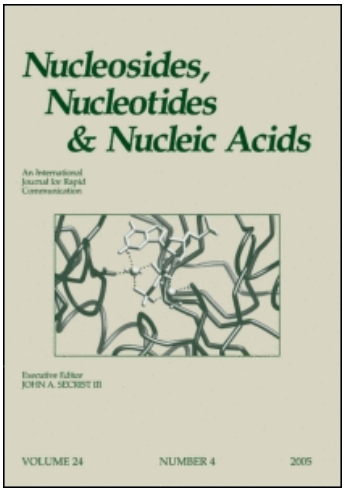

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CHIRAL 1', 2'-*SECO*-NUCLEOSIDES: SYNTHESIS OF D AND L-THREITOL-2'-O-METHYLENYL NUCLEOSIDES

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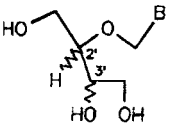
Abstract: 1', 2'-*Seco*-nucleoside derivatives of adenine, cytosine, guanine and thymine with a D or L-threitol side-chain configuration have been synthesized from D or L dimethyl tartarate respectively. Biological evaluation of the four enantiomeric pairs of nucleosides revealed they were inactive against various viruses in cell cultures.

The lack of rational structure-activity relationships in antiviral chemotherapy is at the origin of an intensive synthetic work especially in the field of nucleosides[1]. In this respect the synthesis of new acyclic nucleosides is of uppermost interest owing to the well established activity of some members of this important class of compounds as antiviral agents[2].

Recent studies with both racemic and chiral nucleoside analogues[3] (*i.e.* carba-2'-deoxyguanosine[4], DHBG[5] and DHPG[6]) have shown that the antiviral activity usually resides in only one of the two enantiomers.

Although the syntheses of a few chiral 1', 2'-*seco*-nucleosides have been reported[7-10], erythritol nucleoside derivatives *i.e.* 9-[(1', 3'(S)-dihydroxy-2'(R)-butoxy)methyl]guanine and the N-1 derivative of uracil are only fully described[11] in these series. This paper is devoted to a straightforward synthesis of homochiral 1', 2'-*seco*-nucleosides **13** and **14** having a L or D threitol side-chain with four nucleobases *i.e.* adenine, cytosine, guanine and thymine (Figure 1).



(S, S)–13
(R, R)–14

Figure 1

As schown in scheme 1 the reaction sequence was performed separately on the two enantiomers of dimethyl tartarates **1** (L series) and **2** (D series).

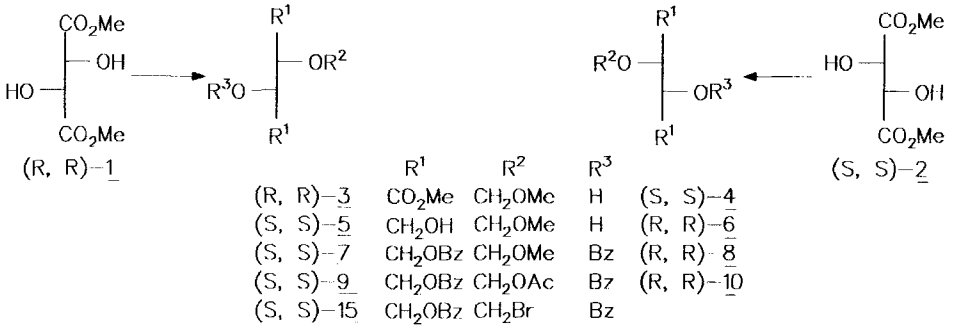
The process will be described here on only one of the two series, namely L, and the experimental section will give detailed results for the enantiomeric compounds.

Compound **1** was treated with dimethoxymethane[12] and phosphorus pentoxide to afford **3** (58% yield). The latter derivative was reduced to **5** by the method of Harnden[13] using $NaBH_4$ in *tert*-butanol in quantitative yield.

