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Single Diastereomers of Polyhydroxylated 9-Oxa-1-azabicyclo[4.2.1]nonanes from Intramolecular 1,3-Dipolar Cycloaddition of ω-Unsaturated Nitrones

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8-Benzyloxymethyl-3,4,5-tribenzoyloxy-9-oxa-1-azabicyclo-[4.2.1]nonane has been prepared as the single diastereoisomer **8** from an intramolecular 1,3-dipolar cycloaddition involving 2-(benzyloxy)acetaldehyde and ω-unsaturated hydroxylamine **7** derived from methyl α-D-glucopyranoside. The analogous 8-methoxycarbonyl 9-oxa-1-azabicyclo[4.2.1]nonane was afforded in a similar manner, from methyl D-galactopyranoside and methyl glyoxylate, as a 3:1 mixture of diastereoisomers **15** and **16**. When conducted in achiral ionic liquid **17** this ratio increased to 8:1, and in chiral ionic liquid **18**, compound **15** was formed exclusively.

Glycosidases are intimately involved in a plethora of metabolic pathways, and the development of glycosidase inhibitors presents an enormous challenge for the treatment of associated disorders, e.g., diabetes, Gaucher's disease, cancer, and viral infections including AIDS.[1-5] Recently, highly oxygenated chiral heterocycles containing nitrogen (also referred to as azasugars, iminosugars, or iminocyclitols) have emerged as potential glycosidase inhibitors worthy of further investigation.[6,7]

Our interest in this field stems from our previous synthetic efforts to prepare chiral azetidines. En route to these compounds, diastereomeric mixtures of hydroxylated chiral 9-oxa-1-azabicyclo-[4.2.1]nonanes were produced through an intramolecular 1,3-dipolar cycloaddition involving ω-unsaturated nitrones derived from D-glucose and 2-furaldehyde.[8] This nitrone-alkene cycloaddition is a well-known powerful tool that has successfully been employed in the literature to construct a variety of isoxazolidines, 1,3-aminoalcohols, and derivatives[9,10] usually starting from carbohydrate precursors.[11,12] Recently, a ring-contracted dihydroxylated 8-oxa-1-azabicyclo[3.2.1]octane and its ring-opened azepane derivative have been found to be effective glycosidase inhibitors.[13]

As highlighted above, because of the increasing biological interest in this class of compounds, we have decided to explore the scope of this intramolecular 1,3-dipolar cycloaddition. Therefore, we have investigated the utility of other aldehydes and sugars, namely, D-glucose and D-galactose, and our findings are presented herein.

We first embarked on investigation of the iodination of methyl α-D-glucopyranoside **1** using the conditions described by Vasella[14-16] and Garegg[17] (Scheme 1). After extensive experimentation, we have found that iodo compound **2** can only be obtained reproducibly in good yields (60%) on a large scale when using a modified procedure that requires careful consideration of reaction conditions (e.g., reagent addition times, temperature, stirring) and a combination of different purification procedures. Subsequent benzoylation of compound **2**[18-20] successfully afforded benzoate **3**.[21-23] The latter halo derivative **3** was then subjected to the Boord–Vasella reaction[14-16,24-28]

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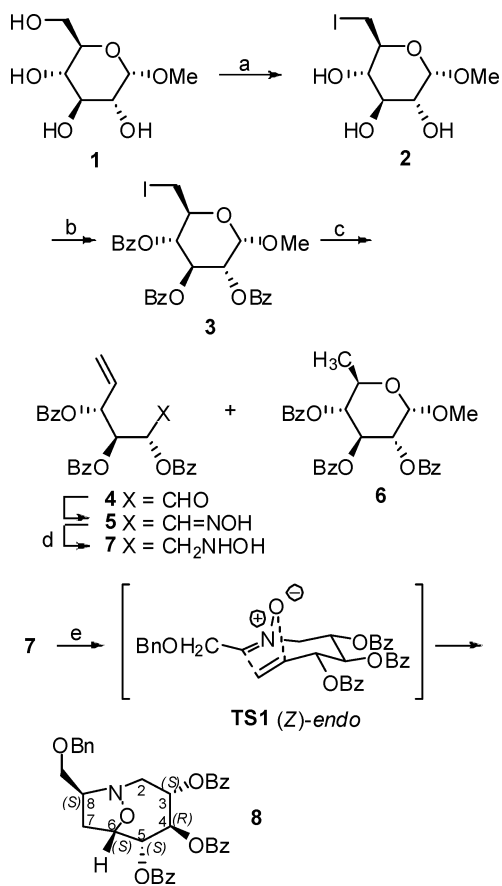|| Heriot-Watt University.

