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Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 19 (2008) 976–983

Oxetane amino acids: synthesis of tetrameric and hexameric carbopeptoids derived from L-ribo 4-(aminomethyl)-oxetan-2-carboxylic acid

Beatrice Lopez-Ortega, Sarah F. Jenkinson, Timothy D. W. Claridge and George W. J. Fleet*

Chemistry Research Laboratory, Department of Chemistry, University of Oxford, Mansfield Road, Oxford OX1 3TA, UK

Received 25 February 2008; accepted 27 March 2008

Abstract—The synthesis of methyl 2,4-anhydro-5-azido-3-*O*-benzyl-5-deoxy-L-ribonate, a δ-2,4-*cis*-oxetane-azido ester scaffold derived from L-arabinose, is reported. Iterative coupling methods were utilised to form homo-oligomers up to the hexamer in order to investigate the secondary structural preferences of these systems.

1. Introduction

Peptides and proteins are involved in a vast array of biological processes and are therefore attractive targets for drug design.[1] Poor bioavailability and metabolic stability of peptidic drugs, however, have resulted in significant limitations. Sugar amino acids (SAA's) are versatile building blocks for the formation of foldamers and peptidomimetics; hence there has been much interest in their synthesis.[2] SAA's have many advantages in the design of peptidomimetics as they are conformationally restricted by their ring size; the backbone functionality can readily be modified to give, for example, chain branching[3] unsaturation[4] and deoxygenation.[5] Many different stereochemistries can be accessed and the acid and amino groups can be introduced at different positions on the ring to allow access to α-, β-, γ- and δ-amino acids (Fig. 1).

The use of δ-SAA's as peptidomimetics was demonstrated by Kessler et al. who investigated the conformational influences of several tetrahydropyran (THP) SAA's on peptide chains by replacing them with the Gly-Gly fragment of Leu-enkephalin.[6] The δ-SAA dipeptide isosteres **1** and **2** (Fig. 2) were seen to induce different secondary structures with **1** inducing a β-turn type structure and **2** inducing a γ-turn type structure. Further investigation into THP[7] and tetrahydrofuran (THF)[8,9] dipeptide isosteres has led to the formation of several biologically active peptidomimetics with much improved metabolic stability.[10]

Foldamers are molecules which display a predisposition towards the formation of well-defined secondary structure in short sequences. Investigations into the synthesis and secondary structure of homo-oligomers of conformationally restricted[11,12] THF and THP SAA's provide many examples of predisposition towards secondary structures in relatively small molecules.[13–15] Ring contraction to the more conformationally stable 4-membered oxetane system may confer more rigidity upon the SAA and hence increase the potential for their oligomers to adopt stable secondary structures. In the case of the *cis* β-amino acid oxetane oligomers derived from D-xylose and L-rhamnose these were seen to adopt helical structures stabilised by 10-membered hydrogen bonds.[16] Investigations into the 2,4-*trans*-oxetane δ-amino acid scaffolds have been reported, however, the oligomers did not appear to adopt well-defined secondary structures stabilised by hydrogen bonding.[17] Here the synthesis of the 2,4-*cis*-oxetane amino acid building blocks and coupling to form homo-oligomers is reported.

2. Synthesis of oxetane amino acid oligomers

Two strategies could be envisaged for the formation of the desired 2,4-*cis*-oxetane amino acid monomers, with the introduction of the azide functionality either before or after

* Corresponding author. E-mail: george.fleet@chem.ox.ac.uk

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doi:10.1016/j.tetasy.2008.03.030

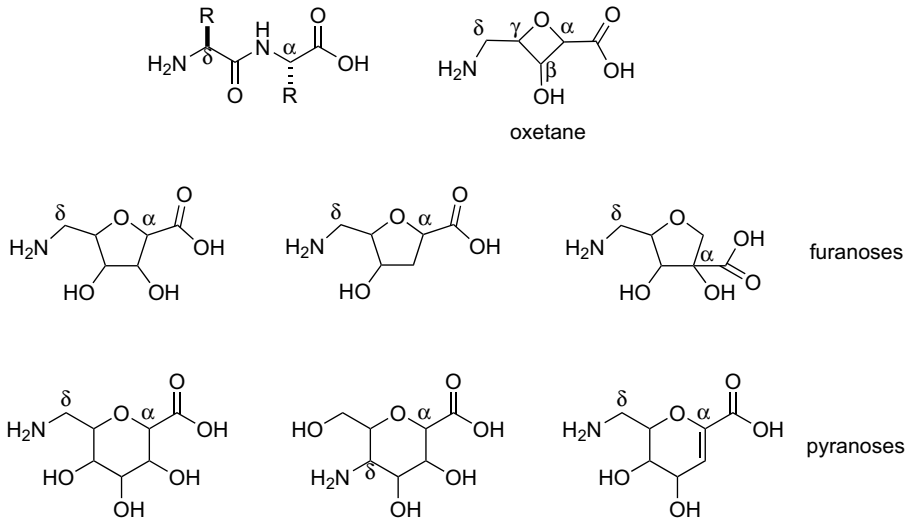


Figure 1. Stereochemically constrained SAA's: examples of the diversity of δ-SAA dipeptide isosteres available.

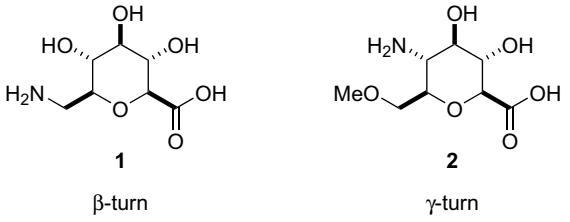
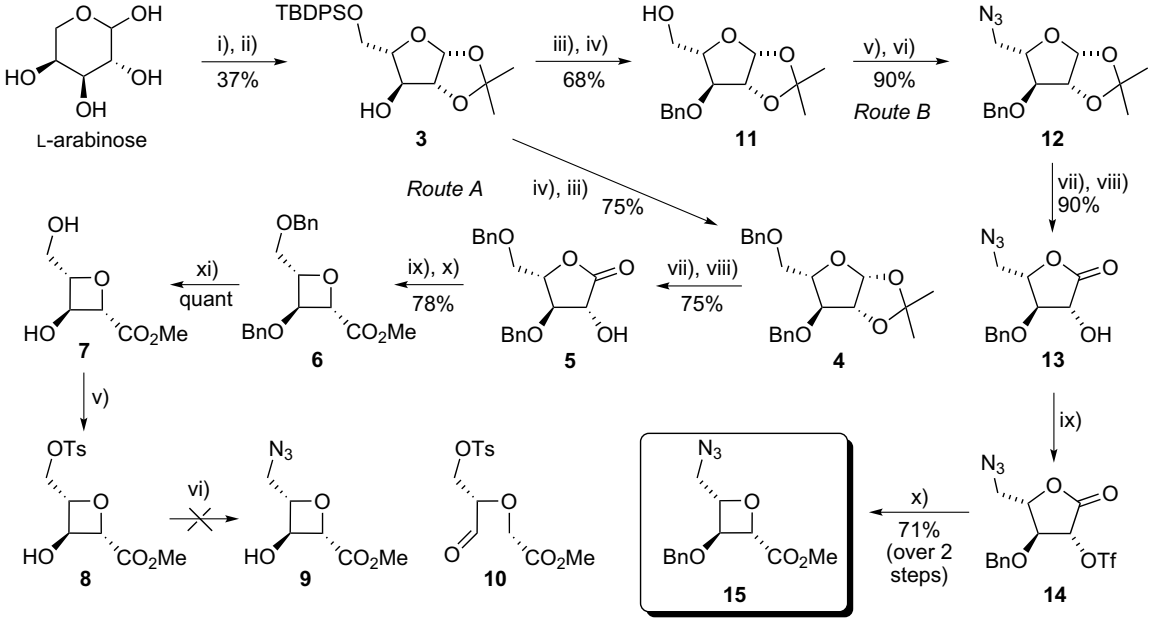


