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1,3-Dipolar cycloaddition reaction of a D-galactose derived nitrone with allyl alcohol: synthesis of polyhydroxylated perhydroazaazulene alkaloids

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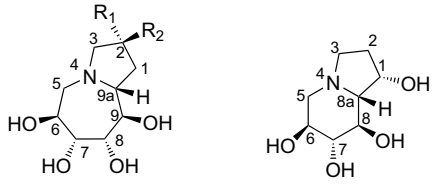
Abstract—Diastereofacial intermolecular 1,3-dipolar cycloaddition of D-galactose derived nitrone with allyl alcohol followed by tosylation afforded, in a 1:1 ratio *endo*- and *exo*-isooxazolidines **4a** and **4b** with complete diastereoselectivity at the nitrone carbon. The N–O bond reductive cleavage and S_N2 displacement afforded the pyrrolidine ring with a galactose appendage that on acetonide cleavage and reductive amino-cyclization afforded pentahydroxylated perhydroazaazulenes **1a** and **1b**.

1. Introduction

Amongst substituted perhydroazaazulenes, a group of hydroxyl-substituted perhydroazaazulenes **1** (Fig. 1) is an emerging class of compounds. These compounds are also considered as higher-ring homologues of polyhydroxylated indolizidine alkaloids. The diverse bioactivities of indolizidine iminosugars,[1] for example, naturally occurring castanospermine[2] **2** and its analogues, as promising glycosidase inhibitors in the treatment of various diseases such as diabetes,[3] cancer[4] and viral infections, including AIDS[5] are known in the literature. This has prompted a structure activity relationship study of hydroxylated perhydroazaazulenes **1**, which are synthesized and evaluated for glycosidase inhibitory activities. In addition, it has been thought that the presence of the polyhydroxylated seven membered ring in **1**, could also exhibit a change in the conformation of the bicyclic system, due to the hydrogen bonding of the hydroxyl groups with the ring nitrogen, causing them to act as DNA minor groove binding ligands as in the case of hydroxylated azepanes.[6] In this respect, Lindsay and Pyne first reported trihydroxy perhydroazaazulenes,[7a] while Gomez-Guillen et al. have reported the syntheses of a hexahydroxy- and pentahydroxy-perhydroazaazulenes.[7b] Another report from Geyer et al. described the synthesis of a tetrahydroxy-octahydro-5-oxo-thiazolo-(3,2-*a*)azepine from D-γ-glucuronolactone and converted it into hexapeptide mimetic, and studied the polyproline II helix conformation.[8] A report from our laboratory describes the synthesis of tetrahydroxy-perhydroazaazulenes using a Johnson–Claisen rearrangement of the D-glucose derived allylic alcohols.[9] As part of our interest in this area,[10] we recently reported the 1,3-dipolar cycloaddition (DC) reaction of 1,4-furanosyl nitrone (obtained from D-glucose) with allyl alcohol in the synthesis of 2-hydroxy-1-deoxycastanospermine analogues.[10c] During this study we noticed that the DC of a nitrone to allyl alcohol occurs with perfect regioselectivity, wherein the oxygen of the 1,3-dipole attacks the more highly substituted carbon of the double bond, while the π-facial stereoselectivity at the



1a, R_1 = OH, R_2 = H
1b, R_2 = OH, R_1 = H

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Figure 1. Iminosugars and analogues.

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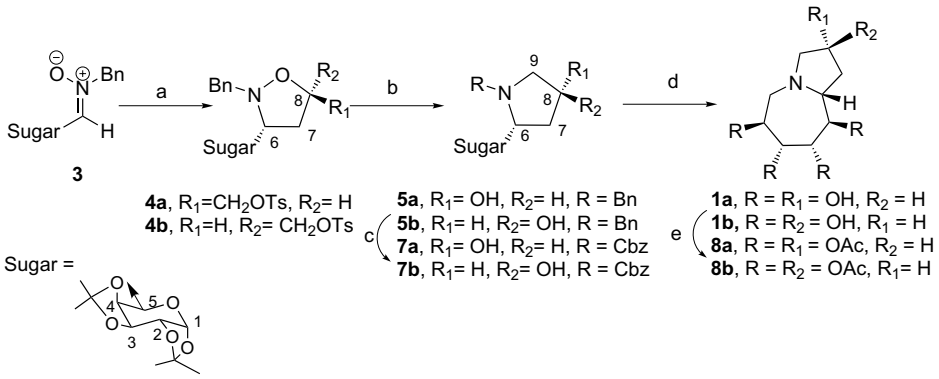


Scheme 1. Reagents and conditions: (a) (i) allyl alcohol, 100 °C, 2.5 h, (ii) TsCl, pyridine, 0 °C to 25 °C, 6 h; (b) Zn, $Cu(OAc)_2$, AcOH, 70 °C, 1 h; (c) (i) $HCOONH_4$, Pd/C, MeOH, 80 °C, 1 h, (ii) CbzCl, $NaHCO_3$, MeOH, 0 °C to 25 °C, 2.5 h; (d) (i) TFA–H_2O (4:1), 25 °C, 2 h, (ii) $HCOONH_4$, Pd/C, MeOH, 80 °C, 1.5 h; (e) Ac_2O, pyridine, DMAP, 0 °C to 25 °C, 12 h.

nitrone and allyl carbon was found to be low, affording all four possible diastereomers. It has been reported by Pedro Merino et al. that the furanosyl nitrones give low π-facial diastereoselectivity, while the pyranosyl nitrones afford high π-facial diastereoselectivity at the prochiral nitrone carbon.[11] With this view in mind, we decided to exploit 1,3-DC reaction[12] of a D-galactose derived nitrone **3** with allyl alcohol which would be regio- and π-facial diastereoselective at the nitrone carbon, while the *endo*- and *exo*-selectivity at the allyl carbon would lead to the formation of *anti*- and *syn*-isoxazolidines. The isoxazolidines thus obtained on tosylation followed by N–O bond reductive cleavage and in situ nucleophilic tosyl substitution would afford pyrrolidines with a D-galactose appendage that on *N*-Cbz protection, cleavage of the acetonide functionalities and reductive amino-cyclization (C6 amino functionality of pyrrolidine with C1-hemiacetal) would lead to the formation of the seven membered ring of the azaazulene skeleton required for the target molecule. Although a few reports are currently available with regard to the use of DC of the nitrones to allyl alcohol,[13] the application of this strategy to nitrone **3** towards the synthesis of perhydroazaazulene analogues, to the best of our knowledge, is still not known. Our efforts in the successful implementation of this methodology for the synthesis of polyhydroxy perhydro azaazulenes **1a** and **1b** are reported herein.[†]

