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Carbanucleosides: synthesis of both enantiomers of 2-(6-chloro-purin-9-yl)-3,5-bishydroxymethyl cyclopentanol from D-glucose

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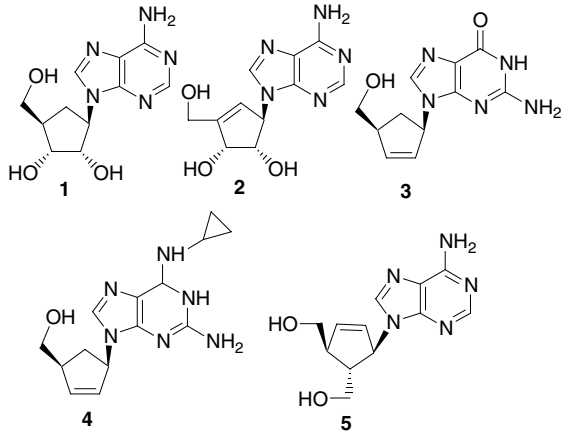
Abstract—The key intermediate 1,2:5,6-di-*O*-isopropylidene-3-deoxy-3β-allyl-α-D-glucofuranose (**8**) could be conveniently prepared through radical induced allyl substitution at C-3 of appropriate 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose derivatives (**7a,b**) and used to synthesize enantiomeric bishydroxymethyl aminocyclopentanols **13** and **19** by the application of a 1,3-dipolar nitrone cycloaddition reaction involving the C-5 or C-1 aldehyde functionality. The products were subsequently transformed into carbanucleoside enantiomers **15** and **21**. The diastereomeric isoxazolidinocyclopentane derivative **20** was similarly converted to carbanucleoside **22**.

Since the isolation of (−)-aristeromycin[1] (**1**) and (−)-neplanocin A[2] (**2**) from natural sources, the area of carbanucleosides[3] has become the focus of attention for synthetic chemists. Many such nucleosides exhibit important antiviral properties against herpes simplex virus (HSV 1 and 2),[4] human cytomegalovirus,[5] hepatitis B virus[6] and human immunodeficiency virus (HIV),[7] which are attributed to their metabolic stability against various cleaving agents and the ability to prevent free radical-induced degradation of the ribose ring of nucleosides or nucleotides by *C*-4′-H abstraction. Among the carbanucleosides, carbovir (**3**),[7] abacavir (**4**),[8] (−) BCA (**5**),[9] carba-5-bromovinyl-2′-deoxyuridine,[10] carba-2′-*para*-fluoro-guanosine[11] and some cyclopentene nucleosides[12] are important due to their potent anti-HIV activity in vitro.



The desired biological activity of a chiral molecule is often recognized to reside in one enantiomer, the other enantiomer being either inactive or showing different activity. Thus, to meet the demand for enantiomerically pure new drugs, drug intermediates and pharmaceuticals, focus has been directed to the synthesis of chiral carbanucleosides in both enantiomeric forms. Realizing this, our group has been actively engaged in enantiodivergent syntheses of various nucleoside analogues[13] from the cheap and easily available starting material 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**6**) using intramolecular nitrone cycloaddition (INC) and ring closing metathesis (RCM) as synthetic tools. As depicted in Figure 1, the appendage of an allyl moiety

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at the C-3 position and INC reaction using the C-1 or C-5 aldehyde could be a very convenient way to synthesize both the enantiomers of the desired carbocyclic nucleosides. According to the procedures reported so far, introduction of an allyl group[14] is achieved through addition to the ketone/epoxide generated at C-3; however, the nucleosides derived by this procedure contain a tertiary carbon at C-3 with hydroxy functionality. To obtain our target bishydroxymethyl substituted nucleoside, which is structurally closer to the naturally occurring carbocyclic nucleosides, direct substitution of the C-3 hydroxyl group by an allyl moiety was needed. It was important to ensure that the allyl group was β-oriented so that cyclization (with the C-5 nitrone) may proceed in the desired manner (to obtain the five-membered carbocyclic backbone); *trans* orientation of the two termini is known to direct cyclization to an alternative mode forming six-membered carbocycles. Once both the enantiomers of a five-membered carbocycle are derived, conversion to their corresponding nucleosides demands only cleavage of the isoxazolidine as well as the furan rings and construction of the nucleoside base through well established methodologies.

