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An *all-cis* 3,4-Dihydroxy-5-aminopiperidine by a Novel Route to Deoxydiamino Sugars

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Abstract: An (*L*)-diaza-1,6-dideoxytalose **7** as a first example of a new synthetic concept for aminodeoxy sugars by destruction of the 5-membered heterocyclic ring of condensed pyridones derived from natural amino acids and an o-bromo-bromomethyl 5-membered heterocycle is reported.

Chiral piperidines with hydroxy and eventually amino substituents are of broad interest as azasugars and as alkaloides. They also exhibit interesting biological activities.[1,2] Known syntheses of this class of compounds are commonly based on sugars as starting material but there are also a number of syntheses starting with naturally occurring amino acids and their derivatives.[3] We report now a first example of a novel approach to enantiopure aminohydroxypiperidines using biogenic α-amino acids as chiral precursors making use of a straight forward synthesis of optically active condensed dihydropyridin-3-ones by reaction of o-bromo-bromomethylaromatics or heterocycles with α-amino esters recently developed in our group.[4] Thus N-alkylation of the N-benzenesulphonyl-alanine methyl ester **1** with 5-bromo-4-bromomethyl-2-phenyloxazole **2** and and cyclisation of the resulting oxazolylamino ester by bromo-lithium exchange gave the oxazolo[4.5-c]pyridone **3**. Reduction of the keto function with $NaBH_4$ allowed stereoselective formation of the *cis*-hydroxy product **4** (*anti*-attack with respect to the methyl group). Since all attempts failed to cleave the oxazole ring reductively,[5] e. g. by catalytic hydrogenation or by sodium in boiling ethanol, or by hydrolysis compound **4** was transformed to the more reactive N-methyloxazolium salt **5**. A modified procedure using 1M aqueous KOH rather than the commonly used aqueous NH_3 [6] turned out to be advantageous to cleave the oxazole ring of **5** hydrolytically creating the third chiral centre again in the *cis* configuration (i. e. *anti*-attack of a proton under formation of **6**). Finally smooth reduction of the keto group of **6** with $NaBH_4$ occurred again in an *anti*-fashion with respect to the other substituents at the ring thus affording the all-*cis* product **7** in enantiomerically pure form representing a (*L*)-diaza-1,6-dideoxytalose. [7] As far as we could find out compound **7** represents the first diazahexose of this configuration.

Investigations of other heterocyclic rings as precursors for heteroatom substituents to the piperidine ring as well as possibilities to synthesise products similar to **7** but with other configurations, e. g. by changing the configuration of the hydroxy group in **4** or with other protective groups are currently underway.

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Dedicated to Professor Dr Henk van der Plas on the occasion of his 70th birthday.

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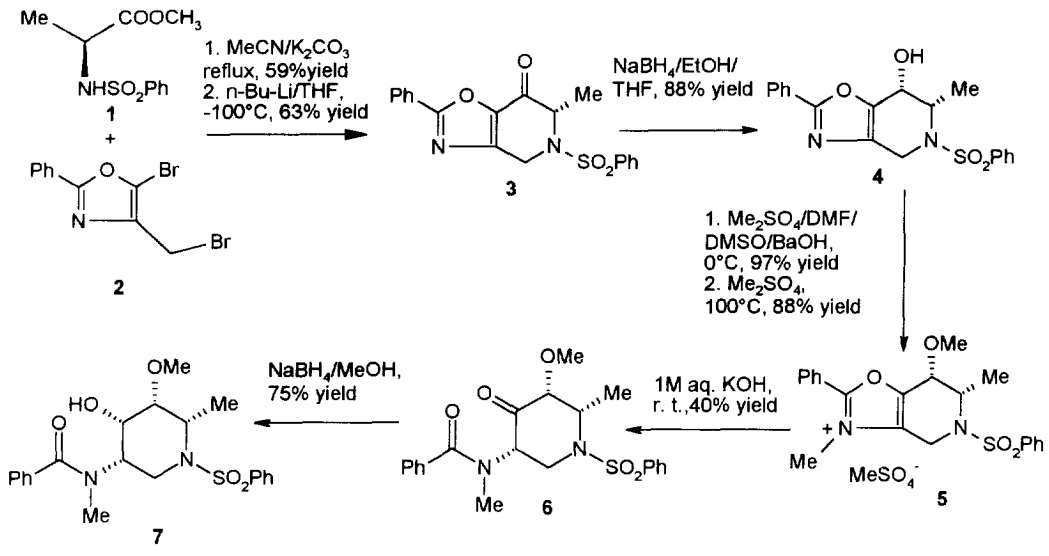

References and Notes

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7. e.e. > 99% (HPLC) *Selected data* for 7: Colourless crystals; mp. 142-143°C (EtOAc/hexane=2/1); $[\alpha]_D^{20} = -14.1$ (c=1, MeOH); δ_H(300 MHz; CD_3COCD_3/Hz) 1.18 (d, J=7.02, 3H, CH_3);); 2.89(s, CHNC$\underline{H}_3$); 3.10(s, CHOC$\underline{H}_3$); 3.32(m C$\underline{H}$OCH$_3$); 3.69(t, J=12.26, 1H, C$\underline{H}$-OH); 3.83(m, C$\underline{H}$-NCH$_3$); 3.88-4.37, (dd, J=4.96, CH_2N); 4.30(m, 1H, C$\underline{H}$CH$_3$); 7.43 (2xCH$_{ar}$); 7.45(2xCH$_{ar}$); 7.64(CH$_{ar}$); 7.66(2xCH$_{ar}$); 7.73(CH$_{ar}$); 7.88 (2xCH$_{ar}$); δ_C(75 MHz; CD_3OD) 13.6 (CH_3); 36(NCH_3); 38 0(CH_2N); 52.0(C$\underline{H}$-NCH$_3$); 54.0(C$\underline{H}$-CH$_3$); 57.2(CH-OC$\underline{H}_3$); 72.0(C$\underline{H}$-OH) 79.7 (C$\underline{H}$-OCH$_3$); 128.4(2xCH$_{ar}$); 130.1(2xCH$_{ar}$); 131 (2xCH$_{ar}$); 131.3 (2xCH$_{ar}$); 134.4 (CH$_{ar}$); 138.0 (CH$_{ar}$); 144.0 (CS); 175.0 ($CONCH_3$). The relative configuration was confirmed by X-.ray crystal analysis of racemic **7** obtained from racemic rather than from enantiopure **3**.

   Full details of the structure determination of racemic have been deposited at the Fachinformationszentrum Karlsruhe, Gesellschaft für Wissenschaftlich-technische Information mbH, D-76344 Eggenstein-Leopoldshafen, Germany. A full literature citation and the reference number CSD 410369 should be quoted for any request of the material.