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Synthesis of functionalized 3-hydroxypiperidines

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ABSTRACT

The synthetic versatility of three chemoenzymatically prepared hydroxypiperidine building blocks has been explored, resulting in a library of enantiopure functionalized piperidines. Key steps involved *N*-acyliminium ion-mediated CC-bond formation and cross-metathesis reactions, after which full deprotection led to the set of free 3-hydroxypiperidines.

1. Introduction

The 3-hydroxypiperidine moiety constitutes a key structural element in various biologically relevant molecules and natural products.[1] Some examples of the latter include the relatively simple substituted 3-hydroxypiperidines such as 5-hydroxypipecolic acid (**1**),[2] 1,3,4-trideoxynojirimycin (**2**),[3] and pseudoconhydrine (**3**, Fig. 1).[4] Pipecolic acid **1** is found in various plants and microorganisms and is a potentially useful scaffold for incorporation into conformationally restricted peptidomimetics.[5] Recently, the azasugar **2** was isolated from the pods of the *Angylocalyx pynaertii*. Pseudoconhydrine (**3**) was isolated from the poisonous hemlock (*Conium maculatum*) and a first total synthesis was already reported in 1949.[6]

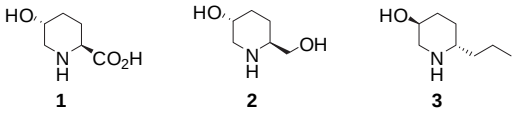
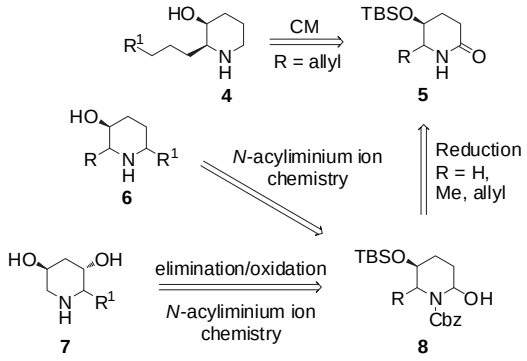


Figure 1.

Although several syntheses of these natural products and related 3-hydroxypiperidines are known,[7] efficient pathways to diversely substituted 3-hydroxypiperidines still form an attractive objective. Earlier in our group a strategy for the synthesis of a 3-hydroxypiperidine moiety was developed and applied in total syntheses of (+)-epiquinamide[8] and (+)-febrifugine.[9] Herewith we wish to report an extension of this methodology resulting in the synthesis of a modest library of diversely substituted piperidines.

We devised a new strategy that would give access to functionalized 3-hydroxypiperidines in a straightforward way. The approach can be divided in two main pathways as depicted in Scheme 1. In the first pathway, 2,3-disubstituted piperidines will be prepared via cross-metathesis (CM) onto the allyl-substited piperidine **5**. The second pathway should give access to piperidines **6** and **7** with different substitution patterns via *N*-acyliminium ion chemistry starting from hemiaminals **8**. In case of the 3,5-dihydroxy compounds **7** this *N*,*O*-acetal is first converted in the enamide followed by diol formation to deliver the *N*-acyliminium ion precursor. Hemiaminals **8** can be formed via Cbz-protection of the piperidines **5**, followed by partial reduction of the lactam. In turn, the lactams **5** can be formed from an enantiopure cyanohydrin via a reductive cyclization as previously described.[8]



Scheme 1. Retrosynthesis.

2. Synthesis of the three building blocks

In earlier investigations we disclosed the efficient formation of the enantiopure cyanohydrin **9** using the hydroxynitrile lyase *Hb*HNL and its conversion into the corresponding *N*,*N*-acetal under reductive conditions.[8] Diazotation in acetic acid gave the *N*,*O*-acetal **10**, which turned out to be suitable for *N*-acyliminium ion-mediated reactions with, for example, allyltrimethylsilane to afford the

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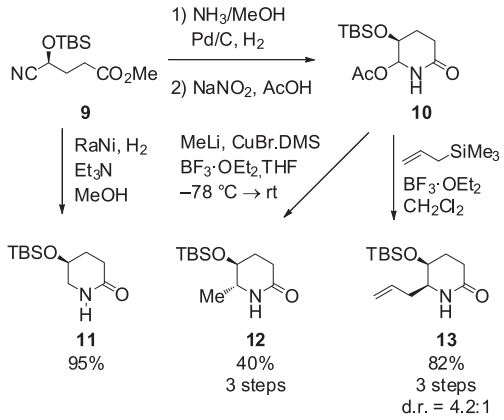
allylated product **13** in 82% over three steps (Scheme 2). In order to extend the scope, *N*,*O*-acetal **10** was now subjected to methyl cuprate to afford product **12** in a moderate yield of 40% over three steps (starting from **9**) as a single diastereoisomer.[10] Varying the conditions (e.g., changing the nucleophile or copper source) gave no improvement in yield. Furthermore, cyclization of the cyanohydrin under influence of Raney nickel and Et_3N gave lactam **11** in 95% yield. With these three building in hand, the stage was set for the diversifications.



Scheme 2. Building block synthesis.

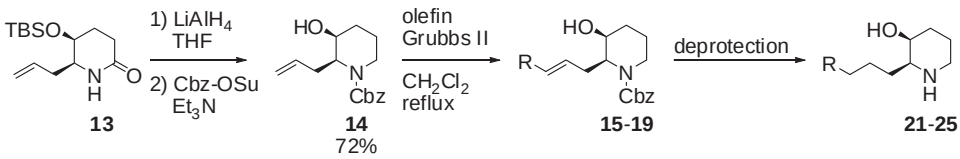
3. Cross-metathesis

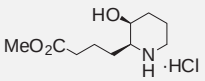
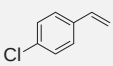
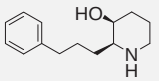
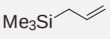
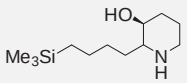
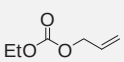
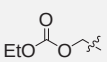
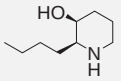
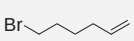
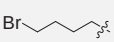
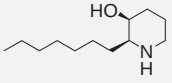
A straightforward way to generate a class of 2,3-disubstituted piperidines proceeds via CM[11] of the allylated piperidine derivative **14**. Its precursor **13** was reduced prior to the CM reaction to facilitate the introduction of more diverse olefins. The reduction was performed with $LiAlH_4$ and proceeded with concomitant desilylation to the free hydroxy substituent. Next, the amine was Cbz-protected in view of its anticipated incompatibility with the CM reaction. Treatment with Cbz–OSu in the presence of triethylamine provided the CM substrate **14** in 72% yield over two steps.

The first cross-metathesis was performed with methyl acrylate under influence of Grubbs-II to give the desired product **15** in 62% yield (Table 1, entry 1). Prompted by this result, other olefins were also subjected to the CM reaction such as 4-chlorostyrene affording olefin **16** in a moderate yield of 55% (entry 3). CM with a more electron-rich alkene, allyltrimethylsilane, gave CM product **17** in a good yield of 70% (entry 4). Next, allyl ethyl carbonate was used to afford olefin **18** in 72% yield (entry 5). In entry 6, the allyl precursor was reacted with 6-bromohex-1-ene to provide bromide **19** in 53% yield. In conclusion, a range of olefins with different functionalities could be successfully coupled to precursor **14** via cross-metathesis.

Next, Cbz deprotection of the CM products was in order. The first attempt to remove the Cbz protecting group was carried out with HBr in acetic acid, but the reactions did not proceed in a clean manner. Therefore, we switched to a hydrogenolysis approach under the influence of Pd/C and hydrogen gas, which would also lead to olefin hydrogenation. The first precursor **15** was subjected to these reductive conditions and indeed the Cbz group was removed. Analysis showed that the product had partially cyclized via attack of the liberated nitrogen onto the methyl ester. Subsequent subjection of the mixture to a basic methanol mixture afforded the fully cyclized product **20** in 78% yield (Table 1, entry 1). Although, addition of HCl during the hydrogenation prevented cyclization so that product **21** was obtained quantitatively (entry 2). Removal of the Cbz group in case of the halogenated compounds **16** and **19** proceeded smoothly, but also both halogens were removed (entries 3 and 6). Entry 4 shows the deprotected silyl-containing product **23**, which was obtained in 79% yield. Surprisingly, hydrogenolysis

Table 1
Cross-metathesis of piperidine **14**



Entry	Olefin	R	Product	Yield (%)	Conditions deprotection[a]	Product		Yield (%)
1			**15**	62	A		**20**	78
2			**15**		B		**21**	100
3			**16**	55	B		**22**	66
4			**17**	70	C		**23**	79
5			**18**	72	B		**24**	100
6			**19**	53	C		**25**	95

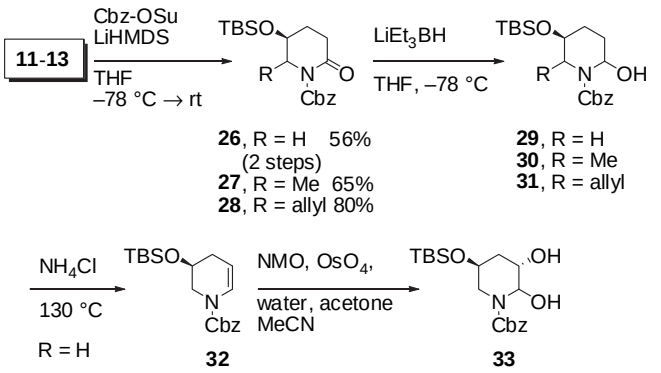
[a] Conditions: (A) (1) Pd/C, 20 bar H_2 (H-Cube) 25 °C, 1 mL/min MeOH; (2) K_2CO_3 (2 equiv), MeOH, 2 h. (B) Pd/C, H_2 (1 atm), HCl (1 equiv), MeOH, 2 h. (C) Pd/C, 20 bar H_2, (H-Cube) 25 °C, 1 mL/min MeOH.

of carbonate **18** led to complete reduction of the carbonate group. In the literature, removal of the carbonate group has been described with Pd(0) via a mechanism similar to the acetate elimination sequence.[12] Presumably, the π-allyl complex is formed under influence of Pd/C, followed by β-hydride elimination and subsequent hydrogenation of the double bond. The reaction proceeded cleanly and afforded product **24** in quantitative yield (entry 5). Thus, a series of 2-alkylated 3-hydroxypiperidines were efficiently prepared in reasonable overall yields.

4. *N*-Acyliminium ion chemistry

The three building blocks **11**–**13** were protected with a Cbz group to facilitate reduction to the *N*,*O*-acetals. Treatment of **11** with Cbz–OSu and LiHMDS gave the Cbz-protected piperidone **26** in 56% over two steps. In the same fashion the methyl substituted (**12**) and the allyl substituted piperidone (**13**) were Cbz-protected in 65 and 80% yield, respectively (Scheme 3). Initially, the formation of the *N*,*O*-acetal was troublesome: performing the reduction with $NaBH_4$[13] gave only the linear amino alcohol due to overreduction. Gratifyingly, use of $LiEt_3BH$ gave the hemiaminal **29** in a clean conversion.[14] Encouraged by this result, the same reaction was performed on the other two building blocks **27** and **28** to produce the *N*-acyliminium ion precursors **30** and **31**. Due to the instability of the hemiaminals, they were used directly without column chromatography in the next *N*-acyliminium ion steps. In all cases, the hemiaminals were obtained as mixtures of diastereoisomers, but exact determination of the ratios appeared impossible due to the presence of rotamers and therefore complex NMR spectra.

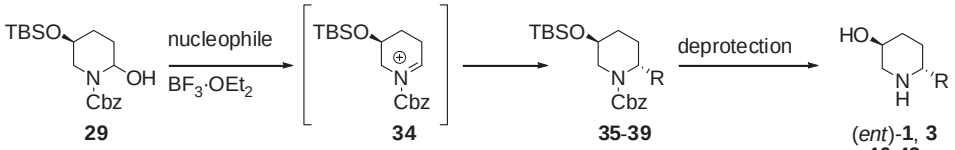
We envisioned that extension of the library of substituted piperidines could be realized via enamide formation and subsequent dihydroxylation of hemiaminal **29**. Heating in the presence of NH_4Cl smoothly afforded enamide **32**.[15] Subsequent epoxidation was attempted with Oxone, but no product was observed. A one-pot epoxidation-ring opening sequence (Oxone, $NaHCO_3$, MeOH) did not lead to the desired product either. The outcome was most of the time unclear due to complex NMR spectra and unstable compounds. Luckily, diol formation under influence of NMO and osmium tetroxide instead afforded triol **33**, which was used in crude form in the subsequent *N*-acyliminium ion reaction.

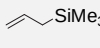
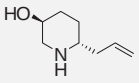
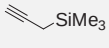
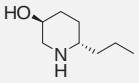
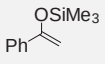
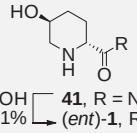
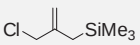
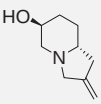


Scheme 3. Synthesis of hemiaminals **29**–**31** and **33**.

Having set the stage for the *N*-acyliminium ion reactions, precursor **29** was reacted with allyltrimethylsilane and $BF_3{\cdot}OEt_2$ to give the allyl-substituted product **35** in 72% yield over two steps as a single diastereoisomer (Table 2, entry 1).[16] Next, different nucleophiles were used to determine the scope of the reaction and prepare a small set of 2,5-disubstituted piperidines. The introduction of an allene via reaction with propargyltrimethylsilane proceeded in a moderate yield of 44% (entry 2). Unfortunately, the reaction with a silyl enol ether did not show any product formation at all (entry 3). Entry 4 shows that it was possible to introduce a cyanide group in a yield of 41%. Finally, a last variation was introduced via reacting 2-(chloromethyl)allyltrimethylsilane with hemiaminal **29** to give **39** in a yield of 68%. In all cases the reaction was completely diastereoselective, with the trans-isomer as the

Table 2
N-Acyliminium ion reactions of hemiaminal **29**



Entry	Nucleophile	R	Product	Yield[a] (%)	Conditions deprotection[b]	Product		Yield (%)
1			**35**	72	A		**40**	78
2			**36**	44	B		**3**	52
3			**37**	n.r.	—	—	—	—
4	$SiMe_3CN$		**38**	41	A	 KOH 61% → **41**, R = NH_2; (*ent*)-**1**, R = OH	**41**	100
5			**39**	68	C		**42**	80

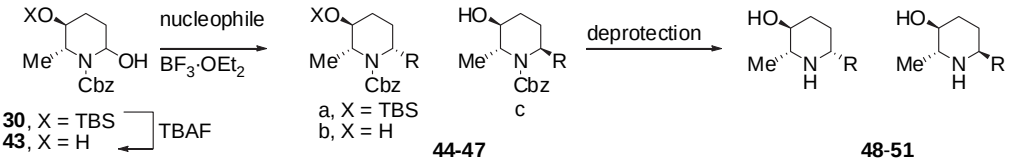
[a] Yield determined over two steps.
[b] Conditions: (A) HBr/acetic acid, 0 °C, 5 min. (B) Pd/C, H_2 (1 atm), HCl (1 equiv), MeOH, 2 h. (C) (1) HBr/acetic acid, 0 °C, 5 min; (2) K_2CO_3 (2 equiv), MeOH, 2 h.