To achieve the desired goal, the allyl group must substitute the C-3 hydroxyl group of **6** with retention of stereochemistry, which is best achieved using radical substitution. Thus, for radical-induced allylation at C-3, we treated phenoxythiocarbonyl ester **7a**[15] or methyl xanthate **7b**,[16] both derived from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**6**), with allyl tri-*n*-butyltin using two different procedures—thermal and photochemical. Thermal radical reaction with methyl xanthate **7b** using AIBN and allyl tri-*n*-butyltin in refluxing toluene was fast (30 min) but yielded a mixture of products, creating tremendous difficulty in separation. Photo-induced radical substitution was also unsuccessful. However, the photochemical conversion of the phenoxythiocarbonyl ester derivative **7a**, carried out at a low temperature (10 °C) using UV light, resulted in a clean reaction with very high yield though requiring a longer time (40 h) for completion. Thus, photochemical allylation of **7a** appeared to be the most useful method. The transformation of **7a** to the allyl derivative **8** with retention of configuration is attributed to the shielding of the α-face of the radical centre by the dioxolane ring system[17] (Scheme 1).

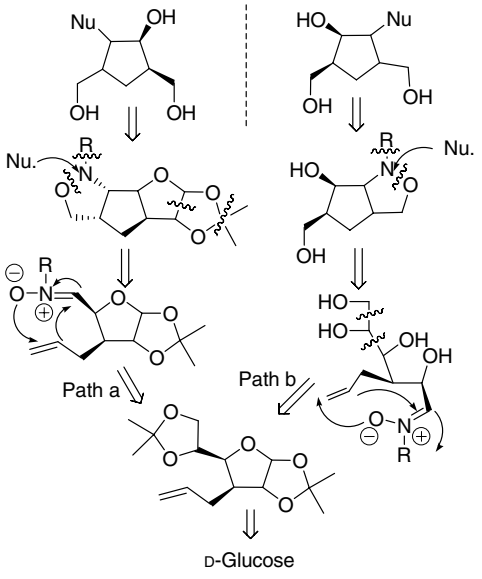
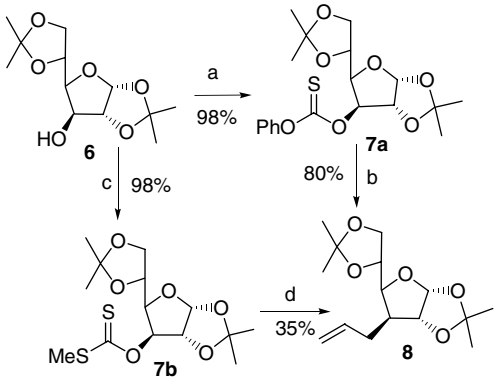


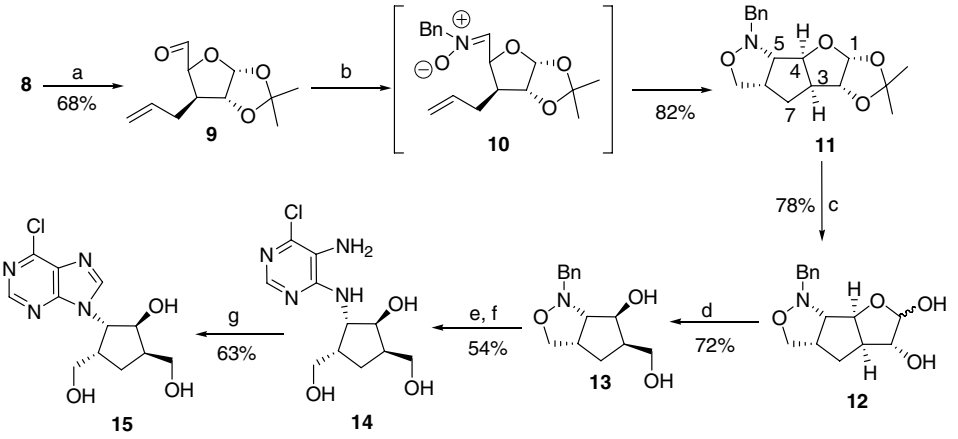
Figure 1. Retrosynthetic analysis for both the enantiomers of a carbanucleoside.