2. Results and discussion

The required nitrone **3** was prepared from D-galactose as reported earlier.[14] The 1,3-DC of **3** to allyl alcohol at 100 °C for 2.5 h afforded an inseparable mixture of isoxazolidines in 90% yield (after chromatographic purification), which upon further treatment with *p*-toluenesulfonylchloride in pyridine afforded an inseparable diastereomeric mixture of tosyloxylated isoxazolidines **4a** and **4b** in the ratio 1:1 as evident from the ^1H NMR spectrum of column purified material (Scheme 1).

In the next step, the mixture of isoxazolidines **4a** and **4b** was subjected to N–O bond reductive cleavage using Zn-acetic acid, which on chromatographic separation afforded the corresponding pyrrolidines **5a** and **5b** in a 1:1 ratio in 84% yield. This one pot two-step reaction of **4** most likely involves the in situ generation of a β-amino alcohol that concomitantly undergoes nucleophilic displacement of the –*O*-tosyl group leading to the formation of 8-hydroxy-pyrrolidine-ring skeleton **5**. Fortunately pyrrolidine **5b**, which has a lower R_f compared to **5a**, was isolated as a crystalline solid. Single crystal X-ray analysis (Fig. 2) established the absolute configurations at the newly generated C6 and C8 stereocentres as (*R*) and (*S*), respectively. Having known the structure of **5b**, the stereochemical assignment in **5a** was derived from the correlation study. For this, we considered oxidizing the C8-hydroxyl groups in **5a** and **5b** to the corresponding C8-keto products that will enable us to determine whether **5a** and **5b** are C6-epimeric are not, and from the X-ray data correlation of **5b**, assign the absolute stereochemistry at C8 in **5a**.

Thus, pyrrolidines **5a** and **5b** were individually subjected to the Swern oxidation (Scheme 2) that afforded the same ketone **6** (confirmed on the basis of the spectral, analytical data and the super imposable IR spectra). As the absolute configuration at C6 in **5b** was established as (*R*), the same absolute configuration (6*R*) was assigned to **5a**, while the absolute configuration at C8 in **5b** was determined to be (*S*) and as **5a** was found to be the C8 epimeric alcohol, the C8 configuration in **5a** was therefore assigned as (*R*).

Pyrrolidines **5a** and **5b** were derived from isoxazolidines **4a** and **4b**, respectively. Therefore it is evident that DC of nitrone **3** to allyl alcohol (and subsequent tosylation) is highly diastereoselective wherein the addition of the allyl alcohol takes place exclusively from the *Re* face of nitrone **3** leading to the formation of *endo*- and *exo*-isoxazolidines in a 1:1 ratio. This observation was found to be analogous to that reported by Merino et al.[11] and Gomez-Guillen et al.[7b] in which the DC of nitrone **3** with methyl acrylate afforded the *Re-endo* cycloadduct as the only isolable product due to the favoured secondary orbital overlap of –COOMe group;[12c] the same effect is absent in the DC of nitrone **3** with allyl alcohol, resulting in the formation of *endo*- and

[†] While our work was in progress, Gomez-Guillen et al. have published a report on the DC of a D-galactose derived nitrone with methyl acrylate towards the synthesis of **1a**.

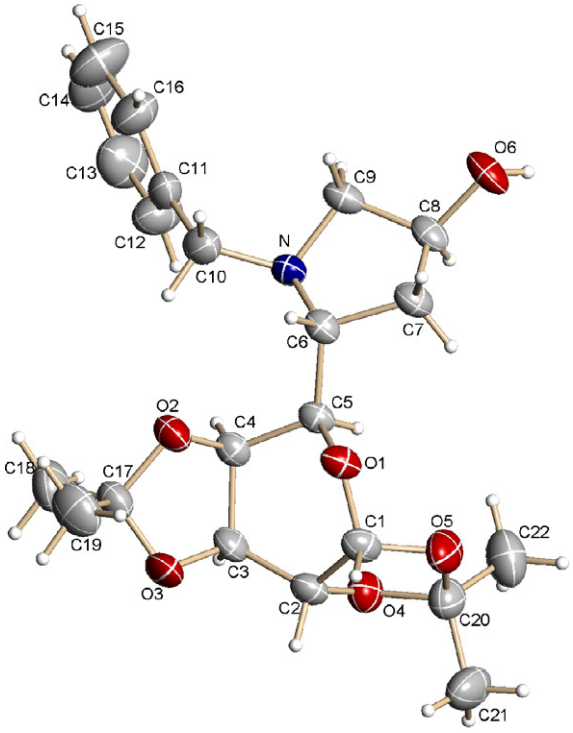
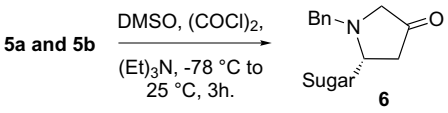


Figure 2. ORTEP diagram of compound **5b**.



Scheme 2.

exo- products in a 1:1 ratio. The above results were compared with our earlier report[10c] on the 1,3-DC of furanosyl nitrone with allyl alcohol and it was noted that pyranosyl nitrone **3** offered high π-facial selectivity when compared to furanosyl nitrone as reported by others.[11]

2.1. Explanation for the observed stereoselectivity in the DC reaction

The observed π-facial diastereoselectivity could be rationalized on the basis of Felkin-Anh like transition states (TS). Out of the four TS, we considered the TS I in which the bulky C-4 substituent is kept perpendicular to C=N and the other TS II, wherein the electronegative pyranose ring oxygen is perpendicular to C=N (Fig. 3). We believe that, in TS I, the approach of the allyl alcohol from the *Re* face of the C=N is favoured over the *Si* face approach in TS II due to the interactions of the bulky C4-substituent, leading to the formation of isoxazolidines with exclusively (*R*)-absolute configuration at the nitrone carbon (C6). The approach of the allyl alcohol in *endo*/*exo* orientation, however, affords **4a** and **4b** in equal amounts.