Figure 2.

the ring contraction (Scheme 1). The key step, the ring closure of an α-triflate of a γ-lactone in basic methanol, is known to form oxetane rings in good yields provided that there is a *trans* relationship between the C-2 and C-3 positions of the oxetane ring formed.[4,18] Thus the initial oxetane target was azido ester **9**.

The protected L-arabinose **3** (Scheme 1) with only the C-3 hydroxyl unprotected was the common intermediate for the two routes.[19] Deprotection of the silyl group, benzylation of the two free hydroxyls, followed by acetonide deprotection and bromine oxidation gave the arabinonolactone **5** in good yield. Activation of the free hydroxyl group as a trifluoromethanesulfonyl ester followed by treatment with basic methanol yielded the desired oxetane ring **6** and provided the desired masked acid functionality, the ester group at C-1.[20] Protection of both the C-3 and C-5 hydroxyl groups prior to the ring closure prevented competitive formation of 3 or 5-membered rings. Deprotection

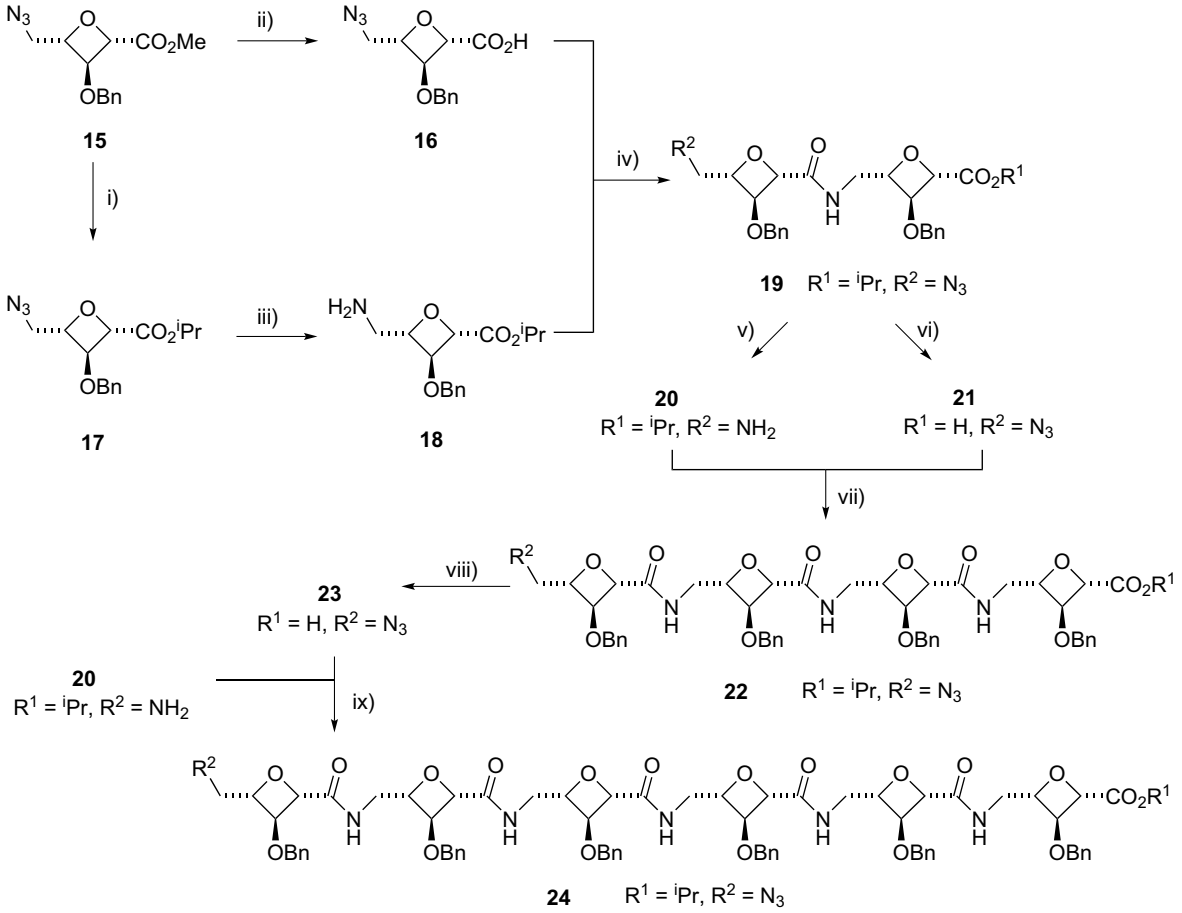


Scheme 1. Reagents and conditions: (i) TBDPSCl, imidazole, DMF, 60 °C, 2 h; (ii) $CuSO_4$, acetone, (±)-camphor sulfonic acid, rt, 4 h; (iii) NaH, BnBr, $^nBu_4NI$, DMF, −10 to 5 °C, 3 h; (iv) $^nBu_4NF$, THF, rt, 2 h; (v) TsCl, pyridine; (vi) NaN_3, DMF; (vii) TFA/H_2O 3:2, rt, 30 min; (viii) Br_2, $BaCO_3$, dioxane–H_2O, 0 °C to rt, 18 h; (ix) Tf_2O, DCM, pyridine, −30 °C, 30 min; (x) MeOH, K_2CO_3, −30 to −10 °C, 1 h; (xi) Pd/C, H_2, MeOH, rt, 45 min.