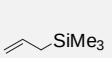
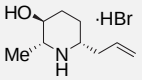
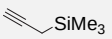
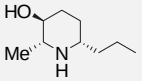
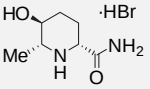
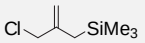
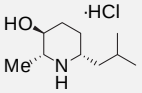
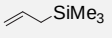
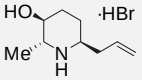
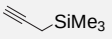
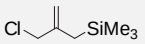
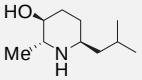
only product.[7a,17] The stereochemistry was elucidated via 2D-NMR experiments on the deprotected compounds.[18]

A pool of 2,5-*trans*-disubstituted piperidines was formed via deprotection of compounds **35**–**39**. To facilitate TBS and Cbz deprotection in a single operation, the compounds were subjected to HBr in acetic acid. First, the allyl-substituted precursor **35** was stirred in HBr/acetic acid, followed by evaporation to afford the desired product **40** in 78% yield (Table 2, entry 1). The Cbz deprotection with HBr/acetic acid in the presence of an allene was more troublesome, since HBr probably reacted with the allene to generate multiple side products. Therefore, in this case Pd/C in combination with hydrogen gas was used to remove the Cbz group and concomitantly reduce the allene to a propyl side chain. Furthermore, via the addition of HCl, the TBS was removed in the same pot to afford pseudoconhydrine (**3**) in 52% yield (entry 2).[7a] The analytical data were identical to those in literature, thereby supporting our stereochemical assignment. Deprotection of the cyanide substituted product **38** proceeded smoothly with HBr in acetic acid, but also the cyanide was converted into the amide **41** (entry 4). Upon treatment with aqueous KOH, amide **41** was converted (61%) into the corresponding acid, the natural product 5-hydroxypipecolic acid (*ent*-**1**).[19] Stirring the 2-(chloromethyl)allyl precursor **39** in HBr/acetic acid afforded a mixture of deprotected compound and cyclized product **42** (entry 5). After the addition of basic methanol, the cyclization was completed to give **42** as a single product in 80% yield.

To further apply the successful *N*-acyliminium ion coupling and expand the variety of piperidines, we subjected hemiaminal **30** to several π-nucleophiles in the presence of $BF_3{\cdot}OEt_2$. First, allyltrimethylsilane was successfully used providing the desired product **44a** in 56% over two steps as a single diastereoisomer (Table 3, entry 1). Second, an allene was introduced in a low yield of 32%, including partial removal of the TBS group (**45b**, 25%). Introduction of two other nucleophiles was somewhat disappointing; reaction with Me_3SiCN proceeded in 40% yield, again as a mixture with and without protecting group. The introduction of 2-(chloromethyl)allyl afforded only the TBS-protected product **47a**, but in a relatively low 30% yield. More encouraging was the diastereoselectivity of the process, in all cases leading to the cis-isomer (with respect to the methyl) as the sole product.[20] The isolation of TBS-deprotected products was taken as an incentive to remove the TBS group prior to the *N*-acyliminium ion reactions. Due to the instability of the hemiaminal, the TBS group was initially removed before the lactam reduction. Interestingly, the TBS turned out to be crucial in the reduction, since applying the successful $LiEt_3BH$ conditions on the free alcohol only led to overreduction. Inversely, reduction followed by TBS deprotection appeared a better alternative providing precursor **43**, which was used in crude form in the *N*-acyliminium ion reactions. As depicted in Table 3, entry 5, the yield of the reaction with allyltrimethylsilane was slightly improved, 63 versus 56%. Unfortunately, the reaction was no longer completely diastereoselective: the products were formed in a 2:1 ratio in favor of the

Table 3
N-Acyliminium ion reactions of hemiaminals **30** and **43**



Entry	s.m.	Nucleophile	R	Product/ratio A/B/C	Yield (%)	Deprotection substrate	Conditions[c]	Product		Yield (%)
1	**30**			**44**/1:0:0	56[a]	**44a**	A		**48**	100
2	**30**			**45**/1:3.5:0	32[a]	**45a**	B		**49**	81
3	**30**	Me_3SiCN	NC	**46**/1:2:0	40[a]	**46a**	A		**50**	100
4	**30**			**47**/1:0:0	30[a]	**47a**	B		**51**	100
5	**43**			**44**/0:2:1	63[b]	**44c**	A		**52**	74
6	**43**			**45**/0:1:1	58[b]	**45c**	C	—		—
7	**43**	Me_3SiCN	NC	**46**/0:>99:0	28[b]	**46a**[d]	—	—		—
8	**43**			**47**/0:1.4:1	66[b]	**47c**	C		**53**	93

[a] Yield determined over two steps.
[b] Yield determined over three steps.
[c] Conditions: (A) HBr/acetic acid, 0 °C, 5 min. (B) Pd/C, H_2 (1 atm), HCl (1 equiv), MeOH, 2 h. (C) Pd/C, H_2 (1 atm), MeOH, 2 h.
[d] For deprotection results, see entry 3.

cis-product. In case of propargyltrimethylsilane the yield was slightly better, 58 versus 32%, but this time there was virtually no selectivity (entry 6). Introduction of the cyanide was problematic, since a complex reaction mixture was formed and a low yield of the cis-product **46b** was obtained (entry 7). More successful was the reaction with 2-(chloromethyl)allyltrimethylsilane providing product **47** in 66% yield and a 1.4:1 diastereomeric ratio (entry 8). Fortunately, the separation of the diastereoisomers was straightforward in all cases and the single diastereoisomers were used in the deprotection step.

Creation of a set of 2-methyl-3-hydroxypiperidines commenced with deprotection of the two allyl-substituted compounds **44a** and **44c**. In both cases, the desired piperidine was obtained in high yield as depicted in Table 3, entries 1 and 5. Removal of the protecting groups in the case of the allene substituent was performed with Pd/C and H_2 in methanol, combined with addition of HCl. The 2,6-*cis*-disubstituted product **49** was obtained in 81% yield (entry 3). Sadly, deprotection of the trans-product **45c** did not provide sufficient material for complete spectroscopic analysis. Next, the cyanide substituted product **46a** was deprotected and converted at the same time into the corresponding amide **50** in quantitative yield (entry 3). Cbz-removal with HBr in acetic acid in case of the 2-(chloromethyl)allyl side chain appeared more troublesome, giving again rise to a mixture of open and cyclized product. This time, however, we were unsuccessful in converting the open product into the corresponding cyclic product upon stirring in basic methanol. On the other hand, reductive removal of the Cbz group was more successful, providing both isomers **47a** and **47c**, and the corresponding products **51** and **53**, respectively, in high yields (entries 4 and 8). In case of the allylated substrate **31**, the yields were disappointing and only TBS-deprotected product was observed. Thus, hemiaminal **31** was subjected to TBAF and the deprotected compound **54** was used in the *N*-acyliminium ion reactions (Table 4). We were delighted to observe a significant improvement in reactivity: for example, the reaction with allyltrimethylsilane proceeded in a yield of 68% with selective formation of the *trans*-product **55** (entry 1). Again, a small library was generated by reacting hemiaminal **54** with different nucleophiles. The reaction with propargyltrimethylsilane proceeded in 62% yield over the three steps (entry 2). Next, the cyanide was introduced in a moderate 50% yield, while the 2-(chloromethyl)allyl was introduced in 62% yield (entries 3 and 4, respectively). In all cases, the trans-isomers were formed as the exclusive products.

Subsequent removal of the protecting groups afforded the 2-allyl-3-hydroxypiperidines as shown in Table 4. Deprotection of the diallylated compound **55** proceeded in 92% yield using HBr in acetic acid (entry 1). The reductive removal of the Cbz group in case of the allene substituent afforded the dipropyl-substituted product **60** in quantitative yield (entry 2). In entry 3, the cyanide-containing compound **57** was deprotected to afford amide **61** in 68% yield. Next, the 2-(chloromethyl)allyl compound was deprotected under reductive conditions to afford the completely reduced product **62** in a yield of 93%.

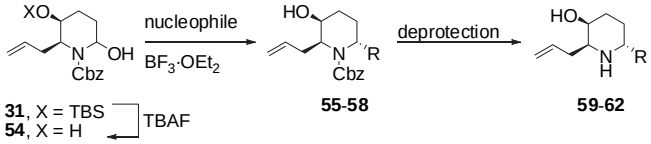
The last set of substituted piperidines was generated via *N*-acyliminium ion-mediated reactions with precursor **33**. First, an allyl substituent was introduced in a diastereoselective manner in 40% yield over four steps (Table 5, entry 1). Somewhat disappointing was the yield of the formation of the allene-substituted compound **64**, where only 9% product was isolated. The cyanide and the 2-(chloromethyl)allyl were both introduced in moderate yields of 21 and 24%, respectively. Thus, the protocol was successfully applied for these four nucleophiles to give the products in a fully diastereoselective manner.

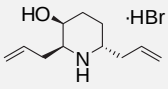
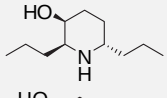
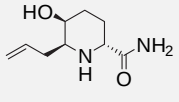
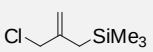
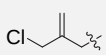
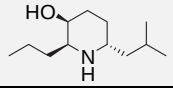
Next, the compounds were deprotected in the same fashion as described earlier in this section. Allylated compound **63** was stirred in HBr/acetic acid to liberate the piperidine **67** in 85% (Table 5, entry 1). The allene was hydrogenated together with hydrogenolysis of the Cbz group to afford piperidine **68** in 95% (entry 2). Next, the Cbz and TBS groups of **65** were removed under the influence of HBr in acetic acid with concomitant conversion of the cyanide into the corresponding amide **69** in 68% yield (entry 3). In entry 4, the 2-(chloromethyl) allylated piperidine was deprotected and after stirring in basic methanol afforded the cyclized product **70** in 59%.

5. Mechanistic considerations

The stereochemical observations of the previous section can be analyzed via the intermediate *N*-acyliminium ion conformations.[21] By considering, such *N*-acyliminium ions can form two half chair conformations as shown for *N*-acyliminium ion precursor **29** in

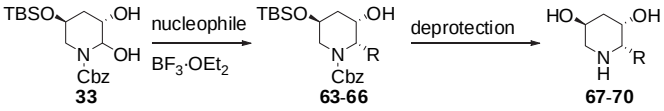
Table 4
N-Acyliminium ion reactions of hemiaminal **54**

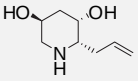
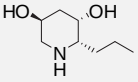
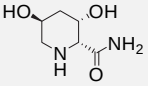
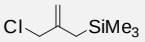
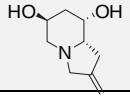


Entry	Nucleophile	R	Product	Yield[a] (%)	Conditions deprotection[b]	Product		Yield (%)
1			**55**	68	A		**59**	92
2			**56**	62	B		**60**	100
3	Me_3SiCN		**57**	50	A		**61**	68
4			**58**	62	B		**62**	93

[a] Yield determined over three steps.
[b] Conditions: (A) HBr/acetic acid, 0 °C, 5 min. (B) Pd/C, H_2 (1 atm), MeOH, 2 h.

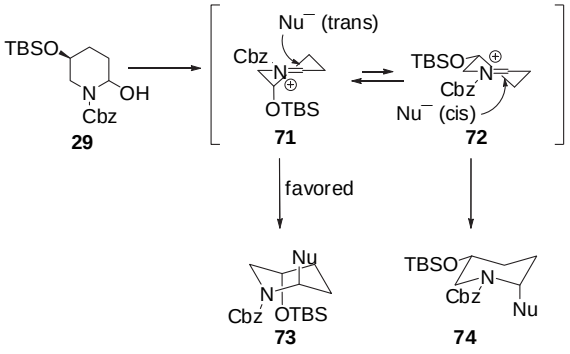
Table 5
N-Acyliminium ion reactions of hemiaminal **33**



Entry	Nucleophile	R	Product	Yield[a] (%)	Conditions deprotection[b]	Product		Yield (%)
1			**63**	40	A		**67**	78
2			**64**	9	B		**68**	52
3	$SiMe_3CN$		**65**	21	A		**69**	100
4			**66**	24	C		**70**	80

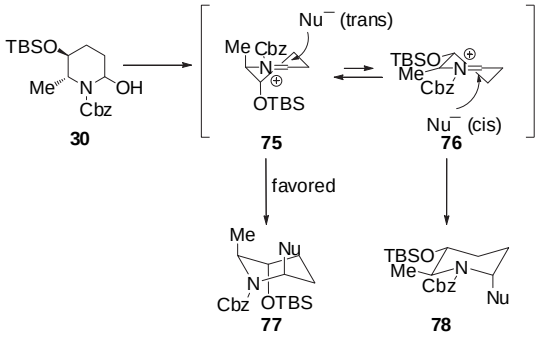
[a] Yield determined over four steps.
[b] Conditions: (A) HBr/acetic acid, 0 °C, 5 min. (B) Pd/C, H_2 (1 atm), HCl (1 equiv), MeOH, 2 h. (C) (1) HBr/acetic acid, 0 °C, 5 min; (2) K_2CO_3 (2 equiv), MeOH, 2 h.

Scheme 4. The pseudoaxial intermediate **71** is favored due to stabilizing electrostatic attraction between the partially negatively charged oxygen atom at the C-4 position and the positively charged carbocation. The nucleophile preferentially attacks from the pseudoaxial side, giving rise to the trans-substituted product **73**. Semi-empirical calculations (MOPAC AM1) of the energy differences between the two intermediates **71** and **72** showed a significant difference of 10.8 kcal/mol in favor of the pseudoaxial product **71**. This is in line with the experimental outcome, in which the trans-products are formed.



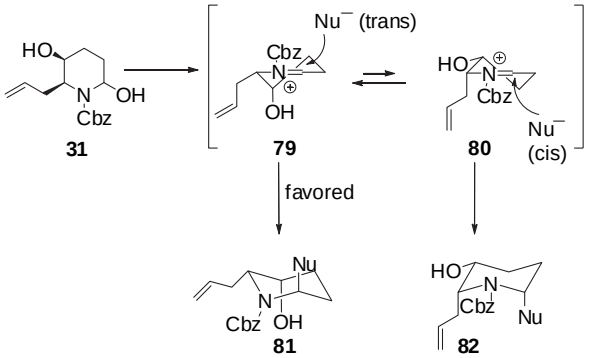
Scheme 4. Stereochemical rationale I.

