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Diastereoselective synthesis of pyrrolidines via 1,3-dipolar cycloaddition of a chiral azomethine ylide

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ABSTRACT

1,3-Dipolar cycloaddition of D-glucose-derived azomethine ylides for the synthesis of chiral pyrrolidines accompanied an unexpected 1,2-elimination in the furanose moiety of the products. The C3′ alkoxy/hydroxy group of the furanose moiety was invariably eliminated under the reaction conditions. Also, in contrast to the previous reports, moderate to good *exo*-diastereoselectivity was observed in the reaction products.

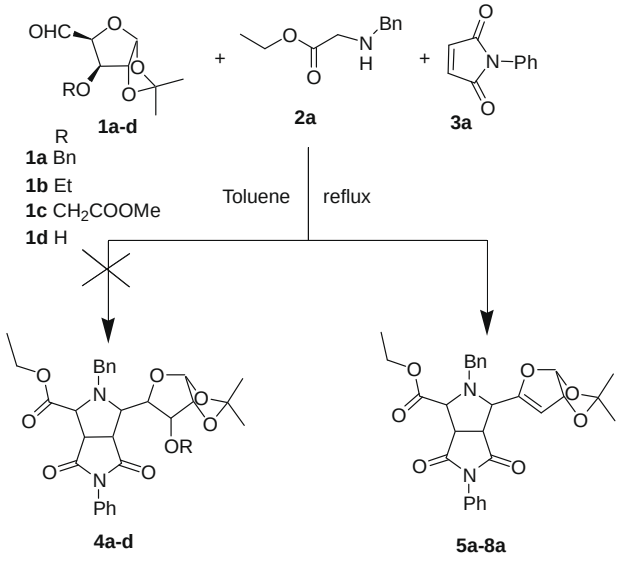
1. Introduction

1,3-Dipolar cycloaddition is one of the simplest approaches for the construction of five-membered heterocyclic ring systems.[1] The high regio- and stereoselectivity observed in the 1,3-dipolar cycloaddition enables it to be one of the powerful tools for synthesis of various chiral natural products.[2] Dipolar cycloaddition of azomethine ylide has been used in many instances for the diastereoselective synthesis of various pyrrolidine-based alkaloids that find applications as chiral building blocks and chiral catalyst in organic synthesis.[3–7] Highly substituted pyrrolidines are well known for their glucosidase inhibitory activity in addition to potent antiviral, antibacterial, antidiabetic and anticancer activities.[8]

The major role played by carbohydrates in various biological processes is evident from the recent advances made in glycobiology.[9] Since carbohydrates occur as constituents of various glycoproteins and glycolipids, the development of carbohydrate-based drugs will be of much use in the treatment of various diseases[10] such as obesity and diabetes.

2. Results and discussion

In continuation of our interest in the 1,3-dipolar cycloaddition reactions for the synthesis of biologically active heterocycles,[11] we intended to explore the chiral version of the same. To this end, we synthesized various 3-*O*-alkyl-1,2-*O*-isopropylidene-xylopentadialdoses starting from D-glucose.[12] Our synthetic strategy was to trap the in situ generated azomethine ylides obtained from the above aldehyde and various *N*-benzyl secondary amines[13] with maleimides to synthesize the chiral pyrrolidine.



Scheme 1.

To evaluate the feasibility of our approach, we refluxed a solution of the aldehyde **1a**, glycine ester **2a** and *N*-phenyl maleimide **3a** in toluene (Scheme 1). ^{1}H NMR spectrum of the crude reaction mixture revealed the presence of four diastereoisomers in the ratio of 58:13:15:14. Flash column chromatography of the mixture resulted in the isolation of three components of which one was found to be an inseparable mixture and the other two components being the pure diastereomers.

