Stereoselective Synthesis of Highly Substituted Piperidines

Christoph Schneider,*[a] Christoph Börner,[a] and Ansgar Schuffenhauer[a]

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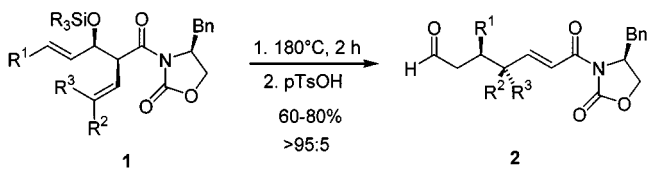
Enantiopure piperidines **4** may be accessed in very good overall yields and high stereoselectivity from the bifunctional products **2** of the silyloxy Cope rearrangement of chiral aldol products **1** by sequential nucleophilic addition of primary amines and subsequent hydrogenation. The reaction is proposed to proceed by initial imine formation followed by an intramolecular aza-conjugate addition to the α,β-unsaturated imide. The stereoselectivity is controlled by A(1.2) strain between the imine *N*-alkyl group and the conjugate double bond. In an alternate approach, polyalkyl-substituted piperidines were prepared by the addition of organozinc reagents to cyanopiperidines readily obtained from the Cope products in the presence of a silver salt.

Introduction

Nitrogen heterocycles enjoy a prominent position in natural product chemistry due to their significant physiological properties which have resulted in numerous medicinal applications.[1] Even the simple piperidine skeleton is contained in a number of biologically active drugs coniine perhaps being the most familiar example. Modern syntheses of piperidines[2] have used hetero Diels–Alder reactions of imines[3] including sequential cross metathesis hetero Diels–Alder reactions,[3i] Lewis acid assisted cyclizations of imines or iminium ions,[4] addition of organometallic reagents to *N*-acylpyridinium salts,[5] and reactions of bicyclic cyanopiperidines and lactams.[6]

We have been actively investigating the synthetic potential of chiral 7-oxo-2-enimides **2** which are formed in good yields and high stereoselectivity from the thermal [3.3]-sigmatropic rearrangement of the requisite aldol products **1** (Scheme 1).[7] Novel synthetic routes towards tetrahydropyrans,[8] polyol chains,[9] terpenols,[10] and cyclohexanes[11] have been devised taking advantage of the functional groups of the Cope products. In this paper we report our efforts to prepare highly substituted and enantiopure piperidines starting from the Cope products **2**.[12]

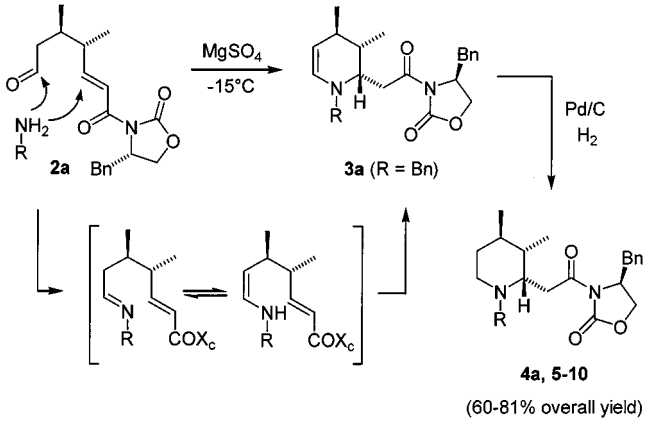


Scheme 1. The silyloxy Cope rearrangement of chiral aldol products

[a] Institut für Organische Chemie der Georg-August-Universität Göttingen
Tammannstrasse 2, D-37077 Göttingen, Germany
Fax: (internat.) + 49-(0)551/399660
E-mail: cschnei1@gwdg.de

