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Development of two diastereoselective routes towards *trans*-4-aminomethyl-piperidin-3-ol building blocks

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Abstract

Two diastereoselective, scaleable routes towards *trans*-3,4-disubstituted piperidines with a 4-hydroxymethyl-3-hydroxy or 4-aminomethyl-3-hydroxy substitution pattern are being described. In the first route, the 3,4-trans configuration was introduced regio- and diastereoselectively via a hydroboration/oxidation sequence starting from 4-hydroxymethylpyridine. In the second route, regioselective epoxide ring opening of *N*-benzyl-3,4-epoxy-piperidine was achieved with LiCN, in situ generated from acetocyanohydrin and $LiNH_2$. The regioselectivity of both the hydroboration and the epoxide ring opening was positively influenced by the presence of the basic piperidine nitrogen. Both routes have been optimized to be performed at large scale.

1. Introduction

In a medicinal chemistry program directed towards 5-HT_4 receptor ligands, we have discovered several potent agonists with excellent gastro-prokinetic activity, which have now progressed to clinical trials, as exemplified by R149402 and R199715 (Fig. 1).[1] Both compounds contain a *trans*-4-aminomethyl-piperidin-3-ol moiety and the large scale preparation of these clinical candidates or their derivatives required a scaleable synthetic route towards *trans*-3,4-disubstituted piperidine building blocks **1** and **2**.

Functionalized piperidines constitute one of the most common fragments present in biologically active compounds of both natural and synthetic origin. This has resulted in a wealth of synthetic methodology for their preparation and incorporation in more complex structures, which has been extensively reviewed.[2] Reports on the synthesis of 3,4-disubstituted piperidines have been surprisingly limited, with only one example of a 4-aminomethyl substituted piperidine, having a cis relationship to a 3-methoxy substituent.[3] The synthesis of *trans*-3,4-disubstituted piperidines with similar functional groups has been described for 4-amino-piperidin-3-ols,[4] but the methodologies used cannot be easily translated into the synthesis of elongated 4-aminomethyl analogues. In this report we describe our evolving efforts towards the synthesis of *trans*-4-aminomethyl-piperidin-3-ol and *trans*-4-hydroxymethyl-piperidin-3-ol containing building blocks **1** and **2**, respectively, resulting in two diastereoselective and scaleable routes towards **1**.

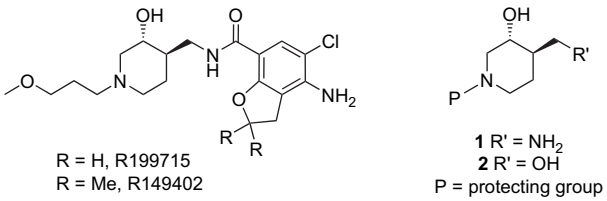

Figure 1.

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2. Results and discussion

The synthesis of *N*-benzyl protected *trans*-**2** (compound **6**, Scheme 1) has been described via reduction of commercially available *N*-benzyl-3-oxo-piperidin-4-carboxylate esters.[3,5] Due to the enolic nature of the 3,4-piperidine bond in these β-keto-esters, invariably a mixture of cis and trans diastereomers is formed with the cis diastereomer as the major product.

Although this route provided access to gram quantities of **2**, the need for larger quantities of both **1** and **2** made it worthwhile to investigate alternative, more diastereoselective routes. In the subsequent sections two different diastereoselective routes will be described.

2.1. Diastereoselective route A

The preparation of piperidines via reduction of pyridines is a commonly used method.[2] The quaternization of the pyridine nitrogen allows for mild reduction conditions, which can be halted at the 3,4-dehydropiperidine (1,2,3,6-tetrahydropyridine) stage.[2,6] The double bond can subsequently be used as a handle for the introduction of substituents on the 3- and/or 4-position. According to this strategy, we started with the quaternization of 4-hydroxymethylpyridine **3** with benzylchloride, followed by reduction of **4** to 3,4-dehydropiperidine **5** (Scheme 1).

Introduction of a 3-substituent in a trans diastereoselective fashion would require a trans anti-Markovnikov addition to the double bond, a requirement fulfilled via a borane addition, followed by oxidation with retention.[7] Indeed, treatment of **5** with an excess of borane, followed by oxidation gave the desired *trans*-3,4-disubstituted piperidine **6** with complete diastereoselectivity in 50% (kilogram scale) to 64% (gram scale) yield after crystallization. According to GC–MS analysis, product **7** was formed as the main side-product in a ~2:1 ratio of **6**:**7**, which was easily removed during work-up via crystallization.

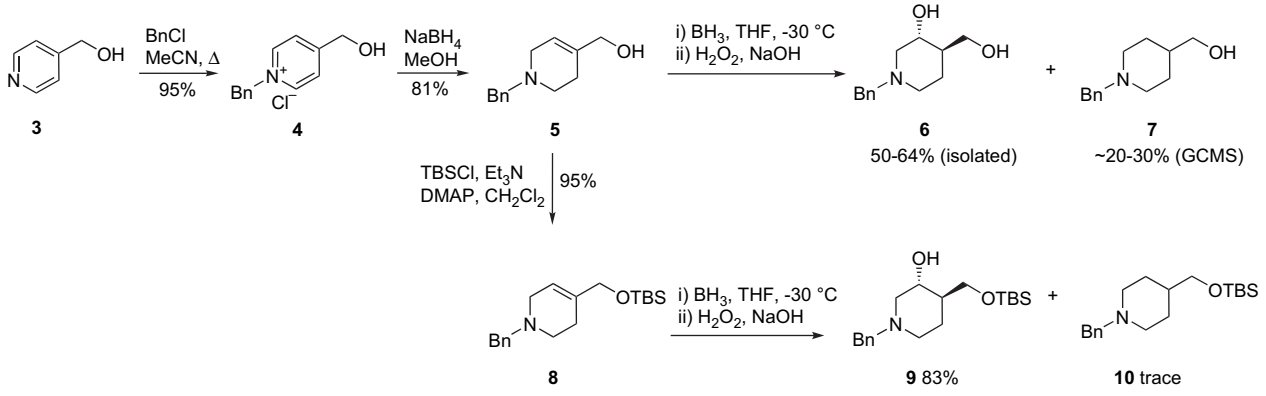
The presence of a basic piperidine and a free hydroxyl group required the use of at least 2 equiv of borane for the reaction to go to completion. This excess of borane could be the cause of the reduction of **5** to **7**. Therefore some borane addition experiments were carried out with a protected hydroxyl group. *tert*-Butyl dimethylsilyl (TBS) protection of **5**, followed by the hydroboration/oxidation sequence, led to a an isolated yield of 83% of **9**. Overreduced **10** was only observed in trace amounts, according to GC–MS analysis. Due to the cost of the required TBS-chloride and the extra protection/deprotection steps, this improvement in yield compared to the reaction of **5** to **6** was eventually not implemented in the scaled-up process.

