# A Synthetic Route to Fully Substituted Chiral Cyclopentylamine Derivatives: Precursors of Carbanucleosides

Ramprasad Ghosh,[a] Joy Krishna Maity,[a] Michael G. B. Drew,[b] Basudeb Achari,[a] Sukhendu B. Mandal*[a]

[a] Chemistry Division, Indian Institute of Chemical Biology (a unit of CSIR), Jadavpur, Kolkata 700 032, India
Fax +91(33)24735197; E-mail: sbmandal@iicb.res.in

[b] Department of Chemistry, University of Reading, Whiteknights, Reading, RG6 6AD, UK

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**Abstract:** Removal of silyl protection from D-glucose derived substrate **6** afforded **7**, which upon acetonide deprotection followed by reaction with *N*-benzylhydroxylamine furnished two isomeric isoxazolidinocyclopentane derivatives via spontaneous cyclization of an in situ generated nitrone. The methyl xanthate derivative of the tertiary hydroxyl group of one isomer was isolated and subjected to radical deoxygenation reaction to form epimeric products, while with the other isomer it underwent spontaneous 1,2-elimination to form a mixture of the two possible endocyclic olefins. Hydrogenolytic cleavage of the isoxazolidine rings of the purified products followed by insertion of 5-amino-4-chloropyrimidine moiety and purine ring construction smoothly afforded structurally unique carbanucleoside analogues. Various spectroscopic methods on the synthesized compounds and X-ray analysis on one important intermediate were used to assign the structures and stereochemistry of the products.

**Key words:** cyclopentylamine, INC reaction, carbanucleosides, D-glucose

Natural nucleosides, susceptible to various enzymes for glycosidic bond cleavage,[1] exist in a dynamic equilibrium between North-type and South-type geometry[2] in solution due to rapid change of the furanose ring in the pseudorotational cycle in which a conformationally unrestricted furanose ring can adopt a number of envelope or twist forms. However, only one conformer is found in the solid state and only one conformer is responsible for forming a nucleoside-enzyme complex, which shows activity. Thus, much attention has been given to structural modifications of nucleosides[3] to confer metabolic stability as well as conformational restriction in the furanose ring. Various analogues of substituted cyclopentane containing carbanucleosides[4–7] have been synthesized for potential antiviral activity.[8] They are inert towards free radical-induced degradation by C-4′-H abstraction[9] as is observed with the ribose ring. The importance of the carbanucleosides has been realized after the isolation of (–)-aristeromycin[10] (**1**) and (–)-neplanocin A (**2**),[11] both displaying antibiotic and antitumor activity, from natural sources (Figure 1). By modifying these biologically active compounds, structurally similar but non-natural synthetic carbanucleoside analogues are generated where the molecular complexity is kept to a minimum whilst improvements are realized in regard to the desired pharmacological activity. Among such nucleosides, carbovir (**3**),[12] abacavir (**4**),[13] (–) BCA (**5**),[14] carba-5-bromovinyl-2′-deoxyuridine,[15] and carba-2′-*ara*-fluoroguanosine[16] are important due to their potent anti-HIV activity in vitro. In addition, many of the intermediate aminocarbocycles have glycosidase inhibitory activity[17] or are used as antibiotics.[18]

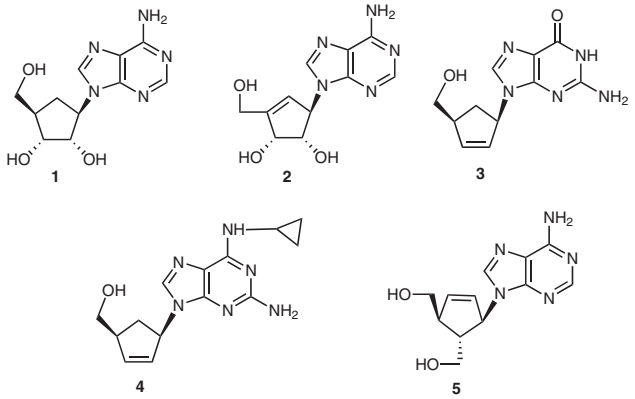


**Figure 1** Structure of some carbanucleosides **1**–**5**

Based on these observations, we describe herein an approach to the synthesis of fully substituted and more crowded cyclopentylamine derivatives, precursors of carbanucleosides, through an application of intramolecular nitrone cycloaddition (INC) reactions[19,20] on an appropriate sugar derived substrate having requisite functionalities at the proper positions.

We started our investigation by synthesizing cyclopentylamine derivatives via INC reaction on D-glucose derived precursors. Toward this end, removal of silyl protection from **6**[21]by tetrabutylammonium fluoride furnished **7** (93%), which upon acetonide deprotection followed by reaction with benzylhydroxylamine (Scheme 1) in refluxing ethanol generated two isomeric isoxazolidinocyclopentane derivatives **9** (36%) and **10** (32%) through the in situ generated 1,3-dipolar enose nitrone **8**. The success of this reaction was evident from the absence of olefinic proton signals and the occurrence of ten aromatic proton signals in the $^1$H NMR spectra of these two products. An alternative bridged [3.2.1] structure, which could have formed through the other mode of cyclization, was ruled out from the absence of upfield proton and carbon signals

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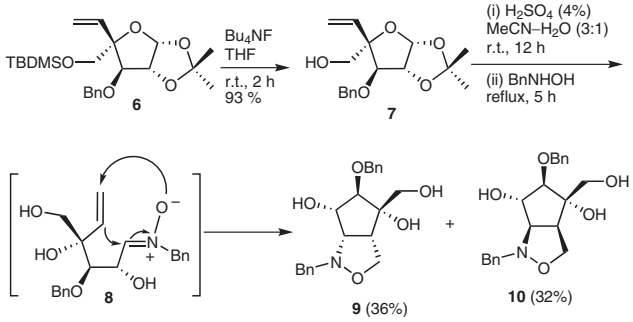
for a methylene group in the $^{1}H$ and $^{13}C$ NMR spectra. Since these isoxazolidino-cyclopentanes belong to the bicyclo[3.3.0]octane system, the ring juncture stereochemistry of *cis* should be energetically favored. Structural confirmation was finally obtained from a single crystal X-ray crystallographic study (the ORTEP diagram is given in Figure 2) of **9**. The structure of **10** was thus settled as indicated in the structure.




**Scheme 1** Cyclopentane derivatives **9** and **10** through INC reaction

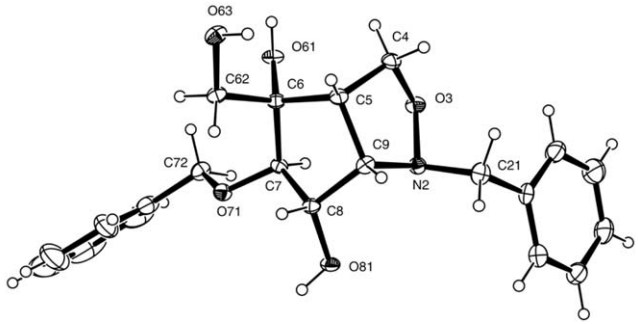
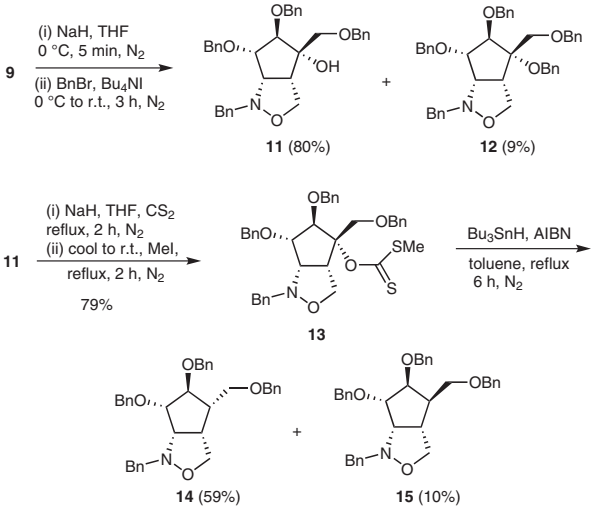



