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Synthesis of a novel *N*-hydroxypyrrolidine using enzyme catalysed asymmetric carbon–carbon bond synthesis

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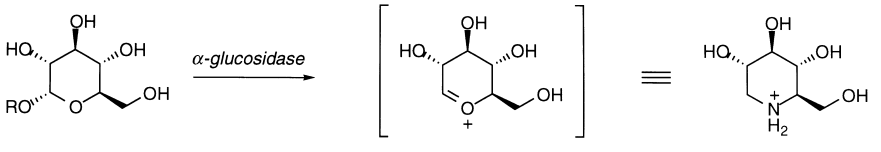
Abstract

N-Hydroxypyrrolidine **5** has been prepared in nine steps starting from 3-*O*-benzylglyceraldehyde **13**. The synthetic route employs *Escherichia coli* transketolase mediated C–C bond synthesis to establish the absolute stereochemistry and a subsequent ring contraction of a 1,2-oxazine **17** to provide the *N*-hydroxypyrrolidine nucleus.

Keywords: imino sugars; transketolase; asymmetric carbon–carbon bond synthesis.

The class of compounds known as 1,1-dideoxyiminoalditols, in which the ring oxygen atom of a sugar is replaced by NH, have proven to be potent inhibitors of a wide range of glycosidases. For example, deoxynojirimycin **1** is a powerful inhibitor of α-glucosidases.[1] The mechanistic basis for the inhibition is believed to be due to a combination of the structural similarity between **1** and D-glucosides **2**, and also the ability to mimic the oxonium ion intermediate **3** by protonation on the nitrogen atom.



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Many types of imino sugars have been reported in the past few years, each with a different spectrum of activity against a range of glycosidases. Recently the synthesis of some *O*-alkylated *N*-hydroxypiperidines **4** was described and the compounds shown to be active against glycosidases.[2]

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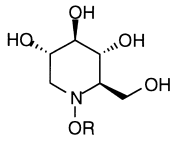
Herein we describe the first synthesis of an *N*-hydroxypyrrolidine **5** which has the same peripheral stereochemistry found in D-glucose.



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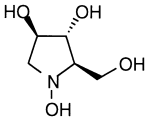

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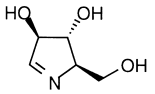

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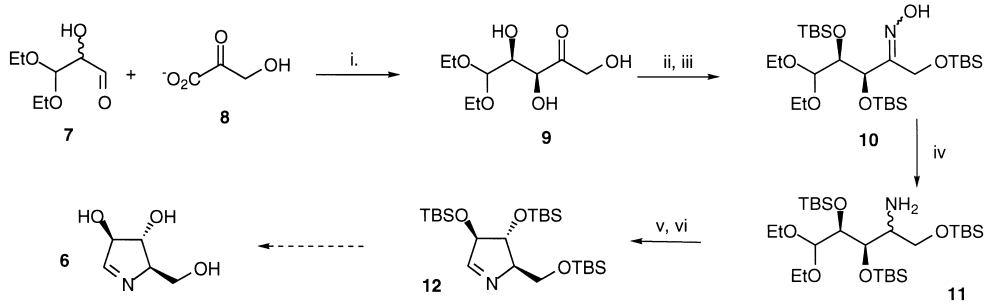
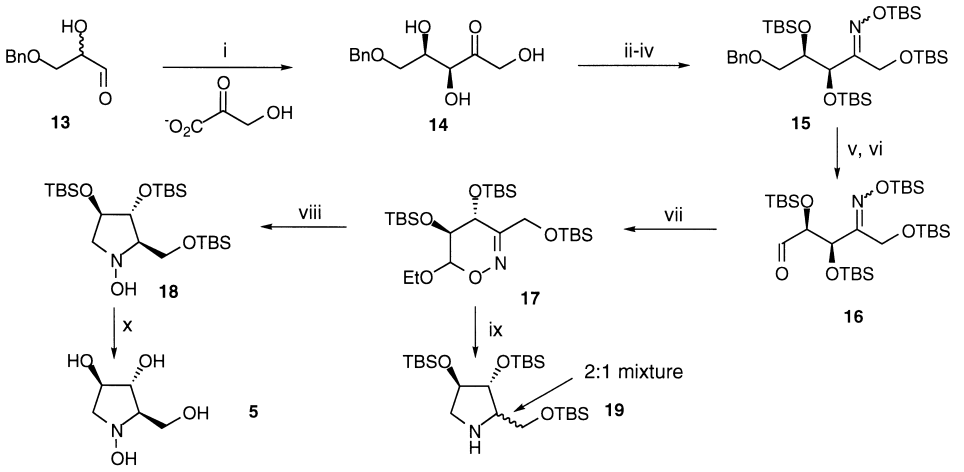
The synthesis of **5** arose out of an attempt to prepare the related imino sugar nectrisine **6**. Our initial planned route to **6** is shown in Scheme 1. Transketolase mediated condensation of (±)-3,3-diethoxy-2-hydroxypropanal **7**[3] with hydroxypyruvate **8** afforded the triol **9** in 56% yield (based on the reactive enantiomer) which was silylated using TBSOTf and Et_3N (74%) followed by treatment with hydroxylamine hydrochloride and $KHCO_3$ in methanol to give the oxime **10** in 82% yield. Reduction of oxime **10** using Raney® nickel proved capricious giving yields of the diastereomeric mixture of amines **11** of up to 65%. The unreliability of the oxime reduction inevitably presented a major obstacle to the successful synthesis of nectrisine, and severely limited the availability of material for subsequent studies. The mixture of diastereomeric amines **11** was readily cyclised (97%) by treatment with iodotrimethylsilane in anhydrous CH_2Cl_2 to give a 3:2 mixture of cyclic imines from which the major diastereomer **12**, bearing the stereochemistry found in nectrisine **6**, was isolated. Unfortunately, treatment of protected imine **12** under a range of desilylation conditions (e.g. TBAF; $AcOH/H_2O/THF$; fluoride resin; HF/acetonitrile) failed to yield a pure sample of nectrisine.