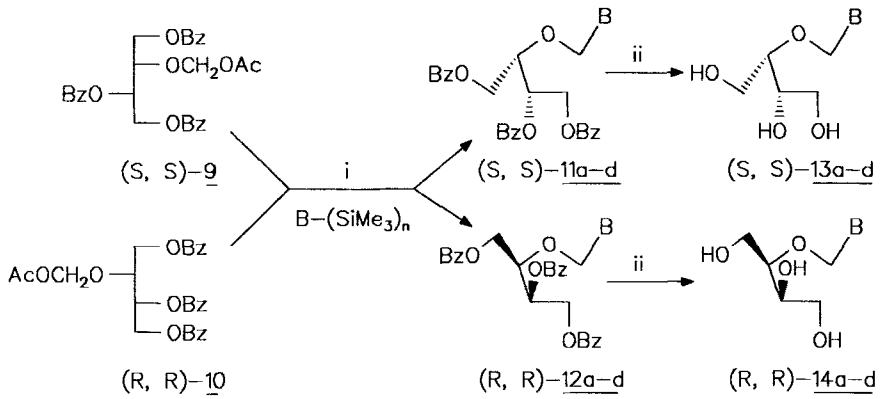
Subsequent benzoylation of **5** gave **7** (64% yield) which was acetoxymethylated to **9** in quantitative yield by acetic anhydride and boron trifluoride etherate at -20°C. The compound **9** was the required synthon used in the next condensation step with the four aforementioned nucleobases. The reaction was accomplished by a solid-liquid phase transfer catalysis method[14-17] with KI-dibenzo-18-crown-6 ether in toluene-acetonitrile (1:1, v/v) (scheme 2).

This efficient procedure gave the expected regiospecific N-1 pyrimidyl or N-9 purinyl acyclonucleosides **11a-d**. Further removal of the benzoyl protecting group was effected with methanolic ammonia to give the free nucleosides **13a-d** in quantitative yields. The regioisomerism of these four compounds was ascertained by means of their UV spectra in two different media[18].

The same sequence of reactions starting from the D-dimethyl tartarate **2** afforded compounds **4**, **6**, **8**, **10**, **12a-d** and **14a-d**, each of



Scheme 1



Scheme 2- a: B= Ad; b: B= Cy; c: B= Gu; d: B= Th; i: KI/dibenzo-18-crown-6 ether, acetonitrile-toluene, reflux; ii: NH_3/MeOH

them having an opposite optical rotation compared to their antipodal series already described earlier. For a comparative purpose of the aforementioned phase transfer glycosylation procedure with the current literature methods, the compound **11d** was also obtained by reaction of the bromo derivative **15** (generated from **9** and bromotrimethylsilane) with trimethylsilylated thymine and triethylamine in dry toluene. This reaction afforded the desired compound **11d** but in lower yield (55 *versus* 87%).

Although biological evaluation showed a marginal activity against herpes simplex virus 1 (HSV1) for compound **13c**, none of the seven other nucleosides had any effect against various DNA and RNA viruses in cell cultures.

EXPERIMENTAL

Dimethyl-[(2R),(3R)-2-methoxymethylenoxy]-tartarate **3**.- To a mixture of L-dimethyl tartarate **1** (18 g, 0.101 mol) and dimethoxymethane (9.83 ml, 0.111 mol) dissolved in anhydrous chloroform (50 ml) was added phosphorous pentoxide (8.51 g, 0.06 mol). The reaction was vigorously stirred 21 h at room temp. and hydrolyzed with ice-water. The organic phase was washed with aqueous sodium bicarbonate, dried ($MgSO_4$) and concentrated under reduced pressure. Compound **3** was obtained after crystallization from pentane-dichloromethane (13 g, 58% yield). $[\alpha]_D^{20}$ +116° (c 2.5, chloroform); R_f 0.43 (methanol-dichloromethane, 3:97); m.p. 73-74°C; ^1H NMR (60 MHz, $CDCl_3$) δ 3.4 (s, 3H, OMe), 3.5 (s, 1H, OH), 3.9 (s, 6H, 2OMe), 4.7 (m, 4H, H-2, H-3, OCH_2O); Anal. Calcd. for $C_8H_{14}O_7$: C, 43.4; H, 6.25. Found: C, 43.24, H, 6.35.

Dimethyl-[(2S),(3S)-2-methoxymethylenoxy]-tartarate **4**.- This compound was obtained (60% yield) following the aforementionned procedure. $[\alpha]_D^{20}$ -116° (c 2.5, chloroform). It showed the same physical and spectral data as compound 3.