**Figure 2** ORTEP diagram of **9** with ellipsoids at 50% probability

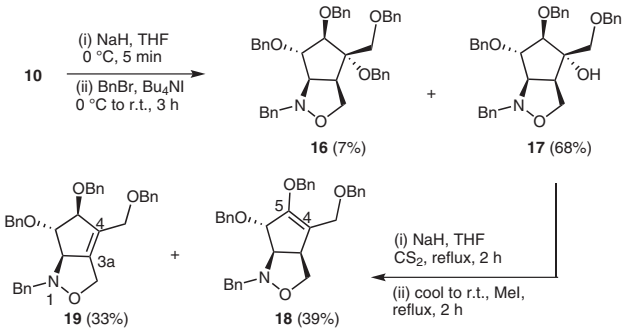
We next turned our attention to deoxygenating the tertiary hydroxyl group generating a number of cyclopentane derivatives with different substitution patterns. Thus, selective benzylation (NaH, BnBr, $Bu_4NI$) to protect the primary and secondary hydroxyl groups of **9** furnished the derivative **11** (Scheme 2) in 80% yield together with the fully substituted minor product **12**. Protection of the hydroxy group in **11** as methyl xanthate (using NaH, $CS_2$, MeI) afforded **13** (79%). Radical-induced reduction of the methyl xanthate group with $Bu_3SnH$ and AIBN furnished a mixture of **14** (59%) and **15** (10%). Formation of **14** as the major product could be anticipated as the approach of the hydrogen radical to the tertiary carbon radical from the *exo*-face of the 5,5-bicycle takes place preferentially due to the hindrance offered by the isoxazolidine ring in the *endo*-face.

Similar benzylation of **10** produced the major product **17** (68%) together with the minor compound **16** (7%). During the preparation of the methyl xanthate of **17** for deoxygenation reaction, the olefinic compounds **18** and **19** were, however, obtained instead in almost equivalent yields



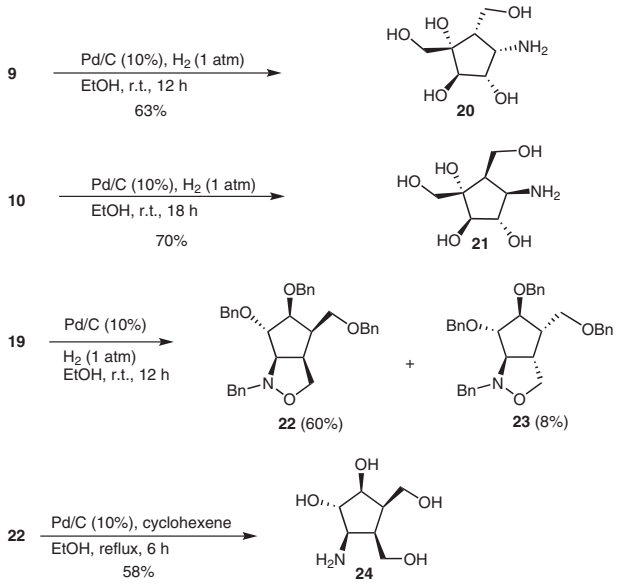

**Scheme 2** Removal of tertiary hydroxy group of **9**

(Scheme 3). The disposition of the double bond was deduced by the appearance of carbon signals in **18** at δ = 117.5 (C-4) and 151.6 (C-5) and in **19** at δ = 128.8 (C-4) and 141.7 (C-3a) in their $^{13}C$ NMR spectra. The facile 1,2-elimination in case of **17** as contrasted with **11** appears to be due to the absence of steric hindrance by the isoxazolidine ring (in the β-face) to cyclic transition state formation in the former case.



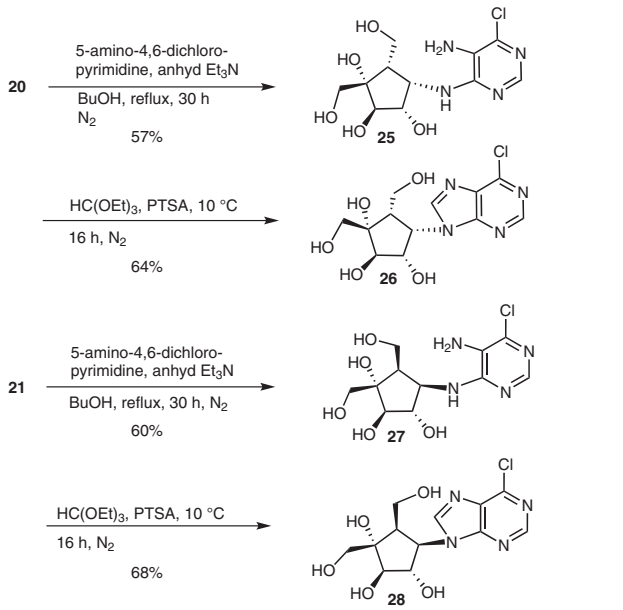

**Scheme 3** Formation of olefins **18** and **19** during the preparation of methyl xanthate on **17**

Cleavage of the isoxazolidine rings and removal of the benzyl protections from **9** and **10** by hydrogenation reaction over Pd/C (Scheme 4) afforded their respective cyclopentylamine derivatives **20** (63%) and **21** (70%). Similar hydrogenolysis reaction on **19** furnished **22** (60%) and **23** (8%) as the double bond reduced products;[22] however, the other olefin **18** failed to afford any desired product and furnished instead a mixture of polymeric products. The product **22** on transfer hydrogenolysis reaction with Pd/C–cyclohexene[23]generated the desired amine derivative **24**. The formation of the *cis*-fused isomer as the major product from the hydrogenation reaction of **19** was expected, as the *trans* stereochemistry is energetically unfavorable.




**Scheme 4** Conversion of **9**, **10**, and **19** to cyclopentylamine derivatives

Finally, to demonstrate the feasibility of converting the aminocyclopentane derivatives to the corresponding nucleoside analogues, we chose the products **20** and **21** (Scheme 5). Coupling reaction of **20** with 5-amino-4,6-dichloropyrimidine in refluxing *n*-butanol in presence of triethylamine produced the pyrimidinyl pentahydroxylated carbocycle derivative **25** (57%). Construction of a purine ring from the pyrimidine ring was accomplished by treatment with triethyl orthoformate in acidic medium to furnish the chloropurine carbanucleoside **26** (64%). The diastereomeric carbanucleoside **28** was obtained (68%) via a similar sequence of reactions, namely, by the reaction of **21** with 5-amino-4,6-dichloropyrimidine to **27** (60%) and its reaction with triethyl orthoformate in acidic condition.




**Scheme 5** Preparation of carbanucleosides **26** and **28** from **20** and **21**

In conclusion, this work describes the application of an INC reaction on a D-glucose derived precursor featuring vinyl and hydroxymethyl functionalities at C-4 and a latent aldehyde moiety at C-1 to produce polyhydroxylated aminocarbocycles. These constitute potential intermediates to synthesize bioactive carbanucleosides and unnatural oligonucleotides. An added advantage of this approach is that the aminocarbocycles may have glycosidase inhibitory activity as well.

Melting points were taken in open capillaries and are uncorrected. $^1$H and $^{13}$C NMR spectra were recorded in $CDCl_3$, $C_5D_5N$, DMSO-$d_6$, $CD_3OD$, or $D_2O$ as solvent using TMS as internal standard. Mass spectra were recorded in ESI and FAB mode. Specific rotations were measured at 589 nm. Pre-coated plates (0.25 mm, silica gel 60 $F_{254}$) were used for TLC analyses. All the solvents were distilled and purified as necessary. Petroleum ether (PE) used refers to the fraction boiling at 60–80 °C.

