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[1,3]-Dipolar intramolecular nitrone olefin cycloaddition reaction of a sugar-derived α,β-unsaturated ester: a new diastereo- and regioselective synthesis of an aminocyclopentitol

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Abstract—The reaction of hemiacetal **2a**, from the sugar derived α,β-unsaturated ester **1a**, with *N*-benzylhydroxylamine hydrochloride in situ generates an *N*-benzylnitrone as a 1,3-dipole, which spontaneously undergoes diastereo- and regioselective intramolecular nitrone olefin cycloaddition to afford a hydroxy functionalised 4-*exo*-ethoxycarbonyl-3-oxa-2-azabicyclo[3.3.0]octane system, a precursor to a hitherto unknown aminocyclopentitol derivative.

Amongst 1,3-dipolar cycloaddition reactions,[1] the intramolecular nitrone olefin cycloaddition (INOC) methodology has received a lot of attention in recent years for the synthesis of novel heterocyclic ring systems and aminocarbocycles with different ring sizes.[2] In the case of simple alkenes containing achiral nitrones, the INOC proceeds well and results in the formation of fused bicyclic isoxazolidines in which the configuration of the olefin dictates and stereoselectivity of product formation.[3] However, the INOC of achiral or chiral nitrones having an electron deficient alkene substituent such as an α,β-unsaturated esters is intriguing and very few examples of this type are known.[4] The stereochemical outcome in such concerted reactions is determined by steric factors and secondary orbital interactions; while the regioselectivity of the cycloaddition is controlled by the transition state invoking both steric and electronic effects. As far as the regiochemical outcome is concerned, there are two possibilities: either the formation of α-oxido ester or β-oxido ester isoxazolidine derivatives. As a part of our continuing interest in nitrone cycloaddition reactions,[5] we have exploited D-glucose derived α,β-unsaturated ester **1** as an appropriate substrate for the INOC. We envisioned that the reaction of hemiacetal **2**, derived from **1** by acetonide cleavage, with *N*-benzyl hydroxylamine hydrochloride would generate the *N*-benzylnitrone (1,3-dipole), which will undergo the INOC reaction in situ with an activated alkene to give an isoxazolidine—a precursor to a five or six membered aminocarbocycle. This class of compounds, namely aminocyclopentitols are known to be powerful inhibitors of glycosidases.[6] In the search for structure–activity relationships, the synthesis and evaluation of the glycosidase inhibitory activities of natural and unnatural analogues of aminocyclitols is a subject of current interest.[7] Our results in this direction are reported herein.

Recently, we have reported the preparation and utility of ethyl 3-*O*-benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-5(*E*)-eno-heptofuranuronoate (**1a**) in the synthesis of polyhydroxylated piperidine and indolizidine alkaloids.[8] The cleavage of the acetonide functionality in **1a** with TFA–water afforded hemiacetal **2a** (anomeric mixture, α:β = 7:3) with the exclusively *E*-geometry at the double bond.[†] The one pot reaction of **2a** with *N*-benzylhydroxylamine hydrochloride (1.0 equiv.) in the presence of sodium acetate (2 equiv.) in aq. ethanol (20%) afforded 4-*exo*-ethoxycarbonyl-3-oxa-2-azabicyclo [3.3.0]octane (α-oxido-ester isoxazolidine) **3** as a white solid in 65% yield (Scheme 1).[‡]

Keywords: nitrones; cycloadditions; cyclitols; isoxazolidines; enzyme inhibitors; glycosidation.

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[†] As indicated from the ^{1}H NMR spectrum the cleavage of the acetonide group in the **la** with TFA–H_2O afforded hemiacetal **2a** as an anomeric mixture (α:β = 7:3) with exclusive *E*-geometry. The same reaction with a mixture of **1a** and **1b** or with **1b** (*Z*-isomer), however, led to hemiacetal **2a** with *E*-geometry as reported by us earlier.[8a] Our attempts to isolate **2b** (*Z*-isomer) in pure form were unsuccessful.

[‡] The reaction afforded an unidentified compound in ~10% yield at a higher R_f value than **3**.