of the benzyl ether protecting groups by hydrogenation proceeded smoothly to give oxetane **7** in good yield (16% over 9 steps). In order to introduce an azide group, to serve as the masked amine, selective activation of the primary alcohol followed by azide displacement was required. Although selective tosylation to give tosylate **8** was successful, subsequent azide displacement did not yield any of the desired azido-ester **9**. The reason for this was unclear; however, β-hydroxy oxetanes are prone to retro-aldol ring opening in basic conditions[17] and it may be that the open chain product **10** (Scheme 1) might have been formed preferentially. The alternative route in which the azide functionality was introduced prior to the ring contraction was therefore investigated. Thus, reaction of **3** with benzyl bromide and sodium hydride in DMF followed by deprotection of the silyl protecting group gave the furanose **11** in which only the C-5 hydroxyl group is free for further manipulation. Activation of the alcohol with tosyl chloride in pyridine at low temperature and subsequent displacement with sodium azide afforded **12** in excellent yield (90% over two steps). Acidic hydrolysis to the lactol and oxidation with bromine gave lactone **13** which on triflation of the free hydroxyl group followed by treatment with potassium carbonate in methanol yielded the desired oxetane monomer unit **15** in 15% over 10 steps.

The synthesis of dimer **19** was accomplished by an iterative coupling procedure in which the amine derived from azido ester **15** was coupled with the acid also derived from azido ester **15** (Scheme 2). For the synthesis of amine **18**, however, transesterification of **15** to **17** was first carried out to avoid intramolecular lactamisation and oligomerisation. The azido ester **15** was therefore treated with potassium carbonate in isopropanol to afford isopropyl ester **17** and then reacted with palladium on carbon under an atmosphere of hydrogen to give the desired amine **18**. The azido ester **15** was also treated with sodium hydroxide in a mixture of tetrahydrofuran and water and then subsequently acidified to yield acid **16**. The acid and amine were used without further purification in the coupling reaction, with *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU) and triethylamine in *N*,*N*-dimethylformamide to give dimer **19** in 89% yield calculated from **17**.

Tetramer **22** was obtained in a similar manner from the coupling of dimer amine **20** and dimer acid **21** with TBTU and triethylamine in 54% yield from the dimer. Finally, hexamer **24** was successfully prepared by treating dimer amine **20** and tetramer acid **23** with TBTU and triethylamine giving hexamer **24** in 64% yield from the dimer.



Scheme 2. Reagents and conditions: (i) ^{i}PrOH, K_2CO_3, rt, 19 h, 85%; (ii) NaOH, H_2O, THF, rt, 6 h; (iii) Pd/C, H_2, AcOEt, rt, 5 h; (iv) TBTU, Et_3N, DMF, rt, 16 h, 89% (from **17**); (v) Pd/C, H_2, AcOEt, rt, 22 h, 87%; (vi) NaOH, H_2O, THF, rt, 5 h; (vii) TBTU, Et_3N, DMF, rt, 2.5 h, 54% (from **19**); (viii) NaOH, H_2O, THF, rt, 3 h; (ix) TBTU, Et_3N, DMF, rt, 18 h, 64% (from **19**).

3. Conclusion

The synthesis of the 2,4-*cis* oxetane azido ester monomer unit **15** was successfully achieved in an overall yield of 15% over 10 steps. This was then subsequently used to form homo-oligomers up to the hexamer, via solution phase iterative coupling, in good yields. The investigations into the secondary structural preferences of these oligomers are described in the following paper.[21]

4. Experimental

4.1. General

Tetrahydrofuran was distilled under an atmosphere of dry nitrogen from sodium benzophenone ketyl or purchased dry from the Aldrich Chemical Company in Sure/Seal™ bottles; dichloromethane was distilled from calcium hydride; pyridine was distilled from calcium hydride and stored over dried 3 Å molecular sieves; hexane refers to 60–80 °C petroleum ether; water was distilled. *N*,*N*-Dimethylformamide was purchased dry from the Aldrich Chemical Company in Sure/Seal™ bottles. All other solvents were used as supplied (analytical or HPLC grade) without prior purification. Reactions performed under an atmosphere of nitrogen or hydrogen gas were maintained by an inflated balloon. A pH 7 buffer was prepared by dissolving KH_2PO_4 (85 g) and NaOH (14.5 g) in distilled water (950 mL). Imidazole was recrystallised from dichloromethane. All other reagents were used as supplied, without prior purification. Thin layer chromatography (TLC) was performed on aluminium sheets coated with 60 F_{254} silica. Sheets were visualised using a spray of 0.2% w/v cerium (IV) sulfate and 5% ammonium molybdate in 2 M sulfuric acid. Flash column chromatography was performed on Sorbsil C60 40/60 silica. Melting points were recorded on a Köfler hot block and are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AM 500 or AMX 500 (^{1}H: 500 MHz and ^{13}C: 125.3 MHz) or where stated on a Bruker AC 200 (^{1}H: 200 MHz and ^{13}C: 50.3 MHz) or Bruker DPX 400 (^{1}H: 400 MHz and ^{13}C: 100.6 MHz) spectrometer in deuterated solvent. Chemical shifts (δ) are quoted in ppm and coupling constants (J) in Hz. Residual signals from the solvents were used as an internal reference. ^{13}C multiplicities were assigned using a DEPT sequence. Infrared spectra were recorded on a Perkin–Elmer 1750 IR Fourier Transform, or Perkin–Elmer Paragon 1000 spectrophotometer using thin films on NaCl plates (thin film) or as KBr disks as stated. Only the characteristic peaks are quoted. Low resolution mass spectra (m/z) were recorded using the following techniques: electrospray ionisation (ES), chemical ionisation (CI, NH_3), or atmospheric pressure chemical ionisation (APCI). ES mass spectra were measured on a Micromass BioQ II-ZS mass spectrometer. CI mass spectra were recorded on a Micromass 500 OAT spectrometer. APCI mass spectra were recorded on a Micromass Platform 1 mass spectrometer via an 'Openlynx' system. High resolution mass spectra (HRMS) were recorded on a Micromass 500 OAT spectrometer by chemical ionisation (CI, NH_3) or a Waters 2790-Micromass LCT mass spectrometer by electrospray ionisation (ES) as stated. For ES mass spectra the spectrometer was operated at a resolution of 5000 full width half height. Positive ion spectra were calibrated relative to PEG with tetraoctylammonium bromide as the internal lock mass. Negative ion spectra were calibrated relative to poly-DL-alanine with Leu-enkephalin as the internal lock mass. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter with a path length of 1 dm. Concentrations are quoted in g/100 mL.