To obtain the corresponding *trans*-4-aminomethyl-piperidin-3-ol building blocks **1**, the conversion of the 4-hydroxymethyl-group into a 4-aminomethyl-group comprised some straightforward functional group transformations.[3] Transformation of the primary hydroxyl group in **6** into a suitable leaving group, such as a tosylate or mesylate, resulted in very unstable compounds, reacting inter- or intramolecularly with the tertiary piperidine nitrogen atom. Therefore, the benzylic protection group in **6** was replaced with a *tert*-butyl carbamate (Boc) group to give **11** in nearly quantitative yield (Scheme 2). Now, tosylation of **11** proceeded cleanly to give **12**. Subsequent displacement of the tosylate with a suitable nitrogen nucleophile would then lead to the required 4-aminomethyl building block. Initially benzylamine was used as the nitrogen nucleophile to give **13** (Scheme 3). This again required a deprotection step to obtain **14**. Similarly, the use of sodium azide would require an extra reduction step to arrive at **14**, and was not considered as an alternative for benzylamine due to its hazardous nature. To avoid the last deprotection step, some experiments were run to directly replace the tosylate with ammonia. After some optimization, this proceeded in high yield via the use of excess ammonia at elevated temperatures in a pressure reactor.

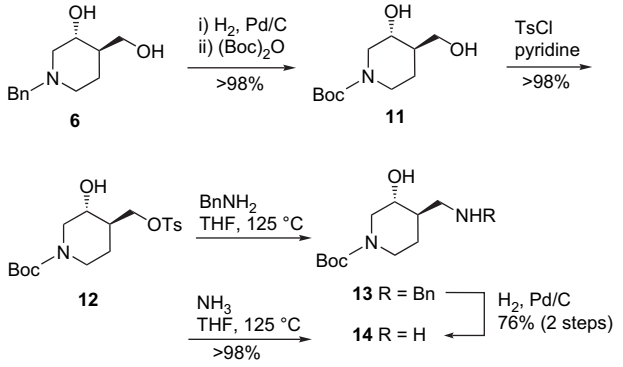
Despite the direct conversion of the tosylate **12** into aminomethylpiperidine **14**, the synthesis of **14** still required a laborious four-step sequence starting from **6**. This prompted the development of an alternative route towards *trans*-4-aminomethyl-piperidin-3-ol building block **2**.

2.2. Diastereoselective route B

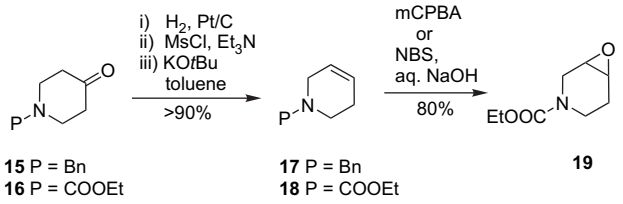
Since an epoxide ring opening also would result in a 3,4-trans relationship between the resulting hydroxyl group and the incoming nucleophile, we started to investigate the formation and opening of 3,4-epoxy-piperidines. Cyanide was chosen as a suitable nucleophile and precursor towards the

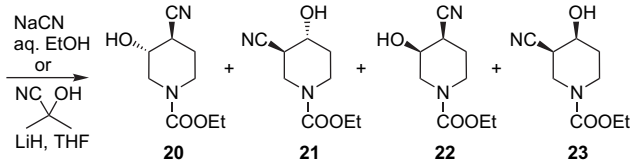


Scheme 1.



Scheme 2.





Scheme 3.

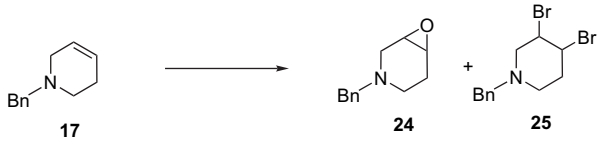
desired aminomethyl functionality.[8] The syntheses of the 3,4-dehydropiperidine intermediates **17**[6,9] and **18**[10] have been described and are mostly high-yielding two-step sequences starting from readily available starting materials. In our hands, access to these compounds was achieved on large scale, starting from the readily available ketones **15** and **16**, respectively (Scheme 3). Catalytic hydrogenation of the ketones in toluene to the corresponding alcohols, followed by dehydration provided the 3,4-dehydropiperidines **17** and **18** in high yields. The low levels of impurities combined with the absence of a solvent switch made this the favoured reaction pathway, especially to tetrahydropyridine **17**.

The epoxidation of the double bond in **17** was anticipated to be difficult with the tertiary amino functionality present. Therefore the first experiments were performed on *N*-ethoxycarbonyl protected epoxide **19**, easily accessible from **18**.[9] Epoxide opening of **19** with NaCN in ethanol/water proceeded smoothly, and resulted in a 4:1 mixture of regioisomers **20** and **21**, with the desired major product **20** arising from nucleophilic attack at the less sterically hindered 4-position. In addition, some epimerization took place, presumably at the α-nitrilic position, resulting in traces of most likely cis isomers **22** and **23** (not isolated). We reasoned that the observed epimerization was most likely due to the formation of a basic alkoxide, formed after epoxide ring opening. A change in reaction conditions from NaCN in protic solvents to LiCN in THF would result in the formation of a more covalent lithium–oxygen bond and possibly suppress the epimerization at the piperidine 4-position.[11] Since LiCN has limited commercial availability and only as a solution in DMF, it was generated in situ by the combination of LiH and acetocyanohydrin.[12] Addition of the epoxide to the LiCN/THF mixture resulted in a fast epoxide ring opening without any observed formation of cis isomers. Unfortunately, still a 4:1 mixture of trans regioisomers **20** and **21** was observed.

At this point we returned to the benzyl protected piperidines (Table 1, Scheme 4). The neighbouring group participation of the piperidine nitrogen with its lone pair in 3,4-epoxy-piperidine **24** could make nucleophilic attack at the 4-position even more preferred than for epoxide **19**.