In the case of the 6-methyl substituted building block, the TBS protecting group turned out be crucial. Due to the trans-substitution pattern of the 6-methyl substituted *N*-acyliminium ion, the two conformers depicted in Scheme 5 are possible. One has both substituents in the axial (**75**) and the other one in the equatorial position (**76**). The axial conformer **75** is favored due to the stabilization of the oxygen substituent, which is confirmed by MOPAC AM1 calculations (conformer **75** is 11.8 kcal/mol lower in energy). With the TBS group present, the nucleophile prefers to attack in a pseudoaxial fashion so that the trans-isomer was formed. After deprotection, the stereoselectivity was lost albeit that there was still a considerable difference in energy between both conformers of 10.8 kcal/mol. Presumably, the nucleophile now reacts from both sides in the pseudoaxial conformer due to comparable steric hindrance from both sides.



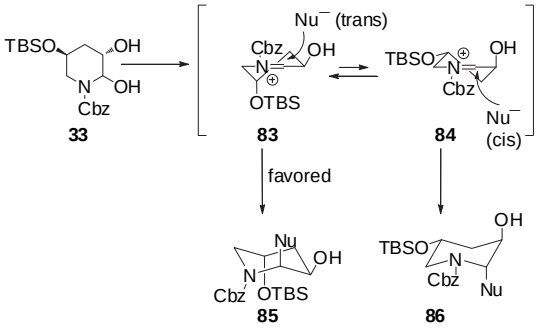
Scheme 5. Stereochemical rationale II.

The 6-allyl-substituted building block was less reactive with the TBS protecting group present. Possibly, the *N*-acyliminium ion is in this case formed with more difficulty due to steric hindrance. This is no longer the case after TBS removal so that the trans-products can be formed. This is also in line with the expectations, in which the pseudoaxial conformer **79** is favored due to the previously described stabilization (Scheme 6). This is confirmed by calculations, showing a 10.5 kcal/mol difference in favor of the pseudoaxial conformer **79**. Due to the cis-relationship between allyl and hydroxyl, both blocking the bottom side of the molecule, there is no interference with the preferred axial attack of the nucleophile.



Scheme 6. Stereochemical rationale III.

The stereochemical outcome in case of the 3,5-dihydroxypiperidine building blocks can be explained in a similar fashion. The substituent in the 3-position prefers the pseudoequatorial and the oxygen in the 5-position the pseudoaxial position, while in both cases the *N*-acyliminium ion is stabilized by orbital interactions (Scheme 7). Calculations (MOPAC AM1) showed indeed an energy difference of 12.2 kcal/mol in favor of conformer **83**. Together with the preferred axial attack, this will give rise to selective formation of the cis-product **85** (with respect to the 3-hydroxy substituent).



Scheme 7. Stereochemical rationale IV.

6. Conclusions

In conclusion, a synthetically versatile approach was developed for the synthesis of diversely substituted piperidines. The first set was achieved via cross-metathesis on the allyl-substituted precursor, followed by subsequent deprotection. The second pathway was based on the formation of the hemiaminals and subsequent introduction of different π-nucleophiles, mostly in a diastereoselective fashion. An extension of this method was realized via the formation of a set of 3,5-dihydroxy trisubstituted piperdines. Thus, a modest library of diversely functionalized piperidines was synthesized in a straightforward manner.

7. Experimental section

7.1. General information

Solvents were distilled from appropriate drying agents prior to use and stored under nitrogen. Reactions were carried out under an inert atmosphere of dry nitrogen or argon. IR spectra were recorded on an ATI Mattson Genesis Series FTIR spectrometer, or a Bruker Tensor 27 FTIR spectrometer. NMR spectra were recorded on a Bruker DMX 300 (300 MHz), and a Varian 400 (400 MHz) spectrometer in $CDCl_3$ solutions (unless otherwise reported). Chemical shifts are given in parts per million with respect to tetramethylsilane (TMS) as internal standard. If stated hydrogenation reactions were conducted in the H-cube hydrogenation reactor from Thalesnano. Optical rotations were determined with a Perkin Elmer 241 polarimeter. High resolution mass spectra were recorded on a JEOL AccuTOF (ESI), or a MAT900 (EI, CI, and ESI).

7.2. (*S*)-5-(*tert*-Butyldimethylsilyloxy)piperidin-2-one (11)

To a solution of cyanohydrin **9** (500 mg, 1.94 mmol) in MeOH (70 mL) were added Et_3N (536 μL, 3.88 mmol) and Raney nickel (50% solution in water, 50 mg) and the resulting suspension was stirred under hydrogen pressure (1 atm) for 3 h. Filtration through Celite and concentration in vacuo afforded the piperidone ring **11**. ^1H NMR ($CDCl_3$, 300 MHz) δ 4.04–3.98 (m, 1H), 3.2–3.12 (m, 2H), 2.52–2.44 (m, 1H), 2.26–2.09 (m, 1H), 1.80–1.78 (m, 2H), 0.83 (s, 9H), 0.01 (s, 6H).

7.3. (5*S*,6*R*)-5-(*tert*-Butyldimethylsilyloxy)-6-methylpiperidin-2-one (12)

A solution of methyl lithium (40 mL 1 M solution in Et_2O, 40.0 mmol) and dimethylsulfide copper bromide (8.1 g, 39.6 mmol) in THF (130 mL) was cooled to −40 °C for 20 min. After cooling to −78 °C, **10** (3.8 g, 13.2 mmol) and $BF_3{\cdot}OEt_2$ (5 mL, 39.6 mmol) were added, the reaction mixture was warmed to rt and stirred overnight. Saturated aqueous NH_4Cl solution (150 mL) and Et_2O (150 mL) were added and the aqueous layer was extracted with Et_2O (3×100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash column chromatography (2:1 to 8:1 EtOAc/heptane) afforded piperidone **12** (1.30 g, 5.3 mmol, 40%). $[\alpha]_D^{20}$ +17 (*c* 3.8, CH_2Cl_2); IR (film) 2958, 2859, 1675, 1100, 836 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 6.99 (br s, 1H), 3.50–3.38 (m, 1H), 3.30–3.25 (m, 1H), 2.46–2.41 (m, 1H), 2.27–2.21 (m, 1H), 1.96–1.95 (m, 1H), 1.84–1.83 (m, 1H), 1.21 (d, *J*=6 Hz, 3H), 0.82 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.5, 70.2, 54.4, 27.5, 25.1, 19.7, 17.4, 13.6, −5.0, −5.4; HRMS (ESI^+) calcd for $C_{12}H_{25}NaNO_2Si$ ($M+Na^+$) 266.1552, found 266.1555.

7.4. (2*S*,3*S*)-2-Allyl-1-benzyloxycarbonyl-3-hydroxypiperidine (14)

To a solution of **13** (296 mg, 1.1 mmol) in THF (30 mL) was added $LiAlH_4$ (105 mg, 2.8 mmol) and the reaction mixture was stirred overnight at 70 °C. The reaction was carefully quenched by addition of H_2O (137 mg, 1.3 mg/mg $LiAlH_4$), aqueous NaOH (15% in H_2O, 137 mg, 1.3 mg/mg $LiAlH_4$), and again H_2O (341 mg, 3.25 mg/mg $LiAlH_4$). The resulting suspension was stirred vigorously for 10 min, filtered, and the filtrate was concentrated in vacuo. The amine was dissolved in CH_2Cl_2 (10 mL) and Cbz–OSu (530 mg, 2.2 mmol) and Et_3N (304 μL, 2.2 mmol) were added. The mixture was stirred overnight followed by the addition of water (10 mL), the organic layer was washed with water (2×10 mL) and dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification via flash column chromatography (3:1 to 1:3 heptane/EtOAc) afforded hydroxypiperidine **14** (220 mg, 0.79 mmol, 72%). $[\alpha]_D^{20}$ +28.9 (*c* 2.0, CH_2Cl_2); IR (film) 3455, 2945, 1748, 1203, 693 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.98–7.33 (m, 5H), 5.74–5.70 (m, 1H), 5.08 (s, 2H), 5.02–4.95 (m, 2H), 4.51–4.48 (m, 1H), 4.01–3.97 (m, 1H), 3.84–3.80 (m, 1H), 2.79–2.75 (m, 1H), 2.45–2.32 (m, 2H), 1.79–1.56 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.3, 134.6, 128.7, 128.3, 127.5, 127.3, 116.4, 72.3, 68.4, 66.6, 54.8, 37.2, 27.6, 25.0; HRMS (ESI) calcd for $C_{16}H_{21}NNaO_3$ ($M+Na^+$) 298.1419, found 298.1414.

7.5. General procedure for the cross-metathesis reactions

Compound **14** was dissolved in CH_2Cl_2 (0.05 M) and argon was bubbled through the solution for 15 min after which Grubbs-II (10 mol %) and the olefin (2 equiv) were added. The solution was heated at reflux overnight followed by concentration in vacuo. The crude product was purified by column chromatography using the indicated solvent mixture.

*7.5.1. (2S,3S)-1-Benzyloxycarbonyl-3-hydroxy-2-((E)-4-methoxy-4-oxobut-2-enyl)piperidine (**15**).* Compound **14** (25 mg, 0.09 mmol) was reacted with methyl acrylate according to the general procedure. Flash column chromatography (3:1 to 1:2 heptane/EtOAc) afforded piperidine **15** (20 mg, 0.056 mmol, 62%). $[\alpha]_D^{20}$ +34.2 (*c* 0.7, CH_2Cl_2); IR (film) 3455, 2958, 1731, 1683, 1160, 702 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.33–7.30 (m, 5H), 6.95–6.89 (m, 1H), 5.89–5.84 (m, 1H), 5.07 (dd, *J*=12.3, 3.0 Hz, 2H), 4.57–4.55 (m, 1H), 3.99–3.97 (m, 1H), 3.84–3.81 (m, 1H), 3.69 (s, 3H), 2.72–2.48 (m, 3H), 1.83–1.25 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.0, 155.0, 145.4, 136.0, 128.0, 127.5, 127.4, 122.5, 68.3, 66.9, 54.4, 51.0, 37.3,

27.2, 26.4, 23.6; HRMS (ESI) calcd for $C_{18}H_{23}NNaO_5$ ($M+Na^+$) 356.1474, found 356.1488.

*7.5.2. (2S,3S)-1-Benzyloxycarbonyl-2-((E)-3-(4-chlorophenyl)allyl)-3-hydroxypiperidine (**16**).* According to the general method, substrate **14** (25 mg, 0.09 mmol) was reacted with 4-chlorostyrene. Flash column chromatography (3:1 to 1:2 heptane/EtOAc) afforded the hydroxypiperidine **16** (19 mg, 0.05 mmol, 55%). $[\alpha]_D^{20}$ +8.2 (*c* 0.5, CH_2Cl_2); IR (film) 3433, 2954, 1744, 1692, 1203, 957 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.39–7.20 (m, 9H), 6.38–6.32 (m, 1H), 6.12–6.09 (m, 1H), 5.11–5.10 (m, 1H), 5.03 (s, 2H), 4.59–4.55 (m, 1H), 4.04–3.99 (m, 1H), 3.89–3.85 (m, 1H), 2.64–2.48 (m, 2H), 1.83–1.54 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.0, 155.2, 130.3, 128.8, 128.3, 128.1, 128.0, 127.5, 137.4, 127.3, 126.8, 72.4, 68.7, 66.7, 55.0, 37.4, 27.4, 26.9; HRMS (ESI) calcd for $C_{22}H_{24}NCl^{35}NaO_3$ ($M+Na^+$) 408.1342, found 408.1351.

*7.5.3. (2S,3S)-1-Benzyloxycarbonyl-3-hydroxy-2-((E)-4-(trimethylsilyl)but-2-enyl)piperidine (**17**).* Substrate **14** (25 mg, 0.09 mmol) was reacted with allyltrimethylsilane according to the general method. Flash column chromatography (3:1 to 1:2 heptane/EtOAc) afforded hydroxypiperidine **17** (20 mg, 0.06 mmol, 70%). $[\alpha]_D^{20}$ +49.6 (*c* 0.32, CH_2Cl_2); IR (film) 3420, 2949, 1748, 1247, 849 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.39–7.33 (m, 5H), 5.47–5.44 (m, 1H), 5.16–5.09 (m, 3H), 4.48–4.42 (m, 1H), 4.02–3.96 (m, 1H), 3.84–3.79 (m, 1H), 2.74–2.73 (m, 1H), 2.38–2.32 (m, 2H), 1.93–1.23 (m, 6H), 0.08 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.1, 136.4, 127.9, 127.4, 127.3, 123.8, 122.5, 68.9, 66.6, 66.6, 55.3, 37.3, 27.4, 26.7, 25.0, −2.2, −2.5; HRMS (ESI) calcd for $C_{20}H_{32}NO_3Si$ ($M+H^+$) 362.2151, found 362.2152.

*7.5.4. (2S,3S)-1-Benzyloxycarbonyl-2-((E)-4-(ethoxycarbonyloxy)-but-2-enyl)-3-hydroxypiperidine (**18**).* According to the general procedure, substrate **14** (25 mg, 0.09 mmol) was reacted with allyl ethyl carbonate. Flash column chromatography (3:1 to 1:2 heptane: EtOAc) afforded hydroxypiperidine **18** (24 mg, 0.065 mmol, 72%). $[\alpha]_D^{20}$ +28.2 (*c* 0.7, CH_2Cl_2); IR (film) 3438, 2958, 1731, 1692, 1251, 603 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.32–7.30 (m, 5H), 5.70–5.60 (m, 2H), 5.13–5.09 (m, 2H), 4.44–4.42 (m, 2H), 4.16 (q, *J*=7.2 Hz, 2H), 4.01–3.96 (m, 1H), 3.83–3.79 (m, 1H), 2.79–2.63 (m, 2H), 2.46–2.33 (m, 2H), 1.81–1.26 (m, 4H), 1.28 (t, *J*=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.6, 155.1, 132.6, 129.4, 128.9, 128.1, 127.5, 125.3, 72.3, 68.5, 67.5, 66.7, 63.4, 54.7, 37.2, 27.2, 26.2, 13.8; HRMS (ESI) calcd for $C_{20}H_{27}NNaO_6$ ($M+Na^+$) 400.1436, found 400.1749.