In the subsequent step, treatment of **5a** with ammonium formate and 10% Pd/C followed by selective amine protec-

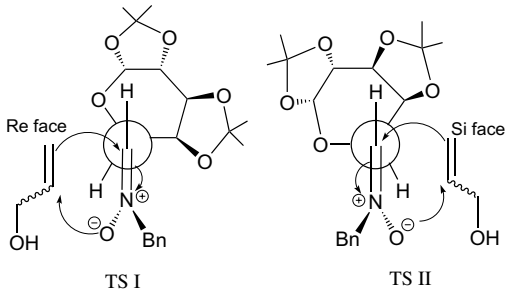


Figure 3. The Felkin-Anh models.

tion with benzyl chloroformate afforded *N*-Cbz protected pyrrolidines **7a** in 80% yield. Finally, **7a** was treated with TFA:H_2O (4:1) and the hemiacetal thus obtained was subjected to hydrogenation (ammonium formate, 10% Pd/C, in methanol reflux) to afford pentahydroxy-perhydroazaazulene **1a** as a viscous liquid. The spectral and analytical data of **1a** were found to be in accordance with that reported.[7b] {$[\alpha]_D^{25} = +7.0$ (*c* 0.5, MeOH) [lit.[7b] $[\alpha]_D^{25} = +6.1$ (*c* 0.5, MeOH)]}. Compound **1a** was treated with acetic anhydride in pyridine to afford per-acetylated derivative **8a**. The same sequence of reactions with **5b** afforded *N*-Cbz protected pyrrolidine **7b**, which on acetonide cleavage and reductive amino-cyclization afforded pentahydroxy-perhydroazaazulene **1b** which was characterized as its peracetyl derivative **8b**. The spectral and analytical data of **7b**, **1b** and **8b** were found to be in agreement with the given structures.

3. Conclusions

In conclusion, the DC of D-galactose derived nitrone **3** with allyl alcohol is highly regio- and *Re* facial stereoselective. However, the *endo*- and *exo*-addition affords *anti*- and *syn*-isoxazolidines in nearly equal amounts. The tosylation of cycloadducts followed by N–O bond reductive cleavage afforded pyrrolidines **5a** and **5b** in high yields, which were converted to the corresponding pentahydroxylated perhydroazaazulenes **1a** and **1b**.

4. Experimental

4.1. General methods

Melting points were recorded with Thomas Hoover melting point apparatus and are uncorrected. IR spectra were recorded with FTIR as a thin film or in Nujol mull or using KBr pellets and are expressed in cm^{-1}. ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded using $CDCl_3$ or D_2O as a solvent. Chemical shifts were reported in δ unit (ppm) with reference to TMS as the internal standard and *J* values are given in Hz. Decoupling and DEPT experiments confirmed the assignments of the signals. Elemental analyses were carried out with C, H-analyzer. Optical rotations were measured using polarimeter at 25 °C. Thin layer chromatography was performed on pre-coated plates (0.25 mm, silica gel 60 F_{254}). Column chromatography was carried out with silica gel (100–200 mesh). The reac-

tions were carried out in oven-dried glassware under dry N_2. Methanol, pyridine, acetone, benzene, toluene, acetonitrile and dichloromethane were purified and dried before use. 10% Pd–C was purchased from Aldrich and/or Fluka. After decomposition of the reaction with water, the work-up involves washing of the combined organic layers with water, brine, drying over anhydrous sodium sulfate and evaporation of solvent at reduced pressure.

4.2. 6,7,9-Trideoxy-6,9-(*N*-benzylimino)-1,2:3,4-di-*O*-isopropylidene-8(*R*)-hydroxy-β-L-*threo*-D-*galacto*-non-1,5-pyranose 5a and 6,7,9-trideoxy-6,9-(*N*-benzylimino)-1,2:3,4-di-*O*-isopropylidene-8(*S*)-hydroxy-α-D-*erythreo*-D-*galacto*-non-1,5-pyranose 5b

