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cis-Stereoselective SmI_2-promoted reductive coupling of keto-nitrones: first synthesis of 1-epitrehazolamine

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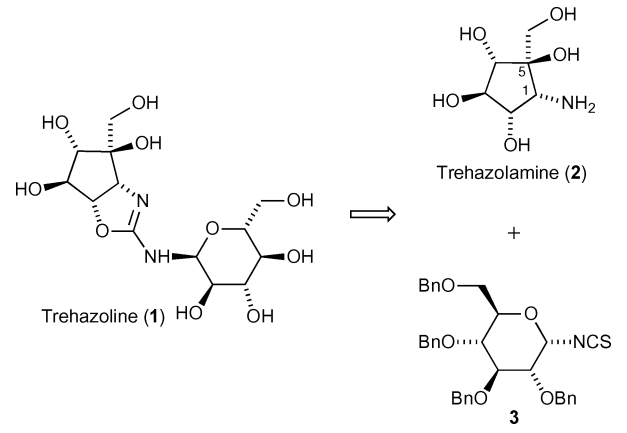
An expeditious synthesis of 1-epitrehazolamine is presented from readily available 2,3,4,6-tetra-*O*-benzyl-D-glucose. The key step involves a samarium diiodide-promoted reductive cyclization of a masked keto-nitrone to form a five-membered ring aminocyclitol. The excellent *cis* selectivity observed in this nitrone–ketone reductive coupling contrasts surprisingly with the *trans* selectivity of ketone–oxime reductive couplings.

Important efforts in the search for novel aminocyclopentitols[1] have been stimulated since this class of compounds has been recognized as modulators of the activity of glycoprocessing enzymes.[1,2] In addition to their implication in specific cell-surface recognition and invasion processes, glycoprocessing enzymes have also been considered carefully as targets for agrochemicals since the discovery in 1991 of trehazoline, isolated from a culture broth of *Micromonospora* sp. SANK 62390[3] and from *Amycolatopsis trehalostatica*.[4]

Trehazoline (**1**) is a pseudodisaccharide in which α-D-glucose is linked to an aminocylopentitol, the trehazolamine (**2**), by an isourea functionality (Scheme 1). Until now, trehazoline has been the best inhibitor (active at nanomolar concentrations) of trehalase, an enzyme (EC 3.2.1.28) that is essential for survival of insects, fungus and nematodes.[5]

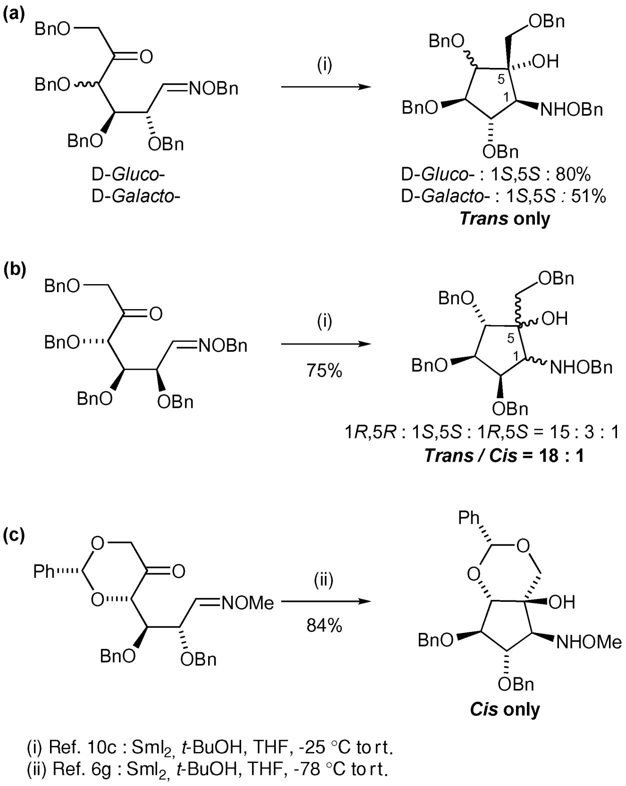


Scheme 1

Although several syntheses of trehazoline (**1**),[6] trehazolamine (**2**)[7] and structural analogues[8] have been reported, 1-epitrehazolamine has not been prepared to date.[9]