Results and Discussion

When the 7-oxo-2-enimide **2a** was treated with benzylamine in toluene at −15°C a smooth condensation reaction took place and the tetrahydropyridine **3a** was formed. Whilst the ^{1}H NMR spectra showed the characteristic signals for the endocyclic enamine double bond (δ = 4.35, δ = 5.89), the compound, however, was too labile for spectroscopic characterization. It was therefore hydrogenated directly (Pd/C, 1 atm H_2) and the piperidine **4a** was obtained essentially as a single stereoisomer in 81% overall yield (Scheme 2). We assume that the amine initially attacks the aldehyde to form the imine which then adds intramolecularly to the conjugate double bond. Supporting evidence for this conclusion comes from the reaction of less nucleophilic amines with **2a**. Thus, aniline and *N*,*N*-dimethylhydrazine were condensed with **2a** to give the corresponding phenylimine and the *N*,*N*-dimethylhydrazone, respectively, in quantitative yield without any indication of cyclization. Sterically more hindered primary amines such as cyclohexylamine also furnished only the imine. Secondary amines, e.g. piperidine, yielded the acyclic enamines exclusively.



Scheme 2. Double nucleophilic addition of primary amines to the 7-oxo-2-enimide **2a**

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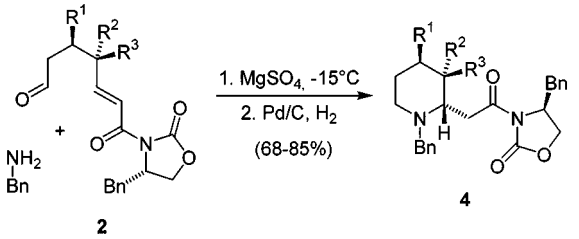
Other primary amines may be employed in this transformation. 4-Methoxy- and (2-chloro)benzylamine as well as *n*-butylamine, isobutylamine, phenylethylamine and (3-methoxy)propylamine all gave the *N*-substituted piperidines **5**−**10** according to the two-step procedure in satisfactory to good overall yields (Scheme 2 and Table 1). The reaction sequence worked better for the *N*-benzyl heterocycles because the corresponding tetrahydropyridines exhibited a higher chemical stability than the *N*-alkyltetrahydropyridines which could not be stored neat, even for a short period of time. Therefore the two-step preparation of the *N*-alkylpiperidines was carried out rapidly in ethyl acetate in such a way that the solution containing the tetrahydropyridine was only filtered to remove the $MgSO_4$ used in the first step and then the enamine directly hydrogenated. The only tetrahydropyridine which was completely stable and could be stored for longer periods of time proved to be the silyl-substituted **3d**, presumably due to the β-effect of silicon.

Table 1. Piperidines **4**−**10** prepared by sequential nucleophilic addition of primary amines to the 7-oxo-2-enimide **2a**

Piperidine	R	(2*S*)/(2*R*)[a]	Yield [%][b]
4a	$C_6H_5CH_2$	> 20:1	81
5	4-MeO−$C_6H_4CH_2$	> 20:1	73
6	2-Cl−$C_6H_4CH_2$	> 20:1	76
7	nC_4H_9	> 20:1	65
8	iC_4H_9	> 20:1	62
9	$C_6H_5CH_2CH_2$	> 20:1	63
10	3-MeO−C_3H_6	> 20:1	60

[a] Determined by ^1H and ^{13}C NMR of the crude products. − [b] Combined yield of both isomers.

Differently substituted 7-oxo-2-enimides **2a**−**g** were condensed with benzylamine and hydrogenated according to the general protocol. The 2,3,4-trisubstituted piperidines **4a**−**g** were obtained in good to excellent overall yields with very high stereocontrol for every case studied (Scheme 3 and Table 2). The major stereoisomer had the (2*S*)-configuration and the C-2-alkyl group in the axial position as unambiguously deduced from ^1H NMR data and is shown explicitly for the piperidines **4c** and **4f** (Figure 1). The coupling constants *J*(2-H/3-H) and *J*(3-H/4-H) were indicative of the relative configuration and conformation. The absolute configuration of the C-3 and C-4 chiral centers could be traced back to the Cope products **2** and the chirality transfer of the sigmatropic process.