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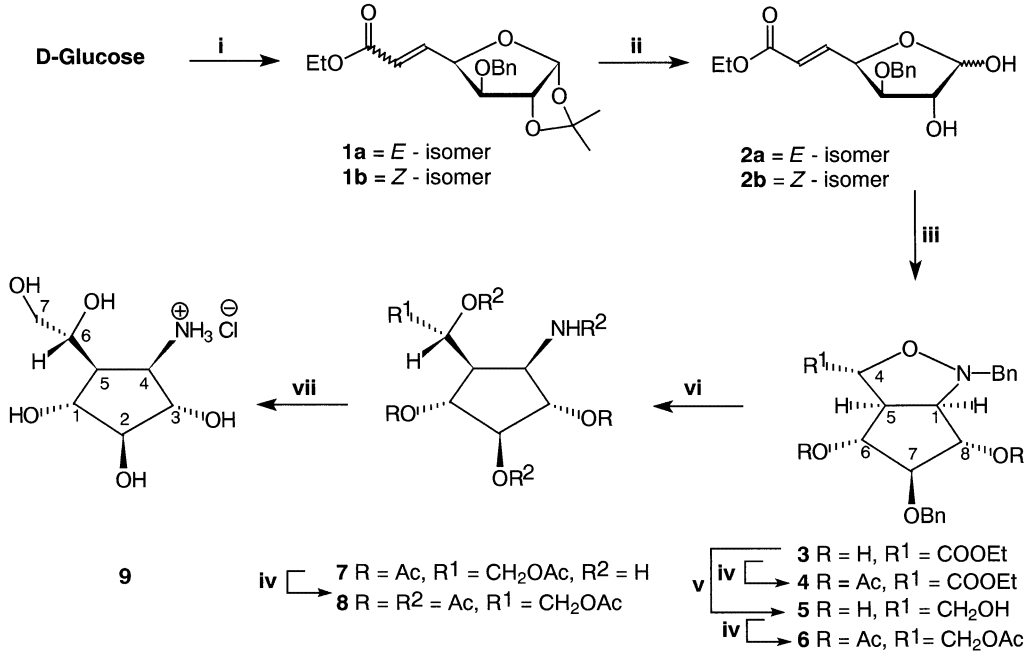

Scheme 1. (i) Ref. 8a; (ii) TFA–H_2O (3:2), 0°C to rt, 2.5 h, 80%; (iii) HN(OH)Bn·HCl (1 equiv.), CH_3COONa (2 equiv.), aq. ethanol, rt for 8 h and then reflux, 4 h, 65%; (iv) Ac_2O (32 equiv.), pyridine (19 equiv.), DMAP (0.01%), rt, 18 h; (v) LAH (5 equiv.), THF, 0°C, 1 h, 83%; (vi) 10% Pd/C, $HCOONH_4$ (7 equiv.), methanol, reflux, 45 min, 84%; (vii) methanolic-HCl, (0.5 M, 0.6 ml), rt, 40 h, 90%.

The spectroscopic and analytical data obtained for **3** were in agreement with the assigned structure.[§] The configurations at the newly generated contiguous stereocentres (C1, C4 and C5) were determined from the high field ^1H NMR, ^{13}C DEPT, TOCSY. However, in order to confirm the assignment, the isoxazolidine **3** was converted to the di-acetyl derivative **4** and the coupling constant information was derived from proton decoupling experiments. In both the compounds **3** and **4**, the high value of $J_{1,5}$ (~9.3 Hz) indicated the five membered *cis* ring fusion. The relative *trans* stereochemical assignment between H-4 and H-5 was established by the low value of $J_{4,5}$ (~4.5 Hz). Similarly, the small values for $J_{5,6}$ (~5.2 Hz) and $J_{1,8}$ (~5.1 Hz) indicated the *trans* relative stereochemistry H-5, H-6 and H-1, H-8, respectively.[¶] The geometry of the starting compound ensures that the substituents at C-6, C-7 and C-7, C-8 are *trans* related supporting the structure

[§] The coupling constant information of isoxazolidine **3** was found to be in good agreement with those reported by Ferrier et al.[4b] for the closely related compound in which they assigned a *cis* configuration at the ring junction and a *trans* relationship between the cyclopentyl substituents at C-1 and C-8 and at C-5 and C-6.