*7.5.5. (2S,3S)-Benzyloxycarbonyl-2-((E)-7-bromohept-2-enyl)-3-hydroxypiperidine (**19**).* Substrate **14** (25 mg, 0.09 mmol) was reacted with 6-bromohex-1-ene following the general procedure. Flash column chromatography (3:1 to 1:2 heptane/EtOAc) afforded hydroxypiperidine **19** (20 mg, 0.048 mmol, 53%). $[\alpha]_D^{20}$ +18.3 (*c* 1.0, CH_2Cl_2); IR (film) 3494, 2941, 1735, 1679, 1216 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.39–7.33 (m, 5H), 5.40–5.35 (m, 1H), 5.10–5.09 (m, 3H), 4.46–4.44 (m, 1H), 4.00–3.95 (m, 1H), 3.83–3.79 (m, 1H), 3.33 (t, *J*=6.6 Hz, 2H), 2.77–2.68 (m, 1H), 2.37–2.33 (m, 2H), 1.94–1.25 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.2, 132.8, 131.7, 128.8, 128.1, 127.5, 126.4, 72.3, 68.7, 66.6, 54.9, 37.2, 33.4, 31.1, 27.3, 26.4, 25.0, 23.7; HRMS (ESI) calcd for $C_{20}H_{28}BrNNaO_3$ ($M+Na^+$) 432.1150, found 432.1159.

7.6. (9*S*,9a*S*)-9-Hydroxyhexahydro-1*H*-quinolizin-4(6*H*)-one (20)

A solution of **15** (50 mg, 0.15 mmol) in MeOH (4 mL) was pumped through the H-cube (20 bar, 25 °C, 1 mL/min) followed by evaporation of the solvent under reduced pressure. The mixture of products was dissolved in MeOH (2 mL) and K_2CO_3 (41 mg, 0.30 mmol) was added. The reaction was quenched after 2 h by the addition of water (2 mL) and CH_2Cl_2 (4 mL) followed by extraction of the aqueous layer with CH_2Cl_2 (3×4 mL). The combined organic layers were dried, filtered, and concentrated in vacuo to afford quinolizinone **20** (20 mg, 0.12 mmol, 78%). $[\alpha]_D^{20}$ −18.6 (*c* 0.59, CH_2Cl_2); IR (film) 3360, 2954, 2867, 1610, 1009 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.81–4.74 (m, 1H), 3.71–3.66 (m, 2H), 3.34–3.30 (m, 1H), 2.47–2.21 (m, 2H), 1.95–1.87 (m, 4H), 1.72–1.58 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.6, 67.6, 59.5, 41.5, 32.5, 31.2, 25.6, 18.9, 18.5; HRMS (ESI) calcd for $C_9H_{16}NO_2$ ($M+H^+$) 170.1181, found 170.1173.

7.7. Methyl 4-((2*S*,3*S*)-3-hydroxypiperidin-2-yl)butanoate hydrochloride (21)

Olefin **15** (40 mg, 0.12 mmol) was dissolved in MeOH (2 mL) and Pd/C (2 mg, 0.019 mmol) and concentrated HCl (4 μL) were added and the mixture was stirred under H_2 (1 atm) pressure for 2 h. The mixture was filtered over Celite and the solvent was evaporated under reduced pressure followed by addition of water (4 mL) and toluene (4 mL). The aqueous layer was washed with toluene (2×4 mL) and concentrated under reduced pressure (azeotropically evaporated twice with toluene) to afford hydroxypiperidine **21** (28 mg, 0.12 mmol, 100%). $[\alpha]_D^{20}$ +7.1 (*c* 0.46, MeOH); IR (film) 3370, 2932, 1726, 1437, 1212, 1001 cm^{-1}; ^1H NMR (D_2O, 300 MHz) δ 4.02–3.99 (m, 1H), 3.57 (s, 3H), 3.26–3.22 (m, 1H), 3.09–305 (m, 1H), 2.92–2.84 (m, 1H), 2.34–2.30 (m, 2H), 1.86–1.82 (m, 2H), 1.71–1.52 (m, 6H); ^{13}C NMR (D_2O, 75 MHz) δ 177.5, 62.6, 58.4, 51.7, 44.0, 32.5, 28.0, 27.9, 19.1, 15.7; HRMS (ESI) calcd for $C_{10}H_{20}NO_3$ ($M+H^+$) 202.1443, found 202.1445.

7.8. (2*S*,3*S*)-2-(3-Phenylpropyl)piperidin-3-ol (22)

Substrate **16** (23 mg, 0.059 mmol) was reacted with Pd/C, following the same procedure as for **21** to afford piperidinol **22** (9 mg, 0.041 mmol, 66%). $[\alpha]_D^{20}$ +7.7 (*c* 0.35, MeOH); IR (film) 3343, 2941, 1454, 702, 598 cm^{-1}; ^1H NMR (D_2O, 300 MHz) δ 7.26–7.16 (m, 5H), 3.99 (m, 1H), 3.25–3.20 (m, 1H), 3.04–3.02 (m, 1H), 2.92–2.84 (m, 1H), 2.59–2.55 (m, 2H), 1.86–1.82 (m, 2H), 1.67–1.48 (m, 6H); ^{13}C NMR (D_2O, 75 MHz) δ 141.7, 128.2, 128.0, 125.7, 62.7, 58.6, 44.0, 34.0, 28.0, 28.0, 25.5, 15.8; HRMS (ESI) calcd for $C_{14}H_{22}NO$ ($M+H^+$) 220.1701, found 220.1698.

7.9. (2*S*,3*S*)-2-(4-(Trimethylsilyl)butyl)piperidin-3-ol (23)

A solution of **17** (26 mg, 0.072 mmol) in MeOH (4 mL) was pumped through the H-cube (20 bar, 25 °C, 1 mL/min) followed by evaporation of the solvent under reduced pressure to afford piperidinol **23** (13 mg, 0.057 mmol, 79%). $[\alpha]_D^{20}$ +27.3 (*c* 0.29, CH_2Cl_2); IR (film) 2928, 1696, 1419, 1242, 827, 616 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.64 (m, 1H), 2.98–2.97 (m, 1H), 2.62–2.61 (m, 1H), 2.49–2.47 (m, 1H), 1.86–1.71 (m, 4H), 1.68–1.29 (m, 8H), −0.04 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 66.3, 60.3, 46.7, 31.9, 31.7, 29.4, 23.6, 20.1, 16.2, −2.1; HRMS (ESI) calcd for $C_{12}H_{28}NOSi$ ($M+H^+$) 230.1940, found 230.1931.

7.10. (2*S*,3*S*)-2-Butylpiperidin-3-ol (24)

Substrate **18** (25 mg, 0.066 mmol) was reacted with Pd/C, following the same procedure as for **23** to afford piperidinol **24** (13 mg, 0.066 mmol, 100%). $[\alpha]_D^{20}$ +25.9 (*c* 0.27, CH_2Cl_2); IR (film) 32.56, 2945, 2850, 1476, 1026, 866 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.65–3.64 (m, 1H), 3.01–2.97 (m, 1H), 2.66–2.58 (m, 1H), 2.49–2.48 (m, 1H), 1.92–1.85 (m, 1H), 1.78–1.67 (m, 2H), 1.50–1.31 (m, 7H), 0.90 (t, *J*=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 66.2, 60.3, 46.7, 31.9, 31.6, 27.7, 22.4, 20.1, 13.6; HRMS (ESI) calcd for $C_9H_{20}NO$ ($M+H^+$) 158.1545, found 158.1545.

7.11. (2*S*,3*S*)-2-Heptylpiperidin-3-ol (25)

A solution of **19** (85 mg, 0.21 mmol) was reacted with Pd/C, following the same procedure as for **23** to afford piperidinol **25** (39 mg, 0.19 mmol, 95%). $[\alpha]_D^{20}$ +20.5 (c 0.19, CH_2Cl_2); IR (film) 2,910, 2854, 1450, 992 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.66 (m, 1H), 3.04–2.99 (m, 1H), 2.64–2.60 (m, 1H), 2.52–2.50 (m, 1H), 1.94–1.90 (m, 2H), 1.88–1.74 (m, 2H), 1.50–1.28 (m, 12H), 0.92 (t, *J*=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 62.7, 58.7, 43.9, 34.8, 31.5, 30.5, 30.4, 28.0, 23.5, 21.5, 17.0, 15.8, 12.9; HRMS (ESI) calcd for $C_{12}H_{26}NO$ ($M+H^+$) 200.2014, found 200.1996.

7.12. (*S*)-1-Benzyloxycarbonyl-5-(*tert*-butyldimethylsilyloxy)-2-oxopiperidine (26)

The crude amide **11** was dissolved in THF (20 mL) and LiHMDS (1.94 mL of a 1 M solution in heptane, 1.94 mmol) was added at −78 °C. After stirring for 30 min, Cbz–OSu (485 mg, 1.94 mmol) was added and the resulting mixture was stirred overnight. The reaction was quenched with water (30 mL) and CH_2Cl_2 (30 mL) and the aqueous layer was extracted with CH_2Cl_2 (2×30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash column chromatography (9:1 to 6:1 heptane/EtOAc) afforded piperidine **26** (395 mg, 1.09 mmol, 56%) as a colorless oil, which solidified upon standing. $[\alpha]_D^{20}$ +6.5 (*c* 1.0, CH_2Cl_2); IR (film) 2945, 2854, 1718, 1296, 832 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.39–7.31 (m, 5H), 5.26 (s, 2H), 4.15–4.13 (m, 1H), 3.73–3.67 (m, 1H), 2.75–2.71 (m, 1H), 2.47–2.43 (m, 1H), 1.93–1.84 (m, 2H), 0.85 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.2, 153.6, 135.0, 128.0, 127.7, 127.5, 67.9, 63.7, 52.4, 30.4, 28.4, 25.2, 17.5, −5.3, −5.4; HRMS (ESI) calcd for $C_{19}H_{29}NNaO_4Si$ ($M+Na^+$) 386.1764, found 386.1787.

7.13. (2*R*,3*S*)-1-Benzyloxycarbonyl-3-(*tert*-butyldimethylsilyloxy)-2-methyl-6-oxopiperidine (27)

Substrate **12** (325 mg, 1.33 mmol) was reacted with Cbz–OSu, following the same procedure as for **26**. Purification via column chromatography (3:1 to 1:1 heptane/EtOAc) afforded piperidine **32** (330 mg, 0.86 mmol, 65%) as a colorless oil. $[\alpha]_D^{20}$ −7.0 (*c* 0.9, CH_2Cl_2); IR (film) 2958, 2854, 1779, 1731, 1264, 832, 776, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.35–7.26 (m, 5H), 5.27 (s, 2H), 4.27–4.25 (m, 1H), 3.89–3.88 (m, 1H), 2.83–2.71 (m, 1H), 2.46–2.37 (m, 1H), 2.05–1.98 (m, 1H), 1.82–1.78 (m, 1H), 1.20 (d, *J*=7 Hz, 3H), 0.84 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.5, 154.0, 135.1, 128.0, 127.6, 127.3, 67.8, 67.7, 58.5, 29.1, 25.1, 24.2, 18.9, 17.4, −5.4, −5.5; HRMS (ESI) calcd for $C_{20}H_{31}NNaO_4Si$ ($M+Na^+$) 400.1920, found 400.1930.

7.14. (2*S*,3*S*)-2-Allyl-1-benzyloxycarbonyl-3-(*tert*-butyldimethylsilyloxy)-6-oxopiperidine (28)

To a solution of amide **13** (500 mg, 1.85 mmol) in THF (20 mL) was added *n*-butyllithium (1.28 mL of a 1.6 M solution in hexane, 2.05 mmol) at −78 °C. After 30 min, Cbz–OSu (1.12 g, 4.63 mmol) was added and the resulted solution was stirred overnight. The reaction was quenched with water (30 mL) and CH_2Cl_2 (30 mL) and the aqueous layer was extracted with CH_2Cl_2 (2×30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification via column chromatography (2:1 to 1:2 heptane/EtOAc) afforded piperidine **28** (602 mg, 1.49 mmol, 80%) as a colorless oil, which solidified upon standing. $[\alpha]_D^{20}$ +30.7 (*c* 2.48, CH_2Cl_2); IR (film) 2949, 2919, 1774, 1713, 1252, 1104, 832, 771 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.35–7.26 (m, 5H), 5.76–5.68 (m, 1H), 5.24 (br s, 2H), 5.04–4.91 (m, 2H), 4.35–4.31 (m, 1H), 4.16–4.08 (m, 1H), 2.66–2.55 (m, 3H), 2.23–2.16 (m, 1H), 1.96–1.92 (m, 2H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.3, 153.7, 135.2, 134.4, 128.5, 128.2, 128.1, 117.6, 68.4, 67.6, 59.1, 33.8, 31.7, 25.7, 25.6, 17.9, 5.1, 5.4; HRMS (ESI) calcd for $C_{22}H_{33}NNaO_4Si$ ($M+Na^+$) 426.2077, found 426.2093.

7.15. (*S*)-1-Benzyloxycarbonyl-3-(*tert*-butyldimethylsilyloxy)-3,4-(2*H*)-dihydropyridine (32)

To a solution of amide **26** (100 mg, 0.28 mmol) in THF (2 mL) was added $LiEt_3BH$ (280 μL of a 1 M solution in THF, 0.28 mmol) at −78 °C. The solution was slowly warmed to −40 °C and quenched after 2 h with water (2 mL) and CH_2Cl_2 (4 mL). The aqueous layer was extracted with CH_2Cl_2 (3×5 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The hemiaminal was heated with NH_4Cl to 130 °C for 2 h. After cooling down the mixture, CH_2Cl_2 (5 mL) was added and the suspension was filtered followed by concentration under vacuo to afford the desired enamide **32**, which was used without further purification.

7.16. General procedure for reduction/*N*-acyliminium ion reaction

A solution of the Cbz-protected lactam in THF (0.1 M) was cooled to −78 °C and $LiEt_3BH$ (1 equiv, 1 M solution in THF) was added. After stirring for 2 h, the reaction was quenched with water and CH_2Cl_2, followed by an extraction of the aqueous layer with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was dissolved in CH_2Cl_2 (0.1 M), cooled to 0 °C, and $BF_3{\cdot}OEt_2$ (3 equiv) and the Me_3Si-nucleophile (5 equiv) were added. The mixture was stirred overnight and water and CH_2Cl_2 were added followed by an extraction of the aqueous layer with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography as indicated.