Scheme 3. Double nucleophilic addition of benzylamine to various 7-oxo-2-enimides **2**

Table 2. Piperidines **4a**−**g** prepared by sequential nucleophilic addition of benzylamine to the 7-oxo-2-enimides **2**

Piperidine	R^1	R^2	R^3	(2*S*)/(2*R*)[a]	Yield [%][b]
4a	CH_3	CH_3	H	> 20:1	81
4b	C_3H_7	CH_3	H	> 20:1	77
4c	Ph	CH_3	H	> 20:1	68
4d	$SiMe_2Ph$	CH_3	H	> 20:1	72
4e	CH_3	C_2H_5	H	> 20:1	81
4f	CH_3	H	CH_3	> 20:1	85
4g	C_3H_7	H	CH_3	> 20:1	81

[a] Determined by ^1H and ^{13}C NMR of the crude products. − [b] Combined yield of both isomers.

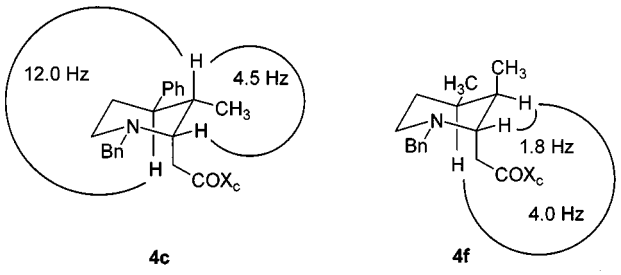


Figure 1. Configuration and conformation of the piperidines **4c** and **4f**

When the same reaction was conducted on the 7-oxo-2-enimide bearing the achiral oxazolidinone, the same sense and a comparable level of stereocontrol was observed which indicates that the stereogenic centers in the chain are responsible for the asymmetric induction. In principle, the reaction may proceed by nucleophilic addition of either the imine or the enamine tautomer to the conjugate double bond. PM3 calculations on both reaction paths clearly reveal that the enamine pathway is at least 10 kcal/mol higher in energy than the imine pathway, which is a good indication that the imine is the actual active species. Assuming that a half-chair conformation resembles the transition structure of the intramolecular addition which is conformationally fixed by the substituents in the chain, two possible transition structures may be drawn (Figure 2). The conjugate double bond can adopt either a pro-axial orientation as in **A**, which eventually leads to the observed product, or the pro-equatorial orientation as in **B**.

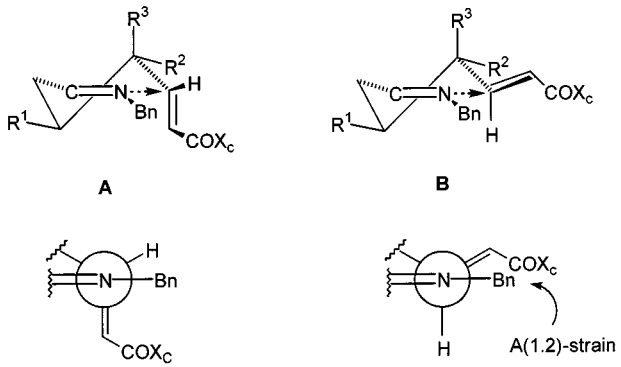
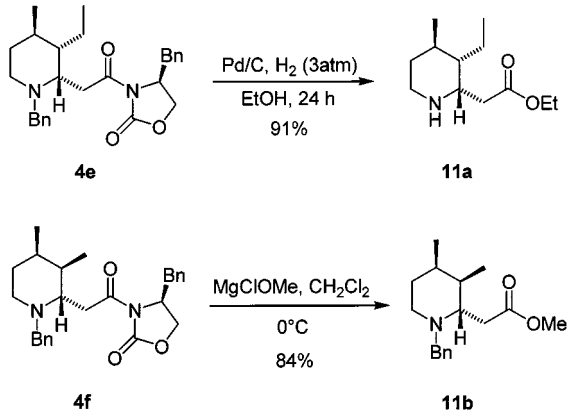


