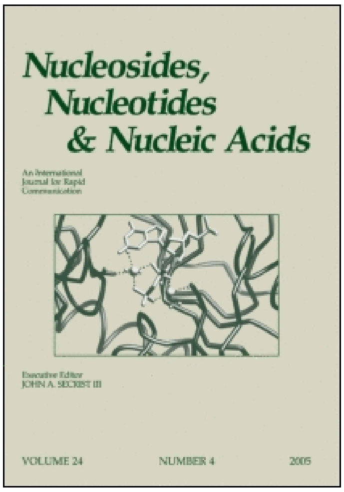


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Enantioselective Synthesis of the Carbocyclic Tetrazole C-Ribonucleosides

Barbara Mohar[a]; Anton Štimac[a]; Jože Kobe[b]
[a] National Institute of Chemistry, Ljubljana [b] Krka, Pharmaceutical and Chemical Works, Novo mesto, Slovenia

To cite this Article Mohar, Barbara , Štimac, Anton and Kobe, Jože(1993) 'Enantioselective Synthesis of the Carbocyclic Tetrazole C-Ribonucleosides', Nucleosides, Nucleotides and Nucleic Acids, 12: 8, 793 — 802
To link to this Article: DOI: 10.1080/07328319308018550
URL: http://dx.doi.org/10.1080/07328319308018550

NUCLEOSIDES & NUCLEOTIDES, 12(8), 793-802 (1993)

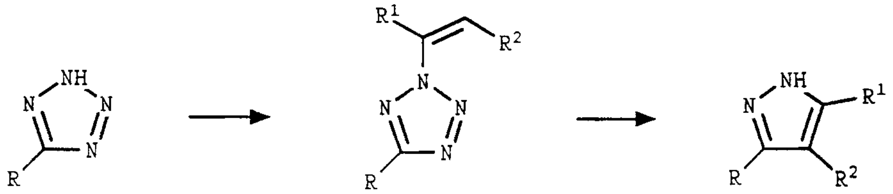
ENANTIOSELECTIVE SYNTHESIS OF THE CARBOCYCLIC TETRAZOLE C-RIBONUCLEOSIDES

Barbara Mohar, Anton Štimac, and Jože Kobe*

National Institute of Chemistry, Hajdrihova 19, 61115 Ljubljana and
Krka, Pharmaceutical and Chemical Works, 68000 Novo mesto, Slovenia.

Abstract: Enantioselective synthesis of the protected derivative of the carbocyclic 5-(β-D-ribofuranosyl)tetrazole **10**, a suitable intermediate for further transformation to the carbocyclic formycin analogs, was accomplished *via* the lactone (+)-**4**.

It has been recently shown, that 5-glycosyl substituted tetrazoles react with electrophiles such as activated alkenes and acetylenes by conjugate addition to give N-1 and/or N-2 alkenyl substituted tetrazoles[1]. Only N-2 alkenyl isomers could be thermally rearranged with concomitant elimination of nitrogen, gaining access to the pyrazole C-nucleosides, which could be further transformed into formycin analogs[2].



In order to test the generality of this approach to C-nucleosides, we extended our investigations also to the structurally related carbocyclic nucleosides[3,4]. Most recently (+)-carbatiazofurin and its enantiomer[5] were found to display cytotoxicity against a breast carcinoma cell line what was the first report on the positive biological leads among carbocyclic C-nucleosides. So far no biological activity was

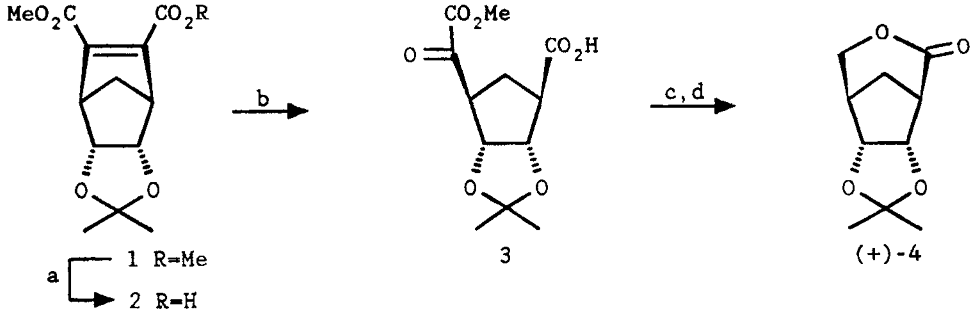
---

This paper is dedicated to Professor Leroy B. Townsend on the occassion of his 60th birthday.