*7.16.1. (2R,5S)-2-Allyl-1-benzyloxycarbonyl-5-(tert-butyldimethylsilyloxy)piperidine (**35**).* Lactam **26** (25 mg, 0.065 mmol) was treated with allyltrimethylsilane as described in the general procedure. Purification via flash column chromatography (18:1 to 8:1 heptane/EtOAc) afforded piperidine **35** (18 mg, 0.07 mmol, 72%). $[\alpha]_D^{20}$ +21.2 (*c* 0.41, CH_2Cl_2); IR (film) 2949, 2850, 1709, 1428, 1238, 849 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.33–7.25 (m, 5H), 5.75–5.69 (m, 1H), 5.14–5.00 (m, 4H), 4.42–4.40 (m, 1H), 3.99–3.98 (m, 1H), 3.86–3.84 (m, 1H), 2.97–2.92 (m, 1H), 2.41–2.16 (m, 2H), 1.70–1.65 (m, 4H), 0.83 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.6, 136.7, 134.9, 134.5, 127.9, 127.2, 116.3, 66.3, 64.2, 49.5, 45.0, 33.7, 26.0, 25.3, 20.9, 17.6, −5.5; HRMS (ESI) calcd for $C_{22}H_{35}NNaO_3Si$ ($M+Na^+$) 412.2284, found 412.2302.

*7.16.2. (2R,5S)-1-Benzyloxycarbonyl-5-(tert-butyldimethylsilyloxy)-2-(propa-1,2-dienyl)piperidine (**36**).* Substrate **26** (106 mg, 0.26 mmol) was reacted with propargyltrimethylsilane, following the general procedure. Flash column chromatography (100:0 to 8:1 heptane/EtOAc) afforded piperidine **36** (44 mg, 0.11 mmol, 44%). $[\alpha]_D^{20}$ +25.7 (*c* 0.18, CH_2Cl_2); IR (film) 2954, 2850, 1696, 1247, 1043, 823 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.31–7.25 (m, 5H), 5.14–5.04 (m, 4H), 4.78–4.75 (m, 2H), 3.98–3.86 (m, 2H), 3.04–3.01 (m, 1H), 1.76–1.49 (m, 4H), 0.85 (s, 9H), 0.07 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 197.8, 155.2, 136.5, 127.9, 127.8, 127.3, 90.1, 71.6, 66.5, 64.2, 48.4, 45.6, 29.3, 26.5, 25.3, 21.4, −5.4; HRMS (ESI) calcd for $C_{22}H_{33}NNaO_3Si$ ($M+Na^+$) 410.2127, found 410.2126.

*7.16.3. (2R,5S)-Benzyloxycarbonyl-5-(tert-butyldimethylsilyloxy)-2-cyanopiperidine (**38**).* According to the general procedure, substrate **26** (106 mg, 0.26 mmol) was reacted with Me_3SiCN. Flash column

chromatography (100:0 to 8:1 heptane/EtOAc) afforded piperidine **38** (40 mg, 0.11 mmol, 41%). $[\alpha]_D^{20}$ +45.1 (*c* 1.1, CH_2Cl_2); IR (film) 2958, 2837, 1718, 1247, 1039, 849 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.34–7.26 (m, 5H), 5.46–5.45 (m, 1H), 5.21–5.10 (m, 2H), 4.05–3.94 (m, 1H), 3.20–3.16 (m, 1H), 2.32–2.22 (m, 1H), 1.90–1.72 (m, 4H), 0.83 (s, 9H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.0, 135.4, 128.0, 127.8, 127.6, 117.0, 67.6, 63.0, 47.2, 43.5, 27.3, 25.1, 22.0, 17.5, −5.5; HRMS (ESI) calcd for $C_{20}H_{30}N_2NaO_3Si$ ($M+Na^+$) 397.1923, found 397.1934.

*7.16.4. (2R,5S)-1-Benzyloxycarbonyl-5-(tert-butyldimethylsilyloxy)-2-(2-(chloromethyl)allyl)piperidine (**39**).* Lactam **26** (106 mg, 0.26 mmol) was reacted with 2-(chloromethyl)allyltrimethylsilane, following the general procedure. Flash column chromatography (100:0 to 8:1 heptane/EtOAc) afforded piperidine **39** (78 mg, 0.18 mmol, 68%). $[\alpha]_D^{20}$ +15.6 (*c* 1.7, CH_2Cl_2); IR (film) 2949, 2846, 1700, 1424, 1234, 840 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.32–7.25 (m, 5H), 5.11–5.07 (m, 4H), 4.93–4.50 (m, 1H), 4.11–3.86 (m, 3H), 2.98–2.94 (m, 1H), 2.58–2.19 (m, 3H), 1.72–1.57 (m, 3H), 1.36–1.31 (m, 1H), 0.84 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.6, 142.0, 136.5, 127.9, 127.7, 127.2, 116.5, 66.4, 64.1, 47.7, 47.4, 44.9, 32.8, 26.1, 25.3, 25.2, 21.6, −5.5, −5.5; HRMS (ESI) calcd for $C_{23}H_{37}Cl^{35}NO_3Si$ ($M+H^+$) 438.2231, found 438.2234.

*7.16.5. (2R,3S,6R)-6-Allyl-1-benzyloxycarboxylate-3-(tert-butyldimethylsilyloxy)-2-methylpiperidine (**44A**).* Amide **27** (70 mg, 0.19 mmol) was reacted with allyltrimethylsilane as described in the general method. Flash column chromatography (100:0 to 3:1 heptane/EtOAc) afforded piperidine **44A** (39 mg, 0.10 mmol, 56%). $[\alpha]_D^{20}$ +7.0 (*c* 0.8, CH_2Cl_2); IR (film) 2958, 2846, 1697, 1415, 1065, 836 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.33–7.25 (m, 5H), 5.79–5.70 (m, 1H), 5.14 (dd, *J*=12.3, 5.7 Hz, 2H), 5.04–4.89 (m, 2H), 4.31–4.25 (m, 1H), 4.22–4.16 (m, 1H), 3.70–3.69 (m, 1H), 2.33–2.25 (m, 2H), 1.82–1.62 (m, 4H), 1.15 (d, *J*=7.2 Hz, 3H), 0.85 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.7, 136.7, 135.6, 127.9, 127.2, 127.1, 116.3, 68.4, 66.3, 53.2, 49.4, 39.2, 25.3, 21.3, 17.6, −5.3, −5.5; HRMS (ESI) calcd for $C_{23}H_{38}NO_3Si$ ($M+H^+$) 404.2634, found 404.2621.

*7.16.6. (2R,3S,6R)-1-Benzyloxycarbonyl-3-(tert-butyldimethylsilyloxy)-2-methyl-6-(propa-1,2-dienyl)piperidine (**45A**).* According to the general procedure, substrate **27** (80 mg, 0.20 mmol) was reacted with propargyltrimethylsilane. Flash column chromatography (100:0 to 8:1 heptane/EtOAc) afforded piperidine **45A** (5 mg, 0.01 mmol, 7%) together with the deprotected piperidine **45B** (14 mg, 0.05 mmol, 25%, analytical data see below). $[\alpha]_D^{20}$ +50.6 (*c* 0.22, CH_2Cl_2); IR (film) 2949, 2846, 1696, 1303, 1087, 620, 421 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.37–7.26 (m, 5H), 5.17–5.14 (m, 3H), 4.97–4.94 (m, 1H), 4.77–4.75 (m, 2H), 4.21–4.17 (m, 1H), 3.71–3.70 (m, 1H), 2.19–2.12 (m, 1H), 1.92–1.82 (m, 1H), 1.64–1.60 (m, 1H), 1.60–1.59 (m, 1H), 1.13 (t, *J*=7.2 Hz, 3H), 0.85 (s, 9H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 206.4, 155.7, 146.8, 127.9, 127.3, 127.2, 93.7, 68.4, 66.4, 53.5, 47.0, 25.7, 21.85, 19.7, 18.1, 15.4, −5.4, −5.5; HRMS (ESI) calcd for $C_{23}H_{35}NNaO_3Si$ ($M+Na^+$) 424.2284, found 424.2273.

*7.16.7. (2R,3S,6R)-1-Benzyloxycarbonyl-3-(tert-butyldimethylsilyloxy)-6-cyano-2-methylpiperidine (**46A**).* Substrate **27** (80 mg, 0.20 mmol) was reacted with Me_3SiCN according to the general procedure. Flash column chromatography (100:0 to 1:1 heptane/EtOAc) afforded piperidine **46A** (10 mg, 0.03 mmol, 13%) together with the deprotected piperidine **46B** (15 mg, 0.05 mmol, 27%, analytical data see below). $[\alpha]_D^{20}$ +38.9 (*c* 0.37, CH_2Cl_2); IR (film) 2962, 2854, 1705, 1415, 1281, 1074, 832, 784 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.37–7.34 (m, 5H), 5.28–5.20 (m, 1H), 5.18 (s, 2H), 4.24–4.21 (m, 1H), 3.80–3.78 (m, 1H), 2.36–2.25 (m, 1H), 2.11–2.01 (m, 1H), 1.76–1.63 (m, 2H), 1.33 (d, *J*=7.5 Hz, 3H), 0.83 (s, 9H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.5, 135.6, 128.1, 127.7, 127.4, 119.6, 67.5, 67.2, 54.1, 39.9, 25.3, 25.2, 22.5, 21.3, 17.5, 16.0, −5.4, −5.6; HRMS (ESI) calcd for $C_{21}H_{32}N_2NaO_3Si$ ($M+Na^+$) 411.2080, found 411.2087.

*7.16.8. (2R,3S,6R)-1-Benzyloxycarbonyl-3-(tert-butyldimethylsilyloxy)-6-(2-(chloromethyl)allyl)-2-methylpiperidine (**47A**).* Substrate **27** (80 mg, 0.20 mmol) was reacted with 2-(chloromethyl)allyltrimethylsilane, following the general procedure. Flash column chromatography (100:0 to 8:1 heptane/EtOAc) afforded piperidine **47A** (20 mg, 0.06 mmol, 30%). $[\alpha]_D^{20}$ +3.3 (*c* 0.72, CH_2Cl_2); IR (film) 2949, 2919, 1696, 1078, 853, 780 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.36–7.31 (m, 5H), 5.16–5.13 (m, 3H), 4.96 (m, 1H), 4.35–4.33 (m, 1H), 4.21–4.19 (m, 1H), 4.06–4.00 (m, 2H), 3.71–3.70 (m, 1H), 2.41–2.37 (m, 2H), 2.14–2.11 (m, 1H), 1.85–1.79 (m, 1H), 1.41–1.36 (m, 2H), 1.17 (d, *J*=7.2 Hz, 3H), 0.85 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.7, 142.4, 136.5, 127.9, 127.5, 127.4, 116.5, 68.3, 66.4, 53.3, 47.9, 47.3, 38.4, 25.3, 21.2, 19.2, 17.6, −5.4, −5.5; HRMS (ESI) calcd for $C_{24}H_{38}Cl^{35}NNaO_3Si$ ($M+Na^+$) 474.2207, found 474.2204.

7.17. General procedure for reduction/TBS removal/*N*-acyliminium ion reaction

To a solution of the Cbz-protected lactam in THF (0.1 M) was added $LiEt_3BH$ (1 equiv 1 M solution in THF) at −78 °C. After stirring for 2 h, the reaction was quenched with water and CH_2Cl_2, followed by an extraction of the aqueous layer with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting oil was dissolved in THF (0.1 M) and TBAF (2 equiv 1 M solution in THF) was added. After stirring for 2 h, water and CH_2Cl_2 were added and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was dissolved in CH_2Cl_2 (0.1 M) and $BF_3\cdot OEt_2$ (3 equiv) and the Me_3Si-nucleophile (5 equiv) were added. After stirring overnight, the mixture was quenched with saturated aqueous $NaHCO_3$ and the solution was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography as indicated.

*7.17.1. (2R,3S,6R)-6-Allyl-benzyloxycarbonyl-3-hydroxy-2-methylpiperidine (**44B**) and (2R,3S,6S)-6-allyl-benzyloxycarbonyl-3-hydroxy-2-methylpiperidine (**44C**).* According to the general method, substrate **27** (100 mg, 0.25 mmol) was reacted with allyltrimethylsilane. Flash column chromatography (5:1 to 1:1 heptane/EtOAc) afforded the product as a separable mixture of diastereoisomers in a ratio of 2:1 (^1H NMR), hydroxypiperidine **44B** (33 mg, 0.11 mmol, 43%) and hydroxypiperidine **44C** (15 mg, 0.05 mmol, 20%).

Compound **44B**: $[\alpha]_D^{20}$ +1.2 (*c* 1.16, CH_2Cl_2); IR (film) 3394, 1661, 1432, 1324, 1078, 1018, 703 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.34–7.33 (m, 5H), 5.73–5.67 (m, 1H), 5.12–4.98 (m, 4H), 4.29–4.25 (m, 2H), 3.77 (m, 1H), 2.31–2.25 (m, 2H), 2.04–1.86 (m, 2H), 1.63–1.46 (m, 2H), 1.19 (d, *J*=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.9, 135.3, 128.0, 127.4, 127.3, 116.6, 67.8, 66.6, 63.0, 49.5, 39.1, 25.3, 20.4, 18.9; HRMS (ESI) calcd for $C_{17}H_{23}NNaO_3$ ($M+Na^+$) 312.1576, found 312.1578.

Compound **44C**: $[\alpha]_D^{20}$ +14.9 (*c* 0.56, CH_2Cl_2); IR (film) 3317, 2936, 1692, 1532, 1260, 1039 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.34–7.33 (m, 5H), 5.83–5.73 (m, 1H), 5.23–5.02 (m, 4H), 3.98–3.94 (m, 2H), 3.78–3.71 (m, 1H), 2.33–2.19 (m, 2H), 1.99–1.96 (m, 2H), 1.65–1.54 (m, 2H), 1.13 (d, *J*=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.4, 136.1, 134.3, 128.0, 127.6, 116.4, 81.0, 78.7, 66.1, 49.8, 39.6, 30.8, 27.8, 15.4; HRMS (ESI) calcd for $C_{17}H_{23}NNaO_3$ ($M+Na^+$) 312.1576, found 312.1565.

*7.17.2. (2R,3S,6R)-1-Benzyloxycarbonyl-3-hydroxy-2-methyl-6-(propa-1,2-dienyl)piperidine (**45B**) and (2R,3S,6S)-1-benzyloxycarbonyl-3-hydroxy-2-methyl-6-(propa-1,2-dienyl)piperidine (**45C**).* Substrate **27** (70 mg, 0.18 mmol) was reacted with propargyltrimethylsilane according to the general method. Flash column chromatography (5:1 to 1:1 heptane/EtOAc) afforded the product as a separable mixture of diastereoisomers in a ratio of 1:1 (^{1}H NMR), hydroxypiperidine **45B** (16 mg, 0.05 mmol, 29%) and hydroxypiperidine **45C** (15 mg, 0.05 mmol, 29%).