Nitrone **3** (2.0 g, 5.5 mmol) and allyl alcohol (3.1 g, 55 mmol) were heated at 100 °C for 2 h. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (*n*-hexane/ethyl acetate = 75/25) to afford a mixture of cycloadducts as a thick liquid (2.1 g, 90%). To a mixture of cycloadducts (2.1 g, 4.9 mmol) in dry pyridine (5 mL), cooled at 0 °C, was added *p*-toluenesulfonylchloride (1.12 g, 5.8 mmol), and stirred at room temperature for 4 h. The reaction mixture was quenched with cold water and extracted with ethyl acetate to give a thick oil that on purification by column chromatography (*n*-hexane/ethyl acetate = 90/10) afforded an inseparable mixture of isoxazolidines as a thick liquid (2.5 g, 87%). Zinc dust (0.56 g, 8.6 mmol) was added to a solution of copper(II) acetate (0.025 g, 0.16 mmol) in glacial acetic acid (1 mL) under a nitrogen atmosphere and the mixture was stirred at room temperature for 10 min until the colour disappeared. The above mixture of isoxazolidines (1.0 g, 1.7 mmol) in glacial acetic acid (1.5 mL) and water (0.5 mL) was added successively and the reaction mixture was heated at 70 °C for 2 h. On cooling to room temperature, the sodium salt of EDTA (0.1 g) was added and the mixture was stirred for 10 min and then made alkaline to pH 10 by addition of 3 M NaOH. Extraction with chloroform, work-up and separation by flash column chromatography by eluting first with *n*-hexane/ethyl acetate = 80/20 gave **5a** (0.307 g, 42%) as a thick oil; $R_f = 0.59$ (hexane/ethyl acetate = 4/6); $[\alpha]_D^{25} = -24$ (*c* 0.41, $CHCl_3$); IR (Neat) 3540–3200, 1632, 1458 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3 + D_2O$) δ 1.21 (s, 3H, CH_3), 1.22 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 2.1 (ddd, $J = 15.3$, 10.2, 5.1 Hz, 1H, H-7a), 2.20–2.38 (m, 2H, H-7b, H-9a), 2.87 (dd, $J = 9.6$, 1.5 Hz, 1H, H-9b), 3.0 (dt, $J = 7.2$, 3.0 Hz, 1H, H-6), 3.45 (d, $J = 13.2$ Hz, 1H, NCH_2Ph), 3.9 (br s, 1H, H-5), 4.11 (d, $J = 2.1$ Hz, 1H, H-4), 4.15 (d, $J = 13.2$ Hz, 1H, NCH_2Ph), 4.24–4.40 (m, 2H, H-2 and H-8), 4.61 (dd, $J = 7.8$, 2.1 Hz, 1H, H-3), 5.63 (d, $J = 4.8$ Hz, 1H, H-1), 7.19–7.38 (m, 5H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.0, 24.8, 25.6, 25.9 (CH_3), 35.5 (C-7), 58.5 (NCH_2Ph), 61.0, 62.2 (C-9, C-6), 68.1, 70.4, 70.6, 70.7, 71.6 (C-2, C-3, C-4, C-5, C-8), 96.3 (C-1), 108.2, 108.6 (O–C–O), 126.5, 127.8, 128.3, 138.9 (Ar), Anal. Calcd for $C_{22}H_{31}NO_6$: C, 65.17; H, 7.71. Found: C, 65.20; H, 7.53.

Further elution with *n*-hexane/ethyl acetate = 78/22 afforded **5b** (0.30 g, 42%) as a white solid; mp = 120 °C; $R_f = 0.60$ (*n*-hexane/ethyl acetate = 4/6); $[\alpha]_D^{25} = +36.0$ (*c* 0.05, $CHCl_3$); IR (Nujol) 3550–3200, 1612, 1454 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3 + D_2O$) δ 1.22 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 1.97 (ddd, $J = 13.5$, 8.4, 6.0 Hz, 1H, H-7a), 2.23 (dt, $J = 13.5$, 6.0 Hz, 1H, H-7b), 2.39 (dd, $J = 10.0$, 5.4 Hz, 1H, H-9a), 3.07 (dd, $J = 10.0$, 5.4 Hz, 1H, H-9b), 3.27 (apparent q, $J = 6.0$ Hz, 1H, H-6), 3.62 (d, $J = 13.5$ Hz, 1H, NCH_2Ph), 3.64 (dd, $J = 6.0$, 1.5 Hz, 1H, H-5), 4.22 (d, $J = 13.5$ Hz, 1H, NCH_2Ph), 4.29 (dd, $J = 5.1$, 2.1 Hz, 1H, H-2), 4.34 (t, 5.4 Hz, 1H, H-8), 4.42 (dd, $J = 8.0$, 1.8 Hz, 1H, H-4), 4.60 (dd, $J = 8.0$, 2.1 Hz, 1H, H-3), 5.56 (d, $J = 5.1$ Hz, 1H, H-1), 7.18–7.21 (m, 5H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.1, 25.0, 25.8, 26.2 (CH_3), 37.5 (C-7), 60.1, 60.9, 61.8 (C-6, C-9, CH_2Ph), 69.5, 70.6, 70.7, 71.1, 77.4 (C-2, C-3, C-4, C-5, C-8), 96.4 (C-1), 108.1, 108.6 (O–C–O), 126.6, 128.0, 128.5, 139.4 (Ar-C). Anal. Calcd for $C_{22}H_{31}NO_6$: C, 65.17; H, 7.71. Found: C, 65.22; H, 7.65.

4.3. Crystal data

Single crystals of compound **5b** were grown by slow evaporation of the solution in chloroform. Colourless crystal of approximate size $0.43 \times 0.11 \times 0.09$ mm was used for data collection on Bruker SMART APEX CCD diffractometer using MoK_α radiation with fine focus tube with 50 kV and 30 mA. Crystal to detector distance 6.05 cm, 512×512 pixels/frame, multiscan data acquisition. Total scans = 5, total frames = 2798, oscillation/frame −0.3°, exposure/frame = 25.0 s/frame, maximum detector swing angle = −30.0°, beam centre = (260.2, 252.5), in plane spot width = 1.24, SAINT integration, θ range = 2.07–25.00°, completeness to θ of 25.0° is 99.9%. SADABS correction applied, $C_{22}H_{31}NO_6$, $M = 405.48$. Crystals belong to monoclinic, space group $P2_1$, $a = 11.5010(6)$, $b = 8.8460(5)$, $c = 11.8760(7)$ Å, $\beta = 114.757(1)°$ $V = 1097.19(11)$ $Å^3$, $Z = 2$, $D_c = 1.227$ mg m^{-3}, $\mu(MoK_\alpha) = 0.089$ mm^{-1}, $T = 293(2)$ K, 12,262 reflections measured, 3857 unique [$I > 2\sigma(I)$], *R* value 0.0456, $wR_2 = 0.0978$. All the data were corrected for Lorentzian, polarization and absorption effects. SHELX-97 (ShelxTL)[ref] was used for structure solution and full matrix least squares refinement on F^2. Hydrogen atoms were included in the refinement as per the riding model.