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SCHEME 1[a]

[a] Reagents and conditions: (a) Ph₃P, I₂, imidazole, PhMe, 70−110 °C, 3 h, 60%; (b) BzCl, py, CH₂Cl₂, 0−25 °C, 16 h, 85%; (c) (1) Zn, various solvents, sonication, 40−60 °C, 4−5 h, (2) NH₂OH·HCl, aq Na₂CO₃, CH₂Cl₂, **5**: 0−65%, **6**: 27−85%; (d) NaBH₃CN, dioxane, MeOH, pH = 1.4−1.5, rt, 45 min; (e) BnOCH₂CHO, PhMe, 4Å molecular sieves, 110 °C, 20 h, 28% overall.

(which involved treatment with activated zinc in various solvents, under sonication).

Surprisingly, despite the fact that there are numerous publications in the literature dealing with this reaction,[14−16,22,23,29,30] an experimentally simple and reliable method suitable for the production of ω-unsaturated aldehyde **4** could not easily be established. We reported previously that although many different reaction conditions worked well on a small scale, increasing the scale of transformation was typically accompanied with a considerable decrease in product yield.[8] We also noted, in the present case, that the nature of the solvent had a dramatic effect on both yield and chemoselectivity of the reaction. That is to say, aldehyde **4** (isolated as a stable oxime **5**,[8] 1:1 *E/Z* mixture) was consistently afforded in 55−65% yield along with the undesired side product **6**[31,32](27−32%) when solutions of **3** in THF−aqueous MeOH or THF or MeCN−aqueous MeOH mixtures were treated with CeCl₃-activated zinc.[23] However,

in neat dioxane, the yield of compound **5** was drastically reduced (12%) while the yield of the concurrent 6-deoxy derivative **6** substantially increased (75%), and in other neat solvents (DMF, MeCN, acetone, diisopropyl ether) compound **6** was produced exclusively (85%). Fürstner et al.[22] have likewise noted that less reactive halo derivatives (e.g., 6-bromo-6-deoxysugars) are prone to reduction.

Finally, oxime **5** was successfully transformed into cycloadduct **8** in a one-pot reaction involving first reduction to the corresponding hydroxylamine **7** using NaBH₃CN at controlled pH (1.4−1.5, in organic phase) followed by condensation of the resulting unstable product with a freshly prepared solution of 2-(benzyloxy)acetaldehyde[33] in dry toluene (**5** → **8**, 28% overall). Cycloadduct **8** was the only isolable compound from the reaction mixture, and the purified substance was a single spot/peak according to TLC, OPLC, and HPLC. The gross structure and the configurations at all newly formed stereocenters were assigned using 1D and 2D NMR measurements (HSQC, HMBC, NOESY) and on the basis of the known configuration of pre-existing stereocenters (3*S*,4*R*,5*S*) that had arisen from the former carbohydrate moiety. In the NOESY spectrum the following protons were found to reside on the top face (relative to the 9-oxa-1-azabicyclo[4.2.1]nonane skeleton as depicted in Scheme 1): H-3/H-2b; H-5/H-6; H-6/H-7b, while protons H-7a/H-8/H-4; H-8/H-2a/H-4 were on the bottom. This clearly demonstrates that proton H-6 and the benzyloxymethyl substituent at position 8 are located on the same side (*β*-) and their absolute configuration is (6*S*,8*S*). Therefore, the configurational preference for this intramolecular 1,3-dipolar cycloaddition was found to parallel that reported previously for the analogous reaction employing a nitrone derived from 2-furaldehyde and D-glucose.[8] It is remarkable, however, that changing a substituent from 2-furyl to benzyloxymethyl at position 8 affects drastically the diastereoselectivity of this 1,3-dipolar cycloaddition: with 2-furyl substituent three difficult-to-separate diastereomers were obtained,[8] whereas the benzyloxymethyl substituent directed the reaction to the exclusive formation of single diastereomer **8**. The formation of the alternative regioisomer (an 8-oxa-1-azabicyclo[4.2.1]nonane with a bridgehead methyne group) was not observed. It is generally assumed that in such cycloadditions the new C−C bond is more developed in the transition state than the C−O bond (cf. Scheme 1, **TS1**) and hence both for steric and electronic reasons, the C−C bond is preferably formed at the less substituted alkene position,[8,13,34,35] although the effects of substituents and ring sizes on the regioselectivity show significant variation.[34,36,37]

In order to expand the repertoire for this reaction we have investigated the corresponding intramolecular 1,3-dipolar cycloaddition for a nitrone prepared from methyl D-galactopyranoside. In this case, functionalization required a slightly different approach as direct halogenation of methyl D-galactopyranoside at position 6 proved to be problematic as a result of steric hindrance exerted by the axial hydroxyl group at position 4.