Compound **45B**: $[\alpha]_D^{20}$ +63.8 (*c* 0.42, CH_2Cl_2); IR (film) 3403, 2988, 1696, 1424, 1285, 1078 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34–7.33 (m, 5H), 5.21–5.09 (m, 3H), 4.96–4.93 (m, 1H), 4.81–4.75 (m, 2H), 4.31–4.28 (m, 1H), 3.78–3.77 (m, 1H), 2.07–1.49 (m, 4H), 1.21 (d, *J*=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 207.4, 155.4, 136.1, 128.1, 127.3, 127.2, 92.0, 81.6, 81.0, 69.2, 66.1, 54.4, 31.3, 27.6, 15.3; HRMS (ESI) calcd for $C_{17}H_{21}NNaO_3$ (M+H$^+$) 310.1419, found 310.1415.

Compound **45C**: $[\alpha]_D^{20}$ +9.1 (*c* 0.68, CH_2Cl_2); IR (film) 3407, 1718, 1268, 1043, 728 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34–7.33 (m, 5H), 5.17–5.16 (m, 3H), 4.81–4.86 (m, 2H), 4.70 (m, 1H), 4.56–4.54 (m, 1H), 4.09–3.98 (m, 1H), 2.06–1.99 (m, 2H), 1.75–1.61 (m, 2H), 1.15 (d, *J*=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 206.3, 155.9, 136.2, 127.9, 127.5, 127.3, 93.3, 76.7, 67.9, 66.7, 53.4, 47.0, 20.9, 19.5, 18.1; HRMS (ESI) calcd for $C_{17}H_{21}NNaO_3$ (M+H$^+$) 310.1419, found 310.1409.

*7.17.3. (2R,3S,6R)-1-Benzyloxycarbonyl-6-cyano-3-hydroxy-2-methylpiperidine (**46B**).* Substrate **27** (70 mg, 0.18 mmol) was reacted with Me_3SiCN according to the general procedure. Flash column chromatography (5:1 to 1:1 heptane/EtOAc) afforded hydroxypiperidine **46B** (14 mg, 0.05 mmol, 28%). $[\alpha]_D^{20}$ +14.7 (*c* 0.61, CH_2Cl_2); IR (film) 3317, 2954, 1709, 1537, 1256, 1082 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34–7.33 (m, 5H), 5.19 (s, 2H), 4.76–4.72 (m, 2H), 4.10–4.08 (m, 1H), 3.85–3.78 (m, 1H), 2.27–2.21 (m, 2H), 1.84–1.80 (m, 1H), 1.60–1.58 (m, 1H), 1.13 (d, *J*=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.3, 135.9, 128.1, 127.7, 127.6, 118.5, 82.7, 66.4, 66.3, 48.9, 30.7, 26.5, 15.7; HRMS (ESI) calcd for $C_{15}H_{18}N_2NaO_3$ (M+Na$^+$) 297.1215, found 297.1219.

*7.17.4. (2R,3S,6S)-1-Benzyloxycarbonyl-6-(2-(chloromethyl)allyl)-3-hydroxy-2-methylpiperidine (**47B**) and (2R,3S,6R)-1-benzyloxycarbonyl-6-(2-(chloromethyl)allyl)-3-hydroxy-2-methylpiperidine (**47C**).* Substrate **27** (70 mg, 0.18 mmol) was reacted with 2-(chloromethyl)allyltrimethylsilane according to the general method. Flash column chromatography (5:1 to 1:1 heptane:EtOAc) afforded the product as a separable mixture of diastereoisomers in a ratio of 1.4:1 (^{1}H NMR), hydroxypiperidine **47B** (24 mg, 0.07 mmol, 39%) and hydroxypiperidine **47C** (17 mg, 0.05 mmol, 27%).

Compound **47B**: $[\alpha]_D^{20}$ −4.6 (*c* 0.69, CH_2Cl_2); IR (film) 3407, 2954, 1692, 1297, 1019, 712 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34–7.33 (m, 5H), 5.16–4.96 (m, 4H), 4.32–4.29 (m, 1H), 4.00–3.95 (m, 2H), 3.80–3.78 (m, 1H), 2.43–2.38 (m, 2H), 2.00–1.61 (m, 4H), 1.21 (d, *J*=8.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.9, 142.1, 136.1, 135.9, 128.0, 127.6, 127.5, 116.8, 116.1, 67.7, 66.9, 53.1, 48.1, 47.1, 38.6, 20.3, 19.2, 18.9; HRMS (ESI) calcd for $C_{18}H_{24}Cl^{35}NNaO_3$ (M+Na$^+$) 360.1342, found 360.1332.

Compound **47C**: $[\alpha]_D^{20}$ +8.3 (*c* 0.71, CH_2Cl_2); IR (film) 3757, 2936, 1701, 1550, 1269 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34–7.33 (m, 5H), 5.16–5.09 (m, 4H), 4.15–3.94 (m, 5H), 3.38–2.34 (m, 2H), 2.05–1.97 (m, 2H), 1.65–1.60 (m, 2H), 1.14 (d, *J*=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.4, 142.2, 136.1, 134.8, 128.0, 127.8, 127.6, 116.0, 81.0, 69.2, 66.2, 54.4, 48.2, 38.7, 31.6, 27.7, 15.6; HRMS (ESI) calcd for $C_{18}H_{24}Cl^{35}NNaO_3$ (M+Na$^+$) 360.1342, found 360.1333.

*7.17.5. (2S,3S,6R)-2,6-Diallyl-1-benzyloxycarbonyl-3-hydroxypiperidine (**55**).* Amide **28** was reacted with allyltrimethylsilane according to the general procedure. Flash column chromatography (5:1 to 1:1 heptane/EtOAc) afforded hydroxypiperidine **55** (32 mg, 0.10 mmol, 68%). $[\alpha]_D^{20}$ −9.8 (*c* 0.30, CH_2Cl_2); IR (film) 2945, 1714, 1506, 1256, 1044, 906, 703 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34 (m, 5H), 5.84–5.71 (m, 2H), 5.11–5.03 (m, 6H), 3.99–3.97 (m, 2H), 3.74–3.72 (m, 1H), 2.34–2.10 (m, 4H), 1.99–1.90 (m, 2H), 1.73–1.54 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.1, 136.2, 134.3, 134.2, 128.0, 127.6, 127.5, 117.1, 116.4, 78.8, 66.2, 52.8, 52.8, 39.7, 37.9, 30.9, 28.4; HRMS (ESI) calcd for $C_{19}H_{25}NNaO_3$ (M+Na$^+$) 338.1732, found 338.1726.

*7.17.6. (2S,3S,6R)-2-Allyl-benzyloxycarbonyl-3-hydroxy-6-(propa-1,2-dienyl)piperidine (**56**).* Substrate **28** (100 mg, 0.25 mmol) was reacted with propargyltrimethylsilane, following the general procedure. Flash column chromatography (5:1 to 1:1 heptane/EtOAc) afforded hydroxypiperidine **56** (48 mg, 0.15 mmol, 62%). $[\alpha]_D^{20}$ −20.2 (*c* 1.5, CH_2Cl_2); IR (film) 3356, 2928, 1692, 1506, 1195, 1056, 664 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36–7.34 (m, 5H), 5.84–5.73 (m, 1H), 5.19–5.03 (m, 5H), 4.82–4.78 (m, 2H), 4.52–4.41 (m, 1H), 4.03–3.99 (m, 1H), 3.77–3.74 (m, 1H), 2.35–2.33 (m, 2H), 2.06–1.96 (m, 2H), 1.81–1.68 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 207.3, 156.1, 136.2, 134.1, 128.0, 127.5, 127.4, 11.7, 92.1, 79.8, 78.8, 66.2, 52.8, 52.4, 37.9, 31.5, 28.0; HRMS (ESI) calcd for $C_{19}H_{23}NNaO_3$ (M+Na$^+$) 336.1576, found 336.1584.

*7.17.7. (2S,3S,6R)-2-Allyl-1-benzyloxycarbonyl-6-cyano-3-hydroxypiperidine (**57**).* According to the general procedure, substrate **28** (100 mg, 0.25 mmol) was reacted with Me_3SiCN. Flash column chromatography (5:1 to 1:1 heptane/EtOAc) afforded hydroxypiperidine **57** (37 mg, 0.12 mmol, 50%). $[\alpha]_D^{20}$ −27.0 (*c* 0.76, CH_2Cl_2); IR (film) 3386, 2945, 1696, 1411, 1303, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36–7.35 (m, 5H), 5.78–5.72 (m, 1H), 5.30–5.01 (m, 5H), 4.54–4.56 (m, 1H), 3.85–3.81 (m, 1H), 2.72–2.61 (m, 2H), 2.07–1.84 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.1, 134.1, 133.5, 128.2, 127.9, 127.8, 118.9, 117.9, 68.2, 67.9, 55.6, 39.1, 29.2, 27.3, 24.0; HRMS (ESI) calcd for $C_{17}H_{21}N_2O_3$ (M+H$^+$) 301.1552, found 301.1556.

*7.17.8. (2S,3S,6R)-2-Allyl-1-benzyloxycarbonyl-6-(2-(chloromethyl)-allyl)-3-hydroxypiperidine (**58**).* Substrate **28** (100 mg, 0.25 mmol) was reacted with 2-(chloromethyl)allyltrimethylsilane according to the general method. Flash column chromatography (5:1 to 1:1 heptane/EtOAc) afforded hydroxypiperidine **58** (56 mg, 0.15 mmol, 62%). $[\alpha]_D^{20}$ −2.2 (*c* 0.56, CH_2Cl_2); IR (film) 3356, 2936, 1713, 1506, 1225, 944 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35 (m, 5H), 5.84–5.75 (m, 1H), 5.18–5.00 (m, 6H), 4.14–4.00 (m, 4H), 3.75–3.73 (m, 1H), 2.37–2.30 (m, 4H), 2.05–1.93 (m, 2H), 1.73–1.56 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.1, 142.3, 136.2, 134.0, 128.0, 127.6, 127.5, 117.2, 116.0, 78.7, 78.2, 66.2, 52.6, 52.6, 48.2, 38.8, 37.8, 31.6, 28.2; HRMS (ESI) calcd for $C_{20}H_{27}Cl^{35}NO_3$ (M+H$^+$) 364.1680, found 364.1706.

7.18. (2*R*,3*R*,5*S*)-2-Allyl-1-benzyloxycarbonyl-5-(*tert*-butyldimethylsilyloxy)-3-hydroxypiperidine (63)

To a solution of **32** (40 mg, 0.1 mmol) in a mixture of acetone, water, and acetonitrile (0.5 mL each) were added NMO (18 mg, 0.15 mmol) and OsO_4 (5 mol %, 17 μL of a solution of 4 wt % in H_2O). The resulting slurry was stirred overnight followed by the addition of CH_2Cl_2 (3 mL) and water (2 mL), the aqueous layer was extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were dried, filtered, and concentrated in vacuo. The crude product was dissolved in CH_2Cl_2 (3 mL) and $BF_3\cdot OEt_2$ (38 μL, 0.3 mmol) and allyltrimethylsilane (80 μL, 0.5 mmol) were added. After stirring overnight, water (5 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2×5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced

pressure. Purification via flash column chromatography (3:1 to 1:3 heptane/EtOAc) afforded hydroxypiperidine **63** (16 mg, 0.04 mmol, 40%). $[\alpha]_D^{20}$ +10.0 (*c* 0.57, CH_2Cl_2); IR (film) 2954, 2859, 1700, 1247, 837 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.35–7.30 (m, 5H), 5.74–5.71 (m, 1H), 5.15–5.01 (m, 5H), 4.58–4.54 (m, 1H), 4.33–4.28 (m, 1H), 3.99–3.95 (m, 2H), 2.88–2.84 (m, 1H), 2.44–2.42 (m, 1H), 2.32–2.25 (m, 2H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.8, 136.4, 134.7, 127.9, 127.4, 127.3, 116.5, 66.6, 65.8, 63.9, 54.5, 43.9, 35.2, 27.1, 25.3, 22.2, −5.6; HRMS (ESI) calcd for $C_{22}H_{36}NO_4Si$ ($M+H^+$) 406.2414, found 406.2422.

7.19. (2*S*,3*S*,5*S*)-1-Benzyloxycarbonyl-5-(*tert*-butyldimethylsilyloxy)-3-hydroxy-2-(propa-1,2-dienyl) piperidine (64)

Substrate **32** (100 mg, 0.28 mmol) was reacted with propargyltrimethylsilane, following the same procedure as for **63**. Flash column chromatography (3:1 to 1:3 heptane/EtOAc) afforded hydroxypiperidine **64** (10 mg, 0.02 mmol, 9%). $[\alpha]_D^{20}$ −12.6 (*c* 0.48, CH_2Cl_2); IR (film) 3408, 2954, 2842, 1701, 1424, 1264, 1109, 840 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.37–7.34 (m, 5H), 5.29–5.05 (m, 3H), 4.84–4.79 (m, 2H), 4.29–4.27 (m, 1H), 4.09–3.94 (m, 2H), 3.75–3.72 (m, 1H), 2.76–2.70 (m, 1H), 2.58–2.54 (m, 1H), 2.01–1.99 (m, 1H), 0.84 (s, 9H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 205.9, 158.0, 130.6, 128.0, 127.6, 127.4, 87.5, 83.6, 68.5, 67.2, 66.9, 49.2, 46.6, 36.2, 25.3, 17.6, −5.2; HRMS (ESI) calcd for $C_{22}H_{33}NNaO_4Si$ ($M+Na^+$) 426.2077, found 426.2062.

7.20. (2*S*,3*S*,5*S*)-1-Benzyloxycarbonyl-5-(*tert*-butyldimethylsilyloxy)-2-cyano-3-hydroxypiperidine (65)

Substrate **32** (100 mg, 0.28 mmol) was reacted with Me_3SiCN, following the same procedure as for **63**. Flash column chromatography (3:1 to 1:3 heptane/EtOAc) afforded hydroxypiperidine **65** (23 mg, 0.08 mmol, 21%). $[\alpha]_D^{20}$ +23.1 (*c* 0.85, CH_2Cl_2); IR (film) 3425, 2911, 2850, 1700, 1424, 1264, 841, 784 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.35–7.34 (m, 5H), 5.59–5.40 (m, 1H), 5.22–5.08 (m, 2H), 4.24–4.17 (m, 1H), 4.11–4.02 (m, 2H), 3.14–3.09 (m, 1H), 2.11–2.06 (m, 1H), 1.82–1.73 (m, 1H), 0.82 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.0, 135.0, 128.1, 127.9, 127.7, 115.1, 67.9, 54.6, 62.0, 50.4, 46.5, 36.7, 25.1, 17.4, −5.5; HRMS (ESI) calcd for $C_{20}H_{31}N_2O_4Si$ ($M+H^+$) 391.2053, found 391.2048.

