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An easy access to spiroannulated glyco-oxetane, -thietane and -azetane rings: synthesis of spironucleosides

Ashim Roy, Basudeb Achari and Sukhendu B. Mandal*

Department of Chemistry, Indian Institute of Chemical Biology, 4 Raja S.C. Mullick Road, Kolkata 700 032, India

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Abstract—The key intermediate **11** derived from D-glucose and possessing bis-mesylmethyl ($MsO{\cdot}CH_2$–) functionality at C-4, was used to generate spirocycles **12**, **13** and **15** via one-step procedures. The spirocompounds **12** and **13** were subsequently converted into the corresponding spironucleosides **24** and **26** in good yield using Vorbrüggen reaction conditions.

The synthesis of structurally modified nucleosides has been emerging as an important area of research because some members show biological activities of medicinal interest.[1] Prominent among these are the spirocyclic nucleosides, which started to draw the attention of synthetic chemists after the isolation of the naturally occurring nucleoside hydantocidin,[2] which possesses a spirocyclic ring at the anomeric centre. Since then, there have been notable contributions from Miyasaka's[3] and Paquette's groups[4] in addition to others,[5] to synthesize 1′-spiro-,[3] 2′-spiro-,[5c] 3′-spiro-[6] and 4′-spironucleoside derivatives[4] as conformationally restricted analogues. The synthesis of nucleosides bearing a spirocycle at *C*-4′ such as **1**–**4** (Fig. 1) has received attention only recently. This class of nucleosides possess several inherent advantages: (i) there is a restriction in conformational flexibility, which may permit the molecule to attain the optimal puckering needed for drug action;[7] (ii) the free radical-induced degradation of nucleosides or nucleotides by *C*-4′–H abstraction is now prevented;[8] and (iii) the compounds are expected to serve as conformationally fixed models, which can be useful for elucidating the glycosidic torsion angle of nucleosides.[9] In our laboratory, we are engaged in the synthesis of a wide variety of nucleosides[10] (carbocyclic, bicyclic, spirocyclic and conformationally locked). The above promising features of *C*-4′ spirocyclic nucleosides prompted us to take up the synthesis of nucleosides containing a four membered ring spirofused at *C*-4′. Although the synthesis of nucleosides that are [5,5] spiro-fused at *C*-4′ is well documented, the [5,4] type of nucleosides have yet to be synthesized. The development of simple and flexible synthetic routes to such systems, therefore, represents a worthwhile task. Towards this endeavour we report herein results on the synthesis of [5,4] fused spirocyclic nucleosides **5** from D-glucose.

Our retrosynthetic analysis (Fig. 2) reveals that nucleophilic displacement of the 1,3-bis-electrophilic synthon **6** would allow construction of the spirocyclic ring. Such

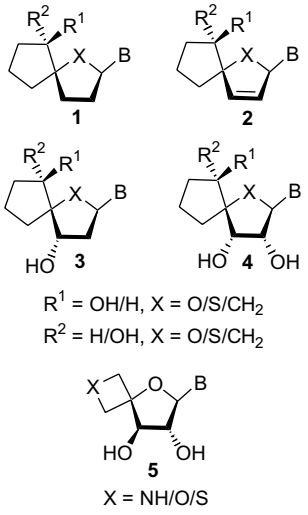

Figure 1. Some structurally unique spironucleosides.

Keywords: Synthesis; Oxetane; Thietane; Azetane; Spironucleosides; D-glucose.
* Corresponding author. Tel.: +91 332473 3491; fax: +91 332473 5197; e-mail: sbmandal@iicb.res.in

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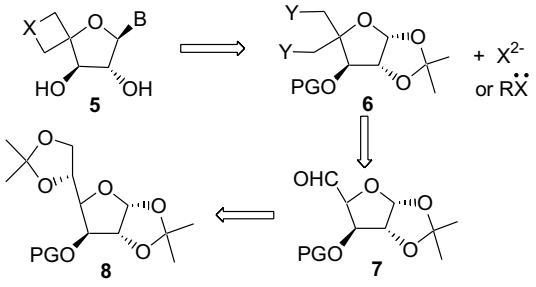
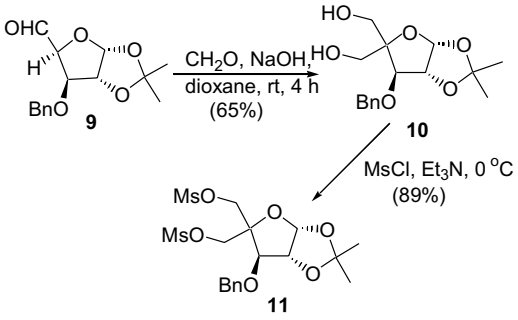


Figure 2. Retrosynthetic analysis of **5**.