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SCHEME 2[a]
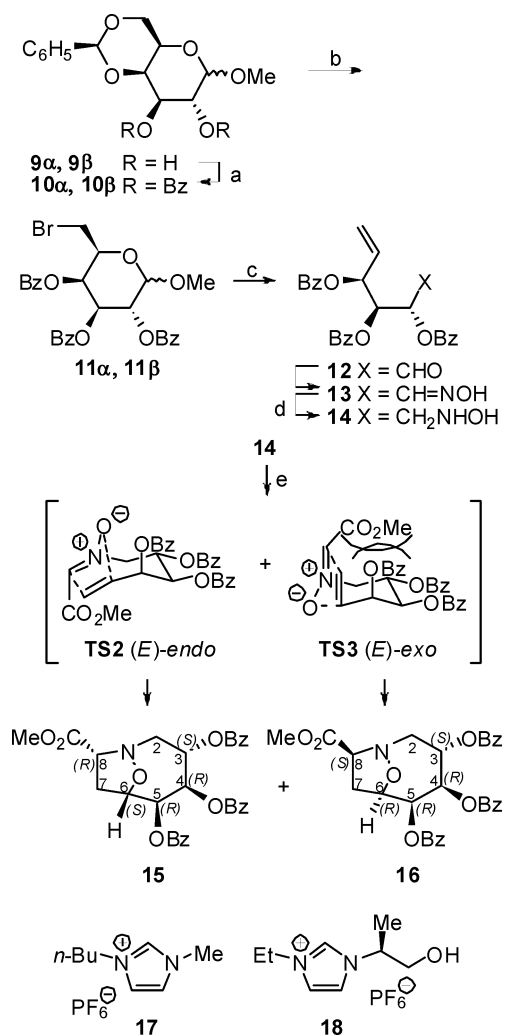
[a] Reagents and conditions: (a) BzCl, py, CH_2Cl_2, 0−25 °C, 4 h, 90%; (b) NBS, $BaCO_3$, $CHCl_3$, $ClCH_2CH_2Cl$, 65 °C, 3 h, 70%; (c) (1) Zn, cat. $CeCl_3$, NH_4Cl, MeOH, THF, sonication, 40 °C, 3 h, (2) $NH_2OH \cdot HCl$, aq K_2CO_3, Et_2O, rt, 16 h, 72% overall; (d) $NaBH_3CN$, MeOH, pH = 1.4−1.5, rt, 1 h; (e) MeO_2CCHO, 4Å molecular sieves, 110 °C, 20 h, PhMe or **17** or **18**, 64−79%

Thus, compound **9**[38] (Scheme 2), which was readily available from methyl D-galactopyranoside, was utilized instead. Following benzoylation, **10**[39] was subjected to Hanessian-type oxidative ring opening[40] using NBS to afford the 6-bromo-6-deoxy derivative **11**, characterized as two separate epimers. The Boord−Vasella ring opening of **11** gave aldehyde **12** (isolated as the stable oxime **13**, 2:1 *E/Z* mixture) in 72% yield. Occasionally, byproducts from this reaction (e.g., the corresponding 6-deoxy pyranose) were also observed, but in most cases this proved to be negligible. Oxime **13** was successfully reduced under conditions identical to those used above for the D-*gluco* derivative ($NaBH_3CN$, MeOH, pH = 1.4−1.5), and the resulting hydroxylamine **14** was condensed without any further purification with a freshly prepared solution of methyl glyoxylate[41] in dry toluene. For this cycloaddition the intermediate

nitrone yielded two cycloadducts, **15** and **16**, in a 3:1 ratio (**13** → **15** + **16**, 64%). Configurational assignment for all newly formed stereocenters was again performed employing 2D NMR techniques. NOESY data revealed the spatial proximity of protons H-2b/H-3; H-6/H-7b/H-8 (top-face) and H-2a/H-4/H-5/H-7a (bottom-face) for **15** and that of protons H-2b/H-3; H-3/H-7b (top-face) and H-2a/H-4; H-4/H-5/H-6; H-5/H-6/H-7a; H-7a/H-8 (bottom-face) for **16**, respectively. This data suggests that the configuration of newly formed stereocenters is (6*S*,8*R*) for **15** and (6*R*,8*S*) for **16**. Steric hindrance between substituents at C-5 and C-8 in **16** (and in the corresponding transition state **TS3**, Scheme 2) probably accounts for the subordinate formation of this compound compared to **15**.

