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Concise, enantiospecific synthesis of (3*S*,4*R*)-3-amino-4-ethylpiperidine as partner to a non-fluoroquinolone nucleus

Michael Reilly,* Donald R. Anthony and Corey Gallagher

Chemical Development, Procter & Gamble Pharmaceuticals, Woods Corners, PO Box 191, Norwich, NY 13815, USA

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Abstract—An enantiospecific, eight-step synthesis of (3*S*,4*R*)-3-amino-4-ethylpiperidine **3** starting from readily available (*S*)-(−)-α-methyl-4-pyridinemethanol **6** has been achieved utilizing an Overman rearrangement of a chiral allylic trichloroacetimidate **13** as the key step. A diastereoselective hydrogenation of the resulting chiral allylic amine **15** afforded predominantly the desired *trans*-substituted piperidine. The conformation of the piperidine along with the directing nature of the amino function are implicated in the selectivity observed.

As part of an ongoing investigation into the synthesis and biological evaluation of 7-substituted, non-fluoro quinolone derivatives within the context of our topoisomerase targeted anti-infectives program, a number of derivatives containing amine functionality in the side chain portion were progressed into development **1** (Fig. 1).[1] Most notably, a variety of differentially substituted, chiral, aminopiperidines **2** were found to exhibit good class activity and were desired in multi-gram quantities for further in vivo evaluation. In particular, a (3*S*,4*R*)-3-amino-4-ethylpiperidine **3** as a partner to the quinolone nucleus was chosen for further exploration.

The research synthesis used to produce this side chain suffered from a variety of drawbacks and was not suitable for the production of larger quantities of the desired piperidine.[2] The synthesis involved employed a lengthy 11-step sequence starting from a D-serine derivative and a tedious chromatography of diastereomers at the end of the synthesis. Moreover, it was retrospectively discovered that significant epimerization of the C3′ chiral center in **3** had occurred during the synthesis resulting in near complete racemization. A concise, enantiospecific synthesis of (3*S*,4*R*)-3-amino-4-ethylpiperidine was therefore necessitated.

Retrosynthetically (Fig. 2) it was envisioned that piperidine **3** could be derived from an externally situated amino olefin **4** via a straightforward hydrogenation

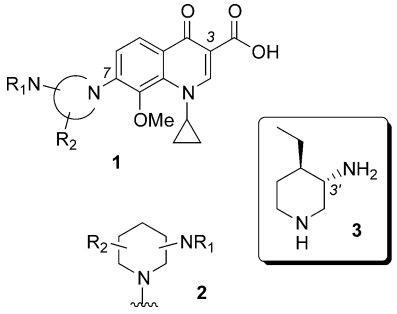

Figure 1. Non-fluoroquinolone derivatives (**1**) and chiral piperidine side chains (**2** and **3**).

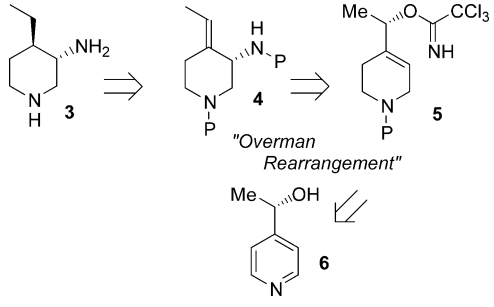

Figure 2. Retrosynthetic dissection of (3*S*,4*R*)-3-amino-4-ethylpiperidine.

Keywords: Overman rearrangement; enantiospecific; pipiridine; 3-amino-4-ethylpiperidine; quinolone; hydrogenation.

* Corresponding author. Tel.: +0-607-335-2918; fax: +0-607-335-2010; e-mail: reilly.m@pg.com