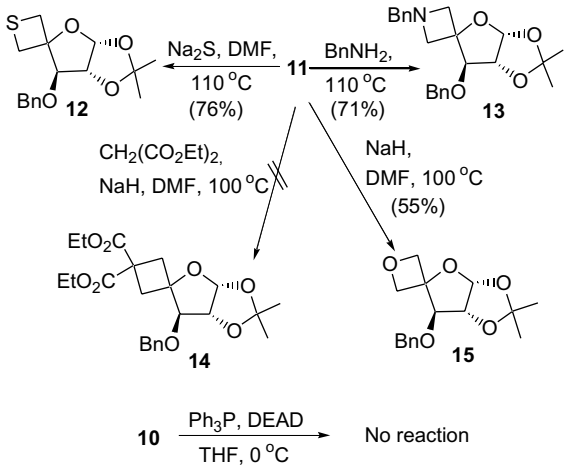
a synthon could easily be derived through a one-carbon insertion into the 3-*O*-protected-5-aldo-1,2-diisopropylidene-α-D-glucofuranose **7**, which is readily synthesized from the 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose derivative **8**.

Based on the above strategy, the key intermediate required for cyclization was prepared (Scheme 1) from the easily accessible 5-aldo-3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose **9**.[11] Treatment of **9** with formalin in the presence of NaOH solution (2 M) afforded the 4-*C*-(hydroxymethyl)-1,2-*O*-isopropylidene-β-L-*threo*-pento-furanose **10** through an aldol-Cannizaro sequence. Subsequently **10** was subjected to mesylation with MsCl and Et_3N to furnish the bis-methanesulfonate **11**. The formation of **10** and **11** was evident from spectral data. In the ^1H NMR spectrum of **10**, the appearance of a 1H singlet at δ 4.12 was attributed to H-3 and the absence of a carbonyl absorption in the 1737 cm^{-1} region of the IR indicated the structure shown. The presence of two three-proton singlets at δ 3.00 and 3.02 confirmed the presence of the bis-methane sulfonate groups in **11**.

When **11** was treated with sodium sulfide (Scheme 2) in dry DMF at 110 °C, it afforded the spirothietane **12**[12] (76%). On the other hand, heating this compound in benzylamine at 110 °C furnished the spiroazetane **13**[12] (71%). However, when **11** was heated with diethyl malonate (DEM) and an excess of NaH in DMF at 110 °C (no reaction at rt), it failed to produce the spirocyclobutane **14**. Instead, the product isolated appeared to be the oxetane **15**[12] (55%). This may be rationalized by assuming that the initial attack of the sulfonate-derived ambident nucleophile (generated from



Scheme 1. Synthesis of 1,2-*O*-isopropylidene-3-*O*-benzyl-bis(4,4-mesylmethyl)-α-D-glucofuranose (**11**).



Scheme 2. Synthesis of spirocycles **12**, **13** and **15**.

11 upon NaH treatment) displaces the other sulfonate to form a putative intermediate (Fig. 3), which during hydrolytic work-up affords **15**. To test whether DEM has any role in fostering oxetane ring formation, compound **11** was heated with NaH in DMF at 100 °C. The formation of the same product in virtually identical yield ruled out any role of DEM in this reaction. To confirm the unusual formation of **15**, we synthesized **15** from **10** following a different reaction sequence as depicted in Scheme 3. Selective protection of one hydroxyl group of **10** with TBDMS-Cl and imidazole at 0 °C followed by mesylation with mesyl chloride and triethylamine furnished the mono-mesylated compound **17**.