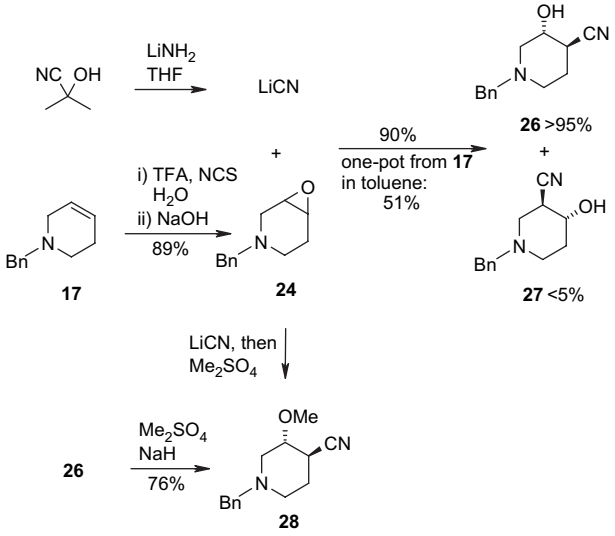
To investigate the epoxide ring opening in **24**, we required a suitable method for the epoxidation of **17**. The use of standard oxidizing agents such as *m*-CPBA led to overoxidation of the piperidine nitrogen. After several attempts a successful epoxidation method was developed with *N*-bromosuccinimide followed by base treatment (Table 1).

Table 1
Optimization experiments for the epoxidation of **20** to **27**



	Reaction conditions[a]	Product ratio (%, GC)	
i	NBS (1 equiv), aqueous dioxane	0	0
ii	NBS (2 equiv), aqueous dioxane	0	53
iii	NBS (3 equiv), aqueous dioxane	0	68
iv	TFA (1 equiv), NBS (1 equiv), aqueous dioxane	<5	>90
v	TFA (1 equiv), NBS (1 equiv), H_2O	>95	0

[a] Product ratio determined after treatment with aqueous NaOH.



Scheme 4.

Reaction of **17** with one or more equivalents of *N*-bromosuccinimide in aqueous dioxane only led to the formation of increasing amounts of dibromide **25** (Table 1, entries i–iii). Two subsequent changes in the reaction conditions were found to be critical for success (Table 1, entries iv and v). Protonation of the basic piperidine nitrogen with trifluoroacetic acid, prior to the addition of *N*-bromosuccinimide, resulted in the formation of epoxide **24** for the first time, albeit in trace amounts.[13] Finally, removal of the organic solvent led to the exclusive formation of epoxide **24**, with traces of unreacted alkene **17** as the only visible impurity. During further optimization for upscaling purposes, *N*-bromosuccinimide was replaced by *N*-chlorosuccinimide, which suppressed the dihalogenation reaction even further, and thus resulted in an improved reproducibility of the reaction.

Subsequent reaction of epoxide **24** with in situ generated LiCN in THF gave product **26** in 90% yield (Scheme 4). Only traces of the regioisomer **27** were present according to GC–MS analysis, thus confirming the positive contribution of the basic piperidine nitrogen to the regioselectivity of the epoxide opening.

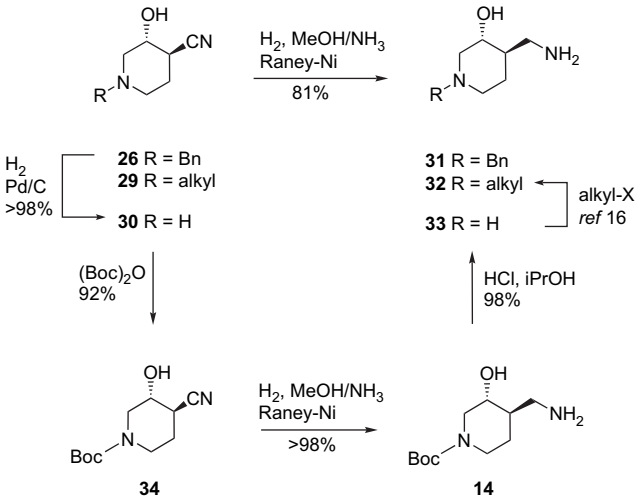
The use of the flammable and moisture sensitive LiH is not feasible for large scale applications. For the in situ generation of LiCN from acetocyanohydrin it has been successfully replaced by alkyllithiums,[14] but these have their own safety drawbacks. For production scale purposes, we replaced LiH with the much more convenient to handle lithium amide. Prior to addition of the epoxide, the reaction mixture was heated to expel the residual ammonia.

Most conveniently, on >100 g scale, the epoxide **24** was not isolated, but the toluene extraction layer, containing **24**, was directly treated with the in situ generated LiCN, to give after crystallization the desired **26** in >97% purity and 51% yield from **17**.

Although most of our final compounds incorporated the free 3-hydroxyl group, we were also interested in making 3-alkoxy piperidine analogues. This could be done by deprotonation of **26** with sodium hydride followed by reaction of the alkoxide with dimethylsulfate. Since the lithium 3-alkoxy-4-cyano piperidine salt is a likely intermediate during the epoxide ring opening of **24** to **26**, we tried to combine this ring opening with a subsequent alkylation in a one-pot procedure. Indeed, this gave the 3-methoxy piperidine **28** as the main product, although always 10–30% of non-alkylated **26** remained present.

Product **26** was subjected to hydrogenolysis (Scheme 5). Depending on the conditions and the catalyst used, either the benzyl group could be selectively removed to give **30**, or the nitrile group could be reduced to compound **31**. *N*-Boc protection of **30**, followed by extensive catalytic hydrogenation led to **14** in excellent yield, and this was found to be the most convenient route towards this intermediate.

The second diastereoselective route described in this paper has now been carried out on kilogram quantities. Starting from building block **15**, *trans*-4-aminomethyl-piperidin-3-ol **14** has been prepared in a seven-step sequence in 60% overall yield. Building block **14** has been used successfully in the synthesis



Scheme 5.

of a large number of potent 5-HT_4 ligands, including the large scale synthesis of R149402 and R199715.[15] As mentioned before, immediate quaternization of pyridine with the ultimately desired alkyl group may shorten the total synthesis of a final compound further via intermediates **29** and **32** by avoiding all protecting group manipulations. Alternatively, fully deprotected **33** can be selectively alkylated at the secondary *N*-piperidine amino group as described before.[16] The most active compounds in our medicinal chemistry program were found to have the 3*S*,4*S* absolute configuration. Further optimisation is currently directed towards the introduction of enantioselectivity in the synthetic route towards **14**.[17]

3. Conclusion

In order to prepare large quantities of *trans*-4-hydroxymethyl- and *trans*-4-aminomethyl-piperidin-3-ol containing building blocks, we have developed two diastereoselective and scaleable routes. Starting from *N*-benzyl 1,2,3,6-tetrahydropyridines, the double bond is used as a handle for the introduction of the *trans*-3,4-substituents via, respectively, a hydroboration/oxidation sequence (route A, Scheme 1) and a regioselective epoxide ring opening (route B, Schemes 4 and 5). The regioselectivity of both the hydroboration and the epoxide ring opening was positively influenced by the presence of the basic piperidine nitrogen. In route B new conditions have been developed for the epoxidation of a double bond in the presence of a basic piperidine nitrogen by protonation of the amino group and using water as the only solvent. An improved, scaleable method for the in situ formation of LiCN has been developed via the reaction of acetocyanohydrin with $LiNH_2$.