### 3-*O*-Benzyl-1,2-*O*-isopropylidene-4-vinyl-β-L-arabinofuranose (7)

To a solution of **6** (664 mg, 1.58 mmol) in THF (50 mL) was added $Bu_4NF$ (494 mg, 1.89 mmol) portionwise and the mixture was stirred at r.t. for 2 h. The solvent was evaporated in vacuo and the residue was extracted with $CHCl_3$ (3 × 30 mL). The $CHCl_3$ solution was washed with brine (2 × 30 mL), dried ($Na_2SO_4$), and concentrated to afford a gummy mass. The crude product was purified by column chromatography on silica gel (100–200 mesh) using EtOAc–PE (17:83) as eluent to afford **7** as a colorless liquid; yield: 452 mg (93%); $[\alpha]_D^{25}$ +20.9 (*c* 0.3, $CHCl_3$).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 1.38 (s, 3 H, $CH_3$), 1.57 (s, 3 H, $CH_3$), 3.52 (d, *J* = 11.8 Hz, 1 H, H-5), 3.62 (d, *J* = 11.8 Hz, 1 H, H-5), 4.16 (d, *J* = 2.5 Hz, 1 H, H-3), 4.57 (d, *J* = 11.8 Hz, 1 H, C*H*$_2$Ph), 4.66 (dd, *J* = 2.8, 4.1 Hz, H-2), 4.74 (d, *J* = 11.8 Hz, 1 H, C*H*$_2$Ph), 5.28 (d, *J* = 11.0 Hz, 1 H, C*H*$_2$=CH), 5.47 (d, *J* = 17.3 Hz, 1 H, C*H*$_2$=CH), 5.90–6.00 (m, 2 H, H-1 and C*H*=CH$_2$), 7.34 (m, 5 H, ArH).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 27.6 ($CH_3$), 28.1 ($CH_3$), 65.6 (C-5), 72.8 (*C*H$_2$Ph), 84.6 (C-3), 86.7 (C-2), 89.5 (C -4), 104.1 (C-1), 114.0 (*C*CH$_3$), 116.6 (*C*H$_2$=CH), 128.0 (2 × CH, Ar), 128.2 (CH, Ar), 128.8 (2 × CH, Ar), 134.9 (*C*H=CH$_2$), 137.9 (C, Ar).

FABMS: *m*/*z* = 329 (M + Na)$^+$.

Anal. Calcd for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24. Found: C, 66.38; H, 7.00.

### (2*S*,3*S*,4*S*,5*R*,6*S*)-1-Benzyl-5-benzyloxy-4-hydroxymethyl-hexahydrocyclopenta[*c*]isoxazole-4,6-diol (9) and (2*R*,3*R*,4*S*,5*R*,6*S*)-1-Benzyl-5-benzyloxy-4-hydroxymethyl-hexahydrocyclopenta[*c*]isoxazole-4,6-diol (10)

Compound **7** (3.50 g, 11.44 mmol) dissolved in 4% $H_2SO_4$ in MeCN–$H_2O$ (3:1, 75 mL) was stirred at r.t. for 12 h. The solution was neutralized with solid $CaCO_3$, filtered, and the filtrate was evaporated to furnish a mixture of anomers as a thick oil. To a solution of this oil (dried over $P_2O_5$) in anhyd EtOH (40 mL) was added *N*-benzylhydroxylamine (4.16 g, 33.84 mmol) and the mixture was heated at reflux for 5 h. The solvent was evaporated to furnish a brown residue, which was purified by silica gel column chromatography (100–200 mesh). Careful elution with EtOAc–PE (2:3) afforded **9** and **10** as crystalline solids.

**9**

Yield: 1.53 g (36%); mp 123–124 °C (EtOAc–PE, 2:3); $[\alpha]_D^{25}$ –154.5 (*c* 0.5, $CHCl_3$).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 2.76 (br s, 1 H, H-3a), 3.02 (t, *J* = 7.5 Hz, 1 H, H-6a), 3.46–3.49 (m, 2 H), 3.75–3.87 (m, 4 H), 3.98 (t, *J* = 6.0 Hz, 1 H), 4.05 (t-like, *J* = 7.5, 8.6 Hz, 1 H), 4.19 (d, *J* = 12.8 Hz, 1 H, NC*H*$_2$Ph), 4.38 (d, *J* = 9.2 Hz, 1 H), 4.61 (d, *J* = 11.3 Hz, 1 H, OC*H*$_2$Ph), 4.81 (d, *J* = 11.3 Hz, 1 H, OC*H*$_2$Ph), 7.32–7.35 (m, 10 H, ArH), signal for 1 H was not discernible.

$^{13}$C NMR (75 MHz, $C_5D_5N$): δ = 57.3 (C-3a), 62.3 (C-3), 65.2 (*C*H$_2$OH), 68.1 (N*C*H$_2$Ph), 74.1 (O*C*H$_2$Ph), 77.7 (C-6a), 81.1 (C-5 or C-6), 83.2 (C-4), 93.6 (C-6 or C-5), 128.9 (CH, Ar), 129.2 (CH, Ar), 129.5 (2 × CH, Ar), 130.1 (2 × CH, Ar), 130.2 (2 × CH, Ar), 131.2 (2 × CH, Ar), 140.5 (C, Ar), 141.4 (C, Ar).

ESIMS: *m*/*z* = 394 (M + Na)$^+$.

Anal. Calcd for $C_{21}H_{25}NO_5$: C, 67.91; H, 6.78; N, 3.77. Found: C, 67.75; H, 6.58; N, 3.51.

**Crystal Data of 9**[24]

$C_{21}H_{25}NO_5$, *M* = 371.42, orthorhombic, space group $P2_12_12_1$, *Z* = 4, *a* = 5.3774(4), *b* = 12.0047(14), *c* = 28.822(4), *U* = 1860.6(4)°, dcalc = 1.326 g/cm$^3$. A set of 5298 independent data were collected with MoKα radiation at 100 K using the Oxford Diffraction X-Calibur CCD System. The crystal was positioned at 50 mm from the CCD. 321 frames were measured with a counting time of 10 s. Data analysis was carried out with the CrysAlis program.[25a] The structure was solved using direct methods with the Shelxs97 program.[25b] The non-hydrogen atoms were refined with anisotropic thermal parameters. The hydrogen atoms bonded to carbon were included in geometric positions and given thermal parameters equivalent to 1.2 times those of the atom to which they were attached. The structure was refined on $F^2$ using Shelxl97 to *R*1 0.0522; *wR*2 0.1193 for 2797 reflections with $I > 2\sigma(I)$.

**10**

Yield: 1.36 g (32%); mp 82–84 °C (EtOAc–PE, 2:3); $[\alpha]_D^{25}$ +27.2 (*c* 0.41, $CHCl_3$).

$^1$H NMR (300 MHz, $C_5D_5N$): δ = 3.63 (dt, *J* = 4.4, 4.8 8.7 Hz, 1 H, H-3a), 3.95 (d, *J* = 13.5 Hz, 1 H), 4.07–4.13 (m, 2 H), 4.22 (d, *J* = 9.0 Hz, 1 H), 4.28 (d, *J* = 11.0 Hz, 1 H, NC*H*$_2$Ph), 4.40 (d, *J* = 6.4 Hz, 1 H), 4.46 (d, *J* = 11.0 Hz, 1 H, NC*H*$_2$Ph), 4.65–4.69 (m, 2 H), 4.96 (d, *J* = 12.0 Hz, 1 H, OC*H*$_2$Ph), 5.03 (d, *J* = 12.0 Hz, 1 H, OC*H*$_2$Ph), 6.43 (br s, 1 H, OH), 6.57 (br s, 1 H, OH), 7.11 (br s, 1 H, OH), 7.18–7.31 (m, 6 H, Ar*H*), 7.45–7.54 (m, 4 H, ArH).

$^{13}$C NMR (75 MHz, $C_5D_5N$): δ = 55.3 (C-3a), 60.4 (C-3), 63.4 (*C*H$_2$OH), 66.2 (N*C*H$_2$Ph), 72.3 (O*C*H$_2$Ph), 75.8 (C-6a), 79.4 (C-5 or C-6), 81.4 (C-4), 91.6 (C-6 or C-5), 127.2 (CH, Ar), 127.4 (CH, Ar), 127.7 (2 × CH, Ar), 128.0 (2 × CH, Ar), 128.3 (2 × CH, Ar), 129.4 (2 × CH, Ar), 138.7 (C, Ar), 139.5 (C, Ar).

