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Efficient, Stereodivergent Access to 3-Piperidinols by Traceless $P(OEt)_3$ Cyclodehydration

Peter H. Huy* and Ari M. P. Koskinen*

Aalto University, School of Chemical Technology, Laboratory of Organic Chemistry, Kemistintie 1, 00076 Espoo, Finland

ari.koskinen@aalto.fi; peter.huy@uni-koeln.de

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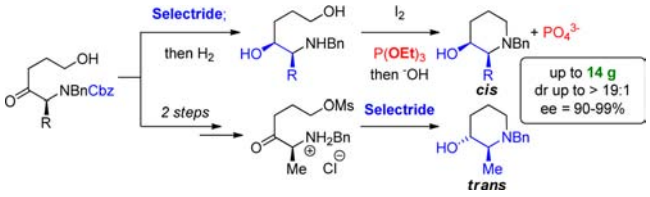
ABSTRACT



A stereodivergent and highly diastereoselective (dr up to >19:1 for both isomers), step economic (5−6 steps), and scalable synthesis (up to 14 g) of *cis*- and *trans*-2-substituted 3-piperidinols, the core motif of numerous bioactive compounds, providing efficient access to the NK-1 inhibitor L-733,060 is presented. Additionally, a "traceless" (referring to the simplified byproduct separation) cyclodehydration realizing simple $P(OEt)_3$ as a substitute for PPh_3 is developed.

1,2-Amino alcohols are a frequent motif found in many pharmacologically active natural products,[1,2] chiral auxiliaries,[3] and catalysts for asymmetric synthesis.[4] Indeed, numerous natural products and other bioactive compounds are derived from a 2-substituted 3-hydroxy piperidine scaffold (as one type of an 1,2-amino alcohol) (Figure 1).[1a−d,2a,2b] Representative examples are the selective nonpeptidic human neurokinin-1 (NK-1) substance P receptor antagonists L-733,060[5] and CP-99,994[6] and the natural products febrifugine (antimalarial)[7] and halofuginone (antiprotozoal, commercial trade names Halocur (lactate salt) and Stenorol (hydrobromide salt)).[8] Other prominent examples are 3-hydroxy pipecolic acids, which serve as (conformationally restricted) substitutes of proline and serine[9] and have been incorporated in various bioactive peptidomimetics,[10] and the iminosugar

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swainsonine, which is inter alia a new potential chemotherapeutic agent.[11] The high importance of further derivatives is underlined by recent patents on analogs of halofuginone as inhibitors for tRNA synthetases.[12]

The majority of the reported[1b−d,13,14] syntheses suffer from some drawbacks: They are elaborate (far more than 10 steps), specific on one of the above-mentioned targets (either in *cis*- or *trans*-configuration), and not proven to be scalable. Considering the versatile pharmacological activities of compounds based on the 3-piperidinol scaffold, the development of a stereodivergent, scalable, and efficient synthetic access is highly desirable.

In the syntheses of potentially new drug candidates scalability is a significant factor to provide sufficient substance amounts for clinical testing.[15] Furthermore, alternatives in reactions driven by the formation of phosphine oxides from phosphines (e.g., the Appel and Mitsunobu reactions) are highly desired to improve atom economy (reduced waste amounts) and to circumvent difficulties in the separation of these byproducts.[16] Numerous protocols have been developed to improve these issues, mostly based on polymer bound or otherwise modified (more complex) phosphines.[16] Surprisingly, in this context simple and inexpensive phosphites ($P(OR)_3$) have only been applied as phosphine substitutes in one single and specific example.[17]

Herein, we report a step economic (5−6 steps), scalable, and stereodivergent synthesis of *trans*- and *cis*-2-substituted 3-piperidinols **A** in high diastereoselectivities (up to > 19:1) and enantiopurities (ee = 90−99%) originating from the ketone intermediates **C** (Figure 1).