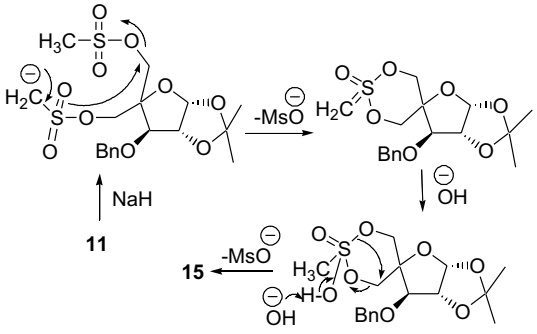
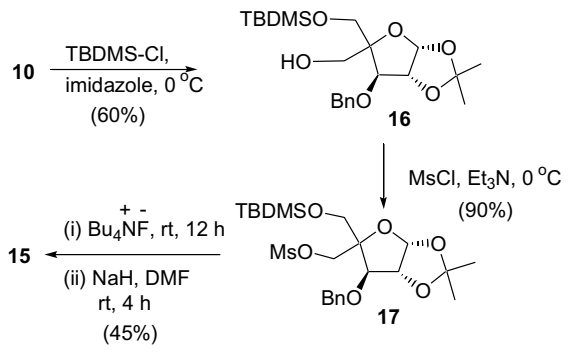


Figure 3. A proposed mechanism for the formation of **15** from **11**.

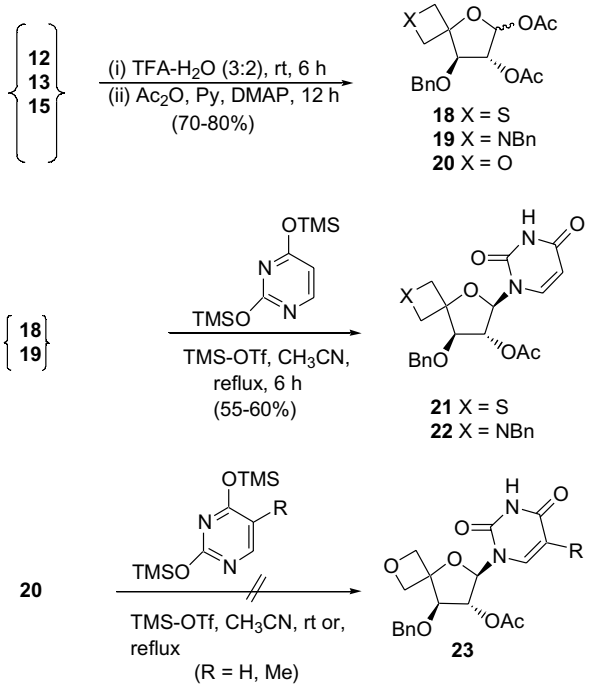


Scheme 3. Alternative synthesis of spirocycle **15**.

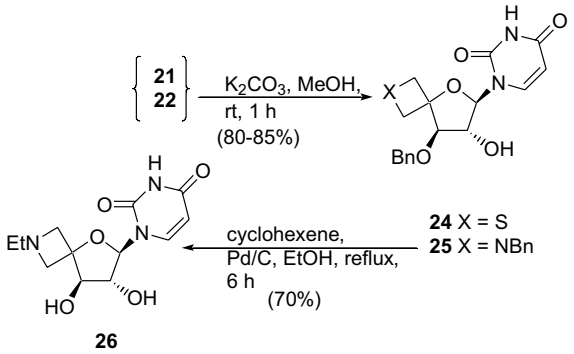
Subsequent deprotection of the TBDMS-group with tetrabutylammonium fluoride and treatment of the product so obtained with NaH in DMF afforded the desired cyclized product **15** (identified from ^{1}H and ^{13}C NMR spectra). However, an attempted synthesis of **15** by treating **10** with DEAD and PPh_3 under Mitsunobu conditions did not succeed (Scheme 2).

Regarding the identification of compounds **12** and **13**, the disappearance of signals in the δ 3.00–3.10 region in their ^{1}H NMR spectra coupled with the appearance of two methylene proton signals in the δ 3.2–3.7 region in addition to extra aromatic proton signals (in the case of **13**) indicated their formation. The ring methylene signals appeared at δ 34.3 and 41.0 in the ^{13}C NMR of **12** but at δ 60.0 and 63.2 in that of **13**. Finally, the presence of an ion peak at m/z 331 $(M+Na)^+$ in the ESI-mass spectrum of **12** and a protonated molecular ion peak at m/z 382 in that of **13** confirmed the structures. The structure of **15** was deduced from similar considerations. Of particular importance was the finding that the chemical shift of the ring methylene protons ($\sim\delta$ 4.6) and carbons (δ 77.2 and 82.5) appeared downfield in the ^{1}H and ^{13}C NMR spectra while the sodiated molecular ion peak was located at m/z 315.