Selective removal of the 5,6-*O*-isopropylidene group of **8** under mild acidic conditions (Scheme 2a) followed by vicinal diol cleavage with $NaIO_4$ in MeOH furnished a sufficiently pure aldehyde **9**, which upon reaction with *N*-BnNHOH afforded **11** through the intermediacy of a non-isolable enose-nitrone **10**. Opening of the 1,2-acetonide of **11** with dilute H_2SO_4 furnished an anomeric mixture of diols **12**, which upon diol cleavage with $NaIO_4$ and $NaBH_4$ reduction of the resulting aldehyde yielded isoxazolidinocyclopentane derivative **13**. Transfer hydrogenolysis of **13** using Pd–C and cyclohexene furnished the corresponding bis-hydroxymethyl aminocyclopentanol, which was used to construct the purine base through a two-step sequence involving coupling with 5-amino-4,6-dichloropyrimidine affording pyrimidine derivative **14** and its cyclization with $HC(OEt)_3$/*p*-TSA, furnishing chloropurine nucleoside **15**.

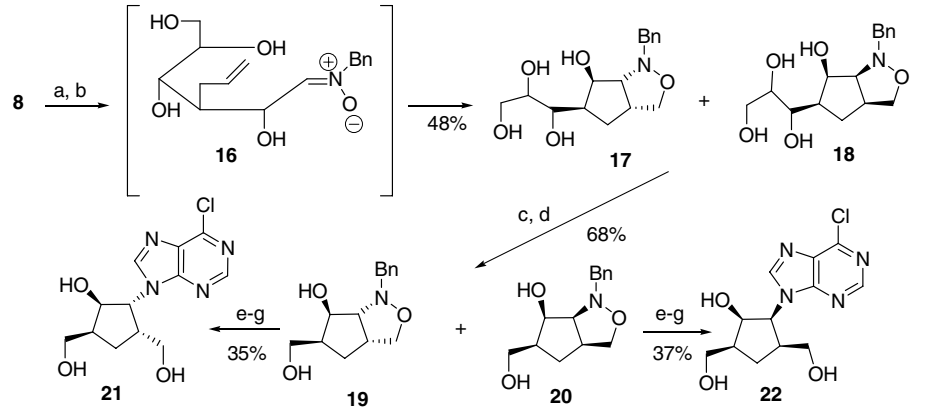
The synthesis of the enantiomer of **13** was carried out using the in situ generated non-isolable nitrone **16** (obtained after removal of both the isopropylidene groups of **8** by overnight stirring with 4% sulphuric acid at room temperature followed by the treatment of an alcoholic solution of the resulting hemi-acetal with *N*-BnNHOH), which spontaneously cyclized to generate a mixture of products[18] **17** and **18** (Scheme 2b). The mixture, without further purification, was reacted with $NaIO_4$ followed by $NaBH_4$ to furnish the corresponding mixture of **19** and **20**, which was separated and purified using column chromatography. In order to obtain chloropurine nucleosides **21** (from **19**) and **22** (from **20**), the procedure followed was similar to that described for **13**.



Scheme 1. Stereospecific *C*-allylation at C-3 of **6**. Reagents and conditions: (a) Phenylchlorothionoformate, pyridine, 0 °C, 2 h; (b) allyl tri-*n*-butyltin, dry benzene, Hanovia lamp (460 W, pyrex glass), 10 °C, 40 h; (c) NaH, CS_2, MeI, THF, rt, 30 min; (d) allyl tri-*n*-butyltin, AIBN, toluene, reflux, 30 min.



Scheme 2a. A synthetic approach to carbanucleoside **15**. Reagents and conditions: (a) (i) Aqueous AcOH (75%), rt, overnight; (ii) aqueous $NaIO_4$, MeOH, rt, 30 min; (b) *N*-benzyl hydroxylamine, benzene, reflux, 4 h; (c) CH_3CN–H_2O–H_2SO_4 (18:6:1), rt, 24 h; (d) (i) aqueous $NaIO_4$, MeOH, rt, 30 min; (ii) $NaBH_4$, MeOH, rt, 2 h; (e) Pd/C (10%), cyclohexene, dry EtOH, reflux, 4 h; (f) 5-amino-4,6-dichloropyrimidine, *n*-butanol, dry Et_3N, reflux, 30 h; (g) triethyl orthoformate, *p*-TSA, dry DMF, 10 °C, 24 h.