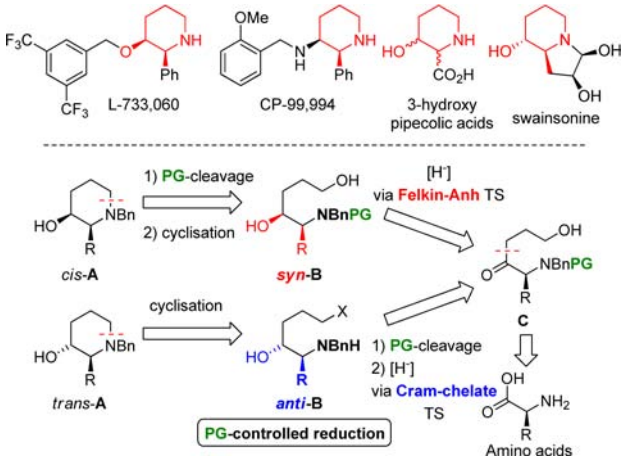

Figure 1. Selected examples for bioactive piperidine derivatives and retrosynthetic analysis of 3-hydroxyl piperidines **A** (X = OH or leaving group, [H⁻] = hydride reducing agent, TS = transition state).

We intended to control the diastereoselectivity in **A** (*cis*/*trans*) through a targeted protecting group (PG) manipulation resulting in the retrosynthetic analysis shown in Figure 1:[18] Reduction of the common precursor ketone **C** (derived from amino acids) should deliver the *syn* amino alcohol **B** according to the Felkin−Anh model (due to the sterically demanding −NBnPG carbamate function). Further PG cleavage and cyclization should give *cis*-**A**. On the other hand, initial deprotection of **C** (to liberate the Lewis basic −NHBn amino moiety) and subsequent reduction toward a Cram chelate transition state should deliver the *anti*-amino alcohol **B**. After subsequent cyclization *trans*-**A** would result.

At the outset L-alanine **1a**, L-phenylalanine **1b**, and L-phenylglycine **1c** were converted to their *N*-benzyl-*N*-Cbz protected derivatives **2a**−**2c** in a novel practical one-pot procedure through the combination of Quitt's reductive benzylation protocol[19] and Schotten−Baumann acylation in 70−79% yield (Scheme 1). Thereby not only one workup was spared, but also the overall yield was improved significantly (e.g., 40% (two steps) → 70% for **2a**).

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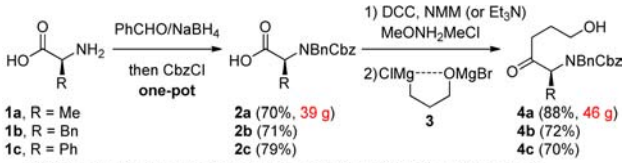
Straightforward amidation of carboxylic acids **2** with DCC and conversion of the resulting Weinreb amides (not shown) with Grignard reagent **3**, which was found to be superior in the final concentration to the reported ClMg*n*PrOMgCl derivative,[20] gave the ketones **4** in good to excellent yields (70−88%, over 2 steps). Notably, with this strategy we saved additional protection and deprotection steps of the free hydroxyl group of **3**.

Scheme 1. Synthesis of Hydroxy Ketones **4**



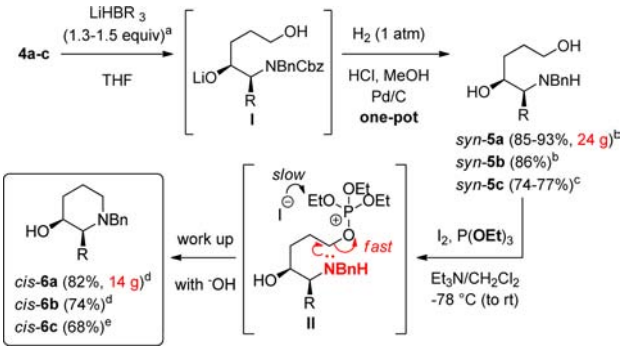
DCC = *N*,*N*′-dicyclohexyl carbodiimide; NMM = *N*-methyl morpholine

Diastereoselective reduction of ketones **4a**−**c** with L-Selectride (**4a**+**b**) and Superhydride (**4c**), respectively, delivered the amino alcohols **I** (Scheme 2). Without isolation of **I** the Cbz-moiety was cleaved through chemoselective hydrogenolysis (in preference over the Bn-group) to result in diols **5a**−**c** in useful to excellent diastereoselectivities (4:1 to >19:1 *syn*/*anti* in accordance to a Felkin−Anh transition state). Subsequently, Appel cyclization[21] (PPh_3/I_2) with careful temperature control (−40 °C to rt) delivered the piperidinols **6a**−**c** in good yields (69−77%). Unfortunately, the byproduct triphenyl phosphine oxide was only separable by chromatography requiring increased amounts of silica gel.