A nucleobase could be successfully installed on **12** and **13** (Scheme 4) by cleavage of the acetonide group, followed by acetylation to form a mixture of the di-acetates, and reaction with 2,4-bis-(trimethylsilyloxy)pyrimidine in the presence of TMS-OTf in CH_3CN under refluxing conditions[13] to furnish the nucleoside derivatives **21**[14] and **22**,[14] the β-orientation of the base being anticipated due to anchimeric assistance by the neighbouring acetoxy group. However, several attempts to install a uracil or thymidine base on **20** were unsuccessful. This may be due to



Scheme 4. Synthesis of spironucleosides **21** and **22**.



Scheme 5. Deprotections of nucleosides **21** and **22**.

the opening of the oxetane ring in the presence of the Lewis acid TMS-OTf. The formation of **21** and **22** was deduced from the appearance of an acetoxy peak in the δ 2.0 ppm region of the ^{1}H NMR spectrum, a doublet in the δ 5.6 region (uracil proton) and a broad singlet in the δ 8–9 region (for the NH). In the ^{13}C NMR spectra of the two compounds, signals for uracil carbons appeared at about δ 89, 140, 150 and 163, as expected.

For deprotection of the nucleosides **21** and **22** (Scheme 5), the acetoxy group was removed with dry K_2CO_3 in MeOH to furnish **24** and **25**. Transfer hydrogenolysis of **24** with cyclohexene was unsuccessful. This may be ascribed to poisoning of the catalyst by the substrate. A similar reaction on compound **25**, however, proceeded smoothly. Interestingly, the product isolated proved to be the *N*-ethyl derivative **26**[15] rather than the expected secondary amine. The incorporation of the ethyl moiety could be rationalized due to the presence of acetaldehyde as an impurity in EtOH, which conceivably could condense with the deprotected amine to form an iminium compound prior to reduction to produce **26**.

In conclusion, this study describes an approach to synthesize nucleosides [5,4] spirofused at C-4′ from a D-glucose precursor. The strategy appears to be capable of providing access to analogues based on ribose, 2-deoxyribose, 2,3-dideoxyribose and 2,3-didehydro-2,3-dideoxyribose frameworks and may be implemented to synthesize such nucleosides with different substitution patterns through judicious selection and manipulation of the sugar derived precursors.