Both routes A and B have been performed at kilogram scale and are optimal for access to either *trans*-4-hydroxymethyl- or *trans*-4-aminomethyl piperidin-3-ols. Depending on the amounts required of these valuable building blocks, or their precursors, these routes can find application for both small and large scale purposes.

4. Experimental

4.1. General

Silica gel column chromatography was performed with Kiesel gel 60 (0.063–0.200 mm) (E. Merck, AG Darmstadt, Germany). ^{1}H NMR spectra were recorded on 360 and 400 MHz spectrometers (Bruker) and chemical shifts (δ) are expressed in parts per million (ppm) with TMS as internal standard. Elemental analysis were carried out on a CarloErba EA1110. Melting points were determined on a Mettler, a Büchi 545, and a Köfler apparatus and are uncorrected. Mass spectral data were obtained from by GC–MS analysis, using an Agilent 6890 series GC, combined with a 5973N Mass Selective Detector. Commercial solvents were used without any pretreatment, including anhydrous solvents where required.

4.2. 1-(Phenylmethyl)-4-pyridinemethanol chloride (*4*)

A solution of 4-pyridinemethanol **3** (200 g, 1.84 mol) in MeCN (1 L) was added to a solution of benzylchloride (279 g, 2.2 mol) in MeCN (1 L) and the reaction mixture was refluxed for 3 h, cooled to room temperature and concentrated under reduced pressure. The residue was suspended in diethyl ether, filtered and dried, yielding crude **4** (411 g, 97%). ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 4.79 (2H, s), 5.86 (2H, s), 7.39–7.48 (3H, m), 7.51–7.59 (2H, m), 8.06 (2H, d, J=6.7 Hz), 9.17 (2H, d, J=6.7 Hz).

4.3. 1-(Phenylmethyl)-4-hydroxymethyl-1,2,3,6-tetrahydro-4-pyridine (*5*)

A solution of **4** (174 g, 0.87 mol) in methanol (2.2 L) was cooled to −20 °C. Sodium borohydride (66 g, 1.75 mol) was added portionwise under a nitrogen atmosphere. The reaction mixture was stirred for 30 min and water (200 mL) was added dropwise. The reaction mixture was partially concentrated under reduced pressure, water was added and the reaction mixture was extracted with CH_2Cl_2. The organic layer was separated, dried on $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (elution CH_2Cl_2), yielding 155 g (87%) of **5**. This could be used as such in the next step. Crystallization from diisopropyl ether afforded pure **5** as a light brown solid, mp 64 °C. ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 1.96–2.03 (2H, m), 2.49 (2H, t, J=5.9 Hz), 2.83–2.88 (2H, m), 3.51 (2H, s), 3.79 (2H, s), 4.67 (1H, br s), 5.50–5.54 (1H, m), 7.21–7.27 (1H, m), 7.27–7.34 (4H, m). Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.56; H, 8.20; N, 6.83.

4.4. (±)-1-(Phenylmethyl)-(trans)-4-hydroxymethyl-piperidin-3-ol (*6*)

A solution of **5** (102 g, 0.5 mol) in THF (1 L) was cooled to −30 °C and was added dropwise under a nitrogen atmosphere to a 1 M solution of borane in THF (1 L, 1 mol) while the reaction mixture was kept at a temperature between −20 and −30 °C. After the addition, the reaction mixture was stirred for 4 h, allowed to warm up to room temperature and stirred at room temperature for 18 h. The reaction mixture was cooled to −10 °C and water (25 mL) was added dropwise. Then, simultaneously, NaOH (3 M in water, 70 mL) and the hydrogen peroxide (30% solution in water, 63.3 mL) were added dropwise while the reaction mixture was kept at a temperature of −10 °C. Again NaOH (50% in water, 140 mL) was added. The reaction mixture was stirred at reflux for 4 h and then cooled and filtered. The filtrate was concentrated under reduced pressure. The resulting precipitate was dissolved in water (500 mL) and saturated with K_2CO_3. The product was extracted with CH_2Cl_2. The resulting solution was dried over $MgSO_4$ and evaporated. The residue, containing predominantly a mixture of **6** and **7** in a 2:1 ratio according to GC–MS, was crystallized from diisopropyl ether/MeCN to yield 56 g (50%) of **6** as a white solid, mp 113 °C. ^{1}H NMR (360 MHz, $CDCl_3$) δ ppm 1.26 (1H, qd, J=13.0, 3.7 Hz), 1.47–1.58 (2H, m), 1.85 (1H, t, J=10.3 Hz), 1.96 (1H, td, J=11.7, 2.8 Hz), 2.81 (1H, br d, J=11.4 Hz), 2.9 (1H, br s), 2.97 (1H, ddd, J=10.7, 4.4, 1.5 Hz), 3.3 (1H, br s), 3.48 (1H, d, J=12.9 Hz), 3.54 (1H, d, J=12.9 Hz), 3.59–3.75 (3H, m), 7.22–7.33 (5H, m). Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.44; H, 8.83; N, 6.33.

4.5. 1-(Phenylmethyl)-4-(tert-butyl-dimethyl-silanyl-oxymethyl)-1,2,3,6-tetrahydropyridine (*8*)

To a solution of **5** (10 g, 0.05 mol) in CH_2Cl_2 (250 mL) were added Et_3N (16 mL, 0.11 mol), and a catalytic amount of DMAP. A solution of *tert*-butyl dimethylsilyl chloride (8.3 g, 0.055 mol) in CH_2Cl_2 (125 mL) was added dropwise and the reaction mixture was stirred at room temperature for 20 h. The mixture was washed with a 1 M aqueous K_2CO_3 solution and the organic layer was dried on $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (elution CH_2Cl_2/MeOH(NH_3) 95:5), yielding 15 g (95%) of **8** as an oil. ^{1}H NMR (360 MHz, $CDCl_3$) δ ppm 0.05 (6H, s), 0.90 (9H, s), 2.06–2.13 (2H, m), 2.58 (2H, t, J=5.9 Hz), 2.96–3.01 (2H, m), 3.58 (2H, s), 4.01–4.05 (2H, m), 5.59–5.64 (1H, m), 7.22–7.37 (5H, m). MS (EI$^+$) *m/z* (rel intensity) 317 (8%, M$^+$), 316 (8%), 302 (4%), 260 (5%), 185 (11%), 172 (100%), 91 (43%).