(2S)-Methoxymethylenoxy-1,(3S),4-butanetriol **5**.- According to the procedure of Hardnen, the diester **3** (11.5 g, 0.051 mol) was dissolved in anhydrous *tert*-butyl alcohol (100 ml) and sodium borohydride (5.16 g, 0.136 mol) was added. Absolute methanol (7 ml) was added in three times (30 min) and the solution was refluxed for 30 min. The reaction was cooled at 0°C and neutralized with 5M HCl (15 ml). The precipitate was filtered off, washed with ethanol and the filtrate evaporated. Compound **5** was obtained as an oil in quantitative yield (8.4 g). $[\alpha]_D^{20}$ +3.3° (c 3, methanol); ^1H NMR (60 MHz, $CDCl_3$) δ 3.4 (s, 3H, OMe), 3.7 (m, 6H, $2CH_2O$, H-2, H-3), 4.1 (s, 3H, 3OH), 4.75 (s, 2H, OCH_2O); Anal. Calcd. for $C_6H_{14}O_5$: C, 43.5; H, 8.25. Found: C, 43.37; H, 8.49.

(2R)-Methoxymethylenoxy-1,(3R),4-butanetriol **6**.- This compound was obtained following the aforementioned procedure. $[\alpha]_D^{20}$ -3° (c 3, methanol). It showed the same physical and spectral data as compound **5**.

1,(3S),4-Tribenzoyloxy-(2S)-methoxymethylenoxybutane **7**.-Benzoyl chloride (162.5 ml, 1.4 mol) was added dropwise at 0°C over 2 h to the triol **5** (23 g, 0.138 mol) dissolved in anhydrous pyridine (450 ml). After stirring at room temp. for 17 h, the reaction mixture was poured in ice-water and the solvent was partially evaporated under reduced pressure and then extracted with dichloromethane. The organic layer was washed with aqueous saturated sodium bicarbonate, then with water, dried ($MgSO_4$) and evaporated. The residue was flash chromatographed on a silica gel column eluted with pentane-dichloromethane (70:30). The *title compound* was obtained as an oil (42 g, 64% yield). R_f 0.42 (dichloromethane); $[\alpha]_D^{20}$ +7.4° (c 2.7, chloroform); ^1H NMR (60 MHz, $CDCl_3$) δ 3.4 s, (3H, OMe), 4.2-4.7 (m, 4H, H-2, H-3, $2CH_2O$), 4.8 (s, 2H, OCH_2O), 7.4-8.0 (m, 15H, aromatic); Anal. Calcd. for $C_{27}H_{26}O_8$: C, 67.83; H, 5.41. Found: C, 67.77; H, 5.48.

1,(3R),4-Tribenzoyloxy-(2R)-methoxymethylenoxybutane **8**.- This compound was obtained following the aforementioned procedure. $[\alpha]_D^{20}$ -7.7° (c 2.7, chloroform). It showed the same physical and spectral data as compound **7**.

1,(3S),4-Tribenzoyloxy-(2S)-acetoxymethylenoxybutane **9**.-Boron trifluoride diethyl ether (1.22 ml, 9.75 mmol) was added in over 40 min to a cooled (-20°C) solution of compound **7** (16 g, 33.4 mmol) in acetic anhydride (3.5 ml, 47 mmol). After 2 h at -20°C, the reaction was hydrolyzed with ice-water, neutralized by a saturated aqueous solution of sodium bicarbonate and extracted with diethyl ether. The organic layer was washed with water, dried (Na_2SO_4) and evaporated under reduced pressure. The *title compound* was obtained as an oil (16.8 g, 98% yield). R_f 0.21 (cyclohexane-diethyl ether, 3:2); $[\alpha]_D^{20}$ +11° (c 1.27, chloroform); ^1H NMR (60 MHz, $CDCl_3$) δ 1.9 (s, 3H, Me), 4.1-4.7 (m, 4H, H-2, H-3, $2CH_2O$), 5.4 (s, 2H, OCH_2O), 7.4-8 (m, 15H, aromatic); Anal. Calcd. for $C_{28}H_{26}O_9$: C, 66.32; H, 5.25. Found: C, 66.39; H, 5.17.

1,(3R),4-Tribenzoyloxy-(2R)-acetoxymethylenoxybutane **10**.-This compound was obtained following the aforementioned procedure. $[\alpha]_D^{20}$ -11.2° (c 1.2, chloroform). It showed the same physical and spectral data as compound **9**.