However, NMR and mass spectral data of the product did not match with the expected structure **4a**. The mass spectra of the products revealed a peak at $m/z = 519$ instead of the expected $m/z = 626$, the difference corresponds to the loss of molecule of

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benzyl alcohol. This was further confirmed from ^{1}H NMR spectrum, which revealed the absence of signal due to benzylic protons (CH_2–Ph). Also, in the furanose moiety only three protons were observed and their chemical shift positions were deshielded. Based on the above facts, the structure of the compound was assigned to be olefins **5a–8a**. Quite interestingly, our strategy furnished the 1,3-dipolar cycloaddition products with an unusual *exo*-diastereoselectivity.[14,15] It is worth mentioning that when the 3-*O*-benzyl group in xylopentadialdose was replaced by ethyl or carbmethoxy methylene group a similar elimination was observed. Elimination occurred even with an unprotected hydroxyl group present at C3′ resulting in the same olefins **5a**–**8a** (Scheme 1, Table 1).

Having ended up with the elimination product in all the above cases, we next treated the ylide obtained from glycine esters **2a**, **2b** with various maleimides **3a–f** (Scheme 2, Table 2). With the ylide derived from glycine ester **2a** (R″ = Et) the pyrrolidines **5a–f** and **8a–f** were obtained as pure diastereomers whereas **6a–f** and **7a–f** were obtained as an inseparable diastereomeric mixture. However, with the ylide derived from ester **2b** (R″ = Bn) all the four diastereomers were separated by flash column chromatography. The overall yield ranged from 67% to 80% with **5a–h** as the major product. When maleimide was replaced by nitrostyrene the cycloaddition products were obtained as an inseparable mixture.

The systematic structural analysis of the four isomers to elucidate the exact regio- and stereochemistry was performed using ^{1}H, ^{13}C and various 2D NMR spectroscopic techniques. The assignment of signals and the regio- and stereochemistry for a representative case (**5g–8g**) is discussed here.[16]

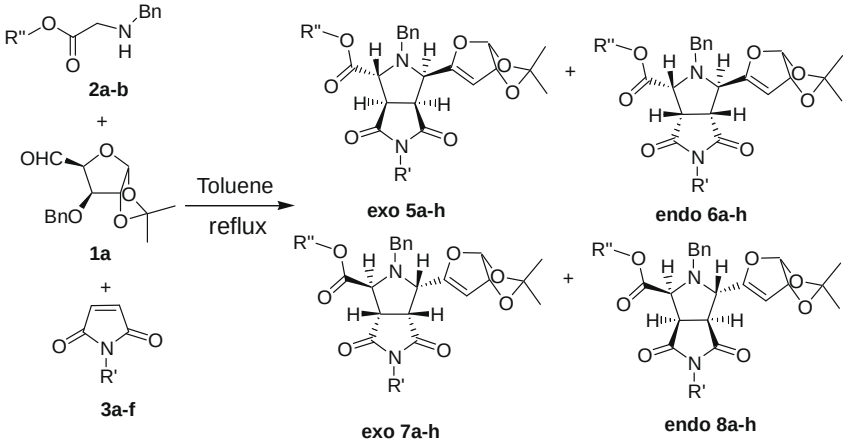
2.1. Structural assignment of diastereoisomers (5g)

In the ^{1}H–^{1}H COSY spectrum of **5g**, the proton at 5.87 ppm (anomeric proton, H-1′) showed correlation with the proton at

Table 1
Cycloaddition of aldehydes **1a**–**d** with glycine ester **2a** and *N*-phenyl maleimide **3a**

Entry	R	Adducts	Products % of diastereoisomers[a]				*exo*/*endo*	Time (h)	Yield[b] (%)
			5a	6a	7a	8a			
1	Bn	**5a–8a**	58	13	15	14	73:27	3	75
2	Et	**5a–8a**	57	14	15	14	72:28	3	70
3	CH_2COOMe	**5a–8a**	55	14	16	15	71:29	4.5	68
4	H	**5a–8a**	56	14	16	14	72:28	6	45

[a] Determined by ^{1}H NMR spectrum of the crude product.
[b] Isolated yield after flash column chromatography.



Scheme 2.

