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A new asymmetric route to substituted piperidines: synthesis of *N*-alkyl-3,4-dihydroxy-5-alkylpiperidines

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Abstract

A facile asymmetric synthesis of *N*-alkyl-3,4-dihydroxy-5-alkylpiperidines has been developed, which is based on an asymmetric alkylation reaction of the SAMP hydrazone of *N*-BOC piperidinone.

Keywords: piperidinone; alkylation; asymmetric synthesis; hydrazones.

Substituted piperidines are common structures in natural and synthetic compounds with an extensive range of biological activities. Among them, polyhydroxylated piperidines have recently received much attention due to their utility as glycosidase inhibitors.[1] For example, isofagomine **1** is a potent β-glucosidase inhibitor.[2] The 3,4,5-trisubstituted piperidine **2** was found to be a potent α-fucosidase inhibitor with a K_i of 6.4 μM.[3] Glucuronic acid analogue **3** has a K_i versus β-glucuronidase of 79 nM.[4] In the course of our study on the development of electronic analogues of the oxocarbenium ion derived from *N*-acetylneuraminic acid,[5] we became interested in developing a synthesis of 1,3,4,5-tetrasubstituted piperidines **4** and **5** (Scheme 1). Although a number of asymmetric routes to substituted piperidines have been developed,[6] asymmetric synthesis of 3,4,5-trisubstituted piperidines is still a challenge since carbohydrate-based approaches can vary in complexity.[2,4,7] The target compounds **4** and **5** contain branched propyl or benzyl C-chains which are not commonly found in carbohydrate building blocks nor would they be readily installed, so we considered a non-carbohydrate approach. This report describes a chiral–hydrazone based asymmetric synthesis of 1,3,4,5-tetrasubstituted piperidines **4** and **5**.

As depicted in Fig. 1, the chiral auxiliary was introduced by condensation of the commercially available ketone **6** with the Enders hydrazine (SAMP) to give the hydrazone **7**.[8] The lithium aza-enolate of hydrazone **7** was prepared with *n*-butyllithium in the presence of *N*,*N*′-dimethylpropyleneurea (DMPU) in THF at −78°C, and was allowed to react with iodopropane or benzyl bromide at −78°C to afford hydrazone **8**, which was unstable on silica gel and was used without any purification for the next step. Cleavage of hydrazone **8** was satisfactorily carried out in a two-phase system containing a saturated

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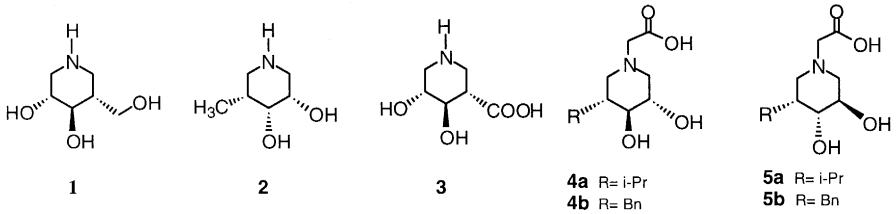

Scheme 1.

aqueous oxalic acid solution and diethyl ether to give ketone **9** in high yield (**9a**: 90% for two steps; **9b**: 87% for two steps).[9] The configuration of the ketone **9** was assigned to be *R*-based on the well-established stereochemical model for alkylation via SAMP/RAMP hydrazones.[8] Kinetic deprotonation of ketone **9** was performed with lithium diisopropylamide (LDA) in THF at −78°C, and reaction of the resulting lithium enolate with TMSCl gave silyl enol ether **10**. The hydroboration–oxidation of silyl enol ether **10**[10] and then desilylation with tetrabutylammonium fluoride (TBAF) gave a mixture of trans-diols **11** and **12** (48% from **9a**, **11a**:**12a**≈1:1 by NMR; 43% from **9b**, **11b**:**12b**≈1:1.3 by NMR) together with monoalcohol **13** as the by-product. Diols **11** and **12** could be separated by careful column chromatography. Alternatively, we used a mixture of diols **11** and **12** for the next reactions without further purification, and very easily carried out the purification procedure by column chromatography of the benzyl esters **15** and **17** (Fig. 2). The relative stereochemistry of diols **11** and **12** was determined by NMR spectroscopy and the structure of **12a** had been unambiguously determined by single-crystal X-ray analysis of its corresponding derivative **17a**. Deprotection of **11** with trifluoroacetic acid (TFA), and then *N*-alkylation with benzyl 2-bromoacetate, gave benzyl esters **15** (64% from **11a**; 55% from **11b**). In the same way, benzyl esters **17** were prepared (61% from **12a**; 49% from **12b**). Compound **17a** gave fine crystals which allowed us to confirm its relative configuration by X-ray analysis. The enantiomeric excesses (ees) of compounds **15a** and **15b** were assigned to be 78 and 63%, respectively by chiral shift experiments with $Eu(tfc)_3$ as the chiral shift reagent. Debenzylation of **15** and **17** by catalytic hydrogenolysis over palladium on carbon was a clean reaction, affording the target compounds **4** and **5** in nearly quantitative yield, respectively.[11] Considering that the series of reactions from silyl enol ether