4.2. 5-*O*-*tert*-Butyldiphenylsilyl-1,2-*O*-isopropylidene-β-L-arabinofuranose 3

L-Arabinose (20 g, 133.3 mmol) was added to a solution of *tert*-butyldiphenylsilylchloride (34.6 mL, 133.3 mmol) and imidazole (18.1 g, 266 mmol) in *N*,*N*-dimethylformamide (265 mL). The mixture was heated to 60 °C for 2 h after which time the resulting solution was poured over HCl (1 M, 280 mL) and extracted with dichloromethane (3 × 150 mL). The organic extracts were washed with water (100 mL) and sodium bicarbonate (satd aq 100 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography to give the lactol as a colourless oil (25 g, 47%). The lactol was subsequently dissolved in acetone (260 mL) and anhydrous copper sulfate (32 g) added. (±)-Camphor-10-sulfonic acid was added until the solution reached pH 2. The mixture was stirred at room temperature for 4 h when TLC (1:1, ethyl acetate/hexane) showed the formation of one major product (R_f 0.51). A further portion of copper sulfate (15 g) was added and after a further 2 h TLC showed full consumption of the starting material. The mixture was neutralised by careful addition of sodium carbonate(s) and filtered through Celite®. The solvent was removed in vacuo and the resulting residue was dissolved in dichloromethane (500 mL), extracted with water (100 mL) and brine (100 mL), dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography and the protected arabinose **3** was obtained as an oil (21.9 g, 78%). $[\alpha]_D^{23} = -5.0$ (c 1.8, $CHCl_3$) {lit.[22] $[\alpha]_D = -5$ (c 1.2, $CHCl_3$)}; ν_{max} (thin film): 3450 (s, OH); δ_H ($CDCl_3$, 200 MHz): 1.08 (9H, s, $OSiPh_2C(CH_3)_3$), 1.29 (3H, s, CCH_3), 1.34 (3H, s, CCH_3), 2.16 (1H, br s, OH), 3.80–3.91 (2H, m, H5), 4.08 (1H, dt, H4, J 2.4, 6.5), 4.43 (1H, d, H3, J 2.2), 4.55 (1H, d, H2, J 4.1), 5.89 (1H, d, H1, J 4.0), 7.34–7.48 (6H, m, ArH), 7.66–7.72 (4H, m, ArH); δ_C ($CDCl_3$, 50 MHz): 19.7 ($OSiPh_2C(CH_3)$), 26.6 (CH_3), 27.3 (CH_3), 64.1 (CH_2), 76.7 (CH), 87.5 (CH), 87.9 (CH), 106.0 (C1), 113.0 ($C(CH_3)_2$), 128.2, 130.3 (2 × ArH), 133.6, 133.7 (ArC), 136.1 (ArH).

4.3. 3-*O*-Benzyl-1,2-*O*-isopropylidene-β-L-arabinofuranose 11

Sodium hydride (295 mg, 7.28 mmol) was suspended in *N*,*N*-dimethylformamide (5 mL) and cooled to −20 °C. A solution of 5-*O*-*tert*-butyldiphenylsilyl-1,2-*O*-isopropylidene-β-L-arabinofuranose **3** (2.07 g, 4.85 mmol) in *N*,*N*-dimethylformamide (10 mL) was added dropwise and the mixture allowed to warm to room temperature over 30 min. The resulting suspension was cooled to −20 °C and $^nBu_4NI$ (215 mg, 0.58 mmol) and BnBr (750 μL,

6.309 mmol) were added. The mixture was stirred for 15 min at −17 °C and then was allowed to warm to room temperature over a period of 30 min. After this time, TLC (1:3, ethyl acetate/hexane) showed no starting material (R_f 0.23) but the formation of one major product (R_f 0.65). The reaction was quenched with ammonium chloride (satd aq 15 mL) and the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (51 mL) and a solution of tetrabutylammoniumfluoride 1.0 M in tetrahydrofuran (9.7 mL, 9.7 mmol) was added. After 2 h at room temperature, TLC (1:3, ethyl acetate/hexane) showed complete consumption of the starting material and the formation of one product (R_f 0.25). Water (25 mL) was added and the mixture was extracted with ether (3 × 100 mL). The combined organic extracts were washed with brine (5 mL), dried over $MgSO_4$ and concentrated in vacuo. A residue was obtained which was purified by column chromatography to give the title compound **11** as a white solid (990 mg, 73%). Found: C, 64.23; H, 7.19; $C_{15}H_{20}O_5$ requires: C, 64.27; H, 7.19; mp: 80–82 °C {lit.[23] mp: 77–78 °C; lit.[24] (for D-enantiomer) mp: 79–80 °C}; ν_{max} (KBr): 3492 (m, OH), 1379 ($C(CH_3)_2$); δ_H ($CDCl_3$, 200 MHz): 1.34, 1.53 (6H, 2 × s, $C(CH_3)_2$); 2.39–2.55 (1H, m, OH), 3.73 (2H, a-t, H5, *J* 5.7), 3.97 (1H, dd, H3, *J* 0.9, 3.3), 4.20 (1H, dt, H4, *J* 3.3, 5.5), 4.60 (2H, AB system $\delta_{5'}$ 4.55, δ_5 4.64, OCH_2Ph, *J* 11.5); 4.68 (1H, dd, H2, *J* 0.9, 4.1), 5.91 (1H, d, H1, *J* 4.1), 7.29–7.37 (5H, m, ArH); δ_C ($CDCl_3$, 50 MHz): 26.2 (CCH_3), 27.0 (CCH_3), 62.6 (CH_2), 71.7 (CH_2), 82.6 (CH), 85.1 (CH), 85.5 (CH), 105.1 (C1), 112.8 ($C(CH_3)_2$), 127.7, 127.9, 128.4 (3 × ArH), 137.1 (ArC); *m*/*z* (APCI+): 303 ($M+Na^+$, 5%), 121 (100%).

4.4. 3-*O*-Benzyl-5-(*p*-toluenesulfonyl)-1,2-*O*-isopropylidene-β-L-arabinofuranose