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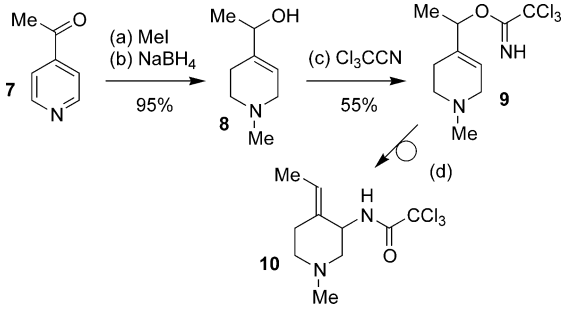
protocol. It was believed that the desired, relative, *trans* geometry could be achieved predominantly during hydrogenation by exploiting the directing nature of the primary amino function.[3] The directing ability of haptophilic groups, such as R–NH_2, during heterogeneous hydrogenation has been well documented and utilized to dramatic effect in the past.[4] The absolute stereochemical control required during the synthesis of the chiral allylic amine **4** could, in turn, be obtained from a similarly chiral allylic alcohol acetimidate **5** via oxygen–nitrogen transposition utilizing a highly selective [3,3]-sigmatropic Overman rearrangement reaction.[5] Owing to the highly organized transition state for this reaction and an analogous carbocyclic example of this rearrangement,[6] it was believed that excellent facial transfer of chirality and control of absolute stereochemistry could be achieved. The chiral allylic alcohol necessary for the present synthesis, though synthetically approachable in a multitude of ways, is represented below as a 1,2,5,6-tetrahydropyridine derivative **5** that could be obtained sequentially from a suitable chiral pyridine[7] **6** via quarternization and subsequent hydride reduction.[8]

Fortunately, for the purposes of our synthesis, both antipodes of chiral α-methyl-4-pyridinemethanol were commercially available.[9] Prior to the consumption of relatively expensive chiral starting materials however, it was decided to explore the conditions for the key Overman rearrangement step. With this in mind, a model study was initiated using the prochiral 4-acetylpyridine **7** as starting material (Scheme 1).

Following literature protocol,[10] treatment of 4-acetylpyridine with methyl iodide led to the intermediate quaternary iodide salt as a solid in 98% yield. Reduction of this salt with sodium borohydride led to the desired 1,2,5,6-tetrahydropyridine derivative **8** in 97% yield. Exposure of the secondary allylic alcohol to trichloroacetonitrile in the presence of catalytic NaH led to the corresponding allylic trichloroacetimidate **9** derivative in 55% yield after silica gel chromatography. Rearrangement under thermal conditions was evaluated in a variety of solvents (Table 1). Refluxing THF, which was amenable to a foreseeable one-pot, trichloroacetimidate formation/rearrangement protocol, failed to give the desired product and only starting material was recovered. The higher boiling solvent toluene afforded only slight solubility of the substrate and, after prolonged heating, decomposition was observed. The use of chlorobenzene as solvent offered excellent solubility and, upon heating at reflux for several hours, afforded the desired rearranged allylic trichloroacetamide **10** in 50% isolated yield. An insoluble, black, tar-like residue, presumed to be due to starting material decomposition, was also observed and believed to be having a deleterious effect on yield. It was supposed that trace acids, either from the solvent or formed during the high temperature procedure, were contributing to the decomposition of the trichloroacetimidate starting material **9**. As a result, modified Overman rearrangement conditions previously reported to inhibit the decomposition of allylic trichloroacetimidates by scavenging trace acid were employed.[11] The addition of 2 mg K_2CO_3/mL solvent to the reaction mixture followed by heating to reflux led to the clean transformation of the allylic acetimidate into the allylic trichloroacetamide **10** in 95% yield and near analytical purity.



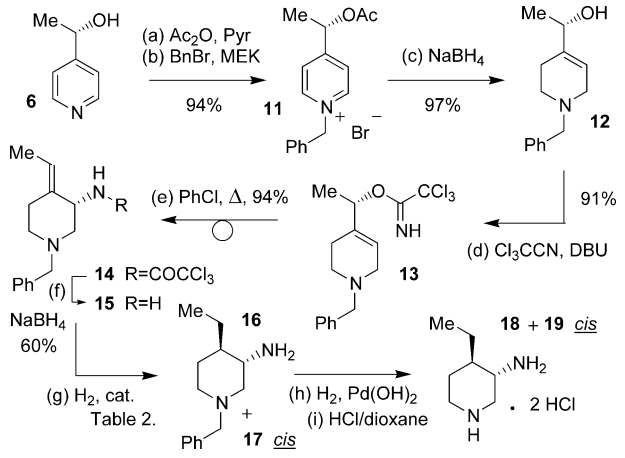
Scheme 1. *Reagents and conditions*: (a) MeI, MeOH, reflux, 98%; (b) $NaBH_4$, MeOH, 5–20°C, 97%; (c) Cl_3CCN, cat. NaH (10 mol%), THF, –15°C, 55%; (d) see Table 1.