4.6. (±)-1-(Phenylmethyl)-(trans)-4-(tert-butyl-dimethyl-silanyloxymethyl)-piperidin-3-ol (*9*)

To a solution of **8** (11 g, 0.036 mol) in THF (300 mL), cooled to −30 °C, was added dropwise a 1 M solution of borane in THF (75 mL, 0.075 mol) under a nitrogen atmosphere while the reaction mixture was kept at a temperature between −20 and −30 °C. After the addition, the reaction mixture was stirred for 3 h, allowed to warm up to room temperature and stirred at room temperature for 20 h. The reaction mixture was cooled to −10 °C and water (1.2 mL) was added dropwise. Then, simultaneously, NaOH (3 M in water, 5 ml) and

hydrogen peroxide (30% solution in water, 4.6 ml) were added dropwise while the reaction mixture was kept at a temperature of −10 °C. Again NaOH (50% in water, 9 ml) was added, followed by water (30 mL). The reaction mixture was stirred at reflux for 3 h and then cooled. The organic layer was separated, dried on $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (elution CH_2Cl_2/MeOH(NH_3) 95:5), yielding 10 g (83%) of **9** as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.05 (3H, s), 0.06 (3H, s), 0.87 (9H, s), 1.18 (1H, qd, J=12.4, 4.0 Hz), 1.43−1.58 (2H, m), 1.82 (1H, t, J=10.2 Hz), 1.92 (1H, td, J=11.6, 2.7 Hz), 2.77 (1H, br d, J=11.3 Hz), 3.01 (1H, ddd, J=10.6, 4.6, 1.6 Hz), 3.50 (2H, s), 3.57−3.68 (2H, m), 3.72 (1H, dd, J=9.9, 4.0 Hz), 4.03 (1H, s), 7.17−7.24 (1H, m), 7.24−7.30 (4H, m).

4.7. (±)-1,1-Dimethylethyl trans-3-hydroxy-4-(hydroxymethyl)-1-piperidinecarboxylate (**11**)

A solution of **6** (486 g, 2.2 mol) in methanol (3 L) was hydrogenated under a hydrogen atmosphere, at 50 °C, with palladium on activated carbon (10%) (25 g) as a catalyst. After uptake of 1 equiv of H_2, the catalyst was filtered off and the filtrate was evaporated, giving 290 g of (±)-*trans*-4-hydroxymethyl-piperidin-3-ol (quantitative yield), which was used in the next reaction step, without further purification. Crystallization from diisopropyl ether afforded pure (±)-*trans*-4-hydroxymethyl-piperidin-3-ol as a white solid, mp 104 °C. ^{1}H NMR (360 MHz, $CDCl_3$) δ ppm 1.12 (1H, qd, J=12.3, 4.3 Hz), 1.55−1.71 (2H, m), 2.44 (1H, dd, J=11.6, 10.1 Hz), 2.58 (1H, dt, J=12.2, 2.5 Hz), 3.0 (1H, br d, J=12.2 Hz), 3.18 (1H, dd, J=11.6, 4.7 Hz), 3.56 (1H, dt, J=10, 4.7 Hz), 3.68 (1H, dd, J=10.5, 8.6 Hz), 3.74 (1H, dd, J=10.5, 4.0 Hz). Anal. Calcd for $C_6H_{13}NO_2$: C, 54.94; H, 9.99; N, 10.68. Found: C, 54.71; H, 10.25; N, 10.57.

A solution of $(Boc)_2O$ (464 g, 2.13 mol) in CH_2Cl_2 (0.5 L) was added dropwise to a solution of the crude intermediate (280 g, 2.13 mol) in CH_2Cl_2 (3 L) at room temperature, while cooling on a waterbath. After the addition, methanol (1 L) was added and the resulting reaction solution was stirred for 1 h at room temperature. The solvent was evaporated to yield 492 g (quantitative yield) of **11**. This could be crystallized from diisopropyl ether, mp 88 °C. ^{1}H NMR (360 MHz, $CDCl_3$) δ ppm 1.16 (1H, qd, J=12.7, 4.4 Hz), 1.44 (9H, s), 1.52−1.71 (2H, m), 2.43−2.58 (1H, m), 2.59−2.77 (1H, m), 3.45−3.56 (1H, m), 3.66 (1H, dd, J=10.3, 8.4 Hz), 3.74 (1H, br d, J=10.3 Hz), 3.89−4.33 (2H, m). Anal. Calcd for $C_{11}H_{21}NO_4$: C, 57.12; H, 9.15; N, 6.06. Found: C, 57.14; H, 9.21; N, 6.01.

4.8. (±)-1,1-Dimethylethyl trans-3-hydroxy-4-[[(4-methylphenyl)sulfonyl]oxymethyl]-1-piperidinecarboxylate (**12**)

To a cooled (−10 °C) solution of **11** (117 g, 0.51 mol) in pyridine (200 mL) was added tosyl chloride (110 g, 0.54 mol) portionwise. The reaction mixture was stirred at room temperature for 1 h. Then CH_2Cl_2 (1.5 L) was added and the mixture was washed with 5% aqueous HCl solution, followed by an aqueous $NaHCO_3$ solution. The organic layer was dried on $MgSO_4$ and concentrated under reduced pressure. Toluene was added to the residue, and the mixture was again concentrated under reduced pressure to give **12** as an oil, which could be used as such in the next step. Crystallization from diisopropyl ether and a small amount of MeCN gave a white solid, mp 111 °C. ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 1.08 (1H, qd, J=13.0, 4.6 Hz), 1.37 (9H, s), 1.53−1.63 (2H, m), 2.36 (1H, br s), 2.42 (3H, s), 2.57 (1H, br s), 3.02−3.13 (1H, m), 3.83 (1H, br s), 3.99 (1H, dd, J=9.5, 7.0 Hz), 3.96 (1H, br s), 4.14 (1H, dd, J=9.3, 2.7 Hz), 5.11 (1H, d, J=5.1 Hz), 7.48 (2H, d, J=8.0 Hz), 7.78 (2H, d, J=8.0 Hz). Anal. Calcd for $C_{11}H_{21}NO_4$: C, 56.09; H, 7.06; N, 3.63. Found: C, 56.27; H, 7.18; N, 3.50.

4.9. (±)-1,1-Dimethylethyl trans-4-(aminomethyl)-3-hydroxy-1-piperidinecarboxylate (**14**)

4.9.1. Two-step procedure from **12**

A mixture of **12** (0.22 mol) and benzylamine (0.084 mol) in THF (100 mL) was stirred for 16 h at 125 °C (autoclave). The reaction mixture was cooled and the solvent was evaporated under reduced pressure. The residue was partitioned between CH_2Cl_2 and an aqueous K_2CO_3 solution. The organic layer was separated, dried on $MgSO_4$, filtered and concentrated under reduced pressure, yielding 15.4 g of 1,1-dimethylethyl (*trans*)-3-hydroxy-4-[[(phenylmethyl)amino]methyl]-1-piperidinecarboxylate **13** together with remaining benzylamine. In order to obtain a pure sample of **13**, after a similar reaction the excess benzylamine was removed via high vacuum distillation, followed by crystallization of the residue in diisopropyl ether, to give pure **13** as a white solid, mp 91 °C. ^{1}H NMR (360 MHz, $CDCl_3$) δ ppm 1.11 (1H, qd, J=13.2, 4.4 Hz), 1.45 (9H, s), 1.46−1.58 (2H, m), 2.49 (1H, br t, J=11.3 Hz), 2.61 (1H, t, J=11.5 Hz), 2.56−2.7 (1H, m), 2.92 (1H, dd, J=12.1, 2.6 Hz), 3.47 (1H, td, J=9.7, 5.1 Hz), 3.75 (1H, d, J=13.0 Hz), 3.87 (1H, d, J=13.0 Hz), 4.06−4.31 (2H, m), 7.25−7.37 (5H, m).