Table 2
Cycloaddition of aldehyde **1a** with glycine ester **2a**–**b** and N-substituted maleimide **3a**–**f**

Entry	R′	R″	Adducts	Products % of diastereoisomer[a]				Time (h)	*exo*/*endo*	Overall yield[b] (%)
				5	**6**	**7**	**8**			
1	Ph	Et	**5a–8a**	58	13	15	14	3.0	73:27	75
2	*p*-MePh	Et	**5b–8b**	59	11	16	14	3.5	75:25	76
3	Bn	Et	**5c–8c**	66	9	16	9	2.5	82:18	80
4	*p*-BrPh	Et	**5d–8d**	54	14	18	14	4.5	72:28	71
5	Me	Et	**5e–8e**	65	10	13	12	2.5	78:22	79
6	H	Et	**5f–8f**	59	13	15	13	4.0	74:26	67
7	Ph	Bn	**5g–8g**	54	15	16	15	3.5	70:30	72
8	*p*-MePh	Bn	**5h–8h**	56	12	16	16	3.5	72:28	70

[a] Determined by ^{1}H NMR spectrum of the crude product.
[b] Isolated yield after flash column chromatography.

5.19 ppm. Also the proton at 5.19 ppm showed correlation with the proton at 5.47 ppm in addition to that with the proton at 5.87 ppm. Hence we assigned the signals at 5.19 ppm to H-2′ and 5.47 ppm to H-3′. In the HMBC spectrum, the above three protons showed contour with carbon at 155.0 ppm and therefore this carbon should be C4′ (Fig. 1). The doublet at δ 4.47 ppm (J = 9.2 Hz) and triplet at 3.59 ppm (J = 8.4 Hz) exhibited HMBC with carbon at 155.0 ppm corresponding to C4′ and hence the protons were assigned as H-3 and H-3a, respectively. The singlet at δ 4.16 ppm and doublet at 3.41 ppm (J = 8.4 Hz) exhibited HMBC contour with carbon at 168.8 ppm corresponding to the ester carbonyl carbon and the protons were assigned as H-1 and H-6a, respectively. Compound **7g** exhibited NMR patterns similar to **5g** (Fig. 2).

2.2. Stereochemical elucidation of the *exo* diastereoisomers (5g)

The stereochemistry of the diastereoisomer **5g** was confirmed as *exo* from the coupling constant values of H-3, H-3a, H-6a and H-1 protons and NOE experiments. In compound **5g**, the coupling constant between H-3 and H-3a was 9.2 Hz and there was no coupling between H-6a and H-1. This shows that the proton H-3 is cis to H-3a and H-1 is trans to H-6a. In one dimensional NOE measurements selective irradiation of H-1 effected enhancement of the signal of H-6a (5.6%) and no enhancement of H-3 proton. Irradiation of H-3 effected enhancement of the signals of H-3a (21.0%), H-3′ (11.2%) and no enhancement of H-1 proton. These facts show that the proton H-3 is cis to H-3a and H-1 is trans to H-6a. Also the protons H-1 and H-3 have anti-relationship (Fig. 3). The structure of **5c** was further confirmed by single crystal X-ray diffraction studies (Fig. 4).[17] The same discussion is applicable to compound **7g** (Fig. 3).

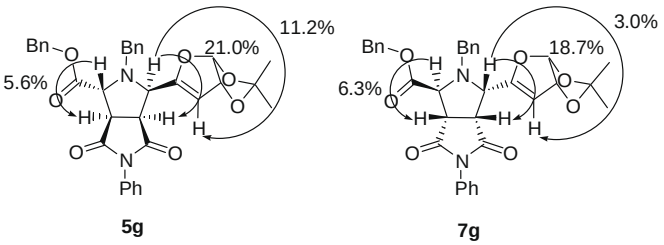


Figure 3. 1-D NOE enhancement of compounds **5g** and **7g**.