One of the most extensively investigated approaches for the synthesis of aminocyclopentitols is the SmI_2-promoted reductive coupling of a ketyl radical anion with an oxime functionality, that affords generally *trans*-aminocyclitols as the sole or major products (Scheme 2, eqn. (a) and (b)).[6h,10] In one case however (Scheme 2, eqn. (c)), a *cis*-aminocyclitol was obtained, resulting apparently from conformational restriction in the starting 5,6-benzylidene ketal-protected keto-oxime.[6g]

Recently, we have disclosed our results on the first SmI_2-promoted cross-coupling of nitrones with carbonyl compounds.[11,12] Evidence was found for the prior reduction of nitrones by SmI_2 followed by coupling of the resulting species to the carbonyl compounds, the process involving an umpolung of the C=N bond of nitrones.[13]



Scheme 2 Stereochemical outcome of the SmI_2-promoted intramolecular reductive coupling of ketone aldoxime ethers.

Surprisingly, in our first examples of intramolecular nitrone–carbonyl couplings,[11,14] products exhibiting a *cis* relationship at the new stereocenters were the only detected. This remarkable selectivity intrigued us and motivated our study of this reaction in the case of highly functionalized, carbohydrate-derived substrates. Herein, we report our preliminary results in this field, that allowed the stereoselective synthesis of 1-epitrehazolamine (**11**) from a new D-glucose-derived keto-nitrone (Scheme 3).

The commercially available 2,3,4,6-tetra-*O*-benzyl-D-glucose (**4**) was readily reduced by $NaBH_4$ to the corresponding glucitol **5**.[15] Swern oxidation then afforded the keto-aldehyde **6**,[6g] that was not isolated (this compound being prone to hydration) but instead was treated directly with one eq. of *N*-benzylhydroxylamine.[16] The formation of the nitrone proved completely regioselective (on the aldehyde *versus* ketone) and the presumed keto-nitrone **7** was isolated in good yield (81% for two steps) as a stable, white powder. However, careful analysis of this product revealed that its actual structure was not **7** but its hydrated counterpart **8**,[17] isolated as a single isomer. The

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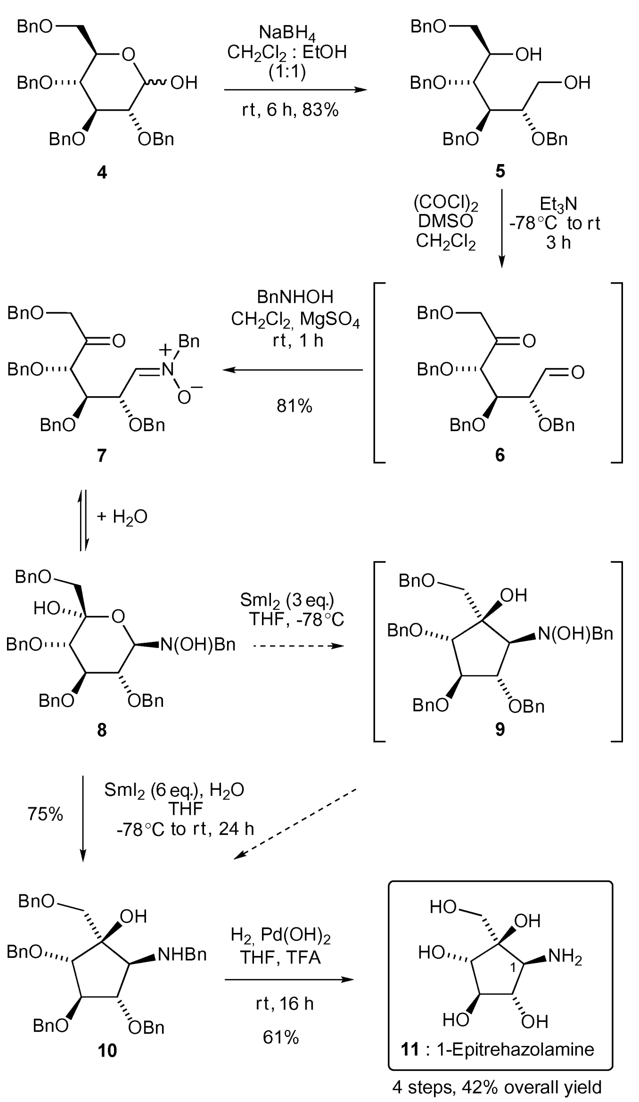