Figure 2. Transition structures **A** and **B** for the aza-conjugate addition of the imino enimides

As the nucleophilic addition of the imine nitrogen atom to the double bond proceeds, the *N*-benzyl group comes into close contact with the pro-equatorial substituent at the neighboring carbon atom of the double bond [developing A(1.2) strain]. In the case of transition structure **A**, the relevant substituent is a hydrogen atom, but in the case of transition structure **B** A(1.2) strain between the *N*-benzyl group and the double bond would develop leading to the destabilization of transition structure **B**.[13] When the R^3 substitutent is a methyl group, as in **4f** and **4g**, additional A(1.3) strain to the α-hydrogen atom of the double bond is involved making transition structure **B** even less favorable.[14]

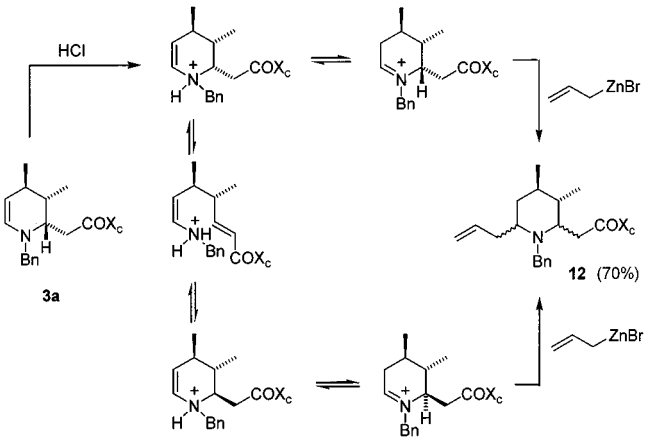
This double nucleophilic addition sequence of primary amines to oxo enimides to furnish piperidines resembles a closely related synthesis of pyrrolidines starting from oxo enoates and primary amines.[15] However, in this case refluxing in cyclohexane was required followed by reduction with $NaCNBH_3$ to give the saturated five-membered heterocycles, presumably by a similar reaction mechanism.

The *N*-benzyl group may be readily removed from the heterocycle by hydrogenation under rather forcing conditions (3 atm hydrogen pressure, 24 h). For example, the *N*-benzylpiperidine **4e** was converted into the unprotected piperidine **11a** with concomitant esterification in 91% yield. No β-lactam formation was observed under these conditions. Esterification may also be achieved with MgClOMe to furnish the methyl ester **11b** in 84% yield (Scheme 4).