2.3. Structural assignment of diastereoisomers (8g)

In the ^{1}H NMR spectrum of compound **8g**, the doublet at δ 4.25 ppm (J = 2.3 Hz) and doublet of doublet at 3.45 ppm (J = 8.4, 1.6 Hz) exhibited HMBC with carbon at 157.0 ppm corresponding to C4′ and hence the protons were assigned as H-3 and H-3a,

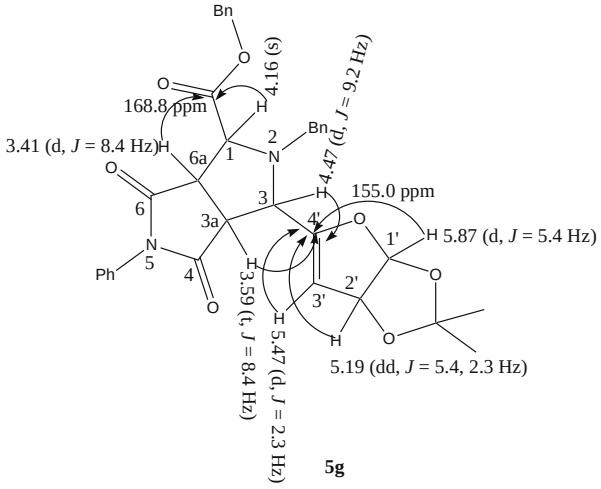


Figure 1. Selective HMBC of compound **5g**.

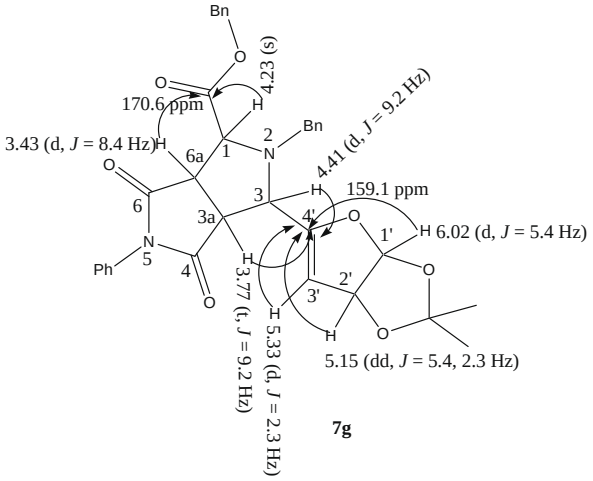


Figure 2. Selective HMBC of compound **7g**.

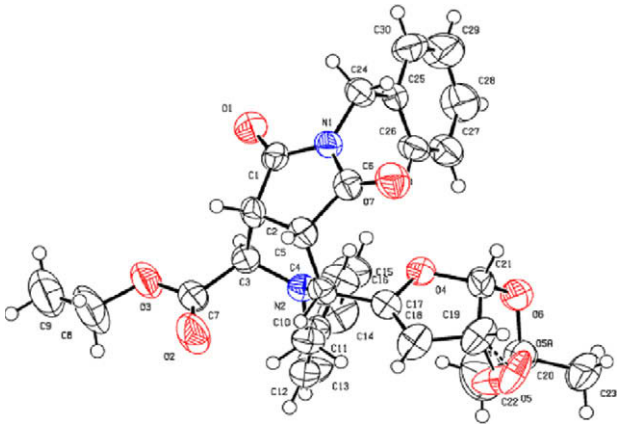


Figure 4. ORTEP diagram of compound **5c**.