Scheme 2b. Synthesis of carbanucleoside **21** (enantiomer of **15**) and diastereomer **22**. Reagents and conditions: (a) CH_3CN–H_2O–H_2SO_4 (18:6:1), rt , 24 h; (b) *N*-benzyl hydroxylamine, EtOH , reflux, 4 h; (c) aqueous $NaIO_4$, MeOH, rt, 30 min; (d) $NaBH_4$, MeOH, rt, 2 h; (e) Pd/C (10%), cyclohexene, dry EtOH, reflux, 4 h; (f) 5-amino-4,6-dichloropyrimidine, *n*-butanol, dry Et_3N, reflux, 30 h; (g) triethyl orthoformate, *p*-TSA, dry DMF, 10 °C, 24 h.

Regarding the structure of **8**, the trans relationship between H-2 and H-3 was established from the appearance of the H-2 signal as a doublet at δ 4.51 ($J = 3.6$ Hz) in the ^{1}H NMR spectrum;[19] this signal is observed as a triplet ($J = 4.0$ Hz) in the case of *cis*-isomers. In the ^{1}H NMR spectrum of **11**,[20] the disappearance of signals for the olefinic protons of the starting material as well as the appearance of signals for *N*-benzylic protons (two doublets at δ 3.85 and 3.97, $J = 13.2$ Hz) and the presence of appropriate aromatic proton signals provided a distinct indication of the success of the INC reaction. The presence of a 2H doublet at δ 4.50 (both $J_{1,2}$ and $J_{3,4} = 3.6$ Hz and $J_{2,3} = 0$ Hz) due to H-2 and H-4, and another doublet at δ 3.59 for H-5 ($J_{5,6} = 7.8$ Hz) confirmed the trans disposition of H-4 and H-5 ($J_{4,5} = 0$ Hz). Since the isoxazolidinocyclopentane is a bicyclo[3.3.0]octane system, the ring juncture stereochemistry should be cis, which is energetically favoured. The other protons in **11** gave appropriate signals in the ^{1}H NMR spectrum. The occurrence of only one upfield signal (at δ 32.2; for C-7) in the ^{13}C NMR spectrum clearly ruled out a bridged structure, which could be formed through the alternative mode of cyclization. Further structural confirmation was obtained from a single crystal X-ray crystallographic study (the ORTEP diagram is given in Fig. 2).[21]

The enantiomeric pairs (**13** and **19**, **15** and **21**)[20] have virtually superimposable IR, ^{1}H NMR, and ^{13}C NMR and optical rotations of equal magnitude but opposite signs. Again, ^{13}C NMR and ESIMS spectra showed **19** and **20** to be isomers each possessing a cyclopentane ring. ^{1}H NMR signals also showed the compounds to be isomeric in nature. The only possible difference between **19** and **20** could be in the two newly generated stereocentres. As the structure of **19** is known from its enantiomeric relationship with **13**, the structure of **20**[20] could be derived very easily keeping in mind the preference for *cis*-fusion of the five-membered rings.

In conclusion, this study describes a linear approach in which both the enantiomers of a carbanucleoside can be synthesized from a D-glucose derived substrate through allyl substitution of the 3-OH group using

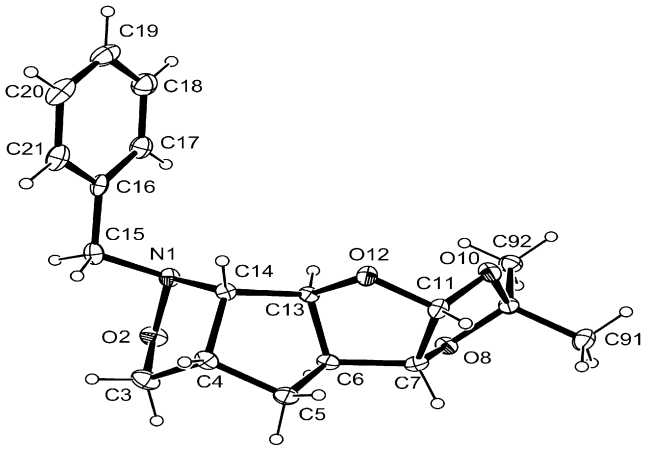


Figure 2. ORTEP diagram of **11**.

radical chemistry and the application of an intramolecular nitrone cycloaddition reaction. This strategy should be useful to synthesize both the enantiomers of the important carbanucleosides applying different strategies of ring closure utilizing the olefin at C-3 and aldehyde at C-5 or C-1. The results may be extended to other systems utilizing different substitution patterns judiciously derived from carbohydrates. These nucleosides could be potential antiviral agents and also be used in the synthesis of unnatural oligonucleotides.