7.21. (2*S*,3*S*,5*S*)-1-Benzyloxycarbonyl-5-(*tert*-butyldimethylsilyloxy)-2-(2-(chloromethyl)allyl)-3-hydroxypiperidine (66)

Substrate **32** (100 mg, 0.28 mmol) was reacted with 2-(chloromethyl)allyltrimethylsilane, following the same procedure as for **63**. Flash column chromatography (3:1 to 1:3 heptane/EtOAc) afforded hydroxypiperidine **66** (30 mg, 0.07 mmol, 24%). $[\alpha]_D^{20}$ +14.6 (*c* 1.4, CH_2Cl_2); IR (film) 3404, 2967, 2846, 1662, 1558, 1242, 1048, 845 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.32–7.30 (m, 5H), 5.13–4.95 (m, 4H), 4.70–4.59 (m, 1H), 4.35–4.29 (m, 1H), 4.18–3.95 (m, 4H), 2.92–2.88 (m, 1H), 2.68–2.62 (m, 1H), 2.38–2.35 (m, 1H), 1.84–1.82 (m, 1H), 1.68–1.65 (m, 1H), 0.84 (s, 9H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.8, 141.8, 136.2, 128.1, 127.9, 127.5, 116.5, 66.7, 65.8, 63.6, 53.0, 47.4, 43.8, 34.9, 25.7, 25.2, 17.5, −5.5; HRMS (ESI) calcd for $C_{23}H_{37}Cl^{35}NO_4Si$ ($M+H^+$) 454.2180, found 454.2168.

7.22. General procedure for deprotection A

HBr (33 wt % in acetic acid, 0.1 M) was added to protected piperidine at 0 °C and the mixture was stirred for 5 min followed by concentration in vacuo. Toluene and water were added and the organic layer was extracted with water. The aqueous layers were combined and concentrated in vacuo to afford the deprotected compound.

7.23. General procedure for deprotection B

The protected piperidine was dissolved in MeOH (0.1 M) and Pd/C (10%) was added and the mixture was stirred under H_2 (1 atm) pressure until completion according to TLC. The mixture was filtered through Celite and the solvent was evaporated under reduced pressure.

7.24. General procedure for deprotection C

The protected piperidine was dissolved in MeOH (0.1 M), Pd/C (10%) and HCl (concentrated, 1 equiv) were added and the mixture was stirred under H_2 (1 atm) pressure until completion according to TLC. The suspension was filtered through Celite and the solvent was evaporated under reduced pressure.

*7.24.1. (3S,6R)-6-Allylpiperidin-3-ol (**40**).* Piperidine **35** (305 mg, 0.78 mmol) was deprotected according to general procedure A. After concentration of the aqueous layers, aqueous NaOH (1 M, 1 mL) and CH_2Cl_2 (5 mL) were added. The aqueous layer was extracted with CH_2Cl_2 (3×5 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the free amine **40** (97 mg, 0.68 mmol, 78%). $[\alpha]_D^{20}$ +12.9 (*c* 0.16, CH_2Cl_2); IR (film) 3286, 2932, 1445, 1030, 909, 607 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.81–5.69 (m, 1H), 5.11–5.05 (m, 2H), 3.67–3.61 (m, 1H), 3.25–3.20 (m, 1H), 2.49–2.35 (m, 2H), 2.21–2.02 (m, 3H), 1.76–1.70 (m, 1H), 1.33–1.16 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 134.9, 117.0, 67.8, 54.6, 53.5, 40.3, 33.7, 30.6; HRMS (ESI) calcd for $C_8H_{16}NO$ ($M+H^+$) 142.1232, found 142.1236.

*7.24.2. (3S,6R)-6-Propylpiperidin-3-ol (**3**).* Allene **36** (45 mg, 0.16 mmol) was deprotected following procedure C followed by addition of aqueous NaOH (1 M, 2 mL) and CH_2Cl_2 (2 mL) and the aqueous layer was extracted with CH_2Cl_2 (2×5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and the solvent was removed under vacuo to give (+)-pseudoconhydrine (**3**) (12 mg, 0.08 mmol, 52%). $[\alpha]_D^{20}$ +10.3 (*c* 0.17, EtOH) (lit. $[\alpha]_D^{29}$ +11.1 (*c* 1.0, EtOH)); IR (film) 3144, 2923, 1454, 1070, 616 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.61 (dt, *J*=10.2, 4.8 Hz, 1H), 3.24–3.18 (m, 1H), 2.47–2.40 (m, 2H), 2.07–2.00 (m, 1H), 1.73–1.71 (m, 3H), 1.63–1.30 (m, 4H), 1.09–0.90 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 68.0, 55.1, 53.6, 38.1, 33.7, 30.8, 18.9, 13.7; HRMS (ESI) calcd for $C_8H_{18}NO$ ($M+H^+$) 144.1388, found 144.1382. Analytical data are in comparison with literature.[7a]

*7.24.3. (2R,5S)-5-Hydroxypiperidine-2-carboxamide hydrobromide (**41**).* Deprotection of compound **38** (40 mg, 0.11 mmol) was performed according to procedure A to afford the desired amine **41** (25 mg, 0.11, mmol, 100%). $[\alpha]_D^{20}$ +2.6 (*c* 0.58, MeOH); IR (film) 3390, 3023, 1683, 1441, 1091, 590 cm^{-1}; ^1H NMR (D_2O, 300 MHz) δ 3.91–3.86 (m, 2H), 3.47–3.41 (m, 1H), 2.83–2.76 (m, 1H), 2.29–2.22 (m, 1H), 2.11–2.02 (m, 1H), 1.83–1.70 (m, 1H), 1.60–1.51 (m, 1H); ^{13}C NMR (D_2O, 75 MHz) δ 170.9, 62.4, 55.9, 46.7, 29.2, 24.2; HRMS (ESI) calcd for $C_6H_{13}N_2O_2$ ($M+H^+$) 145.0985, found 145.0977.

*7.24.4. (2R,5S)-5-Hydroxypipecolic acid (ent-**1**).* Amide **41** (20 mg, 0.09 mmol) was dissolved in MeOH (1 mL), aqueous KOH (2 M, 1 mL) was added and the mixture was stirred overnight followed by concentration under reduced pressure. The residue was suspended in MeOH, filtered, and concentrated in vacuo to afford hydroxypipecolic acid *ent*-**1** (8 mg, 0.056 mmol, 61%). $[\alpha]_D^{20}$ +31.0 (*c* 0.1, MeOH); (lit. (other enantiomer) $[\alpha]_D^{20}$ −33.0 (*c* 2.2, H_2O));[19]

^{1}H NMR (D_2O, 400 MHz) δ 3.68–3.64 (m, 1H), 3.24–3.14 (m, 2H), 2.52–2.46 (m, 1H), 2.07–2.02 (m, 1H), 1.95–1.91 (m, 1H), 1.49–1.34 (m, 2H); ^{13}C NMR (CD_3OD, 75 MHz) δ 178.9, 66.6, 60.0, 51.6, 33.2, 28.9; HRMS (ESI) calcd for $C_6H_{12}NO_3$ ($M+H^+$) 146.0817, found 146.0816.

*7.24.5. (6S,8aR)-2-Methyleneoctahydroindolizin-6-ol (**42**).* Piperidine **39** (78 mg, 0.18 mmol) was deprotected according to procedure A. The resulting mixture was dissolved in MeOH (2 mL) followed by the addition of K_2CO_3 (35 mg, 0.36 mmol). After stirring for 2 h, water (3 mL) and CH_2Cl_2 (3 mL) were added and the aqueous layer was extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash column chromatography (100:0 to 95:5 EtOAc/MeOH) afforded the title compound **42** (22 mg, 0.14 mmol, 80%). $[\alpha]_D^{20}$ −27.4 (*c* 0.13, CH_2Cl_2); IR (film) 2932, 2785, 1553, 1450, 1014, 573 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.89–4.88 (m, 2H), 3.88–3.84 (m, 1H), 3.59–3.54 (m, 1H), 3.27–3.22 (m, 1H), 2.92–2.91 (m, 1H), 2.50–2.45 (m, 1H), 2.16–1.85 (m, 5H), 1.34–1.29 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.1, 105.2, 67.4, 63.1, 59.2, 58.8, 37.2, 33.4, 28.0; HRMS (ESI) calcd for $C_9H_{16}NO$ ($M+H^+$) 154.1232, found 154.1242.

*7.24.6. (2R,3S,6R)-6-Allyl-2-methylpiperidin-3-ol hydrobromide (**48**).* Compound **44A** (24 mg, 0.06 mmol) was deprotected according procedure A to afford deprotected piperidinol **48** (14 mg, 0.06 mmol, 100%). $[\alpha]_D^{20}$ +10.3 (*c* 0.76, MeOH); IR (film) 2941, 1687, 1640, 1445, 1061, 603, 499 cm^{-1}; ^{1}H NMR (D_2O, 300 MHz) δ 5.76–5.64 (m, 1H), 5.18–5.12 (m, 2H), 3.49–3.41 (m, 1H), 3.17–3.12 (m, 1H), 2.96–2.91 (m, 1H), 2.33–2.29 (m, 2H), 2.05–1.98 (m, 2H), 1.49–1.42 (m, 2H), 1.28 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (D_2O, 75 MHz) δ 131.3, 119.4, 68.9, 56.8, 55.6, 36.6, 30.2, 26.2, 14.4; HRMS (ESI) calcd for $C_9H_{18}NO$ ($M+H^+$) 156.1388, found 156.1396.

*7.24.7. (2R,3S,6S)-6-Allyl-2-methylpiperidin-3-ol hydrobromide (**52**).* According to general procedure A, **44C** (13 mg, 0.04 mmol) was deprotected to afford piperidinol **52** (7 mg, 0.03 mmol, 74%). $[\alpha]_D^{20}$ +4.3 (*c* 0.16, MeOH); IR (film) 3420, 2949, 1627, 1070, 850 cm^{-1}; ^{1}H NMR (D_2O, 300 MHz) δ 5.81–5.72 (m, 1H), 5.09–4.99 (m, 2H), 4.09–4.06 (m, 2H), 3.43–3.41 (m, 1H), 2.24–2.21 (m, 2H), 2.04–1.99 (m, 2H), 1.64–1.62 (m, 2H), 1.16 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (D_2O, 75 MHz) δ 134.4, 116.7, 79.6, 78.1, 49.4, 38.5, 30.2, 25.5, 12.7; HRMS (ESI) calcd for $C_9H_{18}NO$ ($M+H^+$) 156.1388, found 156.1387.

*7.24.8. (2R,3S,6R)-2-Methyl-6-propylpiperidin-3-ol (**49**).* Compound **45A** (19 mg, 0.047 mmol) was deprotected according to procedure C. After concentration in vacuo, aqueous NaOH (1 M, 2 mL) and CH_2Cl_2 (2 mL) were added and the aqueous layer was extracted with CH_2Cl_2 (2×5 mL). The combined organic layers were dried over Na_2SO_4, concentrated, and the solvent was removed under vacuo to give piperidinol **49** (6 mg, 0.037 mmol, 81%). $[\alpha]_D^{20}$ +15.3 (*c* 0.07 CH_2Cl_2); IR (film) 2854, 2928, 1458, 1043, 840 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.18–3.11 (m, 1H), 2.54–2.45 (m, 2H), 2.06–2.00 (m, 1H), 1.76–1.71 (m, 1H), 1.24–1.33 (m, 6H), 1.19 (d, *J*=4.5 Hz, 3H), 0.93–0.89 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 73.8, 58.1, 55.6, 38.4, 33.6, 31.3, 18.9, 13.8; HRMS (ESI) calcd for $C_9H_{20}NO$ ($M+H^+$) 158.1545, found 158.1552.

*7.24.9. (2R,5S,6R)-5-Hydroxy-6-methylpiperidine-2-carboxamide hydrobromide (**50**).* Substrate **46A** (25 mg, 0.064 mmol) was deprotected following procedure A to provide piperidine **50** (15 mg, 0.064 mmol, 100%). $[\alpha]_D^{20}$ +15.5 (*c* 0.44, MeOH); IR (film) 3377, 2937, 1683, 1424, 1035, 547 cm^{-1}; ^{1}H NMR (D_2O, 300 MHz) δ 3.91 (dd, *J*=3.2, 12.7 Hz, 1H), 3.55 (dt, *J*=10.8, 4.6 Hz, 1H), 3.05–2.99 (m, 1H), 2.26–2.11 (m, 2H), 1.85–1.67 (m, 1H), 1.62–1.48 (m, 1H), 1.33 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (D_2O, 75 MHz) δ 170.8, 68.2, 56.9, 56.0, 30.2, 25.3, 14.1; HRMS (ESI) calcd for $C_7H_{15}N_2O_2$ ($M+H^+$) 159.1134, found 159.1136.

*7.24.10. (2R,3S,6R)-6-Isobutyl-2-methylpiperidin-3-ol hydrochloride (**51**).* Compound **47A** (20 mg, 0.06 mmol) was deprotected according to procedure C to afford piperidinol **51** (10 mg, 0.06 mmol, 100%). $[\alpha]_D^{20}$ +11.7 (*c* 0.67, MeOH); IR (film) 3960, 2971, 1640, 1454, 1052, 538 cm^{-1}; ^{1}H NMR (D_2O, 300 MHz) δ 3.45–3.44 (m, 1H), 3.33–3.29 (m, 1H), 2.85–2.76 (m, 1H), 1.89–1.86 (m, 2H), 1.46–1.44 (m, 1H), 1.24–1.19 (m, 4H), 1.12 (d, *J*=6.3 Hz, 3H), 0.68–0.62 (m, 6H); ^{13}C NMR (D_2O, 75 MHz) δ 69.1, 56.6, 54.7, 41.0, 30.2, 26.2, 23.3, 21.8, 20.2, 14.5; HRMS (ESI) calcd for $C_{10}H_{22}NO$ ($M+H^+$) 172.1701, found 172.1707.

*7.24.11. (2R,3S,6S)-6-Isobutyl-2-methylpiperidin-3-ol (**53**).* Compound **47C** (16 mg, 0.05 mmol) was reacted with Pd/C, following procedure B to afford piperidinol **53** (8 mg, 0.04 mmol, 93%). $[\alpha]_D^{20}$ −6.6 (*c* 0.32, CH_2Cl_2); IR (film) 3347, 2945, 1666, 1264, 1009, 845 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.12–4.08 (m, 1H), 3.41–3.36 (m, 1H), 3.22–3.18 (m, 1H), 2.61–2.52 (m, 1H), 2.37–2.29 (m, 2H), 1.90–1.86 (m, 2H), 1.51–1.42 (m, 2H), 1.32 (d, J=6.6 Hz, 3H), 0.92–0.86 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 32.0, 28.4, 27.0, 22.6, 22.2, 14.6; HRMS (ESI) calcd for $C_{10}H_{22}NO$ ($M+H^+$) 172.1701, found 172.1696.