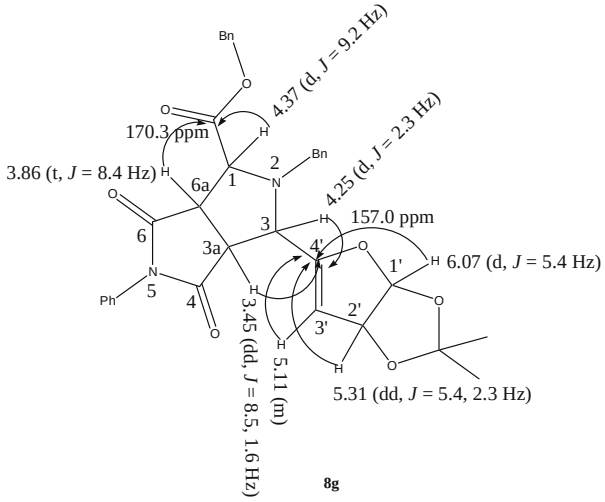


Figure 5. Selective HMBC of compound **8g**.

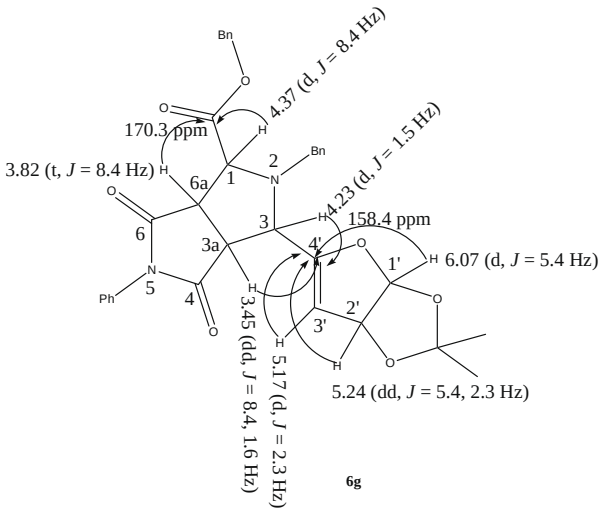


Figure 6. Selective HMBC of compound **6g**.

respectively. The doublet at δ 4.37 ppm (J = 9.2 Hz) and triplet at 3.86 ppm (J = 8.4 Hz) exhibited HMBC contour with carbon at 170.3 ppm corresponding to the ester carbonyl carbon and the protons were assigned as H-1 and H-6a, respectively. (Fig. 5) Compound **6g** exhibited NMR patterns similar to **8g**. (Fig. 6)

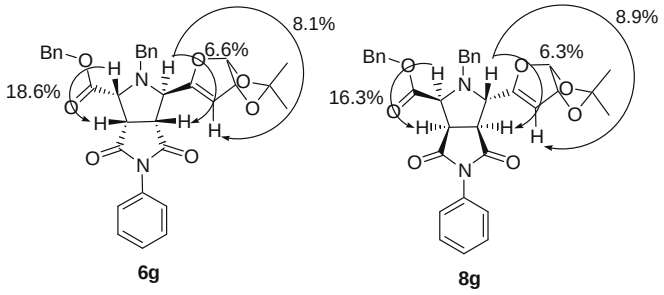


Figure 7. 1-D NOE enhancement of compounds **6g** and **8g**.

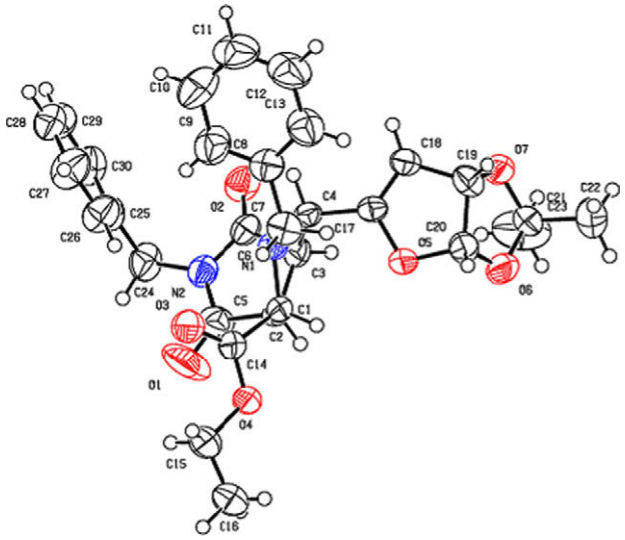


Figure 8. ORTEP diagram of compound **8c**.