1,(3S),4-Tribenzoyloxy-(2S)-bromomethylenoxybutane **15**.- A solution of **9** (4.3 g, 8.49 mmol) in anhydrous dichloromethane (25 ml) was reacted with bromotrimethylsilane (5 ml, 37.8 mmol) at reflux for 12 h. The solution was evaporated under vacuum to give the *title compound* (85% pure as determined by nmr data) which was used in the next step without any further purification. R_f 0.29 (dichloromethane); ^{1}H NMR (60 MHz, $CDCl_3$) δ 4.0-4.7 (m, 6H, H-2, H-3, $2CH_2O$), 5.7 (s, 2H, OCH_2Br), 7.2-8.1 (m, 15H, aromatic).

1-[(1',(3'S),4'-Tribenzoyloxy-(2'S)-butoxy)methyl]thymine **11d** from **15**. - Bis-trimethylsilyl thymine (10.3 mmol) was dissolved in anhydrous dichloromethane (6 ml). To this solution were added anhydrous triethylamine (2.5 ml) and the bromo derivative **15** (8 mmol) in dry toluene (14.5 ml). The reaction mixture was refluxed for 3 h and the solvent was removed under reduced pressure. The resulting oil was refluxed for 30 min in 95% ethanol. The solvent was removed under vacuum and the resulting oil extracted with dichloromethane. The organic layer was washed with water, dried (Na_2SO_4) and evaporated. The resulting oil was flash chromatographed on a silica gel column eluted with dichloromethane and afforded **11d** which was crystallized from absolute ethanol (2.2 g, 57% yield) and had identical physical and spectral data as described for compound **11d** resulting from coupling between silylated thymine and synthon **9**.

Synthesis of protected acyclonucleosides.- General method. To the dried mixture of KI (0.8 mmol) and dibenzo-18-crown-6 ether (0.2 mmol) in toluene (5 ml) were added the trimethylsilylated nucleobase (1 mmol) in dry acetonitrile (2.5 mmol) and the acetylated *pseudo*sugar (1 mmol) in acetonitrile (2.5 ml). The reaction was refluxed for 24 h until no more progress was observed by tlc. The solvents were removed under reduced pressure and the residue was flash chromatographed on a silica gel column eluted with methanol (0 to 4%)-dichloromethane.

9-[(1',(3'S),4'-Tribenzoyloxy-(2'S)-butoxy)methyl]adenine **11a**.-This compound was obtained (78% yield) after chromatography with the aforementioned eluent (3:97). R_f 0.21 (methanol-dichloromethane, 3:97); m.p. 95-97°C (ethanol); $[\alpha]_D^{20}$ +18.7° (c 0.84, chloroform); UV λ max (EtOH, 95%) 259 nm; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.46-4.69 (m, 5H, $2CH_2$, CH), 5.64 (q, 1H, J = 5.1 Hz, CH), 5.80 (q, 2H, J = 11.4 Hz, OCH_2N), 6.72 (br.s, 2H, NH_2), 7.36-7.93 (m, 15H, aromatic), 8.0 (s, 1H, 2-H), 8.13 (s, 1H, 8-H). Anal. Calcd. for $C_{31}H_{27}N_5O_7$: C, 64.31; H, 4.55; N, 12.0. Found: C, 64.02; H, 4.68; N, 12.08.

1-[(1',(3'S),4'-Tribenzoyloxy-(2'S)-butoxy)methyl]cytosine **11b**.-This compound was obtained (87% yield) following the aforementioned procedure. R_f 0.32 (methanol-dichloromethane, 5:95); m.p. >300°C; $[\alpha]_{546}^{20}$+2° (c 2.4, chloroform); UV λ max (EtOH, 95%) 269 nm; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.41-4.65 (m, 5H, $2CH_2$, CH), 5.19 (d, 1H, J = 10.6 Hz, OCH_aN), 5.41 (d, 1H, J = 10.6 Hz, OCH_bN), 5.67 (q, 1H, J = 4.5 Hz, CH), 5.74 (d, 1H, J = 7.3 Hz, 5-H), 7.24-7.96 (m, 18H, aromatic, NH_2, 6-H); Anal. Calcd. for $C_{30}H_{28}N_3O_8$: C, 64.67; H, 5.23; N, 7.45. Found: C, 64.51; H, 5.05; N, 7.52.