ESIMS: *m*/*z* = 372 (M + H)$^+$, 394 (M + Na)$^+$.

Anal. Calcd for $C_{21}H_{25}NO_5$: C, 67.91; H, 6.78; N, 3.77. Found: C, 68.19; H, 6.95; N, 3.55.

**(2*S*,3*S*,4*S*,5*R*,6*S*)-1-Benzyl-5,6-bis(benzyloxy)-4-benzyloxymethylhexahydrocyclopenta[*c*]isoxazol-4-ol (11) and (2*S*,3*S*,4*S*,5*R*,6*S*)-1-Benzyl-4,5,6-tris(benzyloxy)-4-benzyloxymethylhexahydrocyclopenta[*c*]isoxazole (12)**

Oil-free NaH (247 mg, 10.29 mmol) was added portionwise to a solution of **9** (476 mg, 1.29 mmol) in anhyd THF (30 mL) at 0 °C under $N_2$ and the mixture was stirred for 5 min. To the reaction mixture, benzyl bromide (0.31 mL, 2.57 mmol) and $Bu_4NI$ (48 mg, 0.13 mmol) were added and the mixture was stirred at r.t. for 3 h under $N_2$. Excess NaH was destroyed by adding aq $NH_4Cl$ (5 mL) . The solvent was evaporated in vacuo and the residue was extracted with $CHCl_3$ (3 × 25 mL). The $CHCl_3$ solution was washed with $H_2O$, dried ($Na_2SO_4$), and concentrated to afford a liquid, which was purified by column chromatography on silica gel (60–120 mesh). Elution with EtOAc–PE (1:19) furnished **12** and with EtOAc–PE (9:91) afforded **11** as colorless solids.

**11**

Yield: 656 mg (80%); mp 165–166 °C (EtOAc–PE, 1:3); $[\alpha]_D^{25}$ +39.3 (*c* 0.32, $CHCl_3$).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 2.83 (s, 1 H, OH), 3.24 (ddd, *J* = 2.7, 2.7, 7.8 Hz, 1 H, H-3a), 3.37 (d, *J* = 9.3 Hz, 1 H), 3.55 (t-like, *J* = 7.2, 7.7 Hz, 1 H), 3.68 (d, *J* = 9.0 Hz, 1 H), 3.71 (partially merged t, *J* = 7.2 Hz, 1 H), 3.85 (d, *J* = 12.5 Hz, 1 H, NC*H*$_2$Ph), 3.99–4.12 (m, 3 H), 4.29–4.34 (m, 2 H, C*H*$_2$Ph), 4.49–4.63 (m, 3 H, C*H*$_2$Ph), 4.71 (s, 2 H, OC*H*$_2$Ph), 7.20–7.42 (m, 20 H, ArH).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 51.3 (C-3a), 61.1 (C-3), 66.5 (C-6a), 66.8 (N*C*H$_2$Ph), 72.5 (OCH$_2$), 73.3 (O*C*H$_2$Ph), 73.6 (O*C*H$_2$Ph), 74.1 (O*C*H$_2$Ph), 78.5 (C-4), 80.0 (C-6 or C-5), 87.0 (C-5 or C-6), 127.9–128.9 (19 × CH, Ar), 130.3 (CH, Ar), 138.2 (2 × C, Ar), 138.6 (C, Ar), 139.0 (C, Ar).

ESIMS: *m*/*z* = 552 (M + H)$^+$, 574 (M + Na)$^+$.

Anal. Calcd for $C_{35}H_{37}NO_5$: C, 76.20; H, 6.76; N, 2.54. Found: C, 75.95; H, 6.53; N, 2.30.

**12**

Yield: 23 mg (9%); mp 141–142 °C ($CHCl_3$–PE, 1:3); $[\alpha]_D^{25}$ +23.7 (*c* 0.6, $CHCl_3$).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 3.56 (m, 2 × CH), 3.64 (d, *J* = 10.2 Hz, 1 H), 3.79–3.86 (m, 3 H), 4.03 (d, *J* = 12.6 Hz, 1 H) 4.09 (m, 1 H), 4.19 (d, *J* = 12.4 Hz, 1 H, NC*H*$_2$Ph), 4.23 (d, *J* = 9.0 Hz, 1 H), 4.33 (br d, *J* = 8.0 Hz, 1 H), 4.44–4.59 (m, 4 H), 4.71 (t, *J* = 11.7 Hz, 2 H, OC*H*$_2$Ph), 4.83 (d, *J* = 11.7 Hz, 1 H, OC*H*$_2$Ph), 7.25–7.43 (m, 25 H, ArH).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 49.7 (C-3a), 60.8 (C-3), 64.9 (C-6a), 67.2 (OCH$_2$), 67.4 (N*C*H$_2$Ph), 70.9 (O*C*H$_2$Ph), 72.3 (O*C*H$_2$Ph), 73.3 (O*C*H$_2$Ph), 73.9 (O*C*H$_2$Ph), 81.0 (C-5 or C-6), 81.9 (C-4), 87.4 (C-6 or C-5), 127.4–128.8 (24 × CH, Ar), 130.4 (CH, Ar), 136.3 (C, Ar), 138.4 (C, Ar), 138.7 (C, Ar), 139.3 (2 × C, Ar).

ESIMS: *m*/*z* = 642 (M + H)$^+$, 664 (M + Na)$^+$.

Anal. Calcd for $C_{42}H_{43}NO_5$: C, 78.60; H, 6.75; N, 2.18. Found: C, 78.44; H, 6.56; N, 2.05.

**(2*S*,3*S*,4*S*,5*R*,6*S*)-Dithiocarbonic Acid *O*-[1-Benzyl-5,6-bis(benzyloxy)-4-benzyloxymethylhexahydrocyclopenta[*c*]isoxazol-4-yl] Ester *S*-Methyl Ester (13)**

To a solution of **11** (500 mg, 0.91 mmol) in anhyd THF (50 mL) at 0 °C was added NaH (132 mg, 5.5 mmol, 60% suspension in oil) portionwise under $N_2$. After 10 min of vigorous stirring, $CS_2$ (1.1 mL, 18.2 mmol) was added and the mixture was heated at reflux for 2 h. The mixture was cooled to r.t., MeI (0.28 mL, 4.55 mmol) was added and heated at reflux for 2 h. Excess NaH was destroyed by slow addition of cold $H_2O$ (5 mL) and the solvent was evaporated. The residue thus obtained was dissolved in $CH_2Cl_2$ (40 mL) and the solution was repeatedly washed with $H_2O$ (3 × 20 mL), brine (40 mL), and dried ($Na_2SO_4$). The solvent was evaporated to furnish a crude solid, which was purified by silica gel column chromatography (60–120 mesh) using $CHCl_3$–PE (19:1) as eluent to obtain **13** as a yellowish solid; yield: 461 mg (79%); mp 68–71 °C ($CHCl_3$–PE, 1:3); $[\alpha]_D^{25}$ –2.1 (*c* 0.8, $CHCl_3$).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 2.47 (s, 3 H, $CH_3$), 3.56 (t, *J* = 7.5 Hz, 1 H), 3.79–4.04 (m, 5 H), 4.17 (m, 2 H), 4.32 (d, *J* = 12.6 Hz, 1 H, OC*H*$_2$Ph), 4.37 (t, *J* = 8.0 Hz, 1 H and m, 1 H), 4.44 (s, 2 H, OC*H*$_2$Ph), 4.62 (d, *J* = 12.2 Hz, 1 H, OC*H*$_2$Ph), 4.81 (s, 2 H, OC*H*$_2$Ph), 7.13–7.37 (m, 20 H, ArH).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 20.0 ($CH_3$), 50.3 (C-3a), 60.9 (C-3), 65.9 (C-6a), 66.5 (N*C*$H_2$Ph), 68.2 (O*C*$H_2$), 72.3 (O*C*$H_2$Ph), 73.8 (O*C*$H_2$Ph), 74.0 (O*C*$H_2$Ph), 77.7 (C-5 or C-6), 87.6 (C-6 or C-5), 94.1 (C-4), 127.8–130.1 (20 × CH, Ar), 137.4 (C, Ar), 138.2 (C, Ar), 138.9 (C, Ar), 139.1 (C, Ar), 214.6 (*C*$S_2CH_3$).