With the optimized Overman rearrangement conditions in hand, attention was focused on the transformation of chiral (*S*)-(–)-α-methyl-4-pyridinemethanol **6** into the desired optically pure 3-amino-4-ethylpiperidine (Scheme 2). Acetylation of the secondary alcohol with acetic anhydride followed by quarternization with benzyl bromide afforded the quarternary bromide salt **11** as a solid in 94% yield. Reduction of the pyridinium salt with sodium borohydride to afford the 1,2,5,6-tetrahydropyridine intermediate followed by in situ deprotection of the acetate with 1.0N NaOH produced the requisite secondary alcohol **12** in preparation for formation of the chiral trichloroacetimidate ester. The preparation of the trichloroacetimidate ester **13** was improved by treatment of the allylic alcohol with trichloroacetonitrile and DBU to provide a 91% yield

Table 1. Model study on the racemic trichloroacetimidate **9**

Entry	Solvent	Temp. (°C)	Time (h)	Additive	Yield (%) **10**
1	THF	Reflux	24	None	–[a]
2	PhMe	110	20	None	–[b]
3	PhCl	135	15	None	50
4	PhCl	135	15	K_2CO_3	95[c]

[a] No rearrangement product observed.
[b] Substrate only partially soluble, decomposition observed.
[c] 2.0 mg K_2CO_3 per 1.0 mL PhCl added to reaction mixture.



Scheme 2. *Reagents and conditions*: (a) Ac_2O, pyridine, DMAP, DCM, 12 h, 97%; (b) BnBr, 2-butanone, reflux, 12 h, 97%; (c) $NaBH_4$, MeOH, 5–8°C, 3 h, 97%; (d) Cl_3CCN, DBU, DCM, 0°C, 15 h, 91%; (e) PhCl, K_2CO_3, 135°C, 5 h, 94%;[15] (f) $NaBH_4$, EtOH, 1.0N NaOH, 15 h, 60%; (g) H_2, catalyst (see Table 2); (h) H_2, Pearlman's catalyst (see Table 2); (i) 4.0N HCl/dioxane.[16]

after brief chromatography on silica gel. Application of the optimized conditions, discovered earlier for the thermal Overman rearrangement, resulted in the clean transformation of the chiral allylic trichloroacetimidate **13** into the E-olefinic trichloroacetamide **14** in 94% yield.[12] Deprotection of the trichloroacetamide group with sodium borohydride led to the requisite 3-amino-4-ethylidene pyridine **15** in 60% yield.[13] It was decided at this point that the absolute stereochemistry of the piperidine would be determined by conversion to the finished quinolone drug substance[14] **20**, whose absolute stereochemistry was known.

With this in mind, diastereoselective hydrogenation of the exocyclic allylic amine **15** was briefly studied to ascertain the effect of two different heterogeneous catalysts on the *cis*/*trans* ratio (Table 2). Hydrogenation over standard Pd/C (10 wt%) in ethanol at 1 atm H_2 led to the reduction of the olefin **15** with only partial debenzylation observed to give a 1:3 *cis*/*trans* ratio **17**/**16** (entry 1). Subsequent de-benzylation with Pearlman's catalyst (20% wt, entry 3) and treatment of the crude reaction mixture with HCl/dioxane led to the formation of the desired *cis*/*trans* side chain mixture **19**/**18** as the di-HCl salt. The debenzylation reaction in methanol worked similarly, albeit more quickly (entry 3 versus 4). Hydrogenation of the olefin over PtO_2 (entry 2) afforded a 1:5 mixture of *N*-benzyl *cis*/*trans* isomers **17**/**16** which were then subjected to the debenzylation protocol using Pearlman's catalyst in methanol followed by treatment with HCl (entry 5). No further investigation of catalysts was performed; rather the 1:5 ratio of **19**/**18** was deemed acceptable for our purposes and carried forward through the synthesis for determination of the absolute configuration. Multi-gram quantities of the pure *trans* diastereomer, needed for the production of drug substance **20**, could be obtained in 58% yield, however, via careful silica gel chromatography of the *N*-benzyl piperidine mixture **17**/**16** prior to deprotection with Pearlman's catalyst.

The 1:5 *cis*/*trans* mixture from the PtO_2 reduction/$Pd(OH)_2$ debenzylation (entry 5) protocol was carried forward and coupled via aromatic nucleophilic substitution to the quinolone nucleus for absolute and relative structure confirmation. Chiral CE analysis[17] of the final drug substance[14] **20** indicated the desired (3*S*,4*R*) configuration of the amine side chain by comparison with samples of known configuration. High enantiospecificity was also achieved during the synthesis, with <5% of the (3*R*,4*S*) enantiomer observed in the mixture. The *cis*/*trans* ratio of the piperidine mixture was also confirmed by this method to be 1:4.8.