p-Toluenesulfonyl chloride (670 mg, 3.51 mmol) and 4 Å molecular sieves (900 mg) were added to a solution of **11** (656 mg, 2.34 mmol) in pyridine (5.3 mL) at −10 °C. The mixture was allowed to reach room temperature and after 24 h, TLC (1:2, ethyl acetate/hexane) showed one product (R_f 0.49). The mixture was filtered through Celite® and eluted with dichloromethane (200 mL) and the resulting solution was washed with pH 7 buffer (10 mL). The aqueous layer was extracted with ethyl acetate (2 × 100 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography to give 3-*O*-benzyl-5-(*p*-toluenesulfonyl)-1,2-*O*-isopropylidene-β-L-arabinofuranose as a white solid (1.01 g, 99%). Found: C, 60.69; H, 5.98; $C_{22}H_{26}O_7S$ requires: C, 60.81; H, 6.03; $[\alpha]_D^{23} = -15.0$ (*c* 1.1, $CHCl_3$) {lit.[22] $[\alpha]_D^{26} = -22.5 \pm 0.9$ (*c* 1.2, $CHCl_3$), lit.[23] (for D-enantiomer) $[\alpha]_D^{25} = +20.2$ (*c* 0.5, $CHCl_3$)}; δ_H ($CDCl_3$, 200 MHz): 1.28, 1.35 (6H, 2 × s, $C(CH_3)_2$), 2.43 (3H, s, $ArCH_3$), 3.95 (1H, a-d, H3, *J* 2.1), 4.13 (1H, d, H5, *J* 7.0), 4.13 (1H, d, H5′, *J* 5.8), 4.28 (1H, ddd, H4, *J* 2.1, 5.8, 7.0), 4.54 (2H, AB system, OCH_2Ph), 4.60 (1H, a-d, H2, *J* 3.9), 5.86 (1H, d, H1, *J* 3.9), 7.30–7.40 (7H, m, ArH); δ_C ($CDCl_3$, 50 MHz): 21.5 ($ArCH_3$), 25.8 (CCH_3), 26.6 (CCH_3), 68.4 (CH_2), 71.6 (CH_2), 81.9 (CH), 82.1 (CH), 84.3 (CH), 105.9 (C1), 112.6 ($C(CH_3)_2$), 127.7, 127.9, 127.9, 128.4, 129.8 (5 × ArH), 132.4, 136.7, 144.9 (3 × ArC); *m*/*z* (APCI+): 418 ($M-CH_4^+$, 70%), 187 (100%).

4.5. 5-Azido-3-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-β-L-arabinofuranose 12

3-*O*-Benzyl-5-(*p*-toluenesulfonyl)-1,2-*O*-isopropylidene-β-L-arabinofuranose (6.41 g, 14.7 mmol) was dissolved in *N*,*N*-dimethylformamide (37 mL) and NaN_3 (1.43 g, 14.7 mmol) was added. The reaction mixture was heated to 90 °C and after 16 h, TLC (1:4, ethyl acetate/hexane) showed the formation of one product (R_f 0.42). The mixture was cooled to room temperature and water (30 mL) was added. The solvents were evaporated and the resulting residue was dissolved in water (50 mL) and ethyl acetate (200 mL). The aqueous phase was extracted with ethyl acetate (2 × 100 mL) and the combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$ and concentrated. The resulting residue was purified by flash chromatography to give azide **12** as a white solid (4.01 g, 91%). Found: C, 59.23; H, 6.21; N, 13.53; $C_{15}H_{19}N_3O_4$ requires: C, 59.01; H, 6.27; N, 13.76; mp 47–49 °C; $[\alpha]_D^{23} = -55.8$ (*c* 1.1, $CHCl_3$); ν_{max} (KBr): 2092 (s, N_3); δ_H ($CDCl_3$, 200 MHz): 1.35, 1.55 (6 H, 2 × s, $C(CH_3)_2$), 3.39 (1H, dd, H5, *J* 6.1, 12.6), 3.55 (1H, dd, H5′, *J* 6.6, 12.6), 3.94 (1H, dd, H3, *J* 0.5, 3.1), 4.18 (1H, dt, H4, *J* 3.1, 6.4), 4.56 (1H, d, $OCHPh$, *J* 11.8), 4.65 (1H, d, $OCHPh$, *J* 11.8), 4.66 (1H, a-d, H2, *J* 4.6), 5.91 (1H, d, H1, *J* 4.0), 7.28–7.43 (5H, m, ArH); δ_C ($CDCl_3$, 50 MHz): 26.2, 27.0 (2 × $C(CH_3)_2$), 52.3 (C5), 71.9 (OCH_2Ph), 83.0 (CH), 83.2 (CH), 84.8 (CH), 105.7 (C1), 113.0 ($C(CH_3)_2$), 127.8, 128.0, 128.5 (3 × ArH), 136.9 (ArC); *m*/*z* (APCI+): 278 ($M+H^+-N_2$, 45%), 112 (100%).

4.6. 5-Azido-3-*O*-benzyl-5-deoxy-L-arabinono-1,4-lactone 13

Azide **12** (2.65 g, 8.67 mmol), was dissolved in TFA:H_2O, 3:2 (40 mL) and the mixture was stirred at room temperature for 30 min, when TLC (2.5:1, ethyl acetate/hexane) showed no starting material and one product on the baseline. The solvents were removed in vacuo and the resulting residue was co-evaporated with toluene (3 × 100 mL) and dried in vacuo. The crude lactol was dissolved in 1,4-dioxane:water, 2:1 (40 mL) and barium carbonate (5.13 g, 26.01 mmol) was added. The mixture was cooled to 0 °C and bromine (1.34 mL, 26.01 mmol) was added dropwise after which the reaction allowed to warm to room temperature. After 16 h, TLC (1:2.5, ethyl acetate/hexane) showed one product (R_f 0.21). Sodium thiosulfate (satd aq) was added to quench the reaction and the mixture was extracted with ethyl acetate (3 × 150 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography to give lactone **13** as a white solid (2.04 g, 90%). Found: C, 54.66; H, 4.96; N, 15.67; $C_{12}H_{13}N_3O_4$ requires: C, 54.75; H, 4.98; N, 15.96; mp 49–50 °C; $[\alpha]_D^{23} = -158$ (*c* 1.16, $CHCl_3$); ν_{max} (thin film): 3433 (m, br, OH), 2105 (s,

N_3), 1787 (s, C=O); δ_H ($CDCl_3$, 200 MHz): 3.40 (1H, dd, H5, *J* 4.9, 13.8), 3.65 (1H, dd, H5′, *J* 2.8, 13.8), 3.98 (1H, br s, OH), 4.18 (1H, t, H3, *J* 7.9), 4.36 (1H, ddd, H4, *J* 2.8, 4.9, 8.0), 4.63 (1H, d, H2, *J* 8.0), 4.64 (1H, d, OC*H*Ph, *J* 11.7), 4.87 (1H, d, OC*H*Ph, *J* 11.7), 7.29–7.44 (5H, m, ArH); δ_C ($CDCl_3$, 50 MHz): 51.3 (C5), 73.2 (O*C*H_2Ph), 75.0 (CH), 78.6 (CH), 80.7 (CH), 128.6, 128.8, 129.1 (3 × ArH), 137.3 (ArC), 174.8 (C1); *m*/*z* (APCI+): 236 ($M+H^+-N_2$, 20%), 122 (100%).