Scheme 3

configuration of **8** was assigned by comparison to related compounds described in the literature.[18]

In previous work, we demonstrated that the presence of water in reaction mixtures was not detrimental to the SmI_2-induced selective reduction of nitrones and subsequent reductive couplings, and even proved beneficial in several cases.[13] Therefore, compound **8** was treated with SmI_2[19] (3 eq.) to induce intramolecular reductive coupling of the masked keto-nitrone **7**. However, at −78 °C the reaction did not lead to complete disappearance of the starting material after 6 h, while several products appeared on TLC of the reaction mixture. Further analysis showed that over-reduction of the expected *N*-hydroxylamine to the corresponding amine was competing with the reductive cyclization of the starting material. Next, the reaction was performed with an excess of SmI_2 (6 eq.) and the temperature was allowed to raise to room temperature to complete the transformation of hydroxylamine **9** to the amine **10**.† Under these conditions, the aminocyclitol **10** was isolated in 75% yield.[20] Crystals of this product could be obtained (by slow evaporation of a 95 : 5 cyclohexane–CH_2Cl_2 solution) from which X-ray analysis allowed unequivocal assignement of its structure (Fig. 1).[21]

Thus, it was verified that SmI_2-mediated cyclization of the masked keto-nitrone **8** yielded exclusively the corresponding aminocyclitol exhibiting a *cis* relationship (1*S*,5*S*) at the new stereocenters. While four stereoisomers could have arisen from this coupling only one was obtained, in which the amino and the hydroxy groups are *cis* relative to each other and *trans* relative to their vicinal alkoxy neighbouring groups. This stereochemical feature supports the involvement of a chelated transition state for the reaction (Fig. 2).

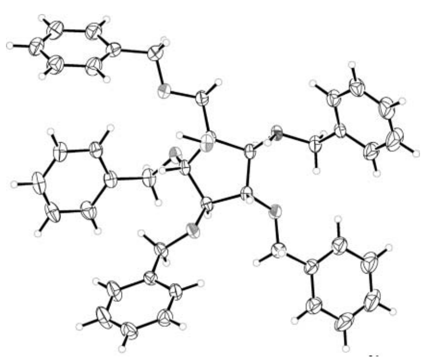

Fig. 1 X-Ray analysis of compound **10**.[21]

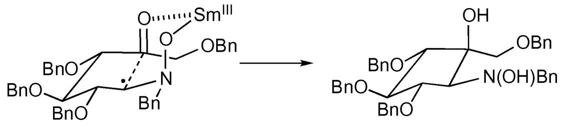

Fig. 2 Proposed chelated transition state for SmI_2-mediated intramolecular nitrone–ketone pinacolic coupling.

While the reductive cyclization of keto-oxime ethers is thought to involve the initial formation of a ketyl radical anion that adds to the C–N double bond of the oxime functionality, we propose that in the present case the initial SET from SmI_2 occurs on the nitrone functionality, in which the basic oxygen atom can strongly coordinate samarium. Such coordination probably facilitates an inner sphere electron transfer to the C–N bond, to produce a radical anion species. Formation of a six-membered chelate in such an intermediate is likely, which would explain the exceptional stereoselectivity of the addition to the carbonyl group, leading to the production of vicinal *cis*-amino alcohols.

Complete debenzylation of **10** by hydrogenation over Pearlman catalyst in the presence of trifluoroacetic acid then produced 1-epitrehazolamine (**11**) in 61% yield.[22]

In conclusion, a stereoselective synthesis of 1-epitrehazolamine has been accomplished in only four steps from 2,3,4,6-tetra-*O*-benzyl-D-glucose (**4**) and in a 42% overall yield. The transformation of 1-epitrehazolamine to the corresponding analogue of trehazoline for biological evaluation is currently underway. This work illustrates once again the versatility of SmI_2 as a selective reducing agent. Fine tuning of reactivity can be achieved with this reagent by using two types of molecules, nitrones and oximes, which are often considered as interchangeable imine equivalents.