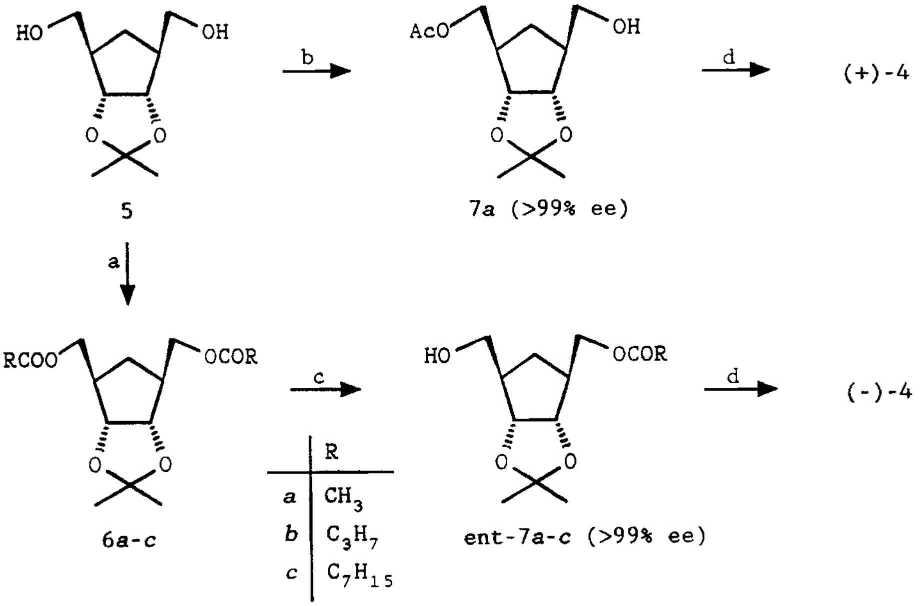
displayed by the rare representatives of this family: (±)-carbapyrazofurin,[6] (±)-carbashowdomycin,[6,7] and (±)-carbaoxazinomycin.[8] These findings certainly support future research in this area.

Reported in this work is the general enantioselective approach to the novel carbocyclic analog of 5-(β-D-ribofuranosyl)tetrazole **10** *via* the appropriate nitrile (-)-**9** in its "natural" configuration with a possibility to extend the synthesis to its antipode (+)-**9**.[9] We reasoned that the Ohno's lactone (+)-**4** might be the most suitable starting material for the preparation of carbocyclic C-nucleosides of the β-D-ribo configuration. (+)-**4** served as a central intermediate in several syntheses of the natural carbocyclic nucleosides (-)-aristeromycin[10] and (-)-neplanocin A[11], since it could be obtained in a homochiral form using different strategies of asymmetric synthesis.[12-16] Taking into account the experimental simplicity and availability of reagents, we selected the original Ohno's procedure[12] (Scheme 1), which made use of the pig liver esterase (PLE) catalyzed asymmetric hydrolysis of the *meso*-diester **1** to make **2**.[17] The half ester **2** thus produced showed an ee *ca* 80% and was further transformed in five stages into the lactone (+)-**4**. This procedure was thus subjected to certain modifications on a synthetic scale (0.4 mol) with respect to the Ohno's small scale experiment.[12] For example, the use of immobilized PLE[18] allowed its easy recovery and reuse for several times without significant loss of the enzymic activity. It was even more important to modify the reduction of keto ester **3** in a way[19], that a slow addition of methanol to the refluxing mixture of **3** and sodium borohydride in *tert*-butanol was introduced instead. Considering these improvements, the lactone (+)-**4** was prepared in 36.5% overall yield from a diester **1**, including recrystallization, which readily provided this key intermediate in optically pure form: $[\alpha]_D^{22}$ +44.4° (*ca* 100% ee).

In addition, we have recently developed another chemico-enzymatic approach[9] to both enantiomeric forms of **4** (Scheme 2). Thus, starting from the readily available *meso*-diol **5**[20] we were able to carry out either enantioselective enzymatic transesterification by vinyl acetate in anhydrous medium to give the chiral monoester **7a** or hydrolysis of its diesters **6a-c** in aqueous medium to give **ent-7a-c**.[21] Several lipases were examined for their hydrolytic and esterification activity and the microbial lipase from *Pseudomonas sp.* (SAM-2) gave the best results in both directions. The absolute configurations of **7a** and **ent-7a-c** were established by their three step transformations involving oxidation, hydrolysis of the ester group, and lactonization into the antipodal lactones (+)- and (-)-**4**, respectively.