[¶] Selected physical data for **3**: white solid, mp = 135°C, $[\alpha]_D = -22.5$ (*c* 0.32, $CHCl_3$); $R_f = 0.37$, (ethyl acetate:hexane = 6:4); ν_{max} (Nujol) 3600–3240 (br.), 1699 cm^{-1}. δ_H ($CDCl_3$, 300 MHz): δ 1.29 (3H, t, $J = 7.0$ Hz, CH_3), 1.57–2.10 (2H, bs, exchanges with D_2O, OH), 3.20 (1H, ddd, $J = 9.3$, 5.2, 4.8 Hz, H-5), 3.44–3.54 (1H, m, H-1), 3.72 (1H, t, $J = 7.6$ Hz, H-7), 3.91 (1H, d, $J = 13.0$ Hz, NCH_2Ph), 3.96–4.04 (1H, m, H-8) 4.13 (1H, dd, $J = 7.6$, 5.2 Hz, H-6), 4.24 (2H, q, $J = 7.0$ Hz, OCH_2CH_3), 4.39 (1H, d, $J = 13.0$ Hz, NCH_2Ph), 4.48 (1H, d, $J = 4.8$ Hz, H-4), 4.73 (2H, ABq, $J = 12.0$ Hz, OCH_2Ph), 7.18–7.40 (10H, m, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.9, 52.4, 54.7, 61.6, 72.5, 74.6, 77.2, 81.2, 89.2, 126.8, 127.7, 127.8, 128.0, 128.2, 128.4, 136.4, 138.2, 171.1. Anal. calcd for $C_{23}H_{27}NO_6$: C, 66.81; H, 6.58. Found: C, 66.69; H, 6.32. For **4**: (ethyl acetate:hexane = 1:1); ν_{max} (Nujol) 1735 cm^{-1}. δ_H ($CDCl_3$, 300 MHz): 1.26 (3H, t, $J = 7.0$ Hz, CH_3), 1.94 (3H, s, CH_3), 2.06 (3H, s, CH_3), 3.33–3.40 (1H, bm, H-5), 3.57–3.65 (1H, bm, H-1), 3.98–4.10 (3H, bm, H-7, NCH_2Ph), 4.20 (2H, q, $J = 7.0$ Hz, OCH_2CH_3), 4.62 (2H, s, OCH_2Ph), 4.75 (1H, d, $J = 4.0$ Hz, H-4), 5.07 (1H, bt, $J = 5.5$ Hz, H-8), 5.25–5.32 (1H, bm, H-6), 7.20–7.38 (10H, m, Ar-H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.0, 20.8, 20.9, 29.7, 53.2, 53.4, 61.5, 72.2, 77.4, 81.1, 85.1, 127.3, 127.6, 127.7, 128.2, 128.3, 128.7, 136.6, 138.7, 169.4, 170.3, 170.7. Anal. calcd for $C_{27}H_{31}NO_8$: C, 65.18; H, 6.28. Found: C, 65.49; H, 6.02. For **6**: white solid, mp = 121°C, $[\alpha]_D = +16.2$ (*c* 0.25, $CHCl_3$); $R_f = 0.63$ (ethyl acetate:hexane = 1:1); ν_{max} (Nujol) 1735 cm^{-1}; δ_H ($CDCl_3$, 300 MHz): 1.97 (3H, s, CH_3), 2.04 (6H, s, CH_3), 2.78 (1H, ddd, $J = 9.3$, 5.3, 4.8 Hz, H-5), 3.38 (1H, bd, $J = 9.3$ Hz, H-1), 3.94 (1H, d, $J = 14.0$ Hz, NCH_2Ph), 4.08 (1H, t, $J = 5.9$ Hz, H-7), 4.12–4.18 (3H, m, CH_2OAc, NCH_2Ph), 4.38–4.44 (1H, m, H-4), 4.61 (2H, ABq, $J = 12.3$ Hz, OCH_2Ph), 5.07 (1H, t, $J = 5.8$ Hz, H-8), 5.15–5.22 (1H, bm, H-6), 7.20–7.40 (10H, m, Ar-H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.9, 21.0, 29.7, 53.6, 59.9, 63.7, 72.1, 72.4, 76.6, 80.0, 86.9, 127.3, 127.5, 127.6, 128.1, 128.2, 136.2, 137.5, 169.4, 170.1, 170.5. Anal. calcd for $C_{27}H_{31}NO_8$: C, 65.18; H, 6.28. Found: C, 65.39; H, 6.55. For **8**: white solid, mp = 118°C, $[\alpha]_D = +38.4$ (*c* 0.25, $CHCl_3$); $R_f = 0.34$ (ethyl acetate:hexane = 1:1); ν_{max} 3600–3220, 1741 cm^{-1}; δ_H ($CDCl_3$, 300 MHz): 2.00 (3H, s, CH_3), 2.05 (3H, s, CH_3), 2.07 (3H, s, CH_3), 2.09 (3H, s, CH_3), 2.10 (6H, s, CH_3), 2.78 (1H, ddd, $J = 7.6$, 7.9, 8.2 Hz, H-5), 4.06 (1H, dd, $J = 12.3$, 6.3 Hz, H-7a), 4.23 (1H, dd, $J = 12.3$, 3.3 Hz, H-7b), 4.58–4.68 (1H, m, H-4), 4.98–5.05 (2H, m, H-2, H-3), 5.24–5.36 (2H, m, H-1, H-6), 6.19 (1H, d, $J = 8.7$ Hz, exchanges with D_2O, NH). The assignment of protons was made by 2D ^1H COSY experiment. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.9, 21.0, 21.1, 21.2, 23.5, 44.9, 52.9, 63.9, 69.3, 76.5, 79.4, 81.5, 170.0, 170.1, 170.4, 170.8. Anal. calcd for $C_{19}H_{27}NO_{11}$: C, 51.23; H, 6.11. Found: C, 51.43; H, 6.30. For **9**: $[\alpha]_D = -19.1$ (*c* 0.20, MeOH); $R_f = 0.19$ (methanol:chloroform = 1:1); ν_{max} (Nujol) 3700–3060 (br.) cm^{-1}; δ_H (D_2O, 300 MHz): 2.14 (1H, ddd or apparent q, $J = 8.0$ Hz, H-5), 3.40–3.85 (7H, m). ^{13}C NMR (D_2O, 75 MHz): δ 43.8, 54.2, 64.4, 69.8, 73.8, 75.9, 79.4. Anal. calcd for $C_7H_{16}ClNO_5 \cdot 3H_2O$: C, 29.63; H, 7.81. Found: C, 29.25; H, 8.12.