Acknowledgements

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12. Procedures for the preparation of spirocycles **12**, **13** and **15**.To a solution of **11** (2.5 g, 5.36 mmol) in dry DMF (15 mL) was added Na_2S (0.63 g, 8.0 mmol) and the mixture was heated at 110 °C for 3 h. The solution was cooled to rt and the solvent was evaporated under reduced pressure. The residue was extracted with $CHCl_3$ (3×30 mL), the combined extract was washed with water (3×30 mL), dried (Na_2SO_4) and evaporated to a gummy mass, which was then purified by column chromatography over silica gel (60–120 mesh). Elution with $CHCl_3$–petroleum ether (1:1) furnished **12** (1.25 g, 76%). For the preparation of **13**, a mixture of **11** (0.95 g, 2.04 mmol) and benzyl amine (15 mL) was heated at 110 °C for 10 h. Usual work-up followed by column chromatography using EtOAc–petroleum ether (3:22) as eluent yielded **13** (0.55 g, 71%). For **15**, oil-free NaH (84 mg) was added portionwise to a solution of **11** (0.8 g, 1.72 mmol) in anhydrous DMF (15 mL) and the mixture was heated at 100 °C for 6 h. Excess NaH was destroyed by slow addition of cold water and the solvent was evaporated. Usual work-up and purification by chromatography over silica gel (60–120 mesh) using $CHCl_3$–petroleum ether (7:3) gave **15** (275 mg, 55%).
Data for **12**: white solid, mp 74–75 °C, $[\alpha]_D^{25}$ −82.6 (*c* 1.3, $CHCl_3$) [found: C, 62.08; H, 6.43. $C_{16}H_{20}O_4S$ requires C, 62.31; H, 6.54]; IR (KBr): ν_{max} 1451, 1380, 1211, 1102, 1075, 859, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.28 and 1.46 ($2 \times s$, $2 \times 3H$, CMe_2), 3.24 (dd, 1H, $J = 2.8$, 9.0 Hz), 3.42 (dd, 1H, $J = 2.8$, 9.5 Hz), 3.61 (d, 1H, $J = 9.5$ Hz), 3.69 (d, 1H, $J = 9.2$ Hz), 4.47 (s, 1H, 3-H), 4.62 (d, 1H, $J = 3.7$ Hz, 2-H), 4.72 and 4.80 ($2 \times d$, $2 \times 1H$, $J = 11.7$ Hz, –O–CH_2), 5.83 (d, 1H, $J = 3.7$ Hz, 1-H), 7.31–7.38 (m, 5H, Ph–H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.6 (CH_3), 26.4 (CH_3), 34.3 (SCH_2), 41.1 (SCH_2), 72.3 (OCH_2), 82.4 (CH), 83.9 (CH), 87.9 (C–O), 105.5 (O–CH–O), 111.8 (O–C–O), 127.5 ($2 \times$ CH), 127.9 (CH), 128.4 ($2 \times$ CH), 137.1 (C); ESIMS: *m*/*z* 331 $(M+Na)^+$. Compound **13**: yellowish gum, $[\alpha]_D^{25}$ −66.5 (*c* 0.71, $CHCl_3$) [found: C, 72.12; H, 7.01; N, 3.61. $C_{23}H_{27}NO_4$ requires C, 72.42; H, 7.13; N, 3.67]; IR (neat): ν_{max} 1494, 1454, 1376, 1310, 1212 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.28 and 1.40 ($2 \times s$, $2 \times 3H$, CMe_2), 3.24 (t-like, 2H, $J = 8.7$, 9.3 Hz), 3.71 (br s, 3H), 3.87 (d, 1H, $J = 7.3$ Hz), 4.31 (s, 1H, 3-H), 4.60 (d, 1H, $J = 3.0$ Hz, 2-H), 4.68 and 4.74 ($2 \times d$, $2 \times 1H$, $J = 11.8$ Hz, –O–CH_2), 5.84 (d, 1H, $J = 3.2$ Hz, 1-H), 7.31–7.34 (m, 10H, Ph–H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.8 (CH_3), 26.6 (CH_3), 60.0 (NCH_2), 63.3 (NCH_2), 65.9 (NCH_2), 72.1 (OCH_2), 81.9 (C–O), 82.4 (CH), 84.8 (CH), 105.1 (O–CH–O), 111.8 (O–C–O), 127.0 (CH), 127.6 ($2 \times$ CH), 127.8 (CH), 128.28 ($2 \times$ CH), 128.35 ($2 \times$ CH), 128.43 ($2 \times$ CH), 137.5 (C), 137.8 (C); ESIMS: *m*/*z* 382 $(M+H)^+$, 404 $(M+Na)^+$. Compound **15**: gummy material, $[\alpha]_D^{25}$ −104.2 (*c* 0.22, $CHCl_3$) [found: C, 65.66; H, 6.78. $C_{16}H_{20}O_5$ requires C, 65.74; H, 6.90]; IR (neat): ν_{max} 1379, 1247, 1213, 1163, 1074, 1020, 972, 860, 752, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.29 and 1.39 ($2 \times s$, $2 \times 3H$, CMe_2), 4.33 (s, 1H, 3-H), 4.60–4.64 (m, 3H), 4.73 (s, 1H), 4.76 (d, 1H, $J = 3.7$ Hz, 2-H), 4.83 (s, 2H, –OCH_2Ph), 5.87 (d, 1H, $J = 3.3$ Hz, 1-H), 7.37 (m, 5H, Ph–H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.7 (CH_3), 26.7 (CH_3), 72.2 (OCH_2Ph), 77.2 (OCH_2), 82.1 (CH), 82.5 (OCH_2), 84.4 (CH), 85.4 (C–O), 105.4 (O–CH–O), 111.9 (O–C–O), 127.8 ($2 \times$ CH), 128.2 (CH), 128.6 ($2 \times$ CH), 137.0 (C); ESIMS: *m*/*z* 315 $(M+Na)^+$.
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14. Compound **21**: foamy solid, $[\alpha]_D^{25}$ −24.3 (*c* 0.46, $CHCl_3$) [found: C, 56.30; H, 4.89; N, 6.70. $C_{19}H_{20}N_2O_6S$ requires C, 56.42; H, 4.98; N, 6.93]; IR (KBr): ν_{max} 3208 (br), 1749, 1688, 1456, 1377, 1223, 1107, 754 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.14 (s, 3H, $OCOCH_3$), 2.98 (d, 1H, $J = 9.0$ Hz), 3.53 (d, 1H, $J = 9.0$ Hz), 3.66 (t-like, 2H, $J = 10.0$, 11.4 Hz), 4.33 (s, 1H, 3′-H), 4.74 and 4.83 ($2 \times d$, $2 \times 1H$, $J = 11.5$ Hz, OCH_2), 5.20 (s, 1H, 2′-H), 5.59 (d, 1H, $J = 7.9$ Hz, 5-H), 6.10 (s, 1H, 1′-H), 7.33–7.39 (m, 6H, Ph–H and 6-H), 8.78 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.2 (CH_3), 34.2 (SCH_2), 39.9 (SCH_2), 72.8