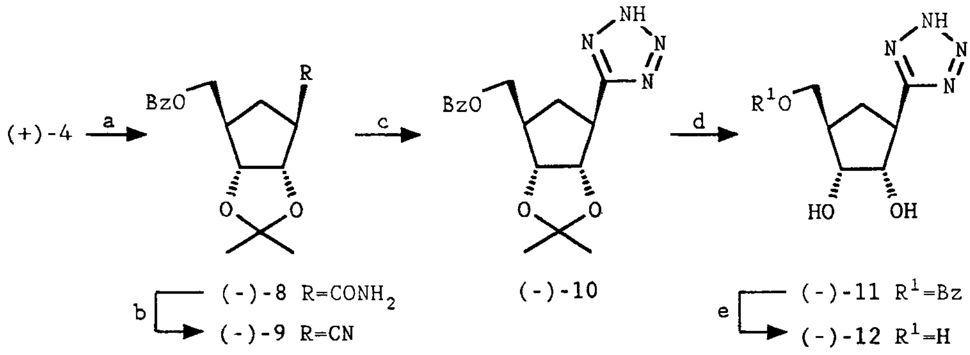


SCHEME 1
(a) immobilized PLE, pH=8, 32°C
(b) O_3/EtOAc
(c) i, $NaBH_4$, t-BuOH/MeOH; ii, $NaIO_4$; iii, $NaBH_4$
(d) Ac_2O/Py; then cryst.



	R
a	CH_3
b	C_3H_7
c	C_7H_{15}

SCHEME 2
(a) $(RCO)_2O/Et_3N$/DMAP/MeCN
(b) lipase SAM-2/vinyl acetate/$(CH_2Cl)_2$, 45°C
(c) lipase SAM-2/H_2O, pH=7, r.t.
(d) i, PDC/DMF; ii, OH^-; iii, Ac_2O/Py



SCHEME 3 (a) i, NH_3/MeOH, r.t.; ii, BzCl/Py, 0°C or Bz_2O/Et_3N/DMAP/MeCN
(b) $(CF_3CO)_2O$/Py/THF, 5°C → r.t.
(c) $LiN_3/PyH^+CF_3COO^-$/Py, 120°C
(d) 2M HCl/MeOH (1:2)
(e) aq. $MeNH_2$

Bz=benzoyl

Having the optically pure lactone (+)-**4** in hand, the synthesis of "natural" enantiomer of the carbocyclic tetrazole nucleoside **10** was realized in a straightforward manner (Scheme 3). Opening of the lactone with ammonia followed by benzoylation gave the protected crystalline amide **8**. The use of benzoic anhydride instead of benzoyl chloride provided cleaner reaction and easier workup in the protection step. The amide **8** was then smoothly dehydrated[22] with trifluoroacetic anhydride to the target nitrile **9**. In the last step, we tried to bring about the azide to nitrile **9** cycloaddition under different conditions and combinations of azides, solvents, and catalysts according to known methods.[23,24] In most cases, however, only moderate conversions to the target tetrazole **10** or its partial decomposition were observed. Fortunately, this reaction could be easily accomplished by using lithium azide (5 equiv.) in pyridine at 120°C when catalyzed by pyridinium trifluoroacetate. Fully deblocked tetrazole **12** was prepared by deisopropylidenation of **10** in acidic medium followed by treatment of the crystalline benzoate **11** with aqueous methylamine. The structures of all new compounds were confirmed by analytical and ^1H, ^{13}C-NMR, and mass spectral data.

The chemistry of **10** closely parallels that of its oxygenated counterpart.[1] Initial experiments show, for example, that **10** reacts with dimethyl 2,3-pentadienedioate to give a 1:4 N-1/N-2 mixture of alkenylated tetrazoles. The utility of the latter in the synthesis of carbocyclic analogs of formycin is currently under investigation.

Experimental Part

Abbreviations. -DMAP, 4-(dimethylamino)pyridine; DMF, N,N-dimethylformamide; PDC, pyridinium dichromate; PLE, pig liver esterase; Py, pyridine.

Materials and methods. -The immobilized PLE (*ca* 31 kUnits) was prepared by the method of Schneider *et. al.*[18] from the soluble PLE (46 kUnits, standard ethyl butyrate; Sigma No. E-3128) and oxirane acrylic beads (12 g, Sigma No. O-7628). Lithium azide was prepared as described previously[25] and dried at 100°C in *vacuo* over P_4O_{10}. Pyridine, acetonitrile, and THF were dried by refluxing with respectively BaO, P_4O_{10}, and $LiAlH_4$, and then distilled. Other reagents and solvents were of commercial purity. Evaporations were conducted in *vacuo* with a rotary evaporator. Flash chromatography was carried out on Silica gel 60 (40-63 μm, Merck) and analytical TLC on precoated plates Silica gel 60 F_{254} (Merck). The spots were visualized by irradiation with UV light (254 nm) or by spraying with 10% H_2SO_4 in ethanol or with 3.5% phosphomolybdic acid in ethanol, and heating.