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Notes and references

† *Typical procedure for the preparation of aminocylopentitol* **10**: a stirred and carefully deoxygenated solution of the hydrated, masked keto-nitrone **8** (0.30 g, 0.455 mmol) in dry THF (59 mL) was cooled to −78 °C under argon. A solution of SmI_2 (0.08 M) in THF (61 mL, 4.08 mmol) was added dropwise, at −78 °C. After stirring the reaction mixture for 2 h at −78 °C, the temperature was slowly raised to room temperature. After 15 h, the reaction was complete. Aqueous saturated $Na_2S_2O_3$ (40 mL) was added and, after stirring for 15 min, the aqueous phase was extracted with EtOAc (3 × 40 mL). The combined organic extracts were washed with aqueous NaCl (40 mL), dried over $MgSO_4$,

filtered and concentrated *in vacuo*. The crude residue was purified by chromatography on silica gel (AcOEt–pentane 1 : 4), to afford the aminocyclitol **10** (0.287 g, 75%) as a white solid.[20]

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9 An *N*-alkoxy-derivative of 1-epitrehazolamine was obtained by SmI_2-promoted reductive cyclization of a 5,6-benzylidene ketal protected keto-oxime: see reference 6g.

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17 Spectral data for compound **8**: white solid, mp 89–90 °C; $[\alpha]_D^{25}$ −24 (*c* 1.73, $CHCl_3$). IR (CH_2Cl_2): 3061, 3037, 2922, 2873, 1608, 1502, 1461, 1355, 1273, 1102, 1077 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 3.55 (d, 1H, J = 10.6 Hz, CH_2OBn), 3.57 (dd, 1H, J = 3.3 Hz and J = 8.3 Hz, *CH*(OBn)CHN), 3.68 (d, 1H, J = 7.8 Hz, *CH*(OBn)C(OH)OCHN), 3.81 (d, 1H, J = 12.2 Hz, NCH_2Ph), 3.98 (d, 1H, J = 10.6 Hz, CH_2OBn), 4.10 (dd, 1H, J = 7.8 Hz and J = 8.3 Hz, *CH*(OBn)CH(OBn)CHN), 4.16 (d,1H, J = 12.2 Hz, NCH_2Ph), 4.26 (d, 1H, J = 11.8 Hz, OCH_2Ph), 4.44 (d, 1H, J = 11.8 Hz, OCH_2Ph), 4.54 (d, 1H, J = 11.8 Hz, OCH_2Ph), 4.64 (d, 1H, J = 11.8 Hz, OCH_2Ph), 4.66 (d, 1H, J = 11.3 Hz, OCH_2Ph), 4.77 (d, 1H, J = 11.1 Hz, OCH_2Ph), 4.79 (d, 1H, J = 11.3 Hz, OCH_2Ph), 4.81 (d, 1H, J = 3.3 Hz, CHN(OH)Bn), 4.91 (d, 1H, J = 11.1 Hz, OCH_2Ph), 7.02–7.05 (m, 2H, $CH_{arom.}$), 7.19–7.33 (m, 21H, $CH_{arom.}$), 7.34–7.41 (m, 2H, $CH_{arom.}$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 62.2 (NCH_2Ph), 68.6 (CH_2OBn), 72.6 (OCH_2Ph), 73.8 (OCH_2Ph), 74.6 (OCH_2Ph), 75.5 (OCH_2Ph), 79.7 (*CH*(OBn)CHN), 80.6 (*CH*(OBn)CH(OH)OCHN), 83.1 (*CH*(OBn)CH(OBn)CHN), 89.9 (*CH*N(OH)Bn), 107.7 (*C*(OH)CH_2(OBn)), 127.5, 127.7, 127.8, 127.9, 128.2, 128.3, 128.4, 128.4, 128.5 and 128.6 (25 × $CH_{arom.}$), 135.9, 137.5, 137.7, 138.3 and 138.7 (5 × $C_{arom.}$). LRMS (DCI) *m/z*: 644.3 $(M + H)^+$; 362.1 $(M + H–BnOH)^+$. Anal. calcd for $C_{41}H_{43}NO_7$: C, 76.49; H, 6.42; N, 2.18. Found: C, 76.25; H, 6.33; O, 2.17%.