9-[(1',(3'S),4'-Tribenzoyloxy-(2'S)-butoxy)methyl]guanine **11c**.-This compound was obtained (88% yield) following the aforementioned procedure. Rf 0.45 (methanol-dichloromethane, 1:9); m.p. 235°C (from ethanol); $[\alpha]_{436}^{20}$ +13.5° (c 1.1 methanol); UV λ max (EtOH, 95%) 252 nm; ^{1}H NMR (250 MHz, DMSO-d_6) δ 4.39-4.67 (m, 5H, $2CH_2$, CH), 5.64 (q, 1H, J = 5.3 Hz, CH), 5.80 (s, 2H, OCH_2N), 6.22 (s, 2H, NH_2), 7.45-7.9 (m, 15H, aromatic), 8.17 (s, 1H, 8-H), 10.84 (s, 1H, NH); Anal. Calcd. for $C_{31}H_{27}N_5O_8$: C, 61.97; H, 4.35; N, 11.6. Found: C, 62.30; H, 4.55; N, 11.71.

1-[(1',(3'S),4'-Tribenzoyloxy-(2'S)-butoxy)methyl]thymine **11d**.-This compound was obtained (87% yield) following the aforementioned procedure. Rf 0.41 (methanol-dichloromethane, 3:97); m.p. 142-143°C (from ethanol); $[\alpha]_D^{20}$ +14° (c 1, chloroform); UV λ max (EtOH, 95%) 264 nm; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.67 (d, 3H, J = 1.3 Hz, Me), 4.53-4.76 (m, 5H, $2CH_2$, CH), 5.20 (d, 1H, J = 10.9 Hz, OCH_aN), 5.43

(d, 1H, J = 10.9 Hz, OCH_bN), 5.72 (q, 1H, J = 5.2 Hz, CH), 7.03 (d, 1H, J = 1.3 Hz, 6-H), 7.4-7.6 (m, 9H, aromatic), 8.0 (m, 6H, aromatic), 8.13 (s, 1H, NH); Anal. Calcd. for $C_{31}H_{28}N_2O_9$: C, 65.05; H, 4.81; N, 4.81. Found: C, 65.03; H, 4.93; N, 4.89.

9-[(1',(3'R),4'-Tribenzoyloxy-(2'R)-butoxy)methyl]adenine **12a**.-This compound was obtained following the aforementioned procedure. $[\alpha]_D^{20}$ -18.4° (c 1.1, chloroform). It showed the same physical and spectral data as compound **11a**.

1-[(1',(3'R),4'-Tribenzoyloxy-(2'R)-butoxy)methyl]cytosine **12b**.-This compound was obtained following the aforementioned procedure. $[\alpha]_{546}^{20}$ -2° (c 3.5, chloroform). It showed the same physical and spectral data as compound **11b**.

9-[(1',(3'R),4'-Tribenzoyloxy-(2'R)-butoxy)methyl]guanine **12c**.-This compound was obtained following the aforementioned procedure. $[\alpha]_{436}^{20}$ -13.2° (c 1.06, methanol). It showed the same physical and spectral data as compound **11c**.

1-[(1',(3'R),4'-Tribenzoyloxy-(2'R)-butoxy)methyl]thymine **12d**.-This compound was obtained following the aforementioned procedure. $[\alpha]_D^{20}$ -14° (c 1.06, chloroform). It showed the same physical and spectral data as compound **11d**.

Debenzoylation of protected nucleosides.- The benzoylated acyclonucleosides were treated with methanolic ammonia at -4°C for 2-4 d. The solvent was removed under reduced pressure and the residue chromatographed on a silica gel column eluted with methanol-dichloromethane (10-20%). The free acyclonucleosides (98% yield) were then cristallized.

9-[(1',(3'S),4'-Trihydroxy-(2'S)-butoxy)methyl]adenine **13a**.-This compound was obtained following the aforementioned procedure. m.p. 200°C (methanol-water); $[\alpha]_D^{20}$ +17.3° (c 1.5, water); UV λmax (EtOH, 95%) 260 nm; ^{1}H NMR (250 MHz, DMSO-d_6) δ 3.21 (t, 2H, J = 5.7 Hz, CH_2), 3.39-3.56 (m, 3H, CH_2, CH), 3.67 (m, 1H, CH), 4.48 (t, 1H, J =

5.5 Hz, OH), 4.56 (d, 1H, J = 5.5 Hz, OH), 4.71 (t, 1H, J = 5.3 Hz, OH), 5.63 (s, 2H, OCH_2N), 7.28 (s, 2H, NH_2), 8.16 (s, 1H, 2-H), 8.24 (s, 1H, 8-H); Anal. Calcd. for $C_{10}H_{15}N_5O_4$: C, 44.35; H, 5.53; N, 25.31. Found: C, 44.60; H, 5.61; N, 26.01.