*7.24.12. (2S,3S,6R)-2,6-Diallylpiperidin-3-ol hydrobromide (**59**).* Substrate **55** (36 mg, 0.12 mmol) was deprotected following procedure A to afford the desired piperidinol **59** (29 mg, 0.11 mmol, 92%). $[\alpha]_D^{20}$ +6.0 (*c* 0.40, MeOH); IR (film) 3317, 2954, 2828, 1406, 1001, 667 cm^{-1}; ^{1}H NMR (D_2O, 300 MHz) δ 5.79–5.71 (m, 2H), 5.22–5.00 (m, 4H), 4.06–3.95 (m, 2H), 3.21–3.18 (m, 1H), 2.47–2.41 (m, 1H), 2.31–1.95 (m, 4H), 1.65–1.63 (m, 3H); ^{13}C NMR (D_2O, 75 MHz) δ 134.6, 131.0, 120.0, 116.7, 78.9, 77.6, 54.0, 38.3, 33.1, 30.3, 28.0; HRMS (ESI) calcd for $C_{11}H_{20}NO$ ($M+H^+$) 182.1545, found 182.1535.

*7.24.13. (2S,3S,6R)-2,6-Dipropylpiperidin-3-ol (**60**).* Compound **56** (13 mg, 0.04 mmol) was reacted with Pd/C, following procedure B to afford piperidinol **60** (8 mg, 0.04 mmol, 100%). $[\alpha]_D^{20}$ −17.3 (*c* 0.38, CH_2Cl_2); IR (film) 3260, 2971, 1649, 1368, 1091, 845 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.04–4.01 (m, 1H), 3.90–3.85 (m, 1H), 3.29–3.28 (m, 1H), 2.42–1.91 (m, 6H), 1.61–1.32 (m, 6H), 0.95–0.89 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 82.8, 64.8, 55.0, 37.5, 36.0, 32.5, 28.6, 19.0, 18.8, 18.2, 17.6; HRMS (ESI) calcd for $C_{11}H_{23}NNaO$ ($M+Na^+$) 208.1677, found 208.1670.

*7.24.14. (2R,5S,6S)-6-Allyl-5-hydroxypiperidine-2-carboxamide hydrobromide (**61**).* Substrate **57** (17 mg, 0.056 mmol) was deprotected following procedure A to afford the desired hydroxypiperidine **61** (11 mg, 0.038 mmol, 68%). $[\alpha]_D^{20}$ +2.4 (*c* 0.53, MeOH); IR (film) 3403, 1692, 1398, 1022, 624 cm^{-1}; ^{1}H NMR (D_2O, 300 MHz) δ 5.77–5.68 (m, 1H), 5.25–5.17 (m, 2H), 4.19–4.18 (m, 1H), 3.90–3.77 (m, 1H), 3.31–3.26 (m, 1H), 2.52–1.92 (m, 6H); ^{13}C NMR (D_2O, 75 MHz) δ 173.9, 131.0, 119.6, 69.4, 62.2, 54.8, 33.0, 28.6, 20.7; HRMS (ESI) calcd for $C_{12}H_{16}N_2NaO_2$ ($M+Na^+$) 207.1110, found 207.1100.

*7.24.15. (2S,3S,6R)-6-Isobutyl-2-propylpiperidin-3-ol (**62**).* Compound **58** (26 mg, 0.07 mmol) was deprotected according procedure B to afford piperidinol **62** (13 mg, 0.065 mmol, 93%). $[\alpha]_D^{20}$ −10.7 (*c* 0.65, CH_2Cl_2); IR (film) 3407, 2963, 1640, 1394, 1091, 417 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.14–4.08 (m, 1H), 3.92–3.87 (m, 1H), 3.05–3.03 (m, 1H), 1.74–1.26 (m, 11H), 1.00–0.88 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 77.7, 55.3, 44.2, 32.2, 31.6, 28.7, 25.4, 25.3, 25.0, 22.5, 22.4, 13.6; HRMS (ESI) calcd for $C_{12}H_{25}NNaO$ ($M+Na^+$) 222.1834, found 222.1835.

*7.24.16. (2S,3S,5S)-2-Allylpiperidine-3,5-diol (**67**).* Piperidine **63** (117 mg, 0.29 mmol) was deprotected according to general

procedure A. After concentration of the aqueous layers, aqueous NaOH (1 M, 1 mL) and CH_2Cl_2 (5 mL) were added. The aqueous layer was extracted with CH_2Cl_2 (3×5 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the free amine **67** (39 mg, 0.25 mmol, 85%). $[\alpha]_D^{20}$ +5.8 (*c* 0.46, MeOH); IR (film) 3282, 2923, 1558, 1090, 603 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 5.84–5.76 (m, 1H), 5.16–5.06 (m, 2H), 4.02–3.96 (m, 1H), 3.95–3.89 (m, 1H), 3.18–3.14 (m, 1H), 2.74–2.70 (m, 1H), 2.49–2.43 (m, 1H), 2.32–2.22 (m, 4H); ^{13}C NMR (CD_3OD, 75 MHz) δ 133.5, 116.7, 64.9, 61.4, 58.0, 50.6, 39.4, 34.1; HRMS (ESI) calcd for $C_8H_{16}NO_2$ ($M+H^+$) 158.1181, found 158.1191.

*7.24.17. (2S,3S,5S)-2-Propylpiperidine-3,5-diol (**68**).* Compound 64 (10 mg, 0.02 mmol) was deprotected according to procedure C. After concentration in vacuo, aqueous NaOH (1 M, 2 mL) and CH_2Cl_2 (2 mL) were added and the aqueous layer was extracted with CH_2Cl_2 (2×5 mL). The combined organic layers were dried over Na_2SO_4, concentrated, and the solvent was removed under vacuo to give piperidinol **68** (3 mg, 0.02 mmol, 95%). $[\alpha]_D^{20}$ +25.0 (*c* 0.06, MeOH); IR (film) 3230, 2812, 1666, 1066, 603 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 4.08–3.95 (m, 2H), 3.21–3.14 (m, 1H), 2.77–2.73 (m, 1H), 2.55–2.48 (m, 1H), 2.24–2.15 (m, 1H), 1.60–1.27 (m, 5H), 0.98–0.93 (m, 3H); ^{13}C NMR (CD_3OD, 75 MHz) δ 65.0, 61.5, 58.0, 50.7, 39.4, 31.9, 18.2, 12.5; HRMS (ESI) calcd for $C_8H_{18}NO_2$ ($M+H^+$) 160.1338, found 160.1338.

*7.24.18. (2R,3S,5S)-3,5-Dihydroxypiperidine-2-carboxamide (**69**).* Piperidine **65** (23 mg, 0.08 mmol) was deprotected according to general procedure A. After concentration of the aqueous layers, aqueous NaOH (1 M, 1 mL) and CH_2Cl_2 (5 mL) were added. The aqueous layer was extracted with CH_2Cl_2 (3×5 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification with an Isolute® Flash SCX-2 ion exchange column (eluents: CH_2Cl_2, MeOH, NH_3/MeOH (1 M)) gave dihydroxypiperidine **69** (10 mg, 0.05 mmol, 68%). $[\alpha]_D^{20}$ +25.3 (*c* 0.08, MeOH); IR (film) 3364, 1640, 1286, 858 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 4.52–4.51 (m, 1H), 4.22–4.16 (m, 1H), 3.93–3.85 (m, 1H), 2.78–2.70 (m, 1H), 2.28–2.15 (m, 1H), 1.71–1.62 (m, 1H), 1.29–1.27 (m, 1H); ^{13}C NMR (CD_3OD, 75 MHz) δ 171.2, 75.0, 64.4, 59.4, 59.0, 38.0; HRMS (ESI) calcd for $C_6H_{12}NNaO_2$ ($M+Na^+$) 183.0746, found 183.0746.

*7.24.19. (6S,8S,8aS)-2-Methyleneoctahydroindolizine-6,8-diol (**70**).* Piperidine **66** (30 mg, 0.07 mmol) was deprotected according to procedure A. The resulting mixture was dissolved in MeOH (1 mL) followed by the addition of K_2CO_3 (14 mg, 0.14 mmol). After stirring for 2 h, water (3 mL) and CH_2Cl_2 (3 mL) were added and the aqueous layer was extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash column chromatography (100:0 to 95:5 EtOAc/MeOH) afforded indolizidine **70** (7 mg, 0.04 mmol, 59%). $[\alpha]_D^{20}$ −20.0 (*c* 0.10, CH_2Cl_2); IR (film) 3369, 2928, 1657, 1087, 1026, 629 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 4.95–4.93 (m, 2H), 4.21–4.16 (m, 1H), 3.99–3.96 (m, 1H), 3.84–3.77 (m, 2H), 3.14–3.07 (m, 1H), 2.87–2.86 (m, 1H), 2.64–2.62 (m, 1H), 2.45–2.38 (m, 2H), 2.19–2.09 (m, 1H), 1.56–1.47 (m, 1H); ^{13}C NMR (CD_3OD, 75 MHz) δ 138.8, 111.3, 73.1, 71.3, 61.6, 53.0, 50.9, 37.4, 35.4; HRMS (ESI) calcd for $C_9H_{16}NO_2$ ($M+H^+$) 170.1181, found 170.1159.

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Supplementary data

The 2D-NMR data of compounds **42**, **50**, **59**, **67**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.05.089. These data include MOL files and InChIKeys of the most important compounds described in this article.

References and notes

1. See, e.g. Strunz, G. M.; Findlay, J. A. In *The Alkaloids*; Brossi, A., Ed.; Acadamic: San Diego, CA, 1986; Vol. 26, p 89.
2. Witkop, B.; Foltz, C. M. *J. Am. Chem. Soc.* **1957**, *79*, 192–197.
3. Yasuda, K.; Kizu, H.; Yamashita, T.; Kameda, Y.; Kato, A.; Nash, R. J.; Fleet, G. W. J.; Molyneux, R. J.; Asano, N. *J. Nat. Prod.* **2002**, *65*, 198–202.
4. Engler, C.; Kronstein, A. *Ber. Dtsch. Chem. Ges.* **1894**, *27*, 1779–1784.
5. Quibell, M.; Benn, A.; Flinn, N.; Monk, T.; Ramjee, M.; Wang, Y.; Watts. *J. Bioorg. Med. Chem.* **2004**, *12*, 5689–5710.
6. Marion, L.; Cockburn, W. F. *J. Am. Chem. Soc.* **1949**, *71*, 3402–3404.
7. (a) Sakagami, H.; Kamikubo, T.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1996**, 1433–1434; (b) Moody, C. J.; Lightfoot, A. P.; Gallagher, P. T. *J. Org. Chem.* **1997**, *62*, 746–748; Löfstedt, J.; Pettersson-Fasth, H.; Bäckvall, J.-E. *Tetrahedron* **2000**, *56*, 2225–2230; (c) Botman, P. N. M.; Dommerholt, F. J.; de Gelder, R.; Broxterman, Q. B.; Schoemaker, H. E.; Rutjes, F. P. J. T.; Blaauw, R. H. *Org. Lett.* **2004**, *6*, 4941–4944; (d) Haddad, M.; Imogai, H.; Larcheveque, M. *J. Org. Chem.* **1998**, *63*, 5680–5683; (e) Jung, J.-C.; Avery, M. A. *Tetrahedron: Asymmetry* **2006**, *17*, 2479–2486; (f) Kim, I. S.; Ji, Y. J.; Jung, Y. H. *Tetrahedron Lett.* **2006**, *47*, 7289–7293.
8. Wijdeven, M. A.; Wijtmans, R.; van den Berg, R. J. F.; Noorduin, W.; Schoemaker, H. E.; Sonke, T.; van Delft, F. L.; Blaauw, R. H.; Fitch, R. W.; Spande, T. F.; Daly, J. W.; Rutjes, F. P. J. T. *Org. Lett.* **2008**, *10*, 4001–4003.
9. Wijdeven, M. A.; van den Berg, R. J. F.; Wijtmans, R.; Botman, P. N. M.; Blaauw, R. H.; Schoemaker, H. E.; van Delft, F. L.; Rutjes, F. P. J. T. *Org. Biomol. Chem.* **2009**, *7*, 2976–2980.
10. Braekman, J.-C.; Charlier, A.; Daloze, D.; Heilporn, S.; Pasteels, J.; Plasman, V.; Wang, S. *Eur. J. Org. Chem.* **1999**, *1*, 1749–1755.
11. Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956.
12. (a) Comins, D. L.; Dinsmore, J. M.; Marks, L. R. *Chem. Commun.* **2007**, 4170–4171; (b) Matsushita, H.; Negishi, E. *J. Org. Chem.* **1982**, *47*, 4161–4165.
13. Vink, M. K. S.; Schortinghuis, C. A.; Luten, J.; van Maarseveen, J. H.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *J. Org. Chem.* **2002**, *67*, 7869–7871.
14. Marin, J.; Didierjean, C.; Aubry, A.; Casimir, J. R.; Briand, J. P.; Guichard, G. *J. Org. Chem.* **2003**, *69*, 130–141.
15. Furukubo, S.; Moriyama, N.; Onomura, O.; Matsumura, Y. *Tetrahedron Lett.* **2004**, *45*, 8177–8181.
16. For excellent reviews on *N*-acyliminium ion chemistry, see, e.g.: (a) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817–3856; (b) Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev.* **2004**, *104*, 2311–2352; (c) Yazici, A.; Pyne, S. G. *Synthesis* **2009**, 339–368; (d) Yazici, A.; Pyne, S. G. *Synthesis* **2009**, 513–541.
17. For *N*-acyliminium ion reactions with similar diastereoselectivity, see: Shono, T.; Matsumura, Y.; Onomura, O.; Sato, M. *J. Org. Chem.* **2002**, *53*, 4118–4121.
18. For 2-D NMR data, see Supplementary data.
19. Kristensen, I.; Olesen Larsen, P.; Erik Olsen, C. *Tetrahedron* **1976**, *32*, 2799–2804.
20. For examples of the formation of 2,6-*cis*-disubstituted piperidines via *N*-acyliminium ion chemistry, see: Shono, T.; Matsumura, Y.; Tsubata, K.; Uchida, K. *J. Org. Chem.* **1986**, *51*, 2590–2592.
21. (a) Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2000**, *1*, 168–169; (b) Strunz, G. M.; Finlay, J. A. In *The Alkaloids*; Brossi, A., Ed.; Academic: New York, NY, 1985; Vol. 26, pp 89–183.