ESIMS: *m*/*z* = 642 $(M + H)^+$.

Anal. Calcd for $C_{37}H_{39}NO_5S_2$: C, 69.24; H, 6.12; N, 2.18. Found: C, 69.03; H, 6.09; N, 2.07.

**(2*S*,3*S*,4*S*,5*S*,6*S*)-1-Benzyl-5,6-bis(benzyloxy)-4-benzyloxymethylhexahydrocyclopenta[*c*]isoxazole (14) and (2*S*,3*S*,4*R*,5*S*,6*S*)-1-Benzyl-5,6-bis(benzyloxy)-4-benzyloxymethylhexahydrocyclopenta[*c*]isoxazole (15)**

To a solution of **13** (60 mg, 0.09 mmol) in toluene (10 mL) were added $Bu_3SnH$ (0.25 mL, 0.94 mmol) and AIBN (2 mg, 0.01 mmol) and the mixture was heated at reflux for 6 h under $N_2$. The solvent was evaporated and the crude mixture was partitioned between MeCN and PE (20 mL, 2:3). The MeCN solution was taken and evaporated to a residue, which was purified by column chromatography (100–200 mesh) using EtOAc–PE (1:24) to yield **15** and **14** as colorless solids.

**14**

Yield: 28 mg (59%); mp 135–136 °C (EtOAc–benzene, 1:3); $[\alpha]_D^{25}$ –57.8 (*c* 0.7, $CHCl_3$).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 2.20–2.26 (m, 1 H, H-3a or H-4), 3.19–3.23 (m, 1 H, H-4 or H-3a), 3.46 (t, *J* = 9.8 Hz, 1 H), 3.55 (t, *J* = 7.2 Hz, 1 H), 3.66–3.74 (m, 2 H), 3.88–4.04 (m, 5 H), 4.22 (d, *J* = 12.0 Hz, 1 H, C*H*$_2$Ph), 4.39 (d, *J* = 12.0 Hz, 1 H, OC*H*$_2$Ph), 4.48 (d, *J* = 12.0 Hz, 1 H, OC*H*$_2$Ph), 4.52 (t, *J* = 12.0 Hz, 2 H, OC*H*$_2$Ph), 4.83 (d, *J* = 11.4 Hz, 1 H, OC*H*$_2$Ph), 7.20–7.42 (m, 20 H, ArH).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 41.8 (C-3a or C-4), 44.8 (C-4 or C-3a), 61.3 (O*C*$H_2$), 65.3 (C-6a), 66.9 (N*C*$H_2$Ph), 69.3 (O*C*$H_2$), 72.2 (O*C*$H_2$Ph), 73.6 (O*C*$H_2$Ph), 73.7 (O*C*$H_2$Ph), 82.6 (C-5 or C-6), 84.6 (C-6 or C-5), 127.9–130.5 (20 × CH, Ar), 137.5 (C, Ar), 138.5 (C, Ar), 138.6 (C, Ar), 139.1 (C, Ar).

ESIMS: *m*/*z* = 558 $(M + Na)^+$.

Anal. Calcd for $C_{35}H_{37}NO_4$: C, 78.48; H, 6.96; N, 2.61. Found: C, 78.31; H, 6.73; N, 2.40.

**15**

Yield: 5 mg (10%); mp 125–127 °C (EtOAc–benzene, 1:3); $[\alpha]_D^{25}$ +98.8 (*c* 0.58, $CHCl_3$).

$^1$H NMR (600 MHz, $CDCl_3$): δ = 2.28 (m, 1 H, H-3a or H-4), 3.50 (br s, 1 H, H-4 or H-3a), 3.79 (br s, 2 H), 3.82 (d, *J* = 8.4 Hz, 1 H), 3.84 (d, *J* = 8.4 Hz, 1 H), 3.94 (q, *J* = 10.2 Hz, 2 H), 4.03 (br t-like, 1 H), 4.12 (t, *J* = 7.2 Hz, 1 H), 4.26 (d, *J* = 8.4 Hz, 1 H), 4.35 (d, *J* = 12.0 Hz, 1 H, OC*H*$_2$Ph), 4.43 (d, *J* = 12.0 Hz, 1 H, OC*H*$_2$Ph), 4.47 (d, *J* = 12.0 Hz, 1 H, OC*H*$_2$Ph), 4.62 (d, *J* = 12.6 Hz, 1 H, OC*H*$_2$Ph), 4.75 (s, 2 H, OC*H*$_2$Ph), 7.15–7.38 (m, 20 H, ArH).

$^{13}$C NMR (150 MHz, $CDCl_3$): δ = 50.3 (C-3a or C-4), 60.6 (O*C*$H_2$), 65.3 (C-4 or C-3a), 67.2 (N*C*$H_2$Ph), 67.9 (O*C*$H_2$), 71.9 (O*C*$H_2$Ph), 73.3 (O*C*$H_2$Ph), 73.6 (O*C*$H_2$Ph), 77.3 (C-6a), 77.8 (C-5 or C-6), 86.5 (C-5 or C-6), 127.3–129.6 (20 × CH, Ar), 137.1 (C, Ar), 137.7 (C, Ar), 138.5 (C, Ar), 138.6 (C, Ar).

ESIMS: *m*/*z* = 536 $(M + H)^+$, 558 $(M + Na)^+$.

Anal. Calcd for $C_{35}H_{37}NO_4$: C, 78.48; H, 6.96; N, 2.61. Found: C, 78.54; H, 6.67; N, 2.37.

**(2*R*,3*R*,4*S*,5*R*,6*S*)-1-Benzyl-4,5,6-tris(benzyloxy)-4-benzyloxymethylhexahydrocyclopenta[*c*]isoxazole (16) and (2*R*,3*R*,4*S*,5*R*,6*S*)-1-Benzyl-5,6-bis(benzyloxy)-4-benzyloxymethylhexahydrocyclopenta[*c*]isoxazol-4-ol (17)**

Compounds **16** and **17** were prepared from **10** according to the previous procedure (described for **11** and **12** from **9**) using the protocol: **10** (750 mg, 2.02 mmol), oil-free NaH (389 mg, 16.9 mmol), anhyd THF (60 mL), benzyl bromide (0.47 mL, 4.04 mmol), and $Bu_4NI$ (72 mg, 0.20 mmol). Purification of the crude mixture by column chromatography on silica gel (60–120 mesh) using EtOAc–PE (7:93) furnished **16** and EtOAc–PE (1:9) mixture gave **17** as colorless solids.

**16**

Yield: 90 mg (7%); mp 120–121 °C (EtOAc–benzene, 1:3); $[\alpha]_D^{25}$ –6.4 (*c* 0.49, $CHCl_3$).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 3.38–3.45 (m, H-3a), 3.67 (d, *J* = 12.6 Hz, 1 H), 3.74 (d, *J* = 11.3 Hz, 1 H), 3.78–3.82 (m, 1 H), 3.96–3.99 (m, 4 H), 4.08–4.14 (m, 2 H), 4.47–4.56 (m, 6 H), 4.69 (d, *J* = 11.8 Hz, 2 H, OC*H*$_2$Ph), 7.18–7.39 (m, 25 H, ArH).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 53.1 (C-3a), 61.1 (C-3), 66.3 (N*C*$H_2$Ph), 67.3 (O*C*$H_2$), 69.1 (O*C*$H_2$Ph), 72.3 (O*C*$H_2$Ph), 72.5 (O*C*$H_2$Ph), 73.6 (C-6a), 74.1 (O*C*$H_2$Ph), 86.3 (C-4), 87.8 (C-5 or C-6), 88.2 (C-6 or C-5), 127.7–130.0 (25 × CH, Ar), 137.1 (C, Ar), 138.4 (C, Ar), 138.6 (C, Ar), 138.9 (C, Ar) 139.5 (C, Ar).