1-[(1',(3'S),4'-Trihydroxy-(2'S)-butoxy)methyl]cytosine **13b**.-This compound was obtained following the aforementioned procedure. m.p>300°C (from methanol-chloroform); $[\alpha]_D^{20}$ +7° (c 1.8, water); UV λ max (EtOH, 95%) 269 nm; ^{1}H NMR (250 MHz, DMSO-d_6) δ 3.28-3.63 (m, 6H, $2CH_2$, 2CH), 4.58 (m, 2H, 2OH), 4.69 (t, 1H, J = 5.1 Hz, OH), 5.15 (q, 2H, J = 9.6 Hz, OCH_2N), 5.7 (d, 1H, J = 7.2 Hz, 5-H), 7.23 d, (2H, J = 26.8 Hz, NH_2), 7.63 (d, 2H, J = 7.2 Hz, 6-H); Anal. Calcd. for $C_9H_{15}N_3O_5$: C, 44.31; H, 6.28; N, 17.32. Found: C, 44.07; H, 6.16; N, 17.13.

9-[(1',(3'S),4'-Trihydroxy-(2'S)-butoxy)methyl]guanine **13c**.-This compound was obtained following the aforementioned procedure. m.p.>300°C (from water); $[\alpha]_D^{20}$ +15.9° (c 1.38, water); UV λ max (EtOH, 95%) 253 nm; ^{1}H NMR (250 MHz, DMSO-d_6) δ 3.23 (t, 2H, J = 5.1 Hz, CH_2), 3.38-3.58 (m, 4H, CH_2, CH), 4.48 (m, 2H, OH), 4.64 (t, 1H, J = 5.8 Hz, OH), 5.43 (s, 2H, OCH_2N), 6.49 (s, 2H, NH_2), 7.78 (s, 1H, 8-H), 10.64 (s, 1H, NH); Anal. Calcd. for $C_{10}H_{15}N_5O_5$: C, 39.94; H, 5.96; N, 23.30. Found: C, 39.60; H, 5.65; N, 23.09.

1-[(1',(3'S),4'-Trihydroxy-(2'S)-butoxy)methyl]thymine **13d**.-This compound was obtained following the aforementioned procedure. m.p. 112-113°C (from methanol-carbon tetrachloride); $[\alpha]_D^{20}$ +7.6° (c 1.3, ethanol, 95%); UV λmax (EtOH, 95%) 264 nm; ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.77 (d, 3H, J = 1.1 Hz, Me), 3.31-3.59 (m, 6H, $2CH_2$, 2CH), 4.5 (m, 2H, OH), 4.64 (t, 1H, J = 5.2 Hz, OH), 5.14 (q, 2H, J = 10.2 Hz, OCH_2N), 7.55 (d, 1H, J = 1.1 Hz, 6-H), 11.27 (s, 1H, NH); Anal. Calcd. for $C_{10}H_{16}N_2O_6$: C, 46.26; H, 6.20; N, 10.51. Found: C, 46.15; H, 6.20; N, 10.76.

9-[(1',(3'R),4'-Trihydroxy-(2'R)-butoxy)methyl]adenine **14a**.-This compound was obtained following the aforementioned procedure. $[\alpha]_D^{20}$ -16.6° (c 1.5, water). It showed the same physical and spectral data as compound **13a**.

1-[(1',(3'R),4'-Trihydroxy-(2'R)-butoxy)methyl]cytosine **14b**.-This compound was obtained following the aforementioned procedure. $[\alpha]_D^{20}$ -7.2° (c 1.8, water). It showed the same physical and spectral data as compound **13b**.

9-[(1',(3'R),4'-Trihydroxy-(2'R)-butoxy)methyl]guanine **14c**.-This compound was obtained following the aforementioned procedure. $[\alpha]_D^{20}$ -15.3° (c 1.37, water). It showed the same physical and spectral data as compound **13c**.

1-[(1',(3'R),4'-Trihydroxy-(2'R)-butoxy)methyl]thymine **14d**.-This compound was obtained following the aforementioned procedure. $[\alpha]_D^{20}$ -7.9° (c 1.38, ethanol, 95%). It showed the same physical and spectral data as compound **13d**.

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