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15. *Preparation of* **7a**: To a cooled solution (0 °C) of 1,2:5,6-di-*O*-isopropylidine-α-D-glucofuranose **6** (500 mg, 1.92 mmol) in dry pyridine (10 mL), phenyl chlorothionoformate (443 mg, 2.56 mmol) was added slowly using a syringe. A yellow precipitate generated during addition was allowed to dissolve by stirring for 1 h. When the solution became transparent, the reaction temperature was raised to rt and stirring was continued for another 30 min. After completion of the reaction (TLC), the solvent was evaporated under reduced pressure and the last traces of pyridine were removed by azeotropic evaporation with toluene. The oily mass thus obtained was then dissolved in DCM (20 mL), washed with water (3 × 10 mL) and dried (Na_2SO_4). The solvent was evaporated under reduced pressure to yield a crude yellow solid, which was finally purified by column chromatography over silica gel (petroleum ether:ethyl acetate 4:1) to afford **7a** (689 mg, 87%) as a colourless solid. $[\alpha]_D^{25}$ −27.5 (*c* 0.74, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.34 (s, 3H), 1.37 (s, 3H), 1.45 (s, 3H), 1.55 (s, 3H), 4.05–4.13 (m, 2H), 4.32 (br s, 2H), 4.78 (d, 1H, $J = 3.7$ Hz), 5.64 (s, 1H), 5.96 (d, 1H, $J = 3.7$ Hz), 7.12 (d, 2H, $J = 7.8$ Hz), 7.30 (t, 1H, $J = 7.3$ Hz), 7.43 (t-like, 2H, $J = 7.8$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.1 (CH_3), 26.1 (CH_3), 26.5 (CH_3), 26.7 (CH_3), 66.9 (CH_2), 72.1 (CH), 79.5 (CH), 82.7 (CH), 84.9 (CH), 104.8 (CH), 109.3 (C), 112.3 (C), 121.6 (2 × CH), 126.6 (CH), 129.5 (2×CH), 153.1 (C), 193.5 (C); ESIMS, *m*/*z*: 419 $(M+Na)^+$. Anal. Calcd for $C_{19}H_{24}O_7S$: C, 57.56; H, 6.10. Found: C, 57.38; H, 5.88.