4.4. 6,7,9-Trideoxy-6,9-(*N*-benzoxycarbonylimino)-1,2:3,4-di-*O*-isopropylidene-8(*S*)-hydroxy-β-L-*threo*-D-*galacto*-non-1,5-pyranose 7a

A solution of compound **5a** (0.20 g, 0.49 mmol), 10% Pd/C (0.075 g) and ammonium formate (0.18 g, 2.9 mmol) in methanol (4 mL) was refluxed for 1 h. The reaction mixture was filtered through Celite and the filtrate was evaporated to give a thick oil. To a solution of amino alcohol (0.15 g, 0.45 mmol) in methanol–water (10 mL, 9:1), cooled to 0 °C, were added benzylchloroformate (0.091 g, 0.60 mmol), sodium bicarbonate (0.114 g, 1.3 mmol) and the solution was stirred for 2.5 h. Methanol was evaporated under reduced pressure. After the usual work-up and further purification by column chromatography (*n*-hexane/ethyl acetate = 90/10), **7a** (0.176 g, 80%) was

obtained as a thick liquid; $R_f = 0.33$ (hexane/ethyl acetate = 7/3); $[\alpha]_D^{25} = 8.0$ (*c* 0.05, $CHCl_3$); IR (Neat) 3600–3250, 1697, 1400 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3 + D_2O$) δ 1.30 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 2.21 (ddd, $J = 15.0$, 10.0, 4.8 Hz, 1H, H-7a), 2.53 (br d, $J = 15.0$ Hz, 1H, H, H-7b), 3.45 (dd, $J = 11.1$, 4.8 Hz, 1H, H-9a), 3.55 (br d, $J = 11.1$ Hz, 1H, H-9b), 4.17 (d, $J = 10.0$ Hz, 1H, H-6), 4.18–4.28 (m, 1H, H-8), 4.3 (dd, $J = 4.8$, 2.1 Hz, 1H, H-2), 4.36 (br d, $J = 8.1$ Hz, 1H, H-4), 4.42 (br s, 1H, H-5), 4.60 (dd, $J = 8.1$, 2.1 Hz, 1H, H-3), 5.1 (ABq, $J =$ 12.3 Hz, 2H, $NCOCH_2Ph$), 7.20–7.5 (m, 5H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.8, 24.7, 25.4, 25.5 (CH_3), 34.0 (C-7), 55.8 (C-9), 58.7 (C-6), 66.2, 66.4 (C-5, CH_2Ph), 69.7, 70.3, 70.6, 71.9 (C-2, C-3, C-4, C-8), 96.0 (C-1), 108.9 (O–C–O), 127.3, 127.48, 127.9, 136.3 (Ar-C), 154.8 (C=O); Anal. Calcd for $C_{23}H_{31}NO_8$: C, 61.46; H, 6.95. Found: C, 61.50; H, 6.99.

4.5. 6,7,9-Trideoxy-6,9-(*N*-benzoxycarbonylimino)-1,2:3,4-di-*O*-isopropylidene-8(*S*)-hydroxy-α-D-*erythreo*-D-*galacto*-non-1,5-pyranose 7b

Compound **5b** (0.15 g, 0.36 mmol) was treated with 10% Pd/C (0.05 g) and ammonium formate (0.13 g, 2.17 mmol), in methanol (3 mL), followed by benzylchloroformate (0.068 g, 0.45 mmol) and sodium bicarbonate (0.083 g, 0.97 mmol), as described in the synthesis of **7a**. Further purification by column chromatography (*n*-hexane/ethyl acetate = 85/15) afforded **7b** (0.12 g, 77%) as a white solid; Mp = 117 °C; $R_f = 0.625$ (hexane/ethyl acetate = 5/5); $[\alpha]_D^{25} = +400$ (*c* 0.03, $CHCl_3$); IR (Nujol) 3600–3200, 1685, 1415, 1346 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3 + D_2O$) δ 1.22 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.96 (ddd, $J = 11.7$, 8.4, 3.0 Hz, 1H), 2.52 (dt, $J = 11.7$, 6.3 Hz, 1H, H-7b), 3.38–3.68 (m, 2H, H-9a, H-9b), 4.13–4.34 (m, 3H, H-6, H-8, H-2), 4.34–4.46 (br s, 2H, H-3, H-4), 4.56 (br d, $J = 7.2$ Hz, 1H, H-3), 5.08 (ABq, $J = 12$ Hz, 2H, CH_2Ph), 5.47 (d, $J = 4.8$ Hz, 1H, H-1), 7.18–7.40 (m, 5H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.5, 25.5, 26.1, 26.3 (CH_3), 35.1 (C-7), 54.9 (C-9), 58.4 (C-6), 66.6, 66.9 (CH_2Ph), 70.9(s), 71.4, 72.5 (C-2, C-3, C-4, C-5), 96.76 (C-1), 109.4 (O–C–O), 128.0, 128.6, 136.9 (Ar-C), 155.5 (C=O).

Due to the presence of the N-Cbz functionality, the ^1H NMR of the compound shows broad signals and ^{13}C NMR shows doubling of signals. Anal. Calcd for $C_{23}H_{31}NO_8$: C, 61.46; H, 6.95. Found: C, 61.66; H, 6.92.

4.6. 6,7,9-Trideoxy-6,9-(*N*-benzylimino)-1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-non-1,5-pyranose 6

To a solution of oxalyl chloride (0.033 g, 0.26 mmol) in CH_2Cl_2 (2 mL) at −78 °C was added DMSO (0.04 g, 0.51 mmol) and the mixture was stirred for 15 min. A solution of alcohol **5a/5b** (0.1 g, 0.23 mmol) in CH_2Cl_2 (3 mL) was added, and the mixture was stirred at −78 °C for an additional 1 h. Triethylamine (0.12 g, 1.1 mmol) was added, and the mixture was allowed to warm to room temperature. Usual work-up followed by purification by column chromatography (*n*-hexane/ethyl acetate = 90/10) afforded **7a** (0.07 g, 70%) as a thick liquid; $R_f = 0.70$ (*n*-hexane/ethyl acetate = 5/5); $[\alpha]_D^{25} = -26.6$ (*c* 0.30, $CHCl_3$); IR (Neat) 1749, 1654 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.38 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 2.57 (dd, $J = 19.2$, 7.5 Hz, 1H, H-7a), 2.70–2.90 (m, 2H, H-9a, H-7b), 3.26 (d, $J = 17.7$ Hz, 1H, H-9b), 3.36 (ddd, $J = 9.9$ Hz, 1H, H-6), 3.49 (d, $J = 12.9$ Hz, 1H, CH_2Ph), 4.14 (br s, 1H, H-5), 4.21 (d, $J = 12.9$ Hz, 1H, CH_2Ph), 4.28 (dd, $J = 7.8$, 2.1 Hz, 1H, H-4), 4.33 (dd, $J = 7.8$, 2.1 Hz, 1H, H-2), 4.63 (dd, $J = 7.8$, 2.1 Hz, 1H, H-3), 5.60 (d, $J = 4.8$ Hz, 1H, H-1), 7.18–7.40 (m, 5H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$); δ 24.3, 24.8, 25.9, 26.3 (CH_3), 39.5 (C-7), 58.4, 60.5, 61.6 (C-6, CH_2Ph, C-9), 65.6 (C-5), 70.5, 71.0, 72.3 (C-2, C-3, C-4), 96.6 (C-1), 108.3, 109.2 (O–C–O), 127.2, 128.3, 128.6, 137.0 (Ar-C); Anal. Calcd for $C_{22}H_{29}NO_6$: C, 65.49; H, 7.24. Found: C, 65.30; H, 7.39.