Scheme 4. Debenzylation and esterification of the piperidines

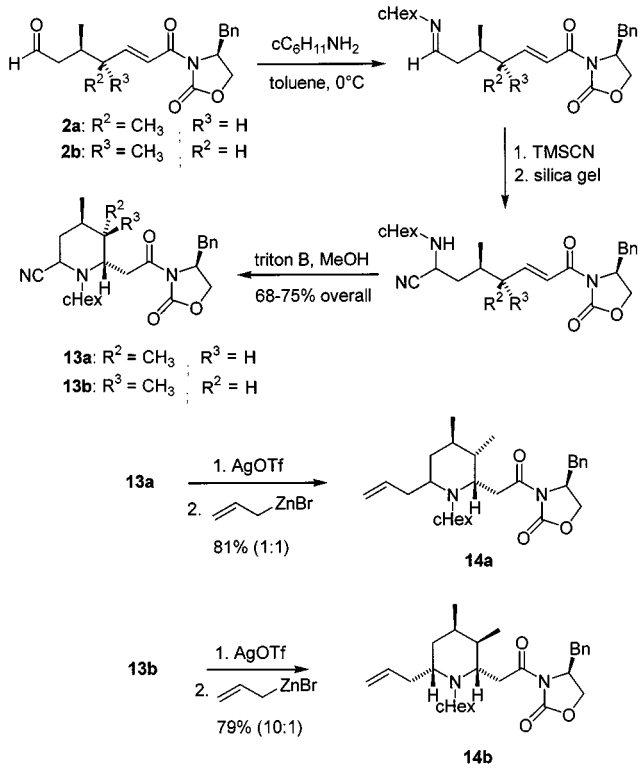
As a method for the synthesis of piperidines with a greater degree of substitution, we decided to make use of the endocyclic enamine double bond. We speculated that it should be possible to either protonate or alkylate the enamine giving iminium ions and subsequently add nucleophiles in the C-6 position of the piperidine ring. Different Brønsted acids and organometallic reagents were investigated. The combination of HCl and allylzinc bromide proved to be best and gave the addition product **12** in 70% yield, albeit as a mixture of 4 stereoisomers with respect to the C-2 and C-6 chiral centers in the piperidine ring. Since protonation of enamines is known[16] to furnish initially the enammonium salts which subsequently isomerize to the more stable iminium ions, it is likely that the enammonium salt, a much better leaving group than amino, underwent a rapid retro Michael reaction with loss of the homogenous stereochemistry at C-2 (Scheme 5). Epimerization at C-2 could not be avoided with any of the Brønsted acids employed.



Scheme 5. Sequential protonation and alkylation of the tetrahydropyridines **3**

The principle reaction, however, had worked well. So we investigated other routes to prepare the desired iminium ions. Cyanopiperidines have been extensively used for the stereoselective synthesis of nitrogen heterocycles by Husson et al.[17] The cyano groups can be replaced by alkyl groups by the action of silver salts and trapping the intermediate iminium salts with Grignard reagents. This strategy required the preparation of the cyanopiperidines which was accomplished in a three-step sequence (Scheme 6). Condensation of the Cope products **2a** and **2b** with cyclohexylamine furnished the corresponding imines, addition of trimethylsilyl cyanide gave the amino nitriles which were then cyclized with Triton B in methanol to give the cyanopiperidines **13a** and **13b** as mixtures of C-2 stereoisomers. The stereoselectivity of the cyclization was > 20:1 in favor of the (6*S*) stereoisomers.

Treatment of **13a** with silver trifluoromethanesulfonate and addition of allylzinc bromide to the intermediate iminium salt gave the 2,3,4,6-tetrasubstituted piperidine **14a** in 81% yield as 1:1 mixture of C-6 stereoisomers. The (2*S*) configuration, however, was completely maintained. Similar treatment of **13b** with allylzinc bromide furnished the piperidine **14b** in 79% yield with high stereoselectivity in favor of the 2,6-*cis*-substituted piperidine. Apparently, the C-3-β-methyl group directed the incoming nucleophile to the α-face of the iminium ion. In order to assign the stereochemistry of **14b** it was converted into the methyl ester **15** and its configuration and conformation deduced from ^1H NMR data (Figure 3). The location of the C-2-, C-3- and C-6-alkyl groups in axial positions appears in contradiction to what might be expected. However, MM3 calculations show very clearly that the usual chair conformation is distorted with the C-2- and C-6-alkyl groups turned away from each



Scheme 6. Synthesis and alkylation of the cyanopiperidines **13**

other. This distortion causes the dihedral angles between 5-H_{ax} and 6-H and 5-H_{eq} and 6-H to be 51° and 69°, respectively, which results in the unusually large coupling constant of J(5-H_{ax}/6-H) = 5.9 Hz. The dihedral angle between 2-H_{eq} and 3-H_{eq} is also increased to 68° and accordingly the coupling constant J(2-H/3-H) reduced to 1.6 Hz. A significant nuclear Overhauser enhancement between the methylene protons of the axial C-2- and C-6-alkyl groups supports a 2,6-*cis*-diaxial configuration. The depicted conformation is also stabilized by the *N*-cyclohexyl group which serves an an additional equatorial substituent.