4.7. Methyl 2,4-anhydro-5-azido-3-*O*-benzyl-5-deoxy-L-ribonate 15

Lactone **13** (1.93 g, 7.46 mmol) was dissolved in dichloromethane (100 mL) and pyridine (1.81 mL, 22.38 mmol). The solution was cooled to −40 °C and triflic anhydride (1.88 mL, 11.19 mmol) was added dropwise. After 30 min, TLC (1:1, ethyl acetate/hexane) showed no starting material (R_f 0.38) but the formation of one product (R_f 0.66). The reaction mixture was diluted with dichloromethane (200 mL) and extracted with HCl (1 M, 100 mL). The aqueous layer was washed with dichloromethane (200 mL) and the combined organic extracts were washed with water (100 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was used in the following step without further purification. The crude triflate **14** was dissolved in methanol (420 mL) and cooled to −25 °C. Potassium carbonate (3.09 g, 22.38 mmol) was added and the mixture was kept between −25 and −10 °C for 30 min and then allowed to warm to 0 °C over 30 min. After this time, TLC (1:1 ethyl acetate/hexane) showed the formation of one product (R_f 0.4). The mixture was filtered through silica and eluted with methanol and concentrated in vacuo. The resulting residue was purified by flash chromatography to give oxetane **15** as a colourless oil (1.47 g, 71% over 2 steps). Found: C, 56.21; H, 5.34; N, 14.84; $C_{13}H_{15}N_3O_4$ requires C, 56.31; H, 5.45; N, 15.15; $[\alpha]_D^{23} = -169$ (*c* 1.25, $CHCl_3$); ν_{max} (thin film): 2105 (s, N_3), 1755 (s, C=O); δ_H ($CDCl_3$, 400 MHz): 3.17 (1H, dd, H5, *J* 3.9, 13.8), 3.47 (1H, dd, H5′, *J* 3.9, 13.8), 3.83 (3H, s, CO_2CH_3), 4.46 (1H, t, H3, *J* 5.2), 4.49 (1H, d, OC*H*Ph, *J* 11.7), 5.02 (1H, d, H2, *J* 5.3), 7.33–7.38 (5H, m, ArH); δ_C ($CDCl_3$, 100 MHz): 52.4 (CO_2CH_3), 52.5 (C5), 72.0 (O*C*H_2Ph), 76.3 (CH), 81.7 (CH), 84.6 (CH), 128.1, 128.3, 128.6 (3 × ArC), 136.7 (ArC), 170.0 (CO_2CH_3); *m*/*z* (APCI+): 158 ($M^+-CH_3-N_2$).

4.8. Isopropyl 2,4-anhydro-5-azido-3-*O*-benzyl-5-deoxy-L-ribonate 17

Azido ester **15** (370 mg, 1.33 mmol) was dissolved in isopropanol (3.5 mL) and potassium carbonate (250 mg, 1.81 mmol) was added. The mixture was stirred at room temperature for 19 h when TLC (3:7, ethyl acetate/hexane) showed no starting material (R_f 0.26) but one major product (R_f 0.53). The reaction mixture was filtered through Celite eluted with ether and concentrated in vacuo. The residue was purified by flash column chromatography to give isopropyl azido ester **17** as a colourless oil (347 mg, 85%). Found : C, 58.93; H, 6.49; N, 13.69; $C_{15}H_{19}N_3O_4$ requires: C, 59.01; H, 6.27; N, 13.76; $[\alpha]_D^{23} = -160$ (*c* 1.5, $CHCl_3$); ν_{max} (thin film): 2104 (s, N_3), 1749 (s, C=O); δ_H ($CDCl_3$, 400 MHz): 1.29, 1.31 (6H, 2 × d, CH(CH_3)$_2$), 3.19 (1H, dd, H5, *J* 4.0, 13.7), 3.46 (1H, dd, H5′, *J* 3.8, 13.7), 4.41 (1H, a-t, H3, *J* 5.1), 4.47 (1H, d, OC*H*Ph, *J* 11.7), 4.69 (1H, d, OC*H*Ph, *J* 11.7), 4.71 (1H, a-dd, H4, *J* 4.5, 8.1), 4.96 (1H, d, H2, *J* 5.2), 5.14 (1H, septet, C*H*(CH$_3$)$_2$, *J* 6.3), 7.30–7.38 (5H, m, ArH); δ_C ($CDCl_3$, 100 MHz): 21.6, 21.6 (2 × C, CH(*C*H$_3$)$_2$), 52.4 (C5), 69.2 (O*C*H(CH$_3$)$_2$), 71.7 (O*C*H_2Ph), 76.3 (CH), 81.9 (CH), 84.3 (CH), 127.9, 128.2, 128.5 (3 × ArH), 136.7 (ArC), 169.1 (C1); *m*/*z* (APCI+): 306 ($M+H^+$, 20%), 170 (100%).

4.9. Isopropyl 2,4-anhydro-5-(2,4-anhydro-5-azido-3-*O*-benzyl-5-deoxy-L-ribononamido)-3-*O*-benzyl-5-deoxy-L-ribonate 19

Azido ester **15** (367 mg, 1.33 mmol) was dissolved in THF (6 mL) and water (1.05 mL) and sodium hydroxide (1 M, 1.5 mL, 1.5 mmol) was added. The mixture was stirred at room temperature for 6 h after which TLC (2:3, ethyl acetate/hexane) showed no starting material (R_f 0.82) but one product on the baseline. The mixture was concentrated in vacuo and the residue was dissolved in water (6 mL) and treated with amberlite resin (IR 120 H^+) for 30 min. The solution was filtered and concentrated to give the crude acid **16** as an oil (399 mg) which was used without further purification.

Azido ester **17** (393 mg, 1.29 mmol) was dissolved in ethyl acetate (17.7 mL) and palladium on carbon (19 mg) was added. The mixture was flushed with hydrogen and after 5 h, TLC (3:7, ethyl acetate/hexane) showed the formation of a single baseline product. The mixture was filtered through Celite®, eluted, ethyl acetate and concentrated in vacuo to give the crude amine **18** (357 mg, 99%) which was used without further purification.