4.7. (2*R*,6*S*,7*R*,8*S*,9*R*,9a*R*)-2,6,7,8,9-Pentahydroxy-perhydroazaazulene 1a

A solution of **7a** (0.20 g, 0.45 mmol) in TFA–H_2O (6 mL, 4:1) was stirred at 25 °C for 4 h. Trifluoroacetic acid was co-evaporated with benzene to furnish a thick liquid. A solution of the above product (0.160 g, 0.43 mmol), 10% Pd/C (0.100 g) and ammonium formate (0.16 g, 2.6 mmol) in methanol (4 mL) was refluxed for 1.5 h. The reaction mixture was filtered through Celite and the filtrate was evaporated. Purification by column chromatography (chloroform/methanol = 85/15) afforded **1a** (0.085 g, 87%) as a thick liquid; $R_f = 0.30$ (methanol); $[\alpha]_D^{25} = +7.0$ (*c* 0.5, MeOH); IR (Neat) 3676–3250 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.8 (dd, $J = 14.0$, 5.1 Hz, 1H, H-1a), 2.66 (ddd, $J = 14.0$, 9.3, 5.1 Hz, 1H, H-1b), 2.71–2.86 (m, 1H, H-5a), 2.92–3.23 (m, 2H, H9a, H3a), 3.25 (d, $J = 11.7$, 1H, H-3b), 3.61 (dd, $J = 13.5$, 6.6 Hz, 1H, H-5b), 3.80 (dd, $J = 9.3$, 6.6 Hz, 1H, H-9), 3.94 (d, $J = 6.6$ Hz, 1H, H-8), 4.20 (d, $J = 6.6$ Hz, 1H, H-7), 4.22 (apparent q, $J = 6.6$ Hz, 1H, H-6), 4.42–4.52 (m, 1H, H-2); ^{13}C NMR (75 MHz, D_2O) δ 41.5 (C-1), 60.1 (C-5), 67.3 (C-3), 69.8, 69.9, 71.3 (C-9, C-6, C-2), 75.8(s), 77.0 (C-7, C-8, C-9); Anal. Calcd for $C_9H_{17}NO_5$: C, 49.51; H, 7.82. Found: C, 49.79; H, 7.77.

4.8. (2*S*,6*S*,7*R*,8*S*,9*R*,9a*R*)-2,6,7,8,9-Pentahydroxy-perhydroazaazulene 1b

A solution of **7b** (0.20 g, 0.45 mmol) in TFA–H_2O (6 mL, 4:1) followed by treatment with 10% Pd/C (0.100 g) and ammonium formate (0.16 g, 2.6 mmol) as described in the synthesis of **1a**, and purification by column chromatography (chloroform/methanol = 80/20) afforded **1b** (0.056 g, 82%) as a thick liquid; $R_f = 0.4$ (methanol); $[\alpha]_D^{25} = +90.9$ (*c* 0.11, MeOH); IR (Neat) 3429–3230 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.95 (dt, $J = 13.5$, 6.9 Hz, 1H, H-1a), 2.14 (ddd, $J = 13.5$, 7.2, 3.9 Hz, 1H, H-1b), 2.46–2.62 (m, 2H, H-3a, H-5a), 2.81 (apparent q, $J = 8.4$ Hz, 1H, H-9a), 3.31 (dd, $J = 12.9$, 6.6 Hz, 1H, H-5b), 3.38 (dd, $J = 11.4$, 5.4 Hz, 1H, H-3b), 3.54 (dd, $J = 9.0$, 6.0 Hz, 1H, H-9), 3.82–3.92 (m, 2H, H-7, H-8), 4.0 (apparent q, $J = 6.8$ Hz, 1H, H-6), 4.26–4.42 (m, 1H, H-2). The

assignments of the signals were confirmed by decoupling experiments. ^{13}C NMR (75 MHz, D_2O); δ 40.5 (C-1), 59.9 (C-3), 63.9 (C-5), 67.6 (C-9a), 68.7, 68.9 (C-2, C-6), 74.8, 75.4, 75.7 (C-7, C-8, C-9). Anal. Calcd for $C_9H_{17}NO_5$: C, 49.31; H, 7.82. Found: C, 49.51; H, 8.01.