Melting points were determined on a Kofler apparatus and are uncorrected. Mass spectra were recorded on an AutospecEQ spectrometer in the fast-atom-bombardment (FAB) mode at the Jožef Stefan Institute, Ljubljana. Microanalyses were performed at the Department of Chemistry, University of Ljubljana. Optical rotations were measured on a Perkin Elmer 241 MC polarimeter. ^1H- (299.94 MHz) and ^{13}C-NMR (75.43 MHz) spectra were recorded with a Varian VXR-300 instrument. Me_4Si was used as an internal reference for solutions in $CDCl_3$ (δ_C 77.00 ppm) or Me_2SO-d_6 (δ_C 39.50 ppm). Sodium 3-(trimethylsilyl)-1-propanesulfonate (DSS) was used as an internal reference ($\delta_{H(Me)}$ and $\delta_{C(Me)}$ 0 ppm) for solutions in D_2O. Chemical shifts and coupling constants were obtained from a first order analysis of the spectra. The spectra were assigned by means of the corresponding ^1H-^1H and ^{13}C-^1H chemical shift correlated spectra.

(1R, 5R, 6R, 7S)-6,7-(isopropylidenedioxy)-3-oxabicyclo[3.2.1]octan-2-one (4). -A mixture of the diester 1[26] (30.0 g, 0.106 mol) in acetone (200 mL) and 0.1 M phosphate buffer (2500 mL, pH 8) was treated with the immobilized PLE (*ca* 31 kUnits), and mechanically stirred at 32°C for 4.5 h. The reaction was terminated by filtration of the enzyme. The aqueous solution was acidified to pH 2 with 2 M HCl and extracted with CH_2Cl_2 (6 x 700 mL). The extract was dried (Na_2SO_4) and concentrated to give the half ester **2** (27.8 g, 97%) as a white solid with mp 115-119°C, $[\alpha]_D^{25}$ -23.5° (*c* 1.17, $CHCl_3$) {ref.[12] mp 115-118°C, $[\alpha]_D^{25}$ -23.8° (*c* 1.17, $CHCl_3$)}. The half ester **2** (104.6 g, 0.39 mol), prepared by repeating of the above procedure using the same immobilized enzyme, was ozonizated in ethyl acetate (1000 mL) as already reported[12] to afford the keto ester **3** (105.0 g) as a slightly yellow syrup. Dry MeOH (300 mL) was added over a period of 5 h to the refluxing mixture of **3** and $NaBH_4$ (32 g, 0.85 mol) in *tert*-butanol (1000 mL). The mixture was refluxed for additional 2 h, then cooled in ice water, and neutralized with 2 M HCl. The white precipitate was dissolved by addition of water (500 mL). $NaIO_4$ (98 g, 0.46 mol) was added and the mixture stirred at r.t. overnight. Another portion of $NaIO_4$ (11 g, 0.05 mol) was added and stirring continued for 2 h. The white precipitate was removed by filtration and washed with MeOH (200 mL). $NaBH_4$ (32 g, 0.85 mol) was added portionwise to the filtrate below 35°C, the mixture was stirred at r.t. overnight, and neutralized with 2 M HCl. Solvents were evaporated to dryness and the residue stirred with pyridine (500 mL) and acetic anhydride (300 mL) at r.t. overnight. The mixture was concentrated and the residue extracted with hot CH_2Cl_2 (5 x 400 mL). The extract was concentrated and the residue treated with sat. aq. $NaHCO_3$ (250 mL). The crude lactone **4** (48 g) was filtered and washed with water. Another portion of this material (14 g) was obtained by extraction of the combined filtrate and washings with CH_2Cl_2 (4 x 250 mL), drying of extracts (Na_2SO_4), and concentration. The crude **4** was purified first by silica gel chromatography using a gradient of EtOAc (0-50%) in CH_2Cl_2, followed by washing of the appropriate combined fractions (47 g) with isopropyl ether (200 mL), and recrystallization from CH_2Cl_2 : Et_2O : n-hexane (1 : 5 : 5). The optically pure title compound **4** (28.2 g, 36.5%) was obtained as large colorless needles with mp 142-143°C, $[\alpha]_D^{22}$ +44.4° (*c* 1.0, $CHCl_3$) {ref.[12] mp 140-141.5°C, $[\alpha]_D^{25}$ +44.4° (*c* 1.0, $CHCl_3$)}. ^1H- and ^{13}C-NMR spectra are in accordance with the literature values.[12]