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20 Spectral data for compound **10**: $[\alpha]_D^{25}$ −15 (*c* 2.10, $CHCl_3$). IR (CH_2Cl_2): 3527, 3412, 3094, 3069, 3029, 2873, 1608, 1502, 1453, 1355, 1273, 1216, 1086, 1029 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 3.19 (d, 1H, J = 7.3 Hz, *CH*NHBn), 3.58 (d, 1H, J = 9.9 Hz, CH_2OBn), 3.62 (d, 1H, J = 9.9 Hz, CH_2OBn), 3.66–3.70 (m, 1H, CH(OBn)*CH*(*OBn*)CHN), 3.80 (s, 2H, NCH_2Ph), 3.83–3.91 (m, 2H, *CH*(OBn)*CH*(OBn)C(OH)CH_2OBn), 4.51 (d, 1H, J = 11.9 Hz, *O*CH_2Ph), 4.53 (d, 1H, J = 12.3 Hz, OCH_2Ph), 4.55 (d, 1H, J = 12.0 Hz, OCH_2Ph), 4.57 (d, 1H, J = 11.9 Hz, OCH_2Ph), 4.63 (d, 1H, J = 12.3 Hz, OCH_2Ph), 4.65 (d, 1H, J = 11.9 Hz, OCH_2Ph), 4.71 (d, 1H, J = 12.0 Hz, OCH_2Ph), 4.75 (d, 1H, J = 11.9 Hz, OCH_2Ph), 7.20–7.33 (m, 25H, $CH_{arom.}$). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 52.7 (NCH_2Ph), 63.2 (*CH*NHBn), 72.1 (OCH_2Ph), 72.4 (OCH_2Ph), 72.9 (OCH_2Ph and CH_2OBn), 73.8 (OCH_2Ph), 76.7 (*C*(OH)CH_2(OBn), 85.3, 85.7 and 88.8 (3 × *CH*(OBn)), 127.0, 127.5, 127.6, 127.7, 127.8, 127.8, 128.2, 128.3, 128.3, 128.4 (25 × $CH_{arom.}$), 138.2, 138.3, 138.4, 138.4 and 140.1 (5 × $C_{arom.}$). LRMS (DCI) *m/z*: 630.4 $(M + H)^+$. Anal. calcd for $C_{41}H_{43}NO_6$: C, 78.19; H, 6.88; N, 2.22. Found: C, 78.22; H, 6.73; N, 2.21%.

21 Crystal data for compound **10**: $C_{41}NO_5H_{43}$, $M = 629.79$, orthorhombic, a (Å) = 5.225(2), b (Å) = 15.283(9), c (Å) = 43.03(1), U = 3436(2) $Å^3$, D ($g.cm^{-3}$) = 1.217, T = 293 K, space group $P2_12_12_1$, $Z = 4$, λ (Å) = 0.71073, 2θ max (deg) = 50, μ (cm^{-1}) 0.79, 15 992 reflexions measured, 6994 unique ($R_{int} = 0.06$), 424 parameters, reflections–parameters ratio: 12.9, $R(F)[I > 2\sigma(I)]$ = 4.8%, $R_W(F)$ [all data] = 5.1%, G. O. F. = 1.84‡.

22 Spectral data for compound **11**: oil, $[\alpha]_D^{25}$ +3 (*c* 0.5, H_2O). IR (neat): 3527, 3412, 3094, 3069, 3029, 2873, 1608, 1502, 1453, 1355, 1273, 1216, 1086, 1029 cm^{-1}. ^1H NMR (300 MHz, D_2O) δ: 3.50 (d, 1H, J = 9.3 Hz, *CH*NH_2), 3.72–3.82 (m, 3H, CH_2OH and *CH*(OH)CHNH_2), 3.96 (d, 1H, J = 7.7 Hz, *CH*(OH)C(OH)CH_2OH), 4.05 (dd, 1H, J = 7.7 Hz and J = 8.1 Hz, *CH*(OH) CH(OH)C(OH)CH_2OH). ^{13}C NMR (75 MHz, D_2O) δ: 57.4 (*CH*NH_2), 64.4 (CH_2OH), 74.7 (*CH*(OH)), 75.4 (*C*(OH)CH_2OH), 78.7 (*CH*(OH)), 81.6 (*CH*(OH)). LRMS (DCI) *m/z*: 179.9 $(M + H)^+$.