The crude **13** was dissolved in methanol (100 mL) and hydrogenated with palladium on carbon (10%, 1 g) as a catalyst at 50 °C under 1 atm hydrogen pressure. After uptake of 1 equiv of H_2, the catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue was crystallized from diisopropyl ether+MeCN, filtered off and dried (vacuum, 40 °C), yielding 4 g (76% over two steps) of **14** as a white solid, mp 178 °C. ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 0.98 (1H, qd, J=12.6, 4.6 Hz), 1.19−1.32 (1H, m), 1.38 (9H, s), 1.59 (1H, dq, J=13.2, 2.8 Hz), 2.25−2.5 (1H, m), 2.53−2.67 (1H, m), 2.59 (1H, dd, J=12.4, 5.5 Hz), 2.67 (1H, dd, J=12.4, 6.6 Hz), 3.15 (1H, td, J=9.9, 4.8 Hz), 3.79−4.00 (2H, m). Anal. Calcd for $C_{11}H_{22}N_2O_3$: C, 57.37; H, 9.63; N, 12.16. Found: C, 57.61; H, 9.80; N, 11.92.

4.9.2. One-step procedure from **12**

A solution of **12** (35 g, 0.09 mol) in THF (250 mL) was treated with liquid NH_3 in an autoclave at 125 °C during 16 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was

partitioned between a 5% aqueous NaOH solution and CH_2Cl_2. The organic layer was separated, dried on $MgSO_4$, filtered and the solvent was concentrated under reduced pressure, yielding **14** (16 g, quantitative yield).

4.10. 1-(Phenylmethyl)-1,2,3,6-tetrahydropyridine (*17*)

A solution of **15** (70 g, 0.37 mol) in toluene (300 mL) was hydrogenated overnight at 40 °C with 5% Pd/C (8.4 g) as a catalyst. After GC analysis showed the complete conversion of **15** to the corresponding alcohol, the reaction mixture was filtered over dicalite and the dicalite washed with toluene (100 mL). To this filtrate, a solution of triethylamine (41 g, 0.405 mol) in toluene (400 mL) was added. The resulting mixture was cooled to 5 °C and mesylchloride (46.5 g, 0.405 mol) was added dropwise over a 20 min period, during which time the temperature increased to 25 °C and a precipitate was formed. The mixture was stirred for an additional 1.5 h at room temperature, and then washed with water (2×200 mL). The organic layer was partially concentrated under reduced pressure to remove 200 mL of solvent. The remaining solution containing the mesylate was diluted with toluene (600 mL) and DMA (400 mL) and KO^{t}Bu (54 g, 0.48 mol) was added. The reaction mixture was stirred for 1.5 h at room temperature, and subsequently washed with water (400 mL) and concentrated under reduced pressure to give 63 g of crude **17**. The residue was distilled (75 °C at 0.15 mbar) to give **17** as an oil (41 g, 64% from **15**). The analytical data were in agreement with those reported in the literature.[9]

4.11. Ethyl 1,2,3,6-tetrahydropyridinecarboxylate (*18*)

Compound **18** was prepared from **16** using the same procedure as described for **17**, with analytical data consistent with those reported in the literature.[10]

4.12. Ethyl 7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate (*19*)

To a solution of **18** (217 g, 1.39 mol) in water (1 L) and dioxane (1 L) was added *N*-bromosuccinimide (261 g, 1.47 mol) portionwise at room temperature. During the addition, the temperature slowly increased to 35 °C. After addition, the reaction was stirred 20 h at room temperature and subsequently extracted with CH_2Cl_2 (3×500 mL). The combined organic layers were washed with brine, dried on $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in THF (700 mL), and a 5% aqueous NaOH solution (3,5 L) was added. The reaction mixture was stirred for 1 h at room temperature, and the product extracted with CH_2Cl_2 (3×300 mL). The combined organic layers were dried on $MgSO_4$ and concentrated under reduced pressure. The residue was distilled under reduced pressure (bp 65 °C at 0.1 mmHg) to yield **23** (189 g, 80%). The analytical data were consistent with those reported in the literature.[9,10]

4.13. Ethyl (±)-(trans)-4-cyano-3-hydroxy-piperidinecarboxylate (*20*) and ethyl (±)-(trans)-3-cyano-4-hydroxy-piperidinecarboxylate (*21*)

To a cooled (0–5 °C) suspension of LiH (0.72 g, 0.09 mol) in THF (75 mL) was added a solution of acetocyanohydrin (8.2 mL, 0.09 mol) in THF (15 mL) under a N_2 atmosphere. The reaction mixture was stirred for 2 h at room temperature, and then a solution of **19** (12.8 g, 0.075 mol) in THF (30 mL) was added dropwise. The reaction mixture was subsequently refluxed for 1 h. After cooling to room temperature, water (200 mL) was added, and the mixture was extracted with CH_2Cl_2 (3×100 mL). The combined organic layers were dried on $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (elution CH_2Cl_2/MeOH(NH_3) 96:4), yielding 12 g (80%) of a 4:1 mixture of **20** and regioisomer **21**. Compound **20** ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 1.17 (3H, t, J=7.0 Hz), 1.54–1.66 (1H, dddd, J=13.2, 11.5, 11.5, 4.4 Hz), 1.99 (1H, dq, J=13.2, 3.4 Hz), 2.65 (1H, br s), 2.72 (1H, ddd, J=11.3, 9.5, 4.0 Hz), 2.82 (1H, br t, J=10.2 Hz), 3.46–3.56 (1H, m), 3.80 (1H, br d, J=13.5 Hz), 3.94 (1H, br s), 4.02 (2H, q, J=7.0 Hz), 5.79 (1H, d, J=5.5 Hz). Compound **21** (identifiable peaks) ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 1.18 (3H, t, J=7.0 Hz), 1.27–1.41 (1H, m), 1.74–1.86 (1H, m), 3.14 (1H, ddd, J=13.5, 9.5, 3.3 Hz), 3.34 (1H, br s), 3.64 (1H, br d, J=13.2 Hz), 5.58 (1H, d, J=5.1 Hz).