(1R, 2S, 3R, 4R)-4-(Benzoyloxymethyl)-2,3-(isopropylidenedioxy)cyclopentane-1-carboxamide (8). *Method A:* -Lactone (+)-**4** (20.0 g, 0.10 mol) was treated with methanolic NH_3 (27%, 200 mL) at r.t. overnight and then the solution was concentrated. Benzoyl chloride (15 mL, 0.12 mol) was added dropwise to the solution of the residue in pyridine (200 mL) below 0°C. The mixture was kept in freezer overnight, then treated with MeOH (5 mL) for 15 min, filtered and concentrated. The residue was dissolved in EtOAc (500 mL), washed with water (2 x 150 mL) and brine (150 mL), and dried (Na_2SO_4). Concentration gave an oily residue, which was chromatographed on silica gel with CH_2Cl_2 and CH_2Cl_2/i-PrOH

(10 : 1) to give 8 (27.2 g, 84%) as a colorless solid, mp 99-101°C (hexane/EtOAc), $[\alpha]_D^{22}$ -25.2° (*c* 1.50, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.32 and 1.53 (2s, 6H, 2 Me), 1.92 (td, 1H, H-5a), 2.29 (td, 1H, H-5b), 2.55 (m, 1H, H-4), 2.83 (ddd, 1H, H-1), 4.36 and 4.40 (2 dd, 2H, $C\underline{H}_2OBz$; J_{gem} 11.3, $J_{4,Ha}$ 6.4, $J_{4,Hb}$ 6.6 Hz), 4.52 (dd, 1H, H-3), 4.75 (dd, 1H, H-2), 5.88 and 6.05 (2 br s, 2H, NH_2), 7.44, 7.57, and 8.04 (3 m, 5H, Ph); $J_{1,2}$ 5.9, $J_{1,5a}$ and $J_{4,5a}$ 11.0, $J_{1,5b}$ and $J_{4,5b}$ 7.1, $J_{2,3}$ 6.8, $J_{3,4}$ 4.4, $J_{5a,5b}$ 13.2 Hz; ^{13}C-NMR ($CDCl_3$) δ 25.00 and 27.45 (2 Me), 31.17 (C-5), 44.31 (C-4), 50.83 (C-1), 65.42 ($\underline{C}H_2OBz$), 82.72 (C-3), 83.22 (C-2), 113.11 ($\underline{C}Me_2$), 128.34, 129.55, 129.91, and 132.99 (Ph), 166.39 ($\underline{C}OPh$), 175.19 ($CONH_2$). HRMS: m/z MH^+calcd for $C_{17}H_{22}NO_5$ 320.1498, found 320.1498.

Anal. Calcd for $C_{17}H_{21}NO_5$ (319.36): C, 63.94; H, 6.63; N, 4.38. Found: C, 63.74; H, 6.66; N, 4.22.

Method B: -Lactone (+)-4 (4.55 g, 23 mmol) was treated with methanolic NH_3 (45 mL) as described above. Benzoic anhydride (Bz_2O) (6.11 g, 27 mmol) and DMAP (90 mg) were added to a solution of the concentrated residue (4.95 g) in a mixture of acetonitrile (40 mL) and Et_3N (4.23 mL, 30 mmol). After 4 h stirring at r.t. additional portions of Bz_2O (2.04 g, 9 mmol) and Et_3N (1.27 mL, 9 mmol) were added and stirring continued for 4.5 h. The mixture was treated with sat. aq. $NaHCO_3$ (80 mL) for 30 min, and the solution was extracted with EtOAc (2 x 100 mL). The extract was washed with water (100 mL) and brine (60 mL), and dried (Na_2SO_4). Concentration afforded a crude product (7.13 g), which was crystallized from n-hexane/EtOAc to give 8 (6.90 g, 94%) as a colorless solid, mp 99-101°C, $[\alpha]_D^{22}$ -25.1° (*c* 1.50, $CHCl_3$).