4.9. (2*R*,6*S*,7*R*,8*S*,9*R*,9a*R*)-2,6,7,8,9-Penta-acetoxy-perhydroazaazulene 8a

To an ice-cooled solution of **1a** (0.04 g, 0.18 mmol) in dry pyridine (0.649 g, 8.2 mmol) were added acetic anhydride (1.65 g, 16 mmol), DMAP (0.0021 g, 0.018 mmol) and the mixture was stirred for 12 h at room temperature. The reaction was decomposed with cold water (2 mL), followed by the usual work-up and further purification by column chromatography (*n*-hexane/ethyl acetate = 90/10) afforded penta-acetate **8a** (0.06 g, 77%) as a thick liquid; $R_f = 0.25$ (*n*-hexane/ethyl acetate = 6/4); $[\alpha]_D^{25} = +208$ (*c* 1.05, $CHCl_3$); IR (Nujol) 1732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.92–2.16 (m, 16H, CH_3), 2.44–2.51 (m, 2H, H-1b, H-5a), 2.53–2.63 (m, 2H, H-3a, H-9a), 3.40 (d, $J = 10.8$ Hz, 1H, H-3b), 3.60 (dd, $J = 13.2$, 6.3 Hz, 1H, H-5b), 5.0 (dd, $J = 9.0$, 6.0 Hz, 1H, H-9), 5.20 (t, $J = 4.5$ Hz, 1H, H2), 5.39–5.78 (m, 3H, H-6, H-7, H-8); ^{13}C NMR (75 MHz, $CDCl_3$); δ 20.8(s), 20.8, 21.8 (CH_3), 31.8 (C-1), 55.1, 61.4, 65.0 (C-3, C-5, C-9a), 69.6, 72.1, 72.6, 73.1, 75.0 (C-2, C-6, C-7, C-8, C-9), 169.2, 169.3(s), 169.5, 170.6 (C=O); Anal. Calcd for $C_{19}H_{27}NO_{10}$: C, 53.14; H, 6.34. Found: C, 53.40; H, 6.60.

4.10. (2*S*,6*S*,7*R*,8*S*,9*R*,9a*R*)-2,6,7,8,9-Penta-acetoxy-perhydroazaazulene 8b

Compound **1b** (0.028 g, 0.126 mmol) was treated with dry pyridine (0.45 g, 5.74 mmol), acetic anhydride (1.15 g, 11.2 mmol), and DMAP (0.0015 g, 0.012 mmol) as described in the synthesis of **8a**. Further purification by column chromatography (*n*-hexane/ethyl acetate = 85/15) afforded **8b** (0.045 g, 83%) as a thick liquid; $R_f = 0.29$ (*n*-hexane/ethyl acetate = 6/4); $[\alpha]_D^{25} = +324.3$ (*c* 0.0185, $CHCl_3$); IR (Neat) 1738 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.88–2.10 (m, 1H, H-1a), 2.04 (s, 3H, CH_3), 2.05 (br s, 6H, CH_3), 2.07 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 2.10–2.18 (m, 1H, H-1b), 2.54–2.74 (m, 2H, H-3a, H-5a), 2.88 (apparent q, $J = 8.4$ Hz, 1H, H-9a), 3.30 (dd, $J = 13.2$, 6.3 Hz, 1H, H-5b), 3.59 (dd, $J = 10.8$, 5.4 Hz, 1H, H-3), 4.86 (dd, $J = 8.7$, 6.3 Hz, 1H, H-9), 5.02–5.18 (m, 2H, H-6), 5.26 (dd, $J = 6.3$, 2.0 Hz, 1H, H-8), 5.32 (dd, $J = 6.6$, 2.0 Hz, 1H, H-8); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7, 20.7, 20.8, 20.8, 21.0 (CH_3), 38.3 (C-1), 56.4, 61.9, 65.3 (C-3, C-5, C-9a) 69.9, 72.3(s), 72.6, 74.4 (C-6, C-7, C-8, C-9, C-2), 169.1, 169.3, 169.3, 169.4, 170.1 (C=O). Anal. Calcd for $C_{19}H_{27}NO_{10}$: C, 53.14; H, 6.34. Found: C, 53.28; H, 6.58.