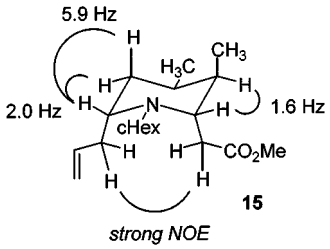
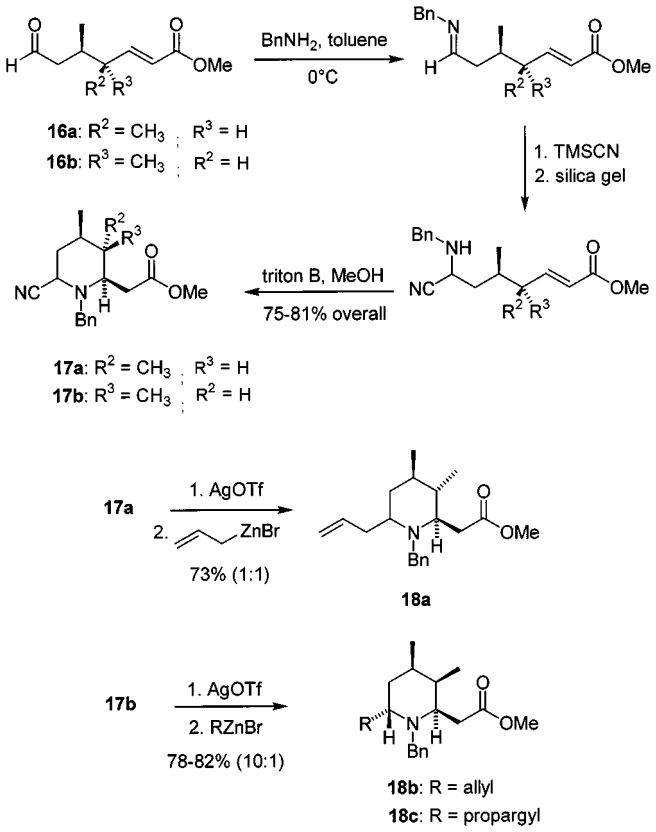


Figure 3. Conformation of the piperidinyl methyl ester **15** according to ^{1}H NMR and MM3 calculations

According to the same general protocol the 7-oxo-2-enoates **16a** and **16b** were converted into the cyanopiperidines **17a** and **17b** which carried the opposite (6*R*) configuration as a result of thermodynamic control by a retro Michael/Michael process (Scheme 7). The facile equilibration of the amino enoates furnishing the C-6 equatorially substituted piperidines is probably due to the lower stability of the ester enolates compared to the imide enolates. A similar observation was made in the synthesis of tetrahydropyrans through intramolecular oxa-conjugate addition reactions.[8] It is interesting to note that the benzylimines were formed quantitatively and no intramolecular conjugate addition of the imines occurred as in the case of the imino enimides. Apparently, the enoates are substantially less reactive towards nucleophiles than the enimides.



Scheme 7. Synthesis and alkylation of the cyanopiperidines **17**

Iminium ion formation through the action of silver trifluoromethanesulfonate followed by addition of allylzinc bromide gave the piperidine **18a** in good chemical yield but as 1:1 mixture of stereoisomers at C-6. The piperidines **18b** and **18c** with a C-6-allyl and -propargyl group, however, were obtained with high stereoselectivity and 2,6-*trans* stereochemistry in 78% and 82% yield, respectively. Again it is apparently the C-3-β-methyl group which shields the upper face of the iminium ion and directs the incoming nucleophile to the bottom face. The assignment of product configuration was facilitated by the characteristic AB system for the diastereotopic *N*-benzylic protons which Hill et al. first recognized as a reliable configurational proof of 2,6-*trans*-piperidines.[18]

Thus, the important 2,6-stereochemistry frequently found in natural products can in certain cases be efficiently and very selectively controlled by the proper choice of the carboxylic acid derivative. In the case of imides a 2,6-*cis* stereochemistry in the piperidines is obtained, whereas esters furnish piperidines with a 2,6-*trans* configuration.