It has been reported that 1,3-dipolar cycloadditions are accelerated when performed in certain ionic liquids.[42] Thus, in an attempt to optimize the above reaction, condensation of hydroxylamine **14** with freshly prepared methyl glyoxylate has also been carried out in the ionic liquid 1-*n*-butyl-3-methyl-1*H*-imidazol-3-ium hexafluorophosphate **17**. Surprisingly, this reaction exhibited improved diastereoselectivity with **15** and **16** being isolated in a 8:1 ratio (**13** → **15** + **16**, 72%). This unexpected finding prompted us to examine the use of the chiral ionic liquid (*S*)-3-ethyl-1-(1-hydroxypropan-2-yl)-1*H*-imidazol-3-ium hexafluorophosphate **18**, prepared in a few steps from L-alanine,[43] in this intramolecular 1,3-dipolar cycloaddition. Thus, when the above cycloaddition was repeated in **18** as a solvent, cycloadduct **15** was unexpectedly obtained as the sole product of the reaction (79% yield). Since their discovery, ionic liquids have gained much popularity owing to their unusual properties, and interest to replace traditional solvents with these new substances is forever increasing.[44,45] However, although the application of ionic liquids in organic chemistry is rapidly expanding, there are currently only a few examples in the literature reporting the use of chiral ionic liquids in asymmetric reactions and the best asymmetric induction obtained so far was 44% ee.[46,47] One can expect a significant transfer of chirality in these solvents due to their high degree of organization. It has been reported that most ionic liquids possess a polymeric structure and are highly ordered H-bonded liquids (three-dimensional networks of anions and cations linked together by hydrogen bonds).[46] In addition, it was recently shown that hydrogen bonding is involved in controlling the *endo*-selectivity of Diels−Alder reactions performed in achiral ionic liquids.[48] Thus, our unprecedented observation that a chiral ionic liquid can shift an asymmetric intramolecular 1,3-dipolar cycloaddition to the exclusive formation of a single diastereomer is therefore a pivotal finding.

In conclusion, 9-oxa-1-azabicyclo[4.2.1]nonanes **8**, **15**, and **16** have been successfully prepared in four steps starting from either methyl α-D-glucopyranoside or methyl D-galactopyranoside, respectively, in overall yields of 9−36%. The key step in their synthesis involved an intramolecular 1,3-dipolar cycloaddition of ω-unsaturated nitrones. Upon optimizing this reaction we have discovered that use of the chiral ionic liquid **18**

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furnished cycloadduct **15** as a single diastereomer in high yield. It is clear from the above study that subtle changes in nature of the substituent and/or configuration of the starting nitrones or solvent have a dramatic effect on the diastereoselectivity of this asymmetric intramolecular 1,3-dipolar cycloaddition. The availability of the above cycloadducts in pure diastereomeric form opens up new avenues in the study of polyhydroxylated 9-oxa-1-azabicyclo[4.2.1]nonanes, and further investigations to exploit this approach in multistep reactions are in progress and will be reported in due course.

Experimental Section

(3S,4R,5S,6S,8S)-8-(Benzyloxymethyl)-9-oxa-1-azabicyclo-[4.2.1]nonane-3,4,5-triyl Tribenzoate (8). To a stirred solution of oxime **5** (3.440 g, 7.27 mmol) in dioxane (300 mL) and MeOH (300 mL) was added NaBH$_3$CN (2.740 g, 43.60 mmol, 6 equiv) while the solution was carefully treated with HCl/dioxane (1.7 M, ~30 mL) to maintain the pH between 1.4 and 1.5 using a combined pH glass electrode for organic solutions. After approximately 45 min, when the reduction stopped (the pH of the reaction mixture did not alter further), the solution was evaporated in vacuo and coevaporated with MeCN (100 mL); the residue was dissolved in a mixture of EtOAc (400 mL) and saturated aqueous Na$_2$CO$_3$ solution (300 mL); and the organic phase was washed with additional Na$_2$CO$_3$ solution (300 mL), water (300 mL), and brine (300 mL), dried (MgSO$_4$), and evaporated in vacuo. If the reaction solution still contains some starting material **5** (TLC), subsequent NaBH$_3$CN (2.740 g, 43.60 mmol, 6 equiv) has to be added and the pH must be maintained for a repeated 30 min period. The unstable hydroxylamine **7** was used immediately without any further purification to avoid its decomposition: R_f 0.60, hexanes−EtOAc 1:1; TLC-MS (*m/z*) 476 (100%, [M + H]$^+$), 498 (12, [M + Na]$^+$). The above hydroxylamine **7** was dissolved in dry toluene (250 mL) and treated with freshly prepared 2-(benzyloxy)acetaldehyde (2 equiv) in the presence of 4 Å molecular sieves and a Dean-Stark water trap. After stirring at 110 °C for 20 h, the solution was filtered, evaporated in vacuo, and coevaporated with MeCN (3 × 50 mL). The residue was purified by silica gel column chromatography [eluent 0−5% (v/v) Et$_2$O in CH$_2$Cl$_2$] to give the title cycloaddition product **8** as a pale yellow oil (1.22 g, 28% overall yield). R_f: 0.33,