ESIMS: *m*/*z* = 642 $(M + H)^+$, 664 $(M + Na)^+$.

Anal. Calcd for $C_{42}H_{43}NO_5$: C, 78.60; H, 6.75; N, 2.18. Found: C, 78.43; H, 6.51; N, 2.01.

**17**

Yield: 757 mg (68%); mp 139–140 °C (EtOAc–benzene, 1:3); $[\alpha]_D^{25}$ +24.1 (*c* 0.46, $CHCl_3$).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 3.14 (s, 1 H, OH), 3.18–3.25 (m, 1 H, H-3a), 3.66 (d, *J* = 9.5 Hz, 1 H), 3.71 (d, *J* = 12.8 Hz, 1 H), 3.77–3.83 (m, 3 H), 3.88 (br s, 1 H), 4.01 (t-like, *J* = 8.3, 9.5 Hz, 1 H), 4.03 (partially merged d, 1 H), 4.11 (dd, *J* = 4.5, 9.0 Hz, 1 H), 4.36 (d, *J* = 12.0 Hz, 1 H, OC*H*$_2$Ph), 4.42 (d, *J* = 12.0 Hz, 1 H, OC*H*$_2$Ph), 4.51 (d, *J* = 12.0 Hz, 1 H, OC*H*$_2$Ph), 4.55 (s, 2 H, OC*H*$_2$Ph), 4.61 (d, *J* = 12.0 Hz, 1 H, OC*H*$_2$Ph), 7.18–7.42 (m, 20 H, ArH).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 55.0 (C-3a), 60.7 (C-3), 66.0 (N*C*$H_2$Ph), 70.3 (O*C*$H_2$), 71.8 (O*C*$H_2$Ph), 72.1 (O*C*$H_2$Ph), 73.2 (C-6a), 73.6 (O*C*$H_2$Ph), 80.7 (C-4), 86.6 (C-5 or C-6), 87.7 (C-6 or C-5), 127.4–129.4 (20 × CH, Ar), 136.7 (C, Ar), 137.5 (C, Ar), 138.1 (2 × C, Ar).

ESIMS: *m*/*z* = 552 $(M + H)^+$, 574 $(M + Na)^+$.

Anal. Calcd for $C_{35}H_{37}NO_5$: C, 76.20; H, 6.76; N, 2.54. Found: C, 75.91; H, 6.57; N, 2.25.

**(2*R*,3*R*,6*S*)-1-Benzyl-5,6-bis(benzyloxy)-4-benzyloxymethyl-3,3a,6,6a-tetrahydro-1*H*-cyclopenta[*c*]isoxazole (18) and (2*R*,5*S*,6*S*)-1-Benzyl-5,6-bis(benzyloxy)-4-benzyloxymethyl-3,5,6,6a-tetrahydro-1*H*-cyclopenta[*c*]isoxazole (19)**

Compound **17** (700 mg, 1.27 mmol) was subjected to a procedure similar to that described earlier (for the conversion of **11** to **13**) using the protocol: (i) NaH (183 mg, 7.6 mmol, 60% suspension in oil), (ii) $CS_2$ (1.53 mL, 25.4 mmol), (iii) MeI (0.40 mL, 6.35 mmol), and (iv) anhyd THF (50 mL) to yield **18** as a brownish liquid and **19** as a white semi-solid mass after purification by silica gel column chromatography (100–200 mesh) using EtOAc–PE as eluents in the ratios of 1:9 and 13:87, respectively.

**18**

Yield: 264 mg (39%); $[\alpha]_D^{25}$ +73.4 (*c* 0.59, $CHCl_3$).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 3.71 (br d, *J* = 6.3 Hz, 1 H), 3.73 (d, *J* = 12.0 Hz, 1 H), 3.79–3.85 (m, 2 H), 4.05–4.18 (m, 6 H), 4.38 (d, *J* = 12.0 Hz, 1 H, OC*H*$_2$Ph), 4.43 (d, *J* = 12.0 Hz, 1 H, OC*H*$_2$Ph), 4.69 (br s, 1 H), 4.73 (d, *J* = 12.0 Hz, 1 H, OC*H*$_2$Ph), 4.97 (d, *J* = 12.0 Hz, 1 H, OC*H*$_2$Ph), 7.12–7.48 (m, 20 H, ArH).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 49.7 (C-3a), 60.1 (C-3), 63.8 ($OCH_2$), 68.7 (N*C*H$_2$Ph), 70.2 (O*C*H$_2$Ph), 70.7 (O*C*H$_2$Ph), 71.7 (O*C*H$_2$Ph), 71.8 (C-6a), 85.2 (C-6), 117.5 (C-4), 127.4–129.7 (20 × CH, Ar), 136.5 (C, Ar), 137.2 (C, Ar), 137.5 (C, Ar), 138.3 (C, Ar), 151.6 (C-5).

ESIMS: *m*/*z* = 556 (M + Na)$^+$.

Anal. Calcd for $C_{35}H_{35}NO_4$: C, 78.77; H, 6.61; N, 2.62. Found: C, 78.49; H, 6.37; N, 2.42.

**19**

Yield: 223 mg (33%); $[\alpha]_D^{25}$ +25.3 (*c* 0.7, $CHCl_3$).

$^1$H NMR (300 MHz, DMSO-$d_6$, 80 °C): δ = 3.80 (br s, 1 H, H-6a), 3.92 (d, *J* = 14.0 Hz, 1 H), 4.00 (d, *J* = 14.0 Hz, 1 H), 4.07–4.20 (m, 3 H), 4.28 (d, *J* = 13.0 Hz, 1 H), 4.34 (d, *J* = 13.0 Hz, 1 H), 4.47–4.56 (m, 4 H), 4.64–4.66 (m, 2 H), 4.91 (br s, 1 H), 7.26–7.53 (m, 20 H, ArH).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 60.4 (C-3 or *C*H$_2$OBn), 62.0 (*C*H$_2$OBn or C-3), 64.5 (N*C*H$_2$Ph), 71.1 (O*C*H$_2$Ph), 71.5 (O*C*H$_2$Ph), 71.6 (O*C*H$_2$Ph), 75.4 (C-6a), 89.6 (C-5 or C-6), 91.6 (C-6 or C-5), 126.3–128.3 (20 × CH, Ar), 128.8 (C-4), 137.2 (C, Ar), 137.7 (C, Ar), 137.8 (C, Ar), 137.9 (C, Ar), 141.7 (C-3a).

ESIMS: *m*/*z* = 534 (M + Na)$^+$, 556 (M + Na)$^+$.

Anal. Calcd for $C_{35}H_{35}NO_4$: C, 78.77; H, 6.61; N, 2.62. Found: C, 78.56; H, 6.48; N, 2.36.

**(1*S*,2*R*,3*S*,4*S*,5*S*)-4-Amino-1,5-bis(hydroxymethyl)cyclopentane-1,2,3-triol (20)**

Pd/C (10%, 60 mg) was added to a solution of **9** (275 mg, 0.74 mmol) in EtOH (20 mL) and the mixture was hydrogenolyzed under atmospheric pressure at r.t. for 12 h. The catalyst was filtered off and the solvent was evaporated to afford **20** as hygroscopic solid; yield: 91 mg (63%); $[\alpha]_D^{25}$ –2.1 (*c* 0.48, MeOH).

$^1$H NMR (300 MHz, $CD_3OD$ + $D_2O$): δ = 2.20 (td, *J* = 6.8, 5.7 Hz, 1 H, H-5), 3.45 (t, *J* = 5.5 Hz, 1 H), 3.59 (s, 2 H), 3.79–3.92 (m, 3 H), 4.00 (d, *J* = 6.0 Hz, 1 H).