4.14. 3-(Phenylmethyl)-7-oxa-3-aza-bicyclo-[4.1.0]heptane (*24*)

A mixture of trifluoroacetic acid (89 mL, 1.15 mol) in water (2 L) was stirred at room temperature. Compound **17** (200 g, 1.15 mol) was added dropwise to the mixture and the resulting suspension was stirred at room temperature for 15 min. *N*-Bromosuccinimide (250 g, 1.4 mol) was added portionwise over 1 h, during which time the temperature increased to 30–35 °C. The reaction mixture was stirred for an additional 30 min. Again *N*-bromosuccinimide (15 g, 0.085 mol) was added portionwise (temperature to 35 °C). The reaction mixture was stirred overnight at room temperature and then decanted and added dropwise to a 20% aqueous NaOH solution (2 L). The mixture was stirred overnight at room temperature. The product was extracted with CH_2Cl_2 (3×600 mL). The combined organic layers were dried on $MgSO_4$, filtered, and concentrated under reduced pressure to yield crude **24** (193 g, 89%), which could be used as such in the next step, or purified further via distillation under reduced pressure (bp 60 °C at 0.1 mmHg). The analytical data were consistent with those reported in the literature.[13] MS (EI$^+$) *m/z* (rel intensity) 189 (34%, M$^+$), 133 (33%), 91 (100%).

4.15. (±)-1-(Phenylmethyl)-(trans)-4-cyano-piperidin-3-ol (*26*)

To a suspension of $LiNH_2$ (15.1 g, 0.66 mol) in THF (600 mL) was added a solution of acetocyanohydrin (60 mL, 0.66 mol) in THF (150 mL) at 40 °C under a N_2 atmosphere.

The reaction mixture was stirred for 0.5 h at 40 °C, cooled to room temperature, and then a solution of **24** (114 g, 0.6 mol) in THF (250 mL) was added dropwise. After complete addition, the reaction mixture was stirred and refluxed for 4 h, then stirred overnight at room temperature. Water was added (2 L) and the mixture was extracted with CH_2Cl_2 (2×1 L). The combined organic layers were dried on $MgSO_4$, filtered, and concentrated under reduced pressure, yielding **26** (128 g, 90%), which could be used as such in the next step, or purified further via crystallization from diisopropyl ether to give a white solid, mp 85 °C. ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 7.23–7.35 (5H, m), 5.51 (1H, d, J=6.0 Hz), 3.52 (1H, d, J=13.3 Hz), 3.48–3.57 (1H, m), 3.42 (1H, d, J=13.2 Hz), 2.86 (1H, ddd, J=10.9, 4.4, 1.6 Hz), 2.72 (1H, d, J=11.5 Hz), 2.44 (1H, ddd, J=12.2, 10.0, 4.1 Hz), 1.98 (1H, dq, J=12.8, 3.3 Hz), 1.88 (1H, td, J=11.6, 2.6 Hz), 1.71 (1H, dd, J=11.0, 9.7 Hz), 1.64 (1H, qd, J=12.5, 4.1 Hz). Anal. Calcd for $C_{13}H_{16}N_2O$: C, 72.22; H, 7.74; N, 12.82. Found: C, 72.19; H, 7.46; N, 12.45.

*4.15.1. One-pot procedure from **17***

To a stirred suspension of **17** (132 g, 0.76 mol) in water (950 mL) was added trifluoroacidic acid (87 g, 0.76 mol) dropwise over a 15 min period. To the resulting clear solution, *N*-chlorosuccinimide (122.5 g, 0.92 mol) was added portionwise, and the reaction mixture was heated to 40 °C overnight. Subsequently, the reaction mixture was cooled to room temperature and a 50% aqueous NaOH solution (245 g, 3 mol) was added dropwise over 15 min, while cooling on a waterbath. During the addition, the temperature rose to 40 °C, and the reaction mixture was subsequently stirred at this temperature for 2 h. Then, the reaction mixture was extracted with toluene (1.15 L), and the organic layer was partially concentrated under reduced pressure to remove 400 mL of solvent to give a remaining solution of epoxide **24** in toluene.

A suspension of $LiNH_2$ (21.1 g, 0.92 mol) in THF (750 mL) was heated to 40 °C for 15 min. Then acetocyanohydrin (78.1 g, 0.92 mol) was added over 15 min and the resulting suspension was stirred at 40 °C for an additional 25 min. To this suspension the solution of **24** in toluene was added, followed by an additional 375 mL of toluene, and the mixture was heated at reflux for 1.5 h. The reaction mixture was cooled to room temperature and washed with two 375-mL portions of water. The organic layer was concentrated under reduced pressure to give crude **26** (137 g). Part of this residue (117 g) was heated to 50 °C and diisopropyl ether (233 mL) was added dropwise over 15 min. Then the homogeneous mixture was heated at reflux for 30 min, cooled to 40 °C and the solution was seeded with crystalline **26**. The mixture was cooled further to room temperature overnight, and the solid product collected via filtration to afford **26** as a beige solid (72 g, 51% overall yield from **17**).

*4.16. (±)-1-(Phenylmethyl)-(trans)-4-cyano-3-methoxy-piperidine (**28**)*

To a solution of **26** (85.6 g, 0.4 mol) in THF (1.4 L) was added NaH (60% in mineral oil, 17.6 g, 0.44 mol) portionwise at room temperature under a N_2 atmosphere. The mixture was stirred for 30 min at room temperature. A solution of dimethylsulfate (41.7 mL, 0.44 mol) in THF (650 mL) was added dropwise to the mixture. The reaction mixture was refluxed for 3 h under a N_2 atmosphere, and then allowed to stand overnight at room temperature. Water (2 L) was added, and the mixture was extracted with CH_2Cl_2 (2×1 L). The combined organic layers were dried on $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was crystallized as from isopropanol/MeCN and oxalic acid, yielding the oxalate of **28** (97 g, 76%), mp 152 °C. CHN calcd/found C 54.99/54.45, H 6.29/6.30, N 8.74/8.50. The oxalate salt was converted into the free base by adding water and Na_2CO_3 followed by extraction of the aqueous layer with CH_2Cl_2. The organic layers were dried on $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was co-evaporated with toluene (2×) to yield **28** (70 g, 76%) as an oil. ^{1}H NMR (360 MHz, $CDCl_3$) δ ppm 1.77–2.09 (4H, m), 2.42 (1H, ddd, J=11.3, 9.2, 4.4 Hz), 2.71–2.81 (1H, m), 3.10 (1H, dd, J=10.8, 3.5 Hz), 3.45 (3H, s), 3.44 (1H, dt, J=9.1, 4.2 Hz), 3.51 (1H, d, J=13.2 Hz), 3.57 (1H, d, J=13.2 Hz), 7.24–7.35 (5H, m).