2.4. Stereochemical elucidation of the *endo* diastereoisomers (8g)

For compound **8g**, the coupling constant between H-3 and H-3a was 2.3 Hz and H-1 and H-6a was 9.2 Hz. In 1-D NOE measurements selective irradiation of H-1 effected enhancement of the signal of H-6a (16.3%). Irradiation of H-3 effected enhancement of the signals of H-3a (6.3%) and H-3′ (8.9%). From the coupling constants and 1D NOE data, the proton H-1 was found to be cis to H-6a and H-3 trans to H-3a (Fig. 7). The structure of **8c** was confirmed through single crystal X-ray diffraction studies (Fig. 8).[18] The same discussion is applicable to compound **6g** (Fig. 7).

In summary, an efficient synthesis of chiral pyrrolidines was accomplished using 1,3-dipolar cycloaddition of a D-glucose-derived azomethine ylide as the dipole. The unusual 1,2-elimination observed in the furanose moiety of the pyrrolidine resulted in the installation of enol ether functionality which is amenable to various synthetic manipulations. Also noteworthy is the fact that the reaction showed an *exo*-diastereoselectivity against the *endo*-diastereoselectivity observed in other similar reported reactions. These chiral carbohydrate tethered pyrrolidines on account of the presence of the masked aldehyde in the vicinity of potential amino group (*N*-Bn) would be the ideal precursors for the synthesis of various indolizidine type alkaloids.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.10.030.