In general, the reaction of alcohols with alkyl phosphites ($P(OR)_3$), activated through oxidants such as iodine, have been reported to give the corresponding phosphates.[22] In order to improve atom economy and side product separation, we rationalized that in the phosphonium intermediate **II** the intramolecular substitution by the amino function (delivering the desired piperidinols **6**) should be significantly faster than the bimolecular reaction of the iodide ion with intermediate **II** as indicated (resulting in the formation of the corresponding undesired phosphates).

Indeed, under optimized conditions the piperidinols **6** were isolated after saponification (during work up) of triethyl phosphate and chromatographic purification in 68−82% yield and high enantiomeric excess (90−99%).[23,24] Interestingly, we observed the strong influence of the ratio of NEt_3/DCM on the yield: For instance, piperidinol **6c** was obtained in 68% yield when using NEt_3/DCM in a 1:1.3 ratio, while a 1:3 solvent mixture gave **6c** in only 22% yield (noteworthily NEt_3 is as cheap as common solvents such as DCM and THF). This can be attributed to the lower solubility of iodine in NEt_3 (which leads to a slower and thus more selective reaction) and general base catalysis: simultaneous deprotonation (through NEt_3) in the cyclization step strongly favors the desired reaction pathway to piperidines **6**.

Scheme 2. Synthesis of *cis*-Piperidinols **6**



[a] R′ = *s*Bu for **4a**+**b** (L-Selectride); R′ = Et for **4c** (Superhydride). [b] dr ≥ 19:1. [c] dr = 4:1. [d] dr ≥ 19:1, ee ≥ 99%. [e] dr = 5.3:1, ee = 90%.

Significantly, 14 g of alanine derived piperidinol *cis*-**6a** was obtained (cyclodehydration with $I_2/P(OEt)_3$) in one batch with no purification of the intermediates (**2a**, **4a** and *syn*-**5a**) and an overall yield of 44%, demonstrating the scalability and high practicability of our sequence. The relative configuration of compounds **5** and **6** was proven by NOE-spectroscopy of piperidinols *cis*-**6a**−**c**, *trans*-**6a**, *cis*- and *trans*-**10**, L-733,060·HCl, and oxazolidinones derived from the aminoalcohols *syn*-**5a** and **5c**.[25]

We wondered if the novel $I_2/P(OEt)_3$ cyclodehydration is also applicable to the synthesis of other heterocycles: Indeed, not only pyrrolidine **8a** (Table 1, entry 1) but also furans **8b** to **8d** (bearing *inter alia* sterically demanding mesityl or two Ph substituents) were obtained in good to excellent yields and purities >90% without any additional purification (Table 1, entries 2−6).

Having developed a short 5-step route leading to *cis*-piperidinols of type **6**, we turned our attention to the *trans* diastereomers of **6** (Scheme 3). Initial reduction studies with the amino ketone (not shown) obtained through Cbz-cleavage of **4a** and basic workup revealed L-Selectride as the best reducing agent again in agreement with a Cram chelate transition state (dr ≥25:1 according to ^{1}H NMR). Disappointingly, the hydroxy piperidine *trans*-**6a** isolated after subsequent Appel cyclization showed a significantly

(20) For the preparation of ClMg*n*PrMg**Cl**, see: Cahiez, G.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1978**, *33*, 3013–3014.

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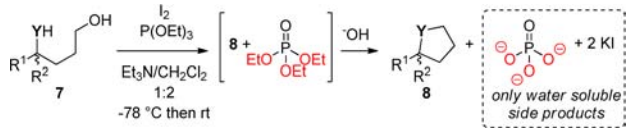
(23) The optical purity was determined with HPLC on a chiral stationary phase and comparison with racemic samples (alanine and phenylglycine derived substrates) or in analogy to the aforementioned amino acid derivatives (phenylalanine deduced substrates). The slight decrease in the optical purity of the phenyl glycine derived piperidinol **6c** occurred in the amidation step (95% *ee*) and the subsequent addition of Grignard reagent **3** (92% *ee*, transformation **2c**→**4c**).

(24) While for the substrates **6a** and **6b** cyclodehydration with $P(OEt)_3$ improved the yield about 5% (compated to PPh_3), cyclization with PPh_3 provided the piperidinol **6c** in a higher yield (77%).