*4.16.1. One-pot procedure from **24***

To a suspension of LiH (0.19 g, 0.024 mol) in THF (100 mL) was added a solution of acetocyanohydrin (2.2 mL, 0.024 mol) in THF (6 mL) under a N_2 atmosphere. The reaction mixture was stirred for 2 h at room temperature, and then concentrated under reduced pressure to afford LiCN as a white solid, which was immediately dissolved in THF (100 mL). To this LiCN solution was added a solution of **24** (3.8 g, 0.02 mol) in THF (5 mL) dropwise under a N_2 atmosphere. Subsequently, the reaction mixture was refluxed for 2.5 h, and then allowed to cool to 40 °C. To this mixture a solution of dimethylsulfate (2.1 mL, 0.022 mol) in THF (5 mL) was added dropwise, and the reaction mixture was refluxed for 3 h under a N_2 atmosphere. Aqueous work-up as above provided a mixture of **28** and **26** in a 9:1 ratio plus traces of remaining epoxide **24**.

*4.17. (±)-trans-4-Cyano-piperidin-3-ol (**30**)*

A solution of **26** (59 g, 27 mol) in methanol (500 mL) was hydrogenated at 40 °C under a starting pressure of 7 atm hydrogen with 10% Pd/C (5 g) as a catalyst. After the reaction had proceeded for about 60% according to LC–MS analysis, further uptake of hydrogen stopped, and the reaction mixture was filtered over dicalite and concentrated under reduced pressure. Then the residue was again subjected to the same hydrogenation conditions, until uptake of 1 equiv of hydrogen in total. Again, the reaction mixture was filtered over dicalite and concentrated under reduced pressure. After co-evaporation with toluene, 35 g (quantitative yield) of **30** was obtained as an oil, which was used as such in the next reaction step. ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 1.51 (1H, qd, J=12.1, 4.2 Hz), 1.92 (1H, dq, J=12.8, 3.2 Hz), 2.16 (1H, dd, J=12.1, 9.5 Hz), 2.30 (1H, td, J=12.2, 2.7 Hz), 2.46–2.54 (1H, m),

2.77 (1H, dt, J=12.5, 3.4 Hz), 2.94 (1H, dd, J=12.1, 4.4 Hz), 3.38 (1H, td, J=9.7, 4.4 Hz). MS (EI^+) *m/z* (rel intensity) 126 (51%, M^+), 97 (11%), 72 (14%), 57 (100%).

*4.18. (±)-1-(Phenylmethyl)-(trans)-4-(aminomethyl)-piperidin-3-ol (**31**)*

Compound **26** (130 g, 0.6 mol) in a 7 N NH_3/MeOH solution (1.5 l) was hydrogenated at 14 °C with Raney nickel as a catalyst (20 g). After uptake of 2 equiv of hydrogen, the catalyst was filtered off and the solvent was evaporated. The residue was dissolved in MeCN and filtered to remove remaining solids. The filtrate was concentrated again under reduced pressure and the residue was treated with diisopropyl ether to afford crystalline **31** (107 g, 81%), mp 74 °C. ^{1}H NMR (360 MHz, $CDCl_3$) δ ppm 1.21 (1H, qd, J=12.4, 4.0 Hz), 1.25–1.39 (1H, m), 1.51 (1H, dq, J=12.7, 2.8 Hz), 1.85 (1H, t, J=10.1 Hz), 1.95 (1H, td, J=11.4, 2.7 Hz), 2.68 (1H, dd, J=12.1, 10.6 Hz), 2.82 (1H, br d, J=11.3 Hz), 2.96 (2H, br s), 3.02–3.09 (2H, m), 3.54 (2H, s), 3.68 (1H, td, J=9.3, 4.4 Hz), 7.20–7.28 (1H, m), 7.28–7.34 (4H, m). Anal. Calcd for $C_{13}H_{20}N_2O$: C, 70.87; H, 9.15; N, 12.72. Found: C, 70.53; H, 9.05; N, 12.46.

*4.19. (±)-trans-4-(Aminomethyl)-piperidin-3-ol (**33**)*

To a solution of **14** (HCl salt, 58 g, 0.22 mol) in isopropanol (2.2 L) was added a 6 N HCl solution in isopropanol (220 mL) and the mixture was refluxed for 30 min. The reaction mixture was concentrated under reduced pressure and the residue coevaporated with toluene (500 mL). The solid residue was suspended in diisopropyl ether. The solid was filtered off and dried in vacuo to give **33** as a double HCl salt (43 g, 98%), mp 237 °C. ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 1.37–1.53 (1H, m), 1.72–1.85 (1H, m), 1.99 (1H, dq, J=14.3, 3.3 Hz), 2.56–2.69 (2H, m), 2.75 (1H, br t, J=11.5 Hz), 3.08 (1H, d, J=9.9 Hz), 3.12–3.23 (2H, m), 3.53–3.66 (1H, m), 5.84 (1H, d, J=4.8 Hz), 8.16 (3H, br s), 9.38 (2H, br s). Anal. Calcd for $C_6H_{14}N_2O\cdot 2HCl$: C, 35.48; H, 7.94; N, 13.79. Found: C, 35.46; H, 7.81; N, 14.33.

*4.20. (±)-1,1-Dimethylethyl trans-4-cyano-3-hydroxy-1-piperidinecarboxylate (**34**)*

To a solution of **30** (32.8 g, 0.26 mol) in methanol (290 mL) was added $(Boc)_2O$ (69 g, 0.32 mol) at room temperature and the reaction mixture was stirred at room temperature overnight. Water (150 mL) was added and the mixture was stirred for an additional 4 h at room temperature. The methanol was evaporated under reduced pressure at room temperature and the resulting mixture was extracted with CH_2Cl_2 (450 mL). The organic layer was dried on Na_2SO_4 and concentrated under reduced pressure to give **34** (54 g, 92%) as an oil, which could be used as such in the next step. ^{1}H NMR (360 MHz, DMSO-d_6) δ ppm 1.39 (9H, s), 1.50–1.62 (1H, m), 1.98 (1H, dq, J=13.4, 3.2 Hz), 2.57 (1H, br s), 2.70 (1H, ddd, J=11.5, 9.5, 3.8 Hz), 2.75 (1H, m), 3.46 (1H, tt, J=9.6, 5.0 Hz), 3.77 (1H, d, J=13.5 Hz), 3.91 (1H, br s), 5.79 (1H, d, J=5.5 Hz).

*4.21. (±)-1,1-Dimethylethyl trans-4-(aminomethyl)-3-hydroxy-1-piperidinecarboxylate (**14**)*

Nitrile **34** could be reduced via catalytic hydrogenation to **14** using the same procedure as described for **31** in quantitative yield. The analytical data were identical to the previously prepared **14** (vide supra).

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