Crude acid **16** and crude amine **18** were dissolved in *N*,*N*-dimethylformamide (9.25 mL) and triethylamine (25 μL, 1.79 mmol) and TBTU (493 mg, 1.54 mmol) was added. The mixture was stirred at room temperature for 16 h after which time the solution was concentrated in vacuo and the resulting residue was purified by column chromatography to give dimer **19** (600 mg, 89% from the isopropyl azide) as a glassy oil. Found: C, 61.73; H, 6.11; N, 10.65; $C_{27}H_{32}N_4O_7$ requires: C, 61.82; H, 6.15; N, 10.68; $[\alpha]_D^{23} = -87.7$ (*c* 0.71, $CHCl_3$); ν_{max} (thin film): 2100 (s, N_3), 1740 (s, HNC=O, I), 1673 (m, HNC=O, II); δ_H ($CDCl_3$, 400 MHz): 1.25, 1.29 (6H, 2 × d, CH(CH_3)$_2$, *J* 6.3), 3.29 (1H, dd, $H5^A$, *J* 4.9, 13.7), 3.47 (1H, dd, $H5'^A$, *J* 3.8, 13.7), 3.53–3.64 (2H, m, $H5^B$), 4.31 (1H, t, H3, *J* 5.3), 4.31 (1H, t, H3, *J* 5.4), 4.45 (1H, d, OC*H*Ph, *J* 11.7), 4.46 (1H, d, OC*H*Ph, *J* 11.8), 4.61 (1H, d, OC*H*Ph, *J* 11.8), 4.72–4.79 (2H, m, $H4^A$, $H4^B$), 4.76 (1H, d, OC*H*Ph, *J* 11.7), 4.93 (1H, d, $H2^B$, *J* 5.3), 4.94 (1H, d, $H2^A$, *J* 5.2), 5.08 (1H, septet, OC*H*(CH$_3$)$_2$, *J* 6.3), 7.14 (1H, a-t, CON*H*, *J* 5.7), 7.29–7.38 (10H, m, ArH); δ_C ($CDCl_3$, 100 MHz): 21.6, 21.7 (2 × CH(*C*H$_3$)$_2$), 41.4 ($C5^B$), 52.5 ($C5^A$), 69.2 (*C*H(CH$_3$)$_2$), 71.6, 71.7 (2 × O*C*H_2Ph), 76.6 (C3), 76.7 (C3), 81.7 ($C2^B$), 83.5 ($C2^A$), 84.1 (C4), 84.5 (C4), 127.8, 128.1, 128.1, 128.5, 128.5 (5 × ArH), 136.7, 136.9 (2 × ArC), 169.4 (C1), 170.2 (C1); *m*/*z* (APCI+): 525.4 ($M+H^+$, 100%).

4.10. Isopropyl 2,4-anhydro-5-[2,4-anhydro-5-azido-3-*O*-benxyl-5-deoxy-L-ribononamido-(N→5)-2,4-anhydro-5-azido-3-*O*-benzyl-5-deoxy-L-ribononamido-(N→5)-2,4-anhydro-5-azido-3-*O*-benzyl-5-deoxy-L-ribononamido-(N→5)]-3-*O*-benzyl-5-deoxy-L-ribonate 22

Dimer **19** (130 mg, 0.25 mmol) was dissolved in ethyl acetate (3.2 mL) and palladium on carbon (9 mg) was added. The reaction was flushed with H_2 and stirred at room temperature for 22 h, after which TLC (3:2, ethyl acetate/hexane) showed the complete conversion of the starting material to one baseline product. The reaction mixture was filtered through Celite, eluted ethyl acetate and concentrated in vacuo. The residue was purified by flash chromatography to yield amine **20** as a colourless oil (107 mg, 87%).

Dimer **19** (125 mg, 0.24 mmol) was dissolved in THF (1.14 mL) and water (200 μL) and sodium hydroxide (1 M, 270 μL, 0.27 mmol) was added. The mixture was stirred at room temperature for 5 h after which TLC (3:2, ethyl acetate/hexane) showed the complete conversion of the starting material to one baseline product. The mixture was concentrated and the residue was dissolved in water (1.1 mL). Amberlite resin (IR120 H^+) was added and the mixture stirred for 30 min, filtered and concentrated in vacuo to give acid **21** which was used without further purification.

Dimer acid **21** and dimer amine **20** were dissolved in DMF (1.59 mL) and triethylamine (42 μL, 0.30 mmol) and TBTU (83 mg, 0.26 mmol) were added. The mixture was stirred at room temperature for 2.5 h when TLC (3:2, ethyl acetate/hexane) showed the formation of one major product (R_f 0.3). The solution was concentrated under reduced pressure and purified by flash chromatography to give tetramer **22** as a colourless oil (130 mg, 62% from the amine). $[\alpha]_D^{22} = -176$ (*c* 0.2, $CHCl_3$); ν_{max} (thin film): 3302 (NH), 2105 (N_3), 1744 (HNC=O, I), 1667 (HNC=O, II); δ_H ($CDCl_3$, 500 MHz): 1.24, 1.27 (6 H, 2 × d, CH(CH_3)$_2$, *J* 6.2), 3.01 (1H, dt, $H5'^B$, *J* 3.8, 14.1), 3.06 (1H, dd, $H5'^A$, *J* 3.4, 14.1), 3.46 (1H, dd, $H5^A$, *J* 3.0, 14.1), 3.55–3.65 (4H, m, $H5^C$, $H5'^C$, $H5^D$, $H5'^D$), 3.90 (1H, ddd, $H5^B$, *J* 9.3, 10.7, 14.1), 4.05 (1H, t, $H3^B$, *J* 4.3), 4.11 (1H, t, $H3^C$, *J* 4.1), 4.37 (1H, d, OC*H*Ph, *J* 11.8), 4.44 (2H, 2 × d, OC*H*Ph, *J* 11.7), 4.49 (1H, d, OC*H*Ph, *J* 11.8), 4.56–4.62 (1H, m, $H4^B$), 4.61 (1H, d, OC*H*Ph, *J* 11.9), 4.61 (1H, d, OC*H*Ph, *J* 11.7),4.69 (1H, m, $H4^A$), 4.70 (1H, d, OC*H*Ph, *J* 11.6), 4.71 (1H, m, $H4^C$), 4.72 (1H, d, OC*H*Ph, *J* 11.8), 4.76 (1H, m, $H4^D$), 4.81 (1H, d, $H2^C$, *J* 4.4), 4.92 (1H, d, $H2^B$, *J* 3.8), 4.93 (1H, d, $H2^D$, *J* 5.6), 5.03 (1H, d, $H2^A$, *J* 5.3), 5.07 (1H, septet, OC*H*(CH_3)$_2$, *J* 6.2), 6.99 (1H, t, NH^B, *J* 4.4), 7.26–7.36 (20H, m, ArH), 8.24 (1H, t, NH, *J* 6.3), 8.34 (2H, t, NH^D, *J* 6.1); δ_C ($CDCl_3$, 125 MHz): 21.7 (1 × OCH(*C*H)), 41.7 (CH_2), 41.8 (CH_2), 52.3 (CH_2), 69.0 (CH), 71.2 (CH_2), 71.4 (CH_2), 71.9 (CH), 77.6 (CH), 77.9 (CH), 78.1 (CH), 81.7 (CH), 83.3 (CH), 83.4 (CH), 83.4 (CH), 84.2 (CH), 84.2 (CH), 84.3 (CH), 84.6 (CH), 127.7, 1278.0, 128.0, 128.1, 128.2, 128.2, 128.5, 238.5 (9 × ArH), 136.6 136.8, 136.9, 136.9 (4 × ArC), 169.5 (HNC=O^A), 170.9, 171.1, 171.7 (3 × HNC=O).

