hz, 8-H_β), 1.97(m ,J=13.5+4+2.5+ 2 Hz, 6-H_β), 2.14(s, OAc), 3.24(t,J=5.5+5.5 Hz, 4-H_2), 3.91(m,J=10+5.5+5.5+ 2.5 Hz, 5-H), 4.18(m,J=4+4+3.5+3.5 Hz, 7-H), 6.01(dd, J=9+2.6 Hz, 1-H).

^{13}C NMR (100 MHz, $CDCl_3$)[16]: δ7.62(C4), 33.55 and 35.16(C6 and C8), 54.85 (C7), 71.12(C5), 90.73(C1), 21.16 and 169.0(OAc).

18b: ^{1}H NMR (400 MHz, $CDCl_3$)[16]: δ1.36(m,J=12+12+11 Hz, 6-H_β), 1.56 (m,J= 12+12+10 Hz, 8-H_β), 2.12(s,OAc), 2.16(m,J=12+4+2+2 Hz, 8-H_α), 2.25(m,J=12 +4 +2+2 Hz, 6-H_α), 3.25(dd,J=6+5.5 Hz, 4-H_2), 3.55(m,J=11+6+5.5+2 Hz, 5-H), 3.64(m,J=12+12+4+4 Hz, 7-H), 5.7(dd,J=10+2 Hz, 1-H).

^{13}C NMR (100 MHz, $CDCl_3$)[16]: δ6.38(C4), 34.16 and 35.87(C6 and C8), 55.08 (C7), 72.88(C5), 92.02(C1), 21.07 and 169.0(OAc).

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16. Atomic numbering refers to that of (+)-1 in Scheme 1.

17. Couplings with fluorine are marked with asterisk.

18. Atomic numbering corresponds to that of the nucleosides as shown on the formula of (-)-7 in Scheme 1.