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15. For metalcatalyzed *exo*-selective 1,3-dipolar cycloaddition see: (a) Peddibhotla, S.; Tepe, J. J. *J. Am. Chem. Soc.* **2004**, *126*, 12776; (b) Oderaotoshi, Y.; Cheng, W.; Fujitomi, S.; Kasano, Y.; Ninakata, S.; Komatsu, M. *Org. Lett.* **2003**, *5*, 5043; (c) Ayerbe, M.; Arrieta, A.; Cossio, F. P. *J. Org. Chem.* **1998**, *63*, 1795.
16. *Experimental procedure for compounds* **5–8**: A mixture of 3-*O*-benzyl-1,2-*O*-isopropylidene-xylopentadialdose **1a** (1.08 mmol), *N*-benzyl glycine ethyl or benzyl ester **2** (1.29 mmol) and *N*-aryl/alkyl maleimide **3** (1.29 mmol) in toluene (15 ml) was refluxed for 3 h. After completion of the reaction, the solvent was evaporated under reduced pressure and the products **5–8** were separated by flash column chromatography using silica gel (230–400 mesh) with ethyl acetate: petroleum ether as an eluent.
2-Benzyl-3-(2,2-dimethyl-3a,6a-dihydro-furo[2,3-d][1,3]dioxol-5-yl)-4,6-dioxo-5-phenyl-octahydro-pyrrolo[3,4-c]pyrrole-1-carboxylic acid benzyl ester (**5g**, **6g**, **7g**, **8g**): *Yield*: 0.451 g (72%):*exo* ***5g****:* Colourless solid; mp 63–65 °C; R_f = 0.54 (50% ethylacetate/petroleum ether); IR (cm^{-1}): 2981, 1717, 1657, 1498, 1384, 1192, 1045; $[\alpha]_D^{30}$ −37.9 (1.18, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 1.38 (s, 3H), 1.39 (s, 3H), 3.41 (d, 1H, *J* = 8.4 Hz, *H*-6a), 3.48 (d, 1H, *J* = 13.0 Hz, −NC*H*H), 3.59 (t, 1H, *J* = 8.4 Hz, *H*-3a), 3.94 (d, 1H, *J* = 13.0 Hz, −NCH*H*), 4.16 (s, 1H, *H*-1), 4.47 (d, 1H, *J* = 9.2 Hz, *H*-3), 5.10 (d, 1H, *J* = 11.5 Hz), 5.19 (dd, 1H, *J* = 5.4, 2.3 Hz, *H*-2′), 5.25 (d, 1H, *J* = 12.3 Hz), 5.47 (d, 1H, *J* = 2.3 Hz, *H*-3′), 5.87 (d, 1H, *J* = 5.4 Hz, *H*-1′), 7.12–7.14(m, 2H, Ar–*H*), 7.21–7.22 (m, 3H, Ar–*H*), 7.32 (d, 2H, *J* = 7.7 Hz, Ar–*H*), 7.35–7.43(m, 6H, Ar–*H*), 7.50 (t, 2H, *J* = 7.7 Hz, Ar–*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.6, 26.0, 45.4, 46.6, 49.6, 59.2, 60.7, 64.8, 80.8, 102.7, 104.9, 110.8, 124.7, 125.5, 126.4, 126.5, 126.7, 126.8, 126.9, 127.2, 127.3, 130.1, 133.2, 135.1, 155.0, 168.8, 172.9, 173.2; ESI-MS (LCQ) *m*/*z* = 581 M^++1. Anal. Calcd for $C_{34}H_{32}N_2O_7$ (580.22): C, 70.33; H, 5.56; N, 4.82. Found: C, 70.50; H, 5.52; N, 4.76.
endo ***6g****:* Colourless solid; mp 60–62 °C; R_f = 0.56 (50% ethylacetate/petroleum ether); IR (cm^{-1}): 2984, 1719, 1659, 1495, 1378, 1196, 1040; $[\alpha]_D^{31}$ +152.9 (0.42, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 1.43 (s, 3H), 1.60 (s, 3H), 3.45 (dd, 1H, *J* = 8.4, 1.6 Hz, *H*-3a), 3.53 (d, 1H, *J* = 13.0 Hz, −NCH*H*), 3.82 (t, 1H, *J* = 8.4 Hz, *H*-6a), 3.91 (d, 1H, *J* = 13.8 Hz, −NC*H*H), 4.23 (d, 1H, *J* = 1.5 Hz, *H*-3), 4.37 (d, 1H, *J* = 8.4 Hz, *H*-1), 5.11 (s, 2H), 5.17 (d, 1H, *J* = 2.3 Hz, *H*-3′), 5.24 (dd, 1H, *J* = 5.4, 2.3 Hz, *H*-2′), 6.07 (d, 1H, *J* = 5.4 Hz, *H*-1′), 7.21–7.25 (m, 7H, Ar–*H*), 7.32–7.34 (m, 4H, Ar–*H*), 7.39 (t, 2H, *J* = 6.9 Hz, Ar–*H*), 7.45 (d, 2H, *J* = 7.7 Hz, Ar–*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.5, 28.4, 47.3, 48.3, 51.7, 59.3, 66.1, 67.5, 82.9, 103.5, 106.7, 112.4, 126.6, 127.4, 128.4, 128.5, 128.6, 128.7, 128.9, 129.1, 129.2, 131.9, 135.1, 137.3, 158.4, 170.3, 175.2, 175.9; ESI-MS (LCQ) *m*/*z* = 581 M^++1. Anal. Calcd for $C_{34}H_{32}N_2O_7$ (580.22): C, 70.33; H, 5.56; N, 4.82. Found: C, 70.52; H, 5.59; N, 4.88.