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18. The crude mixture of **17** and **18** showed appropriate aromatic proton signals in the ^{1}H NMR spectrum and exhibited the pseudomolecular ion peak in the ESIMS spectrum at *m*/*z* 332 $(M+Na)^+$.
19. *Preparation of* **8**: To a stirred solution of **7a** (4.0 g, 10.1 mmol) in benzene (250 ml) was added allyl tri-*n*-butyltin (8.3 g, 25.0 mmol) and the mixture was poured under an Ar atmosphere into a Hanovia flask, equipped with a magnetic stirrer, a cold water circulator and a 460 W filament inside a Pyrex glass. The reaction temperature was set at 10 °C; the UV light was switched on and passed through the Pyrex glass to transmit only the desired wavelength (360 nm) of light. After 40 h, the solvent was evaporated to give a crude oil, which was purified by column chromatography on silica gel (60–120 mesh) using petroleum ether:ethyl acetate (85:15) as the eluent to afford **8** (2.30 g, 80%) as a colourless oily liquid. $[\alpha]_D^{25}$ −21.4 (*c* 0.56, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.30 (s, 3H), 1.35 (s, 3H), 1.42 (s, 3H), 1.52 (s, 3H), 1.87 (m, 1H), 2.43 (m, 2H), 3.93 (dd, 1H, $J = 4.5$, 7.8 Hz), 4.02–4.16 (m, 3H), 4.51 (d, 1H, $J = 3.6$ Hz), 5.06–5.13 (m, 2H), 5.74 (d, 1H, $J = 3.6$ Hz), 5.78 (partially merged m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.7 (CH_3), 26.5 (CH_3), 27.1 (CH_3), 27.2 (CH_3), 30.0 (CH_2), 45.7 (CH), 68.9 (CH_2), 72.7 (CH), 81.0 (CH), 83.9 (CH), 105.2 (CH), 109.7 (C), 111.5 (C), 117.6 (CH_2), 136.1 (CH); ESIMS, *m*/*z*: 307 $(M+Na)^+$. Anal. Calcd for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51. Found: C, 63.10; H, 8.35.
20. Compound **11**: colourless solid. $[\alpha]_D^{25}$ −26.6 (*c* 0.81, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.27 (s, 3H), 1.46 (s, 3H), 1.46–1.52 (partially merged signal, 1H), 1.80 (dd, 1H, $J = 8.4$, 13.2 Hz), 2.84–2.88 (m, 1H), 3.23–3.28 (m, 1H), 3.49 (dd, 1H, $J = 4.8$, 8.4 Hz), 3.59 (d, 1H, $J = 7.8$ Hz), 3.85 (d, 1H, $J = 13.2$ Hz), 3.97 (d, 1H, $J = 13.2$ Hz), 4.16 (t, 1H, $J = 8.4$ Hz), 4.50 (d, 2H, $J = 3.6$ Hz), 5.79 (d, 1H, $J = 3.6$ Hz), 7.24–7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.2 (CH_3), 26.9 (CH_3), 32.2 (CH_2), 47.5 (CH), 48.9 (CH), 60.8 (CH_2), 72.2 (CH_2), 74.9 (CH), 84.0 (CH), 88.8 (CH), 105.6 (CH), 111.3 (C), 127.5 (CH), 128.4 (2 × CH), 129.0 (2 × CH), 136.6 (C); FABMS, *m*/*z*: 318 $(M+H)^+$. Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 68.18; H, 7.18, N, 4.15. Compound **13** : Gum. $[\alpha]_D^{25}$ −48.5 (*c* 0.72, $CHCl_3$); ^{1}H NMR ($CDCl_3$+D_2O, 300 MHz): δ 1.52 (dd, 1H, $J = 6.8$, 12.6 Hz), 1.96–2.07 (m, 1H), 2.33–2.37 (m, 1H), 3.23 (m, 1H), 3.32 (d, 1H, $J = 8.0$ Hz), 3.49 (dd, 1H, $J = 4.8$, 8.5 Hz), 3.75 (dd, 1H, $J = 6.8$, 11.0 Hz), 3.86 (d, 1H, $J = 13.0$ Hz), 3.88 (partially merged dd, 1H, $J = 4.0$, 10.8 Hz), 4.03 (d, 1H, $J = 13.0$ Hz), 4.04 (d, 1H, $J = 4.0$ Hz), 4.17 (t, 1H, $J = 8.0$ Hz), 7.29–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 30.5 (CH_2), 43.7 (CH), 45.5 (CH), 61.3 (CH_2), 61.7 (CH_2), 72.7 (CH_2), 77.8 (CH), 78.6 (CH), 127.4 (CH), 128.3 (2 × CH), 129.0 (2 × CH), 136.9 (C); FABMS, *m*/*z*: 250 $(M+H)^+$. Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.18; H, 7.50, N, 5.34. Compound **15**: Foam. $[\alpha]_D^{25}$ −36.8 (*c* 0.39, MeOH); ^{1}H NMR (D_2O, 300 MHz): δ 1.79–1.95 (m, 2H), 2.50 (m, 1H), 2.72 (m, 1H), 3.19 (br d, 2H, $J = 6.0$ Hz), 3.60 (dd-like, 1H, $J = 7.5$, 10.0 Hz), 3.77 (dd, 1H, $J = 4.8$, 9.8 Hz), 4.94–5.09 (m, 2H), 8.58 (s, 1H), 8.62 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 28.1 (CH_2), 39.5 (CH), 41.2 (CH), 61.5 (CH_2), 61.7 (CH_2), 63.9 (CH), 74.9 (CH), 131.3 (C), 146.8 (CH), 150.6 (C) 152.1(CH), 152.8 (C); ESIMS, *m*/*z*: 321 [$(M+Na)^+$ for Cl^{35}], 323 [$(M+Na)^+$ for Cl^{37}]. Anal. Calcd for $C_{12}H_{15}ClN_4O_3$: C, 48.25; H, 5.06; N, 18.76. Found: C, 48.28; H, 5.00, N, 18.47. Compound **19**: $[\alpha]_D^{25}$ +48.9 (*c* 0.68, $CHCl_3$); IR, ^{1}H and ^{13}C NMR spectra of **19** are practically identical with those of **13**. Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.22; H, 7.43, N, 5.42. Compound **20**: Gum. $[\alpha]_D^{25}$ +43.4 (*c* 0.84, $CHCl_3$); ^{1}H NMR ($CDCl_3$+D_2O, 300 MHz): δ 1.74–1.94 (m, 3H), 3.15 (m, 1H), 3.62 (dd, 1H, $J = 5.4$, 9.4 Hz), 3.69 (dd, 1H, $J = 3.0$, 8.7 Hz), 3.75 (dd, 1H, $J = 5.7$, 11.4 Hz), 3.89–3.95 (m, 3H), 4.11 (dd, 1H, $J = 6.7$, 8.7 Hz), 4.24 (d, 1H, $J = 12.6$ Hz), 7.26–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 30.3 (CH_2), 47.9 (CH), 48.3 (CH), 60.2 (CH_2), 61.5 (CH_2), 71.6 (CH_2), 72.2 (CH), 72.5 (CH), 127.6 (CH), 128.4 (2 × CH), 128.8 (2×CH), 136.6 (C); EIMS, *m*/*z*: 249 $(M)^+$. Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.39; H, 7.47, N, 5.34. Compound **21**: Foam. $[\alpha]_D^{25}$ +37.1 (*c* 0.24, MeOH); ^{1}H and ^{13}C NMR spectra virtually match those of **15**. Anal. Calcd for $C_{12}H_{15}ClN_4O_3$: C, 48.25; H, 5.06; N, 18.76. Found: C, 48.10; H, 4.86; N, 18.61. Compound **22**: Foam.$[\alpha]_D^{25}$ +25.4 (*c* 0.31, MeOH); ^{1}H NMR (D_2O, 300 MHz): δ 1.37–1.48 (m, 1H), 2.07–2.17 (m, 1H), 2.31 (m, 1H), 2.79 (m, 1H), 3.31 (d, 2H, $J = 6.0$ Hz), 3.63 (dd, 1H, $J = 6.0$, 10.8 Hz), 3.78 (dd, 1H, $J = 8.0$, 10.8 Hz), 4.46 (t, 1H, $J = 3.6$ Hz), 5.23 (dd, 1H, $J = 4.0$, 10.0 Hz), 8.67 (s, 1H), 8.87 (s, 1H); ^{13}C NMR (DMSO-d_6, 150 MHz): δ 28.6 (CH_2), 40.7 (CH), 44.9 (CH), 58.6 (CH), 60.3 (CH_2), 61.9 (CH_2), 71.7 (CH), 129.9 (C), 147.8 (CH), 148.7 (C), 151.3 (CH) 152.8 (C); ESIMS, *m*/*z*: 321 [$(M+Na)^+$ for Cl^{35}], 323 [$(M+Na)^+$ for Cl^{37}]. Anal. Calcd for $C_{12}H_{15}ClN_4O_3$: C, 48.25; H, 5.06; N, 18.76. Found: C, 47.98; H, 4.88; N, 18.53.
21. Crystallographic data, **11**: MF = $C_{18}H_{23}NO_4$, M = 317.37, orthorhombic, space group $P2_12_12_1$, $a = 6.9512$ (5), $b = 13.4852$ (10), $c = 17.3143$ (13) Å, $U = 1623.0$ (2) Å^3, $Z = 4$, calcd = 12.99 g cm^{-3}. 4741 Independent reflections were measured using MoKα radiation at 150 K on an Oxford Instruments X-Calibur CCD diffractometer and refined to R1 0.0522. wR 2 0.1022. Torsion angle between H-13 and H-14 is −99.1 and between H-4 and H-14 is 9.4. Crystal data have been deposited at the Cambridge Crystallographic Data Centre with reference number CCDC 619424. Data can be obtained via www.ccdc.cam.ac.uk/data_request/cif.