Scheme 1. Reagents: (i) transketolase, TPP, Mg^{2+}, pH 7.0 (pH stat); (ii) TBSOTf, Et_3N; (iii) $NH_2OH{\cdot}HCl$, $KHCO_3$; (iv) H_2/Raney Ni; (v) TMSI; (vi) SiO_2 chromatography

In view of the problems with the oxime reduction step we turned our attention to an alternative route that began with transketolase mediated coupling of (±)-3-*O*-benzylglyceraldehyde **13** with hydroxypyruvate yielding 5-*O*-benzyl-D-xylulose **14**[4] in 80% yield on a 2–3 g scale (Scheme 2). Triol **14** was converted to silylated oxime **15** by a sequence of silylation (TBSOTf, Et_3N, 83% yield), oxime formation (hydroxylamine hydrochloride, $KHCO_3$, 71% yield, 2:1 mixture of (*E*)-and (*Z*)-geometric isomers) and finally treatment with TBSOTf and Et_3N (95% yield). Debenzylation of oxime ether **15** proved surprisingly problematic. The most effective catalyst proved to be 10% palladium-charcoal which resulted in complete debenzylation of **15** within 24 h under an atmosphere of H_2, though appreciable amounts of catalyst (40–50 weight%) were found to be necessary to obtain a rapid, efficient conversion. The alcohol product was isolated by filtration

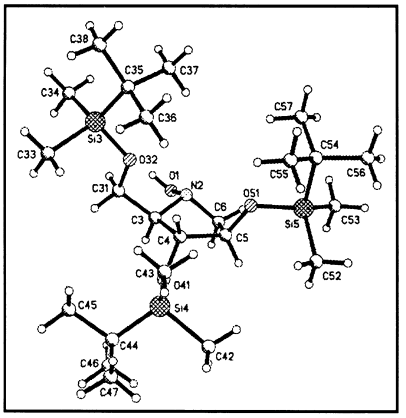
of the reaction mixture through Celite® and found to be >90% pure by ^{1}H and ^{13}C NMR analysis (^{1}H NMR suggesting an 1:1 mixture of double bond isomers), and was isolated in near-quantitative yield as a clear or yellow oil which slightly solidified after prolonged evacuation on a high-vacuum line. Oxidation of the alcohol was accomplished either under Swern conditions (40–60%) or by using NaOCl and TEMPO (cat.) in a two-phase reaction mixture (66%) to give aldehyde **16**.

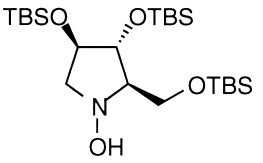


Scheme 2. Reagents: (i) transketolase, TPP, Mg^{2+}, pH 7.0 (pH stat); (ii) TBSOTf, Et_3N; (iii) $NH_2OH{\cdot}HCl$, $KHCO_3$ (iv) TBSOTf, Et_3N (v) H_2/Pd; (vi) NaOCl, TEMPO or Swern; (vii) $(EtO)_3CH$, *p*TsOH; (viii) $NaCNBH_3$; (ix) H_2/Pd (x) HF

The aldehyde **16** was then treated with triethyl orthoformate and *p*-toluenesulfonic acid (cat.) in EtOH with the intention of preparing the corresponding diethyl acetal although the reaction resulted in the unexpected formation of the oxazine **17**. Assignment of the 1,2-oxazine structure **17** was made on the basis of the following evidence. ^{1}H NMR integrals were consistent with the presence of three TBS groups and a single ethoxy group per molecule; a molecular ion of *m*/*z* 534 [MH^+] consistent with the molecular formula $C_{25}H_{55}NO_5Si_3$ was observed in the CI mass spectrum; furthermore a C=N stretch at ν_{max} 1585 cm^{-1} (comparable to that reported for the C=N stretches of a range of unsaturated 1,2-oxazines[5]) was observed, implying that addition or other reaction across the oxime double bond had not taken place.[6]