3. The *cis* relationship of the -COOEt group at C-4 and the -OH functionality at C-6 was also indicated by the IR spectrum of isoxazolidine **3**. This showed a low value for the ester carbonyl (1699 cm^{-1}) indicating the presence of intramolecular hydrogen bonding. In agreement with this, in the acetate **4**, such hydrogen bonding is destroyed as -OH is converted to -OAc. The ester carbonyl now appeared only at 1735 cm^{-1}. In the subsequent step, reduction of the ester functionality in **3** with LAH in THF afforded alcohol **5** which was immediately acetylated to give the triacetate **6** as a white solid in 81% yield.¶ The concomitant reductive cleavage of the N–O bond and the hydrogenolysis of the benzyl groups in **6**, with 10% Pd/C using ammonium formate as a hydride donor in refluxing methanol, yielded the triacetylated amino alcohol **7** which on treatment with Ac_2O in pyridine gave peracetylated amino alcohol **8** as a white solid.¶ The structure and stereochemistry of the compound **8** was confirmed by 2D NMR experiments and the configurations were found to be 1*R*,2*S*,3*S*,4*R*,5*R*, and 6*R*. Treatment of **8** with methanol–HCl (0.5 M) at reflux for 40 h gave aminocyclopentitol **9** as a colourless, semisolid, amine-hydrochloride. The analytical and spectroscopic data¶ were found to be in agreement with the proposed structure **9**.

The overall two-step transformation of **2a** involves the in situ generation of an *N*-benzyl nitrone at the hemiacetal carbon, which spontaneously undergoes INOC leading to the formation of the kinetically controlled (fused) bicyclo[3.3.0]octyl derivative **3** over the (bridged) bicyclo[3.2.1]octane system **10**. We presume that the transition state (TS) **A** (Fig. 1) that assumes product-like geometry is stabilised by the significant σ overlap between the nitrone oxygen and C-6; and between C-1 and C-5 during the formation of these bonds in isoxazolidine **3**, with the *exo*-ethoxycarbonyl functionality, in a concerted pathway.[3,4,9] The steric destabilisation of the TS **B**, required for the formation of a strained ring system, presumably precludes the formation of bridged bicyclo[3.3.1]octane derivative **10**. In TS **A** the C–N sigma bond has an equatorial-like disposition, while in TS **B** this bond has an axial-like disposition.

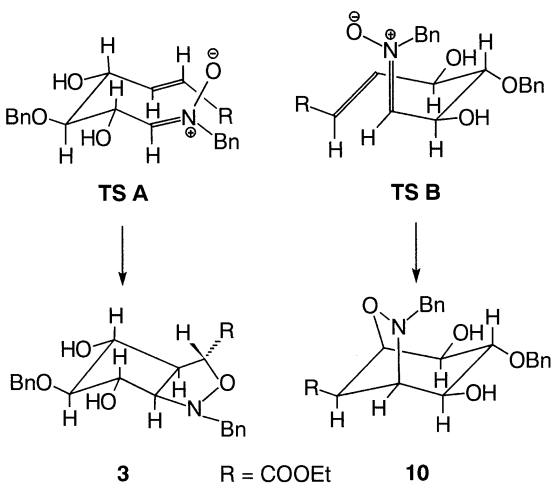

Figure 1.

In conclusion, we have demonstrated that the easily available D-glucose derived α,β-unsaturated ester **2a** could be easily converted to the hydroxy-functionalised 4-*exo*-ethoxycarbonyl-3-oxa-2-aza bicyclo[3.3.0]octyl derivative **3** via the INOC pathway. The isoxazolidine **3** thus obtained was transformed in to the hitherto unknown aminocyclopentitol **9** in good yield. The easy availability of starting material, few steps and high yield of the products makes this approach practicable, even on a multi-gram scale.

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