(1S, 2S, 3R, 4R)-4-(Benzoyloxymethyl)-2,3-(isopropylidenedioxy)cyclopentane-1-carbonitrile (9). -Trifluoroacetic anhydride (4.8 mL, 36 mmol) was added dropwise to a stirred solution of 8 (10.0 g, 31 mmol) and pyridine (5.0 mL, 62 mmol) in THF (50 mL) at a temperature below 5°C. The mixture was stirred at r. t. for 3 h, concentrated, and partitioned between CH_2Cl_2 (250 mL) and water (150 mL). Organic phase was dried (Na_2SO_4) and concentrated to give **9** (9.12 g, 97%) as an oil, $[\alpha]_D^{22}$ -31.7° (*c* 1.49, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.32 and 1.49 (2s, 6H, 2 Me), 1.99 (td, 1H, H-5a), 2.50 (td, 1H, H-5b), 2.64 (quasi d of quintets, 1H, H-4), 2.98 (dt, 1H, H-1), 4.38 and 4.45 (2 dd, 2H, $C\underline{H}_2OBz$; J_{gem} 11.4, $J_{4,Ha}$ 6.5, $J_{4,Hb}$ 7.0 Hz), 4.63 (dd, 1H, H-3), 4.86 (dd, 1H, H-2), 7.46, 7.59, and 8.05 (3 m, 5H, Ph); $J_{1,2}$ 4.1, $J_{1,5a}$, $J_{1,5b}$, $J_{4,5a}$, and $J_{4,5b}$ 7.4, $J_{2,3}$ 6.3, $J_{3,4}$ 3.2, $J_{5a,5b}$ 13.6 Hz; ^{13}C-NMR ($CDCl_3$) δ 24.64 and 26.97 (2 Me), 31.63 (C-5), 34.96 (C-1), 44.69 (C-4), 64.30 ($\underline{C}H_2OBz$), 82.58 (C-3), 83.56 (C-2), 112.99 ($\underline{C}Me_2$), 120.49 (CN), 128.44, 129.61, 129.65, and 133.23 (Ph), 166.19 (CO). HRMS: m/z MH$^+$calcd for $C_{17}H_{20}NO_4$ 302.1392, found 302.1398.

Anal. Calcd for $C_{17}H_{19}NO_4$ (301.35): C, 67.76; H, 6.35; N, 4.65. Found: C, 67.62; H, 6.32; N, 4.69. Analytical sample, mp 81.5-82.5°C, was obtained by crystallization from isopropyl ether.

5-[(1'S, 2'S, 3'R, 4'R)-4-(Benzoyloxymethyl)-2,3-(isopropylidenedioxy)cyclopentan-1-yl]-1H-tetrazole (10). -A solution of **9** (5.00 g, 17 mmol), LiN_3 (4.0 g, 83 mmol), and pyridinium trifluoroacetate (3.80 g, 20 mmol) in pyridine (25 mL) was heated in a pressure tube at 120°C for 3.5 h and concentrated. The residue was dissolved in water (150 mL), acidified to pH 4, and washed with CH_2Cl_2 (2 x 100 mL) to remove the unreacted **9**. The aqueous solution was continuously extracted with EtOAc for 1 d, the extract was dried (Na_2SO_4), and concentrated. The residue was chromatographed on silica gel with a gradient of MeOH (0 - 10%) in CH_2Cl_2 to give **10** (5.02 g, 88%) as a light yellow foam, R_F 0.5 (5 : 1 CH_2Cl_2/MeOH); $[\alpha]_D^{22}$ -27.8° (*c* 1.29, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.32 and 1.53 (2s, 6H, 2 Me), 2.14 (td, 1H, H-5'a), 2.65 (td, 1H, H-5'b), 2.73 (m, 1H, H-4'), 3.67 (td, 1H, H-1'), 4.40 (d, 2H, $C\underline{H}_2OBz$; J_{vic} 6.2 Hz), 4.67 (dd, 1H, H-3'), 4.95 (t, 1H, H-2'), 7.45, 7.57, and 8.06 (3 m, 5H, Ph); $J_{1',2'}$ 6.5, $J_{1',5'a}$ and $J_{4',5'a}$ 10.5, $J_{1',5'b}$ and $J_{4',5'b}$ 6.5, $J_{2',3'}$ 6.5, $J_{3',4'}$ 4.3, $J_{5'a,5'b}$ 12.7 Hz; ^{13}C-NMR ($CDCl_3$) δ 25.06 and 27.42 (2 Me), 33.29 (C-5'), 41.09 (C-1'), 44.67 (C-4'), 65.41 ($\underline{C}H_2OBz$), 82.70 (C-3'), 84.57 (C-2'), 113.87 ($\underline{C}Me_2$), 128.51, 129.66, 130.20, and 133.32 (Ph), 158.10 (C-5), 166.84 (CO). HRMS: m/z MH$^+$calcd for $C_{17}H_{21}N_4O_4$ 345.156, found 345.157.