CH$_2$Cl$_2$−Et$_2$O 95:5. [α]$_D$: −26 (*c* = 0.5, MeOH). IR (CaF$_2$, thin film): 990 (w), 1026 (m), 1069 (m), 1096 (s), 1177 (w), 1261 (s), 1278 (s), 1315 (m), 1451 (m), 1493 (w), 1584 (w), 1601 (w), 1724 (s), 2859 (w), 2942 (w), 3030 (w), 3057 (w) cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$, δ, ppm, superscripts * and # denote interchangeable assignments): 2.25 (1H, ddd, $J_{6,7b\#}$ = 8.7 Hz, $J_{7a,7b}$ = 13.5 Hz, $J_{7b,8\#}$ = 4.6 Hz, H-7b); 2.96 (1H, ddd, $J_{6,7a*}$ = 2.8 Hz, $J_{7a,7b}$ = 13.5 Hz, $J_{7a,8*}$ = 8.6 Hz, H-7a); 3.14 (1H, dd, $J_{2a,2b}$ = 14.1 Hz, $J_{2a,3}$ = 7.7 Hz, H-2a); 3.41 (1H, dd, $J_{8,1'a}$ = 6.4 Hz, $J_{1'a,1'b}$ = 9.4 Hz, H-1'a); 3.60 (1H, dd, $J_{8,1'b}$ = 7.3 Hz, $J_{1'a,1'b}$ = 9.4 Hz, H-1'b); 3.75 (1H, m, H-8); 4.24 (1H, dd, $J_{2a,2b}$ = 14.1 Hz, $J_{2b,3}$ = 5.5 Hz, H-2b); 4.57 (1H, d, $J_{2'a,2'b}$ = 11.9 Hz, H-2'a); 4.66 (1H, d, $J_{2'a,2'b}$ = 11.9 Hz, H-2'b); 4.86 (1H, ddd, $J_{5,6}$ = 5.8 Hz, $J_{6,7b\#}$ = 8.7 Hz, $J_{6,7a*}$ = 2.8 Hz, H-6); 5.66 (1H, dd, $J_{4,5}$ = 8.1 Hz, $J_{5,6}$ = 5.8 Hz, H-5); 5.84 (1H, ddd, $J_{2a,3}$ = 7.7 Hz, $J_{2b,3}$ = 5.5 Hz, $J_{3,4}$ = 9.4 Hz, H-3); 5.99 (1H, dd, $J_{3,4}$ = 9.4 Hz, $J_{4,5}$ = 8.1 Hz, H-4); 7.37 (14H, m, arom); 7.90 (6H, m, arom). ^{13}C NMR (126 MHz, CDCl$_3$, δ, ppm): 32.8 (C-7); 59.1 (C-2); 67.6 (C-8); 69.1 (C-3); 72.6 (C-4); 73.1 (C-1'); 73.2 (C-5); 73.4 (C-2'); 77.1 (C-6); 127.7−128.3 (arom); 129.0 (arom C$_q$); 129.1 (arom C$_q$); 133.0 (arom); 133.1 (arom); 133.2 (arom);138.0 (arom C$_q$); 165.1 (CO); 165.1 (CO); 165.5 (CO). NOESY (connected protons, relative to the 9-oxa-1-azabicyclo-[4.2.1]nonane skeleton): top-face H-3/H-2b; H-5/H-6; H-6/H-7b; bottom-face H-7a/H-8/H-4; H-8/H-2a/H-4. LRMS (*m/z*): 608 (100%, [M + H]$^+$), 630 (25, [M + Na]$^+$). HRMS (FAB, glycerol): calcd for C$_{36}$H$_{34}$NO$_8^+$ [M + H]$^+$ *m/z* 608.22789, found *m/z* 608.2310. Anal. Calcd for C$_{36}$H$_{33}$NO$_8$ (607.649): C, 71.16; H, 5.47; N, 2.31. Found: C, 71.03; H, 5.59; N, 2.48%.

Supporting Information Available: Experimental procedures and characterization data for all compounds and copies of 1D ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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