$^{13}$C NMR (75 MHz, $CD_3OD$): δ = 47.1 (C-5), 54.3 (C-4), 57.7 (CH*C*H$_2$OH), 65.3 (C*C*H$_2$OH), 78.8 (C-3 or C-2), 81.1 (C-1), 86.1 (C-2 or C-3).

ESIMS: *m*/*z* = 194 (M + H)$^+$.

**(1*R*,2*S*,3*R*,4*R*,5*S*)-4-Amino-1,5-bis(hydroxymethyl)cyclopentane-1,2,3-triol (21)**

A solution of **10** (200 mg, 0.54 mmol) in EtOH (10 mL) was hydrogenolyzed over Pd/C (10%, 85 mg) under atmospheric pressure at r.t. for 18 h. The catalyst was filtered off and the solvent was evaporated to afford **21** as hygroscopic material; yield: 73 mg (70%); $[\alpha]_D^{25}$ +39.6 (*c* 0.28, MeOH).

$^1$H NMR (300 MHz, $CD_3OD$): δ = 2.32 (td, *J* = 6.8, 7.5 Hz, 1 H, H-5), 3.47 (d, *J* = 6.3 Hz, 1 H), 3.53 (d, *J* = 8.1 Hz, 1 H), 3.69–3.85 (m, 5 H).

$^{13}$C NMR (75 MHz, $CD_3OD$): δ = 51.1 (C-5), 57.7 (C-4), 58.2 (CH*C*H$_2$OH), 62.5 (C*C*H$_2$OH), 81.4 (C-1), 85.3 (C-2 or C-3), 85.6 (C-3 or C-2).

ESIMS: *m*/*z* = 216 (M + Na)$^+$.

**(2*R*,3*R*,4*R*,5*S*,6*S*)-1-Benzyl-5,6-bis(benzyloxy)-4-benzyloxymethylhexahydrocyclopenta[*c*]isoxazole (22) and (2*R*,3*S*,4*S*,5*S*,6*S*)-1-Benzyl-5,6-bis(benzyloxy)-4-benzyloxymethylhexahydrocyclopenta[*c*]isoxazole (23)**

Pd/C (10%, 100 mg) was added to a solution of **19** (200 mg, 0.38 mmol) in EtOH (15 mL) and hydrogenated with $H_2$ under atmospheric pressure at r.t. for 12 h. The catalyst was filtered off, the solvent evaporated, and the residue was purified by silica gel column chromatography (100–200 mesh). Elution with EtOAc–PE in the ratios of 1:19 and 7:93 afforded **22** and **23**, respectively, as colorless thick liquids.

**22**

Yield: 122 mg (60%); $[\alpha]_D^{25}$ +130.2 (*c* 0.52, $CHCl_3$).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 2.65 (t-like, *J* = 6.0, 6.8 Hz, 1 H, H-3a or H-4), 3.32 (t-like, *J* = 6.7, 7.3 Hz, 1 H, H-4 or H-3a), 3.59 (m, 1 H), 3.63 (d, *J* = 8.6 Hz, 1 H), 3.73–3.79 (m, 2 H), 3.85 (d, *J* = 3.7 Hz, 2 H), 3.97 (t, *J* = 8.5 Hz, 1 H), 4.12–4.16 (m, 2 H), 4.20 (d, *J* = 11.8 Hz, 1 H, C*H*$_2$Ph), 4.28 (d, *J* = 11.8 Hz, 1 H, OC*H*$_2$Ph), 4.34 (d, *J* = 11.9 Hz, 1 H, OC*H*$_2$Ph), 4.49 (s, 2 H, OC*H*$_2$Ph), 4.59 (d, *J* = 11.9 Hz, 1 H, OC*H*$_2$Ph), 7.14–7.44 (m, 20 H, ArH).

$^{13}$C NMR (75 MHz, $CD_3OD$): δ = 43.7 (C-3a or C-4), 47.8 (C-4 or C-3a), 61.2 ($OCH_2$), 66.8 (N*C*H$_2$Ph), 67.2 ($OCH_2$), 71.3 (O*C*H$_2$Ph), 71.4 (O*C*H$_2$Ph), 73.2 (O*C*H$_2$Ph), 75.8 (C-6a), 83.8 (C-5 or C-6), 87.2 (C-6 or C-5), 127.5–129.9 (20 × CH, Ar), 137.2 (C, Ar), 138.5 (C, Ar), 138.7 (C, Ar), 138.8 (C, Ar).

ESIMS: *m*/*z* = 536 (M + H)$^+$, 558 (M + Na)$^+$.

Anal. Calcd for $C_{35}H_{37}NO_4$: C, 78.48; H, 6.96; N, 2.61. Found: C, 78.25; H, 6.73; N, 2.22.

**23**

Yield: 16 mg (8%); $[\alpha]_D^{25}$ –50.2 (*c* 0.45, $CHCl_3$).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 2.13 (br s, 1 H, H-3a or H-4), 3.07 (br s, 1 H, H-4 or H-3a), 3.46 (br t, 1 H), 3.55–3.57 (m, 2 H), 3.76–3.87 (m, 3 H), 4.06–4.16 (m, 3 H), 4.37–4.56 (m, 5 H), 4.72–4.76 (m, 1 H), 7.17–7.42 (m, 20 H, ArH).

$^{13}$C NMR (150 MHz, $CDCl_3$): δ = 45.0 (C-3a or C-4), 47.2 (C-4 or C-3a), 69.7 ($OCH_2$), 70.7 (N*C*H$_2$Ph), 71.9 (C-6a), 71.9 ($OCH_2$), 72.5 (O*C*H$_2$Ph), 73.1 (2 × O*C*H$_2$Ph), 77.0 (C-5 or C-6), 81.9 (C6 or C-5), 127.4–129.7 (20 × CH, Ar), 136.8 (C, Ar), 138.4 (C, Ar), 138.5 (C, Ar), 138.7 (C, Ar).

ESIMS: *m*/*z* = 536 (M + H)$^+$ and 558 (M + Na)$^+$.

Anal. Calcd for $C_{35}H_{37}NO_4$: C, 78.48; H, 6.96; N, 2.61. Found: C, 78.29; H, 6.79; N, 2.40.

**(1*S*,2*S*,3*R*,4*R*,5*R*)-3-Amino-4,5-bis(hydroxymethyl)cyclopentane-1,2-diol (24)**

To a solution of **22** (70 mg, 0.13 mmol) in EtOH (8 mL) were added cyclohexene (1.0 mL) and Pd/C (10%, 36 mg), and the mixture was heated at reflux for 6 h. The catalyst was filtered off and the solvent was evaporated in vacuo to yield a crude residue, which was purified by reverse phase (LiChroprep RP-18, particle size 25–40 μm) column chromatography using $H_2O$ as eluent to furnish **24** as thick gum; yield: 13 mg (58%).

$^1$H NMR (300 MHz, $D_2O$): δ = 2.34–2.38 (m, 1 H, H-3a or H-4), 2.63–2.71 (m, 1 H, H-4 or H-3a), 3.18–3.27 (m, 2 H), 3.40–3.48 (m, 2 H), 3.95–4.08 (m, 2 H), 4.21 (dd, *J* = 4.0, 6.0 Hz, 1 H).

ESIMS: *m*/*z* = 200 (M + Na)$^+$.

**(1*S*,2*R*,3*S*,4*S*,5*S*)-4-(5′-Amino-6′-chloropyrimidin-4′-ylamino)-1,5-bis(hydroxymethyl)cyclopentane-1,2,3-triol (25)**

To a solution of **20** (90 mg, 0.47 mmol) in *n*-BuOH (15 mL) were added 5-amino-4,6-dichloropyrimidine (116 mg, 0.71 mmol) and

$Et_3N$ (1.5 mL), and the solution was heated at reflux for 30 h under $N_2$. The solvent was evaporated and the residue was dissolved in $H_2O$ (10 mL). The aqueous solution was washed with $CHCl_3$ (2 × 15 mL) to remove free pyrimidine base and evaporated to thick oil. Purification by reverse phase (LiChroprep RP-18, particle size 25–40 μm) flash column chromatography with $H_2O$ yielded **25** as a foamy solid; yield: 85 mg (57%); mp 190–195 °C (dec.); $[\alpha]_D^{25}$ –21.4 (*c* 0.53, MeOH).