Anal. Calcd for $C_{17}H_{20}N_4O_4$ (344.37): C, 59.29; H, 5.85; N, 16.27. Found: C, 59.06; H, 5.86; N, 16.18.

5-[(1'S, 2'S, 3'R, 4'R)-4-(Benzoyloxymethyl)-2,3-(dihydroxy)cyclopentan-1-yl]-1H-tetrazole (11). -A solution of **10** (470 mg, 1.36 mmol) in MeOH (10 mL) containing 2 M HCl (5 mL) was stirred at r.t. for 4.5 h. The mixture was concentrated to 1/3 of its volume, diluted with water (10 mL) and extracted with EtOAc (20 mL). The extract was washed with water (2 x 5 mL) and evaporated to dryness. The crude product was crystallized from EtOAc to give **11** (276 mg, 66.5%) as colorless crystals with mp 152-153°C; R_F 0.3 (5 : 1 CH_2Cl_2/MeOH); $[\alpha]_D^{22}$ -35.3° (*c* 1.56, MeOH); ^{1}H-NMR (Me_2SO-d_6, D_2O treated) δ 1.70 (ddd, 1H, H-5'a), 2.38 (td, 1H, H-5'b), 2.47 (m, 1H, H-4'), 3.48 (td, 1H, H-1'), 3.94 (t, 1H, H-3'), 4.08 (dd, 1H, H-2'), 4.33 and 4.40 (2 dd, 2H, $C\underline{H}_2OBz$; J_{gem} 11.0, $J_{4',Ha}$ and $J_{4',Hb}$ 5.9 Hz), 7.56, 7.70, and 8.01 (3 m, 5H, Ph); $J_{1',2'}$ and $J_{1',5'b}$ and $J_{4',5'b}$ 8.0,

$J_{1',5'a}$ 10.1, $J_{2',3'}$ and $J_{3',4'}$ 5.0, $J_{4',5'a}$ 8.1, $J_{5'a,5'b}$ 12.7 Hz; ^{13}C-NMR (Me_2SO-d_6, D_2O treated) δ 29.35 (C-5'), 38.89 (C-1'), 43.50 (C-4'), 66.39 (<u>C</u>H_2OBz), 73.57 (C-3'), 77.00 (C-2'), 129.23, 129.63, 130.05, and 133.90 (Ph), 158.29 (C-5), 166.46 (CO). HRMS: m/z MH^+calcd for $C_{14}H_{17}N_4O_4$ 305.1250, found 305.1252.

Anal. Calcd for $C_{14}H_{16}N_4O_4$ (304.31): C, 55.26; H, 5.30; N, 18.41. Found: C, 55.11; H, 5.19; N, 18.81.

5-[(1'S, 2'S, 3'R, 4'R)-2,3-dihydroxy-4-(hydroxymethyl)cyclopentan-1-yl]-1H-tetrazole (12). -A solution of 11 (130 mg, 0.43 mmol) in 40% aq. $MeNH_2$ (5 mL) was stirred at r.t. for 1.5 h and concentrated. The residue was dissolved in water (15 mL) and washed with CH_2Cl_2 (4 x 15 mL). The aqueous solution was acidified with Dowex 50W-X8 (H^+ form) and stirred at r.t. overnight. The resin was filtered and the filtrate was concentrated to provide the title compound **12** (75 mg, 88%) as a colorless hygroscopic foam, R_F 0.07 (5 : 1 CH_2Cl_2/MeOH); $[\alpha]_D^{22}$ -55.9° (*c* 2.1, H_2O); ^{1}H-NMR (D_2O) δ 1.62 (ddd, 1H, H-5'a), 2.32 (m, 1H, H-4'), 2.46 (td, 1H, H-5'b), 3.60 (td, 1H, H-1'), 3.66 and 3.72 (2 dd, 2H, C<u>H</u>$_2$OH; J_{gem} 11.2, $J_{4',Ha}$ 6.3 $J_{4',Hb}$ 6.4 Hz), 4.05 (dd, 1H, H-3'), 4.21 (dd, 1H, H-2'); $J_{1',2'}$ 8.8, $J_{1',5'a}$ 11.0, $J_{1',5'b}$ and $J_{4',5'b}$ 8.8, $J_{2',3'}$ 5.4, $J_{3',4'}$ 3.7, $J_{4',5'a}$ 8.3, $J_{5'a,5'b}$ 13.0 Hz; ^{13}C-NMR (D_2O) δ 31.21 (C-5'), 41.00 (C-1'), 48.75 (C-4'), 65.87 (<u>C</u>H_2OH), 76.14 (C-3'), 79.22 (C-2'), 160.67 (C-5). HRMS: m/z MH^+calcd for $C_7H_{13}N_4O_3$ 201.0988, found 201.0986.