Reduction of 1,2-oxazines using hydrogenation over Raney® nickel[7] had been shown to yield highly-substituted five-membered heterocycles (proline analogues), useful in the synthesis of ACE inhibitors. Treatment of 1,2-oxazine **17** under analogous conditions yielded the trisilylated derivatives **19** as a mixture of diastereomers (2:1) in 59% overall yield. Of potentially greater interest, however, were reductive processes which did not cleave the N–O bond, and consequently left the oxazine ring structure intact. The reduction of the C=N bond of 6-silyloxy-and 6-alkoxy-1,2-oxazines with sodium cyanoborohydride in acetic acid has been reported to proceed without cleavage of the N–O bond.[8] Reduction of 1,2-oxazine **17** with sodium cyanoborohydride in acetic acid yielded the *N*-hydroxypyrrolidine **18** as a single diastereoisomer and crystalline solid (37%). The X-ray structure of **18** (R-factor of 18%) showed unambiguously that a ring contraction had occurred and that the product contained a five-membered ring. The stereochemistry at the new chiral centre in the product was clearly shown to be (*R*), with all substituents adopting a pseudo-equatorial arrangement about the five-membered ring (Fig. 1).





18

Figure 1. X-Ray structure of protected *N*-hydroxypyrrolidine **18**

Ring contractions of 1,2-oxazines upon treatment with $NaBH_3CN$ have not previously been reported. However similar processes have been observed under acidic conditions[9] yielding nitrones or pyridine *N*-oxides, depending on the nature of the substituent at C-6 of the oxazine, and in the reduction of 6-silyloxy-1,2-oxazines under aprotic conditions using DIBAL-H to yield *N*-hydroxypyrrolidines.[10]

Finally desilylation of **18** was achieved by treatment with aqueous HF in 1:1 acetonitrile/THF which yielded the fully desilylated product **5** in quantitative yield.[11] Evaluation of the activity of **5** as a glycosidase inhibitor is currently in progress.

Acknowledgements

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3. Synthesis of aldehyde **7**: glyceraldehyde diethyl acetal (2.41 g, 14.7 mmol) and TEMPO (50 mg, 0.33 mmol) were dissolved in 1:1 ethyl acetate/toluene (160 cm^3) and cooled to 0°C with stirring. Benzyl trimethylammonium chloride (523 mg, 2.81 mmol), NaBr (335 mg, 3.25 mmol) and saturated aqueous $NaHCO_3$ (35 cm^3) were added. The resulting two-phase mixture was treated dropwise with a solution made up of 1.1 M NaOCl solution (15 cm^3), saturated aq. $NaHCO_3$ (15 cm^3) and brine (20 cm^3) (solution pH 8.6) over a 1 h period, at a rate just sufficient to maintain a yellow colour in the solution. Upon completion of addition of buffered NaOCl, the mixture was subjected to continuous extraction with EtOAc for 15 h. The organic layer was separated, washed with saturated aq. $NaHCO_3$ (20 cm^3) and brine (20 cm^3), dried ($MgSO_4$), concentrated in vacuo, and purified by chromatography on silica [EtOAc (neat)]. The aldehyde (±)-**7** was isolated as a yellow-orange oil: 409 mg (17%); δ_H (300 MHz; D_2O) 1.26 (6H, t, *J* 6.0, CH_3), 3.57 (1H, dd, *J* 4.0 and 5.5, CH(OD)), 3.59–3.73, 3.74–3.90 (4H, m, CH_3CH_2), 4.64 (1H, d, *J* 5.5, $CH(OEt)_2$), 5.07 (1H, d, *J* 4.0, $CH(OD)_2$); δ_C (75.5 MHz; D_2O) 13.8, 13.9 (CH_3), 64.0, 64.1 (CH_3CH_2), 72.9 (CH(OD)), 88.5 ($CH(OD)_2$), 101.7 ($CH(OEt)_2$). Jung, M. E.; Andrus, W. A.; Ornstein, P. L. *Tetrahedron Lett*. **1977**, *18*, 4175.

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11. Experimental data for *N*-hydroxypyrrolidine **5**: δ_H (200 MHz; D_2O) 2.69 (1H, dt, J 6.5, 11.0, 2-H), 3.08 (2H, d, J 7.5, 5-H), 3.66 (2H, d, J 6.5, CH_2O_H), 3.75 (1H, dd, J 5.5, 11.0, 3-H), 4.05 (1H, m, 4-H); δ_C (150.8 MHz; D_2O) 59.6, 63.0, 74.7, 75.1, 77.4; *m*/*z* (CI) 150 [MH^+], 98, 82; (Found: *m*/*z* (CI) [MH^+] 150.0766. $C_5H_{11}NO_4$ requires *m*/*z* (CI) [MH^+] 150.0766).