4.11. Isopropyl 2,4-anhydro-5-[2,4-anhydro-5-azido-3-*O*-benxyl-5-deoxy-L-ribononamido-(N→5)-2,4-anhydro-5-azido-3-*O*-benzyl-5-deoxy-L-ribononamido-(N→5)-2,4-anhydro-5-azido-3-*O*-benzyl-5-deoxy-L-ribononamido-(N→5)-2,4-anhydro-5-azido-3-*O*-benzyl-5-deoxy-L-ribononamido-(N→5)-2,4-anhydro-5-azido-3-*O*-benzyl-5-deoxy-L-ribononamido-(N→5)]-3-*O*-benzyl-5-deoxy-L-ribonate 24

Tetramer **22** (107 mg, 0.11 mmol) was dissolved in tetrahydrofuran (524 μL) and water (90 μL). Sodium hydroxide (1 M, 120 μL, 0.12 mmol) was added and the mixture was stirred for 3 h at room temperature, when TLC (3:2, ethyl acetate/hexane) showed the complete conversion of the starting material to one baseline product. The mixture was concentrated under reduced pressure and the residue was dissolved in water (600 μL) and treated with amberlite resin (IR 120 H^+). After 30 min, the mixture was filtered and concentrated under reduced pressure to give acid **23**, which was used without further purification.

Dimer **19** (57 mg, 0.11 mmol) was dissolved in ethyl acetate (1.4 mL) and palladium on carbon (5 mg) was added. The mixture was flushed with hydrogen and the mixture was stirred at room temperature for 16 h when TLC (3:2, ethyl acetate/hexane) showed complete conversion of the starting material to one baseline product. The mixture was filtered through Celite, eluted ethyl acetate, and concentrated under reduced pressure to give amine **20** which was used without further purification.

Amine dimer **20** and tetramer acid **23** were dissolved in DMF (800 μL) and triethylamine (21 μL, 0.15 mmol) and TBTU (41 mg, 0.13 mmol) were added. After 18 h TLC (4:1, ethyl acetate/hexane) showed the formation of one major product (R_f 0.3). The mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography to give hexamer **24** (100 mg, 64%) as a colourless oil. $[\alpha]_D^{23} = -158$ (*c* 0.3, $CHCl_3$); ν_{max} (thin film): 3297 (m, NH), 2105 (s, N_3), 1743 (s, HNC=O, I), 1660 (m, HNC=O, II); δ_H ($CDCl_3$, 500 MHz): 1.23, 1.25 (6H, 2 × d, CH(CH_3)$_2$, *J* 6.2), 2.99 (1H, dd, $H5'^A$, *J* 3.2, 14.2), 2.94 (1H, a-dt, $H5'^B$, *J* 3.7, 14.0), 3.27 (1H, ddd, $H5'^D$, *J* 4.0, 4.5, 14.0), 3.36 (1H, ddd, $H5'^C$, *J* 3.0, 5.0, 14.0), 3.45 (1H, m, $H5'^E$), 3.45 (1H, dd, $H5^A$, *J* 2.7, 14.2), 3.60 (2H, m, $H5^F$,$H5'^F$), 3.68 (1H, ddd, $H5^E$, *J* 6.5, 10.5, 14.2), 3.75 (1H, ddd, $H5^C$, *J* 7.5, 11.5, 14.0), 3.81 (1H, ddd, $H5^D$, *J* 8.0, 11.0, 14.0), 3.92 (1H, ddd, $H5^B$, *J* 9.2, 11.5, 14.0), 4.04–4.06 (3H, m, $H3^B$, $H3^C$, $H3^D$), 4.10 (1H, t, $H3^E$, *J* 4.2), 4.34 (1H, t, $H3^A$, *J* 5.5), 4.36 (1H, t, $H3^F$, *J* 5.2), 4.39 (1H, d, OC*H*Ph, *J* 12.0), 4.42 (1H, d, OC*H*Ph, *J* 11.5), 4.43 (1H, d, OC*H*Ph, *J* 12.0), 4.45 (1H, d, OC*H*Ph, *J* 10.0), 4.48 (1H, d, OC*H*Ph, *J* 10.0), 4.50 (1H, d, OC*H*Ph, *J* 12.0), 4.56 (1H, a-dt, $H4^B$, *J* 3.5, 11.5), 4.62 (1H, d, OC*H*Ph, *J* 12.0), 4.70 (1H, d, OC*H*Ph, *J* 11.5), 4.70–4.80 (9H, m, 4 × OC*H*Ph, $H4^A$, $H4^C$, $H4^D$, $H4^E$, $H4^F$), 4.83 (1H, d, $H2^E$, *J* 4.0), 4.86 (1H, d, $H2^A$, *J* 5.0), 4.88 (1H, d, $H2^D$, *J* 4.0), 4.88 (1H, d, $H2^B$, *J* 4.5), 4.90 (1H, d, $H2^F$, *J* 5.0), 4.94 (1H, d, $H2^C$, *J* 4.5), 5.05 (1H, septet, C*H*(CH_3)$_2$, *J* 6.2), 6.99 (1H, dd, NH^B, *J* 4.5, 9.0), 8.43 (1H, a-t, NH^C, *J* 6.5), 8.49 (1H, a-t, NH^F, *J* 6.2), 8.55 (1H, a-t, NH^E, *J* 6.2), 8.62 (1H, dd, NH^D, *J* 5.5, 7.5); δ_C ($CDCl_3$, 125 MHz): 21.7 (×2) (2 × CH(*C*H_3)$_2$),

41.7, 41.8, 41.9 (5 × C5), 52.3 ($C5^{A}$), 68.9 ($CH(CH_3)_2$), 71.3 (×2), 71.4, 71.6, 72.1 (6 × O*C*HPh), 76.5, 78.0, 78.3, 78.4 (×2), 78.6, 81.7, 83.3, 83.4, 83.5, 84.2, 84.3 (×2), 84.5, 84.6, 84.9 (16 × CH), 127.7, 127.9, 128.0 (×3), 128.2 (×3), 128.4, 128.5 (×2), 128.6 (13 × ArH), 136.6, 136.8, 136.9, 137.0 (6 × ArC), 169.5 ($HNC{=}O^{A}$), 171.2 ($HNC{=}O^{F}$), 171.5 ($HNC{=}O^{E}$), 171.7 ($HNC{=}O^{B}$), 171.8 ($HNC{=}O^{C}$), 172.3 ($HNC{=}O^{D}$).

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