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References

1. (a) Elbein, A. D.; Molyneux, R. J. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley-Interscience: New York, 1987; Vol. 5; (b) Howard, A. S.; Michael, J. P. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1986; Vol. 28, Chapter 3; (c) Michael, J. P. *Nat. Prod. Rep.* **1990**, *9*, 485–523.
2. (a) Zho, H.; Hans, S.; Cheng, X.; Mootoo, D. R. *J. Org. Chem.* **2001**, *66*, 1761–1767; (b) Svansson, L.; Johnston, B. D.; Gu, J.-H.; Patrik, B.; Pinto, B. M. *J. Am. Chem. Soc.* **2000**, *122*, 10769–10775; (c) Izquiedro, I.; Plaza, M. T.; Robles, R.; Mota, A. J. *Tetrahedron: Asymmetry* **1998**, *9*, 1015–1027; (d) Kang, S. H.; Kim, J. S. *J. Chem. Soc., Chem. Commun.* **1998**, 1353–1354; (e) Kefalas, P.; Grierson, D. S. *Tetrahedron Lett.* **1993**, *34*, 3555–3558; (f) Ina, H.; Kibayashi, C. *J. Org. Chem.* **1993**, *58*, 52–61; (g) Burgess, K.; Chaplin, D. A.; Henderson, I.; Pan, Y. T.; Elbein, A. D. *J. Org. Chem.* **1992**, *57*, 1103–1109; (h) Furneaux, R. H.; Mason, J. M.; Tyler, P. C. *Tetrahedron Lett.* **1995**, *36*, 3055–3058.
3. (a) Truscheit, E.; Frommer, W.; Junge, B.; Muller, L.; Schmidt, D. D.; Wingender, W. *Angew. Chem.* **1981**, *20*, 744–761; (b) Furneaux, R. H.; Gainsford, G. J.; Mason, J. M.; Tyler, P. C.; Hartley, O.; Winchester, B. G. *Tetrahedron* **1997**, *53*, 245–268.
4. Humphries, M. J.; Matsumoto, K.; White, S. L.; Olden, K. *Cancer Res.* **1986**, *46*, 5215–5222.
5. (a) Karpas, A.; Fleet, G. W. J.; Dwek, R. A.; Petursson, S.; Namgoong, S. K.; Ramsden, N. G.; Jacob, G. S.; Rademacher, T. W. *Proc. Nat. Acad. Sci.* **1988**, *85*, 9229–9233; (b) Walker, B. D.; Kowalski, M.; Goh, W. C.; Kozarsky, K.; Krieger, M.; Rosen, C.; Rohrschneider, L.; Haseltine, W. A.; Sodroski, J. *Proc. Natl. Acad. Sci.* **1987**, *84*, 8120–8124; (c) Sunkara, P. S.; Bowling, T. L.; Liu, P. S.; Sjoerdsma, A. *Biochem. Biophys. Res. Commun.* **1987**, *148*, 206–210.
6. Johnson, H. A.; Thomas, N. R. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 237–241.
7. (a) Lindsay, K. B.; Pyne, S. G. *Tetrahedron* **2004**, *60*, 4173–4176; (b) Torres-Sanchez, M. I.; Borrachero, P.; Cabrera-Escribano, F.; Gomez-Guillen, M.; Angulo-Alvarez, M.; Dianez, M. J.; Estrada, M. D.; Lopez-Castro, A.; Perez-Garrido, S. *Tetrahedron: Asymmetry* **2005**, *16*, 3897–3907.
8. (a) Tremmel, P.; Geyer, A. *J. Am. Chem. Soc.* **2002**, *124*, 8548–8549; (b) Gavard, O.; Hersant, Y.; Alais, J.; Duverger, V.; Dilhas, A.; Bascou, A.; Bonnaffe, D. *Eur. J. Org. Chem.* **2003**, 3603–3620; (c) Geyer, A.; Bockelmann, D.; Weissenbach, K.; Fischer, H. *Tetrahedron Lett.* **1999**, *40*, 477–578.
9. Markad, S. D.; Karanjule, N. S.; Sharma, T.; Sabharwal, S. G.; Puranik, V. G.; Dhavale, D. D. *Org. Bio. Chem.* **2006**, *4*, 2549–2555.
10. (a) Karanjule, N. S.; Markad, S. D.; Shinde, V. S.; Dhavale, D. D. *J. Org. Chem.* **2006**, *71*, 4667–4670; (b) Karanjule, N. S.; Markad, S. D.; Dhavale, D. D. *J. Org. Chem.* **2006**, *71*, 6273–6276; (c) Karanjule, N. S.; Markad, S. D.; Sharma, T.; Sabharwal, S. G.; Puranik, V. G.; Dhavale, D. D. *J. Org. Chem.* **2005**, *70*, 1356–1363.
11. Merino, P.; Franco, S.; Merchan, F. L.; Romero, P.; Tejero, T.; Uriel, S. *Tetrahedron: Asymmetry* **2003**, *14*, 3731–3743.
12. For reviews on the 1,3-dipolar cycloaddition of nitrones, see: (a) Pellissier, H. *Tetrahedron* **2007**, *63*, 3235–3285; (b) Ruck-Braun, K.; Tonia, H. E.; Wierschem, F. *Chem. Soc. Rev.* **2005**, *34*, 507–516; (c) Gothelf, K. V.; Jorgensen, K. A. *Chem.*

Rev. **1998**, *98*, 863–910; (d) Confalone, P. N.; Huie, E. M. *Org. React.* **1988**, *36*, 1–173; (e) Torseel, K. B. G. In *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*; Feuer, H., Ed.; VCH: Weinheim, 1988; (f) Ferrier, R. J.; Middleton, S. *Chem. Rev.* **1993**, *93*, 2779–2831; (g) Osborn, H. M.; Gemmell, N.; Harwood, L. M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2419–2438; (h) Frederickson, M. *Tetrahedron* **1997**, *53*, 403–425; (i) Adams, J. P.; Box, D. S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 749–764; (j) Karlsson, S.; Hogberg, H. E. *Org. Prep. Proceed. Int.* **2001**, *33*, 103–172; (k) Koumbis, A. E.; Gallos, J. K. *Curr. Org. Chem.* **2003**, *7*, 585–628; (l) Padwa, A.; Pearson, W. H. *J. Nat. Prod.* **2004**, *67*, 1074; (m) Padwa, A.; Pearson, W. H. *Org. Process Res. Dev.* **2004**, *8*, 293; (n) Padwa, A.; Pearson, W. H. *J. Am. Chem. Soc.* **2002**, *124*, 12633–12634; (o) *Cycloaddition Reactions in Organic Synthesis*; Carruthers, W., Ed.; Tetrahedron Organic Chemistry Series; Pergamon Press: New York, 1990; Vol. 8, pp 269–314; (p) *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press: London, 1988; Vol. 1, 1990 Vol. 2, 1993; Vol. 3; (q) Gothelf, K. V. In *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jorgensen, K. A., Eds.; Wiley-VCH: Weinheim, 2002; Chapter 6, pp 211–247; (r) Kanemasa, S. In *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jorgensen, K. A., Eds.; Wiley-VCH: Weinheim, 2002, Chapter 7, pp 249–300; (s) Kanemasa, S.; Nishiuchi, M.; Kamimura, A.; Hori, K. *J. Am. Chem. Soc.* **1994**, *116*, 2324–2329.

13. (a) Singh, R.; Singh, S.; Bhella, A. K.; Sexana, M.; Faruk, A. S.; Ishar, M. P. S. *Tetrahedron* **2007**, *63*, 2283–2291; (b) Merino, P.; Tejero, T.; Laguna, M.; Cerrada, E.; Moreno, A.; Lopez, J. A. *Org. Bio. Chem.* **2003**, *1*, 2336; (c) Kumar, K. R. R.; Mallesha, H.; Rangappa, K. S. *Synth. Commun.* **2003**, *33*, 1545; (d) Ding, X.; Taniguchi, K.; Ukaji, Y.; Inomata, K. *Chem. Lett.* **2001**, *5*, 468; (e) Ooi, H.; Urushibara, A.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *Org. Lett.* **2001**, *3*, 953.
14. (a) Dondoni, A.; Franco, S.; Junquera, F.; Merchan, F.; Merino, P.; Tejero, T. *Synth. Commun.* **1994**, *22*, 2537–2550; (b) Borrachero, P.; Cabrera, F.; Dianez, M. J.; Estrada, M. D.; Gomez-Guillen, M.; Lopez-Castro, A.; Moreno, J. M.; de Paz, J. L.; Perez-Garrido, S. *Tetrahedron: Asymmetry* **1999**, *10*, 77–78.