Conclusions

A straightforward and stereoselective synthesis of highly substituted and enantiopure piperidines has been developed which takes advantage of the bifunctional products of the silyloxy Cope rearrangement of aldol products. Sequential nucleophilic addition of primary amines to the chiral 7-oxo-2-enimides **2** furnished − via the imines − tetrahydropyridines **3** in one step which were hydrogenated to give the 2,3,4-trisubstituted piperidines **4** in good overall yields and with essentially complete stereocontrol. That sequence was proven to be a highly efficient and easy to perform piperidine synthesis. Efforts to prepare 2,3,4,6-tetrasubstituted piperidines **14** and **18** were successful when cyanopiperidines, readily available from the Cope products in a three-step synthesis, were treated with silver trifluoromethanesulfonate and organozinc reagents.

Experimental Section

General: Air- and/or moisture-sensitive reactions were carried out under N_2 using flame-dried glassware. Solvents were distilled directly prior to use from the appropriate drying agents. The preparation of the Cope products **2** and **17** has been reported elsewhere. All reactions were monitored by thin-layer chromatography (TLC) carried out on precoated silica gel SIL G/UV_{254} plates (Macherey-Nagel & Co.) and visualized with UV light and 1% aqueous $KMnO_4$. Products were purified by flash chromatography on Macherey-Nagel & Co. silica gel 32−63 (particle size 0.032−0.063 mm). − ^1H and ^{13}C NMR spectra were recorded with a Varian VXR 200 (200 MHz), Bruker AMX 300 (300 MHz) and Varian VXR 500 (500 MHz) in $CDCl_3$ at 25°C with TMS as internal standard. − IR spectra of evaporated films were recorded with a Bruker IFS 25 FT-IR instument. − UV spectra were recorded with a Perkin−Elmer Lambda 9 spectrometer. − Optical rotations were measured with a Perkin−Elmer 241 polarimeter. − Mass spectra were taken at 70 eV (EI) or 200 eV (DCI/NH_3) with a Finnigan MAT 95A spectrometer. − Microanalyses were carried out by the microanalytical laboratory of the Institut für Organische Chemie der Universität Göttingen.

Methods of Calculation: The PM3[19] calculations were performed with a PC Version of Mopac 6. The 32 bit PC version was compiled by V. Lobanov and is available from ftp://ftp.osc.edu/chemistry/software/MS-WIN95-NT/mopac6. The transition structures were located by examining the reaction path of the retro-aza Michael reaction by stepwise elongation of the C−N bond. The resulting preliminary transition structure geometries were then fully optimized using the NLLSQ and the TS keywords. The FORCE keyword was used to assert that each transition structure had exactly one imaginary force constant. MM3 calculations were performed with the Alchemy 2000 package from Tripos, Inc.

General Procedure for the Synthesis of the *N*-Benzylpiperidines 4: A mixture of the 7-oxo-2-enimide **2** (0.30 mmol) and benzylamine (32 mg, 0.30 mmol) or the substituted benzylamines, respectively, was stirred in 4 mL of toluene containing a small amount of $MgSO_4$ at −15°C for 1 h. $MgSO_4$ was removed by filtration and the filtrate concentrated in vacuo. The residue was dissolved in 4 mL of ethanol and hydrogenated with H_2 (1 atm) in the presence of Pd/C (32 mg, 10%) for 45 min. The reaction mixture was filtered and the solvent removed in vacuo. The residue was purified by silica gel column chromatography (diethyl ether/pentane, 1:2) to afford the piperidines **4** as colorless oils.