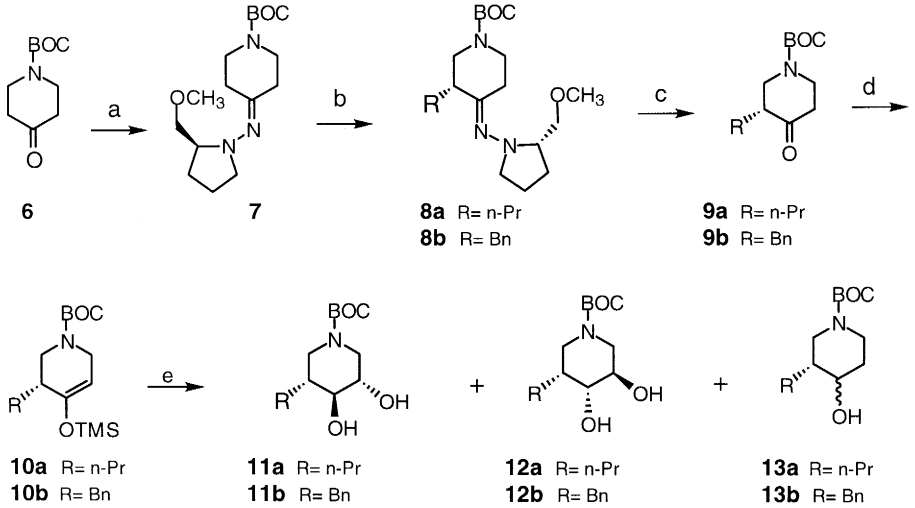

Fig. 1. Reagents and conditions: (a) SAMP, toluene, $MgSO_4$, 90%; (b) (i) BuLi, THF–DMPU, −78°C, 2 h; (ii) 1-iodopropane or benzyl bromide, −78°C–rt; (c) sat. oxalic acid, ethyl ether, rt; (d) (i) LDA, THF, −78°C; (ii) TMSCl, −78°C–rt; (e) (i) $BH_3 \cdot SMe_2$, THF, 0°–rt; (ii) H_2O_2, NaOH; (iii) TBAF, THF, rt

10a to compounds **4a** and **5a** should be racemization free, we estimated that the enantiomeric excess of compounds **4a**/**5a** was 78% and of compounds **4b**/**5b** was 63%. Further, ees for alkylated piperidinones **9a** and **9b** must have been at least 78 and 63%, respectively.[12]

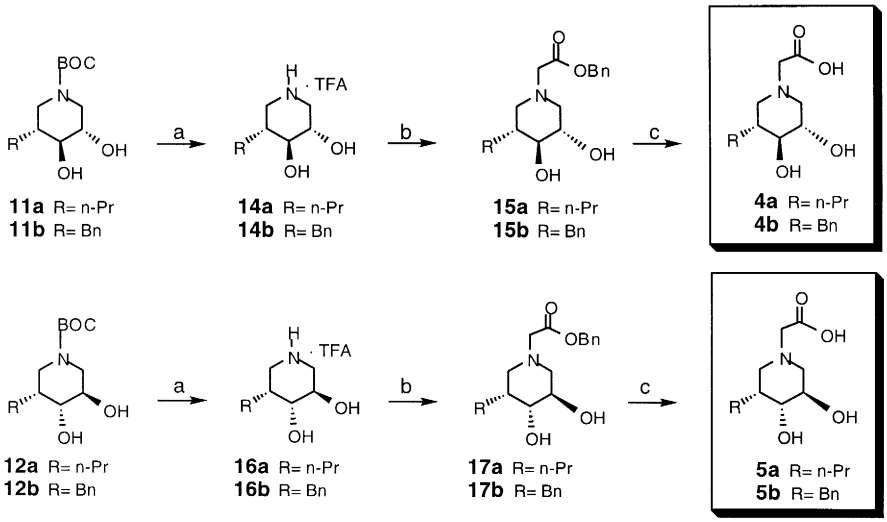

Fig. 2. Reagents and conditions: (a) TFA, CH_2Cl_2; (b) $BrCH_2CO_2Bn$, K_2CO_3, *n*-Bu_4NI (cat.), DMF, rt; (c) H_2, Pd/C, EtOAc

In conclusion, we have described a new asymmetric route to 1,3,4,5-tetrasubstituted piperidines which allows for flexible 5-alkyl-substitution with fair to good enantiomeric excesses. The availability of this new entry to polysubstituted piperidines should assist in the further development of piperidine derivatives as a biologically important class of compounds. Further application of this methodology to the synthesis of sialyltransferase and other glycosyltransferase inhibitors is underway in our laboratory.

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11. Selected data for **15a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (m, 5H), 5.14 (d, J=2.1 Hz, 2H), 3.4–3.8 (m, 3H), 3.3 (br s, 2H), 2.9–3.1 (m, 3H), 2.17 (t, J=10.5 Hz, 1H), 1.96 (t, J=11.1 Hz, 1H), 1.62–1.76 (m, 2H), 1.03–1.37 (m, 4H), 0.89 (t, J=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.14, 135.49, 128.54, 128.35, 78.18, 72.13, 66.38, 58.64, 57.85, 56.81, 40.79, 31.79, 19.99, 14.33; HRMS calcd for $C_{17}H_{26}NO_4$ (M^++H): 308.1862; found: 308.1861. For **4a**: ^{1}H NMR (300 MHz, *d*-DMSO)

δ 3.28–3.36 (m, 1H), 3.14 (d, J=2.4 Hz, 2H), 2.93–3.00 (m, 2H), 2.75 (t, J=9.6 Hz, 1H), 2.12 (t, J=10.8 Hz, 1H), 2.01 (t, J=11.4 Hz, 1H), 1.65 (m, 1H), 1.46 (m, 1H), 1.33 (m, 1H), 1.16 (m, 1H), 1.01 (m, 1H), 0.85 (t, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz, *d*-DMSO) δ 170.19, 76.58, 70.75, 58.70, 57.49, 55.98, 39.50, 31.46, 19.57, 14.34; HRMS calcd for $C_{10}H_{20}NO_4$ (M^++H): 218.1392; found: 218.1392.

12. We tried to use various chiral shift reagents to directly determine the enantiomeric purity of **9a**, **9b**, **17a** and **17b**, but were unable to obtain satisfactory results.