exo ***7g****:* Less amount of *endo* **8g** was present; viscous liquid; R_f = 0.59 (50% ethylacetate/petroleum ether); IR (cm^{-1}): 2989, 1718, 1660, 1497, 1375, 1196, 1045; $[\alpha]_D^{26}$ −57.5 (0.64, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 1.39 (s, 3H), 1.48 (s, 3H), 3.43 (d, 1H, *J* = 8.4 Hz, C*H*-6a), 3.52 (d, 1H, *J* = 13.8 Hz, −NC*H*H), 3.77 (t, 1H, *J* = 9.2 Hz, *H*-3a), 4.02 (d, 1H, *J* = 12.3 Hz, −NCH*H*), 4.23 (s, 1H, *H*-1), 4.41 (d, 1H, *J* = 9.2 Hz *H*-3), 5.09 (d, 1H, *J* = 12.3 Hz), 5.15 (dd, 1H, *J* = 5.4, 2.3 Hz, *H*-2′), 5.25 (d, 1H, *J* = 12.3 Hz), 5.33 (d, 1H, *J* = 2.3 Hz, *H*-3′), 6.02 (d, 1H, *J* = 5.4 Hz, *H*-1′), 7.07–7.08(m, 2H, Ar–*H*), 7.21–7.24 (m, 3H, Ar–*H*), 7.29 (d, 2H, *J* = 7.7 Hz, Ar–*H*), 7.34–7.41(m, 6H, Ar–*H*), 7.47 (t, 2H, *J* = 7.7 Hz, Ar–*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.6, 27.8, 47.7, 48.5, 52.1, 61.4, 63.3, 66.8, 82.7, 100.7, 106.6, 112.7, 126.4, 127.8, 128.3, 128.5, 128.6, 128.7, 128.8, 129.1, 129.2, 131.9, 135.1, 137.1, 159.1, 170.6, 174.0, 175.1; ESI-MS (LCQ) *m*/*z* = 581 M^++1. Anal. Calcd for $C_{34}H_{32}N_2O_7$ (580.22): C, 70.33; H, 5.56; N, 4.82. Found: C, 70.42; H, 5.63; N, 4.72.
endo ***8g****:* Colourless solid; mp 138–140 °C; R_f = 0.65 (50% ethylacetate/petroleum ether); IR (cm^{-1}): 2984, 1718, 1662, 1495, 1385, 1190, 1044; $[\alpha]_D^{30}$ +93.2 (0.60, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 1.43 (s, 6H), 3.41 (d, 1H, *J* = 13.0 Hz, −NC*H*H), 3.45 (dd, 1H, *J* = 8.5, 1.6 Hz, *H*-3a), 3.84 (d, 1H, *J* = 13.0 Hz, −NC*H*H), 3.86 (t, 1H, *J* = 8.4 Hz, *H*-6a), 4.25 (d, 1H, *J* = 2.3 Hz, *H*-3), 4.37 (d, 1H, *J* = 9.2 Hz, *H*-1), 5.09–5.16 (m, 3H), 5.31 (dd, 1H, *J* = 5.4, 2.3 Hz, *H*-2′), 6.07 (d, 1H, *J* = 5.4 Hz, *H*-1′), 7.22–7.26(m, 7H, Ar–*H*), 7.32–7.37 (m, 5H, Ar–*H*), 7.41 (d, 1H, *J* = 6.9 Hz, Ar–*H*), 7.45 (t, 2H, *J* = 7.6 Hz, Ar–*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.8, 28.5, 29.7, 47.4, 51.9, 59.5, 66.3, 67.5, 83.1, 103.9, 106.2, 112.3, 126.7, 127.5, 128.3, 128.4, 128.5, 128.6, 128.8, 129.0, 129.2, 131.8, 135.1, 137.3, 157.0, 170.3, 175.3, 175.9; ESI-MS (LCQ) *m*/*z* = 581 M^++1. Anal. Calcd for $C_{34}H_{32}N_2O_7$ (580.22): C, 70.33; H, 5.56; N, 4.82. Found: C, 70.22; H, 5.52; N, 4.87.
17. Crystallographic data for the structure **5c** in this Letter have been deposited with the Cambridge Crystallographic Data centre as supplemental Publication No. CCDC-689250. Copies of the data can be obtained, free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 01223 336033 or email: deposit@ccdc.cam.ac.uk).
18. Crystallographic data for the structure **8c** in this Letter have been deposited with the Cambridge Crystallographic Data centre as supplemental Publication No. CCDC-699267. Copies of the data can be obtained, free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 01223 336033 or email: deposit@ccdc.cam.ac.uk).