(OCH_2), 79.9 (CH), 82.6 (CH), 88.9 (CH), 89.1 (C–O), 102.9 (O–CH–N), 128.6 (2 × CH), 128.9 (CH), 129.1 (2 × CH), 136.7 (C), 140.5 (6-CH), 150.5 (4-CO), 163.6 (2-CO), 169.9 (O–CO); ESIMS: *m*/*z* 427 $(M+Na)^+$. Compound **22**: foamy solid, $[\alpha]_D^{25}$ −14.3 (*c* 0.58, $CHCl_3$) [found: C, 65.15; H, 5.61; N, 8.59. $C_{26}H_{27}N_3O_6$ requires C, 65.40; H, 5.70; N, 8.80]; IR (KBr): ν_{max} 3196 (br), 1749, 1693, 1453, 1375, 1224, 1110, 754 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.10 (s, 3H, $OCOCH_3$), 3.16 (d, 1H, $J = 7.5$ Hz), 3.27 (d, 1H, $J = 7.9$ Hz), 3.38 (d, 1H, $J = 5.9$ Hz), 3.67 (s, 2H), 3.84 (d, 1H, $J = 6.3$ Hz), 4.14 (s, 1H, 3′-H), 4.67 and 4.73 (2 × d, 2 × 1H, $J = 11.5$ Hz, OCH_2), 5.19 (s, 1H, 2′-H), 5.54 (d, 1H, $J = 8.3$ Hz, 5-H), 6.04 (s, 1H, 1′-H), 7.26–7.40 (m, 11H, 2 × Ph–H and 6-H), 8.41 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.7 (CH_3), 59.1 (NCH_2), 63.0 (NCH_2), 64.3 (NCH_2), 72.0 (OCH_2), 79.2 (CH), 82.6 (O–C–O), 83.3 (CH), 88.3 (CH), 102.1 (O–CH–N), 127.3 (CH), 127.7 (CH), 127.8 (CH), 128.0 (CH), 128.2 (CH), 128.3 (2 × CH), 128.5 (2 × CH), 128.9 (CH), 136.6 (C), 137.1 (C), 140.1 (6-CH), 150.2 (4-CO), 163.4 (2-CO), 169.4 (O–CO); ESIMS: *m*/*z* 478 $(M+H)^+$.

15. Compound **26**: foamy solid, $[\alpha]_D^{25}$ −7.2 (*c* 0.27, MeOH) [found: C, 50.77; H, 5.93; N, 14.68. $C_{12}H_{17}N_3O_5$ requires C, 50.88; H, 6.05; N, 14.83]; IR (KBr): ν_{max} 3384 (br), 1689, 1635, 1465, 1419, 1267, 1107, 1062 cm^{-1}; ^1H NMR (Py-d_5, 300 MHz): δ 0.93 (t, 3H, J= 7.0 Hz, CH_3), 2.48 (q, 2H, $J = 7.0$ Hz, CH_2), 3.26 (d, 1H, $J = 7.3$ Hz), 3.34 (d, 1H, $J = 7.4$ Hz), 3.97 (d, 1H, $J = 6.9$ Hz), 4.24 (d, 1H, $J = 7.9$ Hz), 4.84–5.20 (4 × H merged with solvent peak), 5.87 (d, 1H, $J = 8.1$ Hz, 5-H), 6.60 (s, 1H, 1′-H), 8.09 (d, 1H, $J = 8.1$ Hz, 6-H), 13.30 (br s, 1H, NH); ^{13}C NMR (Py-d_5, 75 MHz): δ 13.1 (CH_3), 54.0 (NCH_2), 60.6 (NCH_2), 65.8 (NCH_2), 79.3 (CH), 82.2 (CH), 85.1 (C–O), 93.0 (CH), 101.7 (O–CH–N), 141.9 (6-CH), 152.2 (4-CO), 164.7 (2-CO); ESIMS: *m*/*z* 284 $(M+H)^+$.