(25) See Supporting Information for further details.

diminished enantiomeric excess (32%).[25] This result was somewhat surprising, because reductions of structurally related secondary amino ketones[18c,d] were previously reported to proceed without a decrease in enantiopurity. However, the observed racemization might be explained through an intermolecular enamine formation.[25]

Table 1. Preliminary Substrate Scope of the $I_2/P(OEt)_3$-Cyclodehydration



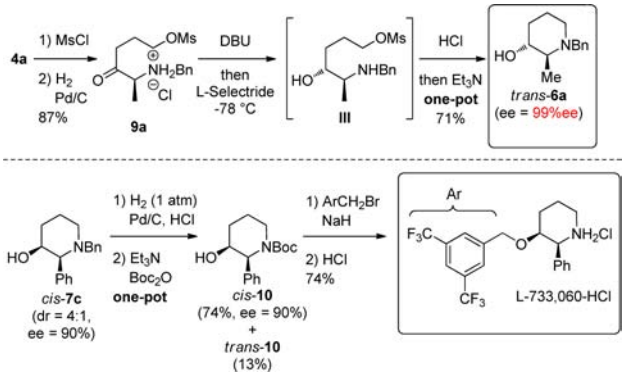
entry	substrate	Y	R^1	R^2	yield[a]
1	**7a**	NBn	H	H	81%[b]
2	*rac*-**7b**	O	Ph	H	92%
3	*rac*-**7c**	O	*o*ClPh	H	88%
4	*rac*-**7d**	O	*p*BrPh	H	83%
5	*rac*-**7e**	O	Mes	H	84%
6	**7f**	O	Ph	Ph	82%

[a] Isolated yields, purity >90% according to crude ^{1}H NMR. [b] $OP(OEt)_3$ was removed by washing with EtOAc.

To gain access to the piperidine *trans*-**6a** in high ee, hydroxy ketone **4a** was subjected to mesylation and Cbz-cleavage to give the hydrochloride **9a**, which cannot racemize through an enamine equilibrium due the protonation of the amino function. To our delight, subsequent liberation of the free amine through DBU at low temperature, immediate L-Selectride reduction (giving intermediate **III**), HCl quenching, and NEt_3-induced cyclization afforded the piperidine *trans*-**6a** in an excellent ee (>99%)[23] and as a single diastereomer according to crude ^{1}H NMR. Although the reduction is performed in the presence of a free hydroxy function and 1 equiv of DBU-H^+, only 1.5 equiv of L-Selectride were necessary for a quantitative conversion. Thus we assume a Cram chelate transition state is formed through an amine N−H proton rather than an amide N−Li lithium cation (which would result from deprotonation of the amino group by L-Selectride and would therefore require at least 2 equiv of the reducing agent).

In order to probe the practicability of our sequence, we synthesized L-733,060 as its hydrochloride salt as depicted in Scheme 3. After cleavage of the Bn-group and Boc-protection in one pot, the diastereomers *cis*- and *trans*-**10** were easily separated by flash chromatography. The resulting alcohol *cis*-**10** was converted to the desired target through etherification and cleavage of the Boc-group. With 8 steps our sequence is one of the shortest syntheses reported to date.[13a−c] Furthermore, with the carbamate *cis*-**10** (synthesized in 6 rather than 8 steps) we also achieved a formal total synthesis of CP-99,994.[26]

Scheme 3. Synthesis of *trans*-Piperidinol **6a** and of L-733,060



In conclusion, we have developed a stereodivergent and highly diastereoselective (dr up to 19:1 for both isomers), scalable, and practical (up to 14 g of **6a** without any purification of intermediates) synthesis of *cis*- and *trans*-3-piperidinols **6**, which represent a key structural motif in various natural products and other bioactive target compounds. Thereby, high step economy (5−6 steps) was achieved by establishing several novel one-pot procedures (**1**→**2**, **4**→**5**, **9a**→*trans*-**6a**) and avoiding any protection of the OH-functions. From piperidinol **6c** the NK-1 inhibitor L-733,060 was prepared in three further steps. Additionally, a unique cyclodehydration procedure replacing PPh_3 through $P(OEt)_3$ to improve atom economy (166 compared to 262 g/mol) and to allow separation of the oxidized side product ($OP(OEt)_3$) through saponification (no similar literature precedents known) was established. Currently, we are exploiting our piperidinol **6** synthesis to other pharmacologically relevant targets and are investigating the substrate scope of the $I_2/P(OEt)_3$-cyclization procedure.

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Supporting Information Available. Experimental procedures and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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