$^1$H NMR (300 MHz, $CD_3OD$ + $D_2O$): δ = 2.00 (ddd, *J* = 5.6, 5.9,12.0 Hz, 1 H, H-5), 3.63 (d, *J* = 6.0 Hz, 1 H), 3.66 (d, *J* = 6.0 Hz, 1 H), 3.96–4.13 (m, 3 H), 4.44 (d, *J* = 10.3 Hz, 1 H), 4.85 (d, *J* = 10.5 Hz, 1 H), 7.95 (s, 1 H, H-2′).

$^{13}$C NMR (150 MHz, $D_2O$): δ = 50.2 (C-5), 55.4 (C-4), 56.8 (CH*C*$H_2$OH), 63.3 (C*C*$H_2$OH), 80.1 (C-1), 83.1 (C-2 or C-3), 85.0 (C-3 or C-2), 123.5 (C-5′), 140.2 (C-6′), 149.8 (C-2′), 154.1 (C-4′).

ESIMS: *m*/*z* = 343 (M + Na)$^+$ for $^{35}$Cl and 345 (M + Na)$^+$ for $^{37}$Cl.

Anal. Calcd for $C_{11}H_{17}ClN_4O_5$: C, 41.19; H, 5.34; N, 17.47. Found: C, 41.00; H, 5.14; N, 17.19.

**(1*S*,2*R*,3*S*,4*S*,5*S*)-4-(6′-Chloropurin-9′-yl)-1,5-bis(hydroxymethyl)cyclopentane-1,2,3-triol (26)**

A solution of **25** (60 mg, 0.19 mmol) in anhyd DMF (5 mL) was treated with $HC(OEt)_3$ (2.5 mL) and PTSA (44 mg, 0.23 mmol). The mixture was stirred at 10 °C for 16 h under $N_2$. The solvent was evaporated in vacuo and the gummy residue was dissolved in MeOH (10 mL) and neutralized by stirring with Dowex-1 $OH^-$ resin for 5 min at r.t. The neutralized methanolic solution was filtered and the solvent was evaporated to give a crude residue, which was purified by reverse phase (LiChroprep RP-18, particle size 25–40 μm) flash column chromatography using $H_2O$ as eluent to furnish **26** as a white foamy solid; yield: 40 mg (64%), mp 160–162 °C (dec.); $[\alpha]_D^{25}$ –65.8 (*c* 0.5, MeOH).

$^1$H NMR (300 MHz, $CD_3OD$ + $D_2O$): δ = 1.94 (ddd, *J* = 5.6, 5.9, 12.6 Hz, 1 H, H-5), 3.48–3.65 (m, 1 H), 3.82–4.17 (m, 4 H), 4.39 (d, *J* = 10.2 Hz, 1 H, H-3), 5.34 (d, *J* = 10.5 Hz, 1 H, H-4), 8.49 (s, 1 H, H-8′), 8.56 (s, 1H, H-2′).

$^{13}$C NMR (150 MHz, $D_2O$): δ = 50.5 (C-5), 55.4 (C-4), 56.8 (CH*C*$H_2$OH), 62.9 (C*C*$H_2$OH), 80.0 (C-1), 81.0 (C-2 or C-3), 82.3 (C-3 or C-2), 130.9 (C-5′), 148.1 (C-8′), 150.1 (C-6′), 151.9 (C-2′), 153.0 (C-4′).

ESIMS: *m*/*z* = 353 (M + Na)$^+$ for $^{35}$Cl and 355 (M + Na)$^+$ for $^{37}$Cl.

Anal. Calcd for $C_{12}H_{15}ClN_4O_5$: C, 43.58; H, 4.57; N, 16.94. Found: C, 43.38; H, 4.39; N, 16.70.

**(1*S*,2*R*,3*S*,4*R*,5*R*)-4-(5′-Amino-6′-chloropyrimidin-4′-ylamino)-1,5-bis(hydroxymethyl)cyclopentane-1,2,3-triol (27)**

The preparation of **27** was carried out following the earlier procedure (described in the preparation of **25** from **20**) using **21** (70 mg, 0.36 mmol), 5-amino-4,6-dichloropyrimidine (89 mg, 0.54 mmol), *n*-BuOH (15 mL), and $Et_3N$ (1.0 mL). Workup and purification yielded **27** as amorphous solid; yield: 69 mg (60%); mp 198–201 °C (dec.); $[\alpha]_D^{25}$ –102.0 (*c* 0.25, MeOH).

$^1$H NMR (600 MHz, $D_2O$): δ = 2.58 (dd, *J* = 3.6, 6.0 Hz, 1 H, H-5), 3.67 (d, *J* = 11.4 Hz, 1 H), 3.70 (d, *J* = 6.0 Hz, 2 H), 3.80 (d, *J* = 12.0 Hz, 1 H), 3.91 (d, *J* = 6.6 Hz, 1 H), 4.18 (t, *J* = 7.2 Hz, 1 H), 4.66 (dd, *J* = 6.6, 9.0 Hz, 1 H), 7.91 (s, 1 H, H-2′).

$^{13}$C NMR (150 MHz, $D_2O$): δ = 49.3 (C-5), 56.8 (C-4), 57.8 (CH*C*$H_2$OH), 61.8 (C*C*$H_2$OH), 81.1 (C-1), 82.6 (C-2 or C-3), 83.3 (C-3 or C-2), 123.5 (C-5′), 141.2 (C-2′), 149.0 (C-6′), 155.0 (C-4′).

ESIMS: *m*/*z* = 343 (M + Na)$^+$ for $^{35}$Cl and 345 (M + Na)$^+$ for $^{37}$Cl.

Anal. Calcd for $C_{11}H_{17}ClN_4O_5$: C, 41.19; H, 5.34; N, 17.47. Found: C, 41.10; H, 5.09; N, 17.23.

**(1*S*,2*R*,3*S*,4*R*,5*R*)-4-(6′-Chloropurin-9′-yl)-1,5-bis(hydroxymethyl)cyclopentane-1,2,3-triol (28)**

Conversion of **27** to **28** was done (according to the earlier method described in the preparation of **26** from **25**) using **27** (100 mg, 0.31 mmol), $HC(OEt)_3$ (4 mL), PTSA (75 mg, 0.39 mmol) to furnish **28** as a foamy solid; yield: 70 mg (68%); mp 187–180 °C (dec.); $[\alpha]_D^{25}$ –83.5 (*c* 0.30, MeOH).

$^1$H NMR (600 MHz, $D_2O$): δ = 2.58 (dd, *J* = 4.2, 7.2 Hz, 1 H, H-5), 3.61 (d, *J* = 11.4 Hz, 2 H), 4.02 (d, *J* = 12.6 Hz, 1 H), 4.21 (t, *J* = 9.0 Hz, 2 H), 4.61 (d, *J* = 7.8 Hz, 1 H, H-3), 5.06 (t, *J* = 7.2 Hz, 1 H, H-4), 8.45 (s, 1 H, H-8′), 8.53 (s, 1 H, H-2′).

$^{13}$C NMR (150 MHz, $D_2O$): δ = 49.4 (C-5), 56.9 (C-4), 58.0 (CH*C*$H_2$OH), 63.1 (C*C*$H_2$OH), 78.6 (C-1), 80.2 (CH), 80.9 (CH), 130.1 (C-5′), 148.2 (C-8′), 148.9 (C-6′), 150.5 (C-2′), 154.0 (C-4′).

ESIMS: *m*/*z* = 353 (M + Na)$^+$ for $^{35}$Cl and 355 (M + Na)$^+$ for $^{37}$Cl.

Anal. Calcd for $C_{12}H_{15}ClN_4O_5$: C, 43.58; H, 4.57; N, 16.94. Found: C, 43.31; H, 4.40; N, 16.71.

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