It is believed that the diastereoselectivity achieved during the hydrogenation of the olefin is due, at least in part, to the interaction of the haptophilic amino group with the catalyst surface. Since the allylic amine group would be axially disposed due to $A^{(1,3)}$ strain, it could easily interact with the catalyst surface providing delivery of hydrogen predominantly from the same side. The more electrophilic nature of PtO_2 (Adams' catalyst) and greater affinity toward the amine function could possibly explain the greater facial selectivity achieved with the use of this catalyst.

In conclusion, a concise, stereo- and enantiospecific synthesis of (3*S*,4*R*)-3-amino-4-ethylpiperidine has been achieved in eight steps utilizing a highly selective Overman rearrangement as the key transformation. Application of this synthesis to the (3*R*,4*S*)-antipodal isomer has also been achieved with similar results.

Table 2. Hydrogenation of **15** to **17**/**16**; debenzylation to **19**/**18**: conditions and yields[a]

Entry	Solvent	Catalyst	Time (h)	*cis*/*trans*	Yield (%)[b]
1	EtOH	Pd/C	12	1:3 (**17**/**16**)	91[c]
2	EtOH	PtO_2	12	1:5 (**17**/**16**)	95
3	EtOH	$Pd(OH)_2$	20	1:3 (**19**/**18**)	95[d]
4	MeOH	$Pd(OH)_2$	12	1:3 (**19**/**18**)	95[d]
5	MeOH	$Pd(OH)_2$	12	1:5 (**19**/**18**)	92[d]

[a] All hydrogenations performed under 1 atm H_2 at 25°C.
[b] Combined yield.
[c] Slight debenzylation was observed.
[d] Isolated as the di-HCl salt (4.0N HCl/dioxane).

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12. Due to the chair-like transition state adopted during the Overman rearrangement and the equatorial disposition of the methyl group resulting from the minimization of a 1,3 diaxial interaction with the bulky trichloromethyl group, the E isomeric olefin is expected along with retention of facial selectivity during the oxygen–nitrogen transposition.
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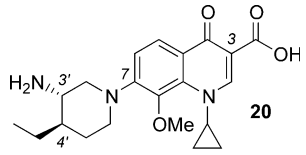
14. Comparison of our sample to the quinolone structure of known configuration shown below was used to establish absolute stereochemistry.



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15. A typical procedure for the Overman rearrangement of trichloroacetimidate **13** is as follows: A solution of the trichloroacetimidate (1.1 g, 3.0 mmol) was dissolved in 150 mL dry chlorobenzene. To this solution was added 0.30 g of anhydrous granular K_2CO_3 (2 mg per mL PhCl). The mixture was heated to 135°C for 5 h and was then cooled to ambient temperature. The reaction solution was filtered through a pad of Celite and concentrated in vacuo to a pale brown oil **14** (1.0 g, 94%). ^{1}H NMR (300 MHz, $CDCl_3$) was consistent with the desired structure and shows the Overman rearranged product **14** in excellent purity.
16. Selected spectroscopic and analytical data for 3(*S*),4(*R*)-*trans*-3-amino-4-ethylpiperidine dihydro-chloride **18**: ^{1}H NMR (300 MHz, CD_3OD) δ 3.64 (dd, 1H, $J=12.1$ Hz, 3.9 Hz), 3.46 (bd, 1H, $J=12.9$ Hz), 3.39–3.28 (m, 1H), 3.09–2.99 (m, 2H), 2.17 (bd, 1H, $J=13.4$ Hz), 1.83–1.72 (m, 2H), 1.60–1.46 (m, 1H), 1.37–1.25 (m, 1H), 0.99 (t, 3H, $J=7.3$ Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 50.5, 46.1, 44.9, 40.3, 26.6, 24.5, 10.3; MS (+ESI): $m/z=129$ (M+H).
17. Chiral capillary electrophoresis (CE) conditions: Agilent CE system, Voltage −20 kV, 200 mbar injection of a 0.1 mg/mL sample, $\lambda=298$ nm. Running buffer: 5% (w/v) highly sulfated-γ-cyclodextrin (HSCD, Beckman) in a 25 mM phosphate buffer pH 2.5. Capillary: Bared fused silica total length 64.5 cm, effective length 56.0 cm, 50 μm i.d. with a 150 μm detection window.