Anal. Calcd for $C_7H_{12}N_4O_3$ (200.20): C, 42.00; H, 6.04. Found: C, 42.06; H, 5.98. Analytical sample, mp 114-115°C, was obtained by crystallization from acetonitrile.

Acknowledgments: This investigation was supported by the Ministry of Science and Technology of Slovenia (Grant Nos. 33-0330 and CI-01513). We thank dr. Bogdan Kralj from Jožef Stefan Institute for mass spectra determinations.

REFERENCES AND NOTES

1. Prhavc, M., Townsend, L.B., Kobe, J. *Nucleosides&Nucleotides* **1991**, <u>10</u>, 729.
2. Prhavc, M. *Dissertation,* University of Ljubljana, Ljubljana, 1993. Presented in part at the 10th International Round Table "Nucleosides, Nucleotides and their Biological Applications", Park City, Utah, September 1992.
3. Marquez, V.E., Lim, M.I. *Med. Res. Rev.* **1986**, <u>6</u>, 1.
4. Borthwick, A.D., Biggadike, K. *Tetrahedron* **1992**, <u>48</u>, 571.

5. Dishington, A.P., Humber, D.C., Stoodley, R.J. *J. Chem. Soc. Perkin Trans.1* **1993**, 57.
6. Just, G., Kim, S. *Tetrahedron Lett.* **1976**, 1063.
7. Saksena, A.K., McPhail, A.T., Onan, K.D. *Tetrahedron Lett.* 1981, 2067.
8. Katagiri, N., Tomura, M., Haneda, T., Kaneko, C. *J. Chem. Soc., Chem. Commun.* 1987, 1422.
9. A detailed report will be published separately.
10. *Synform* **1989**, 7, 192.
11. *Synform* 1989, 7, 225.
12. Arita, M., Adachi, K., Ito, Y., Sawai, H., Ohno, M. *J. Am. Chem. Soc.* 1983, 105, 4049.
13. Arai, Y., Hayashi, Y., Yamamoto, M., Takayama, H., Koizumi, T. *Chem. Lett.* 1987, 185; *idem., J. Chem. Soc. Perkin Trans. 1* **1988**, 3133.
14. Arai, Y., Hayashi, K., Koizumi, T., Shiro, M., Kuriyama, K. *Tetrahedron Lett.* **1988**, 6143; Arai, Y., Hayashi, K., Matsui, M., Koizumi, T., Shiro, M., Kuriyama, K. *J. Chem. Soc. Perkin Trans. 1* **1991**, 1709.
15. Katagiri, N., Haneda, T., Hayasaka, E., Watanabe, N., Kaneko, C. *J. Org. Chem.* **1988**, 53, 226; *idem., Chem. Pharm. Bull.* **1988**, 36, 3867.
16. Helmchen, G., Hady, A.F.A., Hartmann, H., Karge, R., Krotz, A., Sartor, K., Urmann, M. *Pure&Appl. Chem.* **1989**, 61, 409.
17. For another approach to the half ester **2** on a large scale using pig liver acetone powder see: Adachi, K., Kobayashi, S., Ohno, M. *Chimia* **1986**, 40, 311.
18. Laumen, K., Reimerdes, E.H., Schneider, M. *Tetrahedron Lett.* **1985**, 407.
19. Soai, K., Oyamada, H., Takase, M., Ookawa, A. *Bull. Chem. Soc. Jpn.* **1984**, 57, 1948.
20. Just, G., Reader, G., Chalard-Faure, B. *Can. J. Chem.* **1976**, 54, 849.
21. For a closely related work on the enzymatic hydrolysis/transesterification of 1,2-cycloalkanedimethanol derivatives see: Ader, U., Breitgoff, D., Klein, P., Laumen, K.E., Schneider, M.P. *Tetrahedron Lett.* **1989**, 1793.
22. Campagna, F., Carotti, A., Casini, G. *Tetrahedron Lett.* **1977**, 1813.
23. Finnegan, W.G., Henry, R.A., Lofquist, R. *J. Am. Chem. Soc.* 1958, 80, 3908.
24. Bernstein, P.R., Vacek, E.P. *Synthesis* **1987**, 1133.
25. Hofman-Bang, N. *Acta Chem. Scand.* **1957**, 11, 581.
26. Danishefsky, S., Hirama, M., Gombatz, K., Harayama, T., Berman, E., Schuda, P.F. *J. Am. Chem. Soc.* **1979**, 101, 7020.

Received 4/28/93
Accepted 6/10/93