Piperidine 4a: Yield 102 mg (81%). − R_f = 0.46 (diethyl ether/pentane, 1:2). − $[\alpha]_D^{20}$ = +10.0 (*c* = 0.30, $CHCl_3$). − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.87 (d, *J* = 6.8 Hz, 3 H, CH_3), 0.91 (d, *J* = 5.8 Hz, 3 H, CH_3), 1.30−1.43 (m, 3 H, 4′-H, 5′-H_2), 1.74 (mc, 1 H, 3′-H), 2.58 (ddd, *J* = 12.5 Hz, *J* = 5.0 Hz, *J* = 3.0 Hz, 1 H, 6′-H), 2.75 (dd, *J* = 13.5 Hz, *J* = 9.5 Hz, 1 H, benzyl-H), 2.77 (dt, *J* = 3.0 Hz, *J* = 12.5 Hz, 1 H, 6′-H), 2.95 (dd, *J* = 15.5, *J* = 4.5 Hz, 1 H, C*H*−COX_c), 3.32 (dd, *J* = 13.5 Hz, *J* = 3.5 Hz, 1 H, benzyl-H), 3.32 (dd, *J* = 15.5 Hz, *J* = 8.0 Hz, 1 H, C*H*−COX_c), 3.53 (dt, *J* = 8.0 Hz, *J* = 4.5 Hz, 1 H, 2′-H), 3.58 (d, *J* = 13.0 Hz, 1 H, *N*-benzyl-H), 3.79 (d, *J* = 13.0 Hz, 1 H, *N*-benzyl-H), 4.04 (dd, *J* = 9.0 Hz, *J* = 8.0 Hz, 1 H, 5-H), 4.10 (dd, *J* = 9.0, 3.5 Hz, 1 H, 5-H), 4.61 (ddt, *J* = 9.5 Hz, *J* = 8.0 Hz, *J* = 3.5 Hz, 1 H, 4-H), 7.25 (m, 5 H, phenyl-H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.88 (CH_3), 19.80 (CH_3), 30.27 (C-5′), 31.93 (C-3′), 32.00 (CH_2−COX_c), 37.81 (benzyl-C), 38.04 (C-4′), 45.46 (*N*-benzyl-C), 55.46 (C-4), 58.50 (C-6′), 60.07 (C-2′), 65.87 (C-5), 126.7, 127.2, 128.0, 128.6, 128.9, 129.4, 135.4, 140.1 (phenyl-C), 153.3 (C-2), 172.9 (C-1′). − IR (film): $\tilde{\nu}$ = 2962 cm^{-1}, 2920 (CH), 1786, 1700 (C=O), 1386, 1374, 1352 (CH, CH_3), 744, 700 (phenyl). − EI-MS; *m*/*z*: 420 (6) [M^+], 202 (58) [M^+ − CH_2COX_c], 91 (100) benzyl]. − $C_{26}H_{32}N_2O_3$ (420.24): calcd. C 74.26, H 7.67; found C 74.54, H 7.56.

Piperidine 4b: Yield 105 mg (77%). − R_f = 0.43 (diethyl ether/pentane, 1:2). − $[\alpha]_D^{20}$ = −4.6 (*c* = 0.5, $CHCl_3$). − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.3 Hz, 3 H, 3′′-H_3), 0.90 (d, *J* = 7.5 Hz, 3 H, CH_3), 1.00−1.33 (m, 4 H, 1′′-H_2, 2′′-H_2), 1.35−1.54 (m, 3 H, 4′-H, 5′-H_2), 1.82 (mc, 1 H, 3′-H), 2.60 (dt, *J* = 12.5, 2.5 Hz, 1 H, 6′-H), 2.75 (dd, *J* = 13.5 Hz, *J* = 9.5 Hz, 1 H, benzyl-H), 2.77 (dt, *J* = 3.0 Hz, *J* = 12.5 Hz, 1 H, 6′-H), 2.94 (dd, *J* = 15.5 Hz, *J* = 4.5 Hz, 1 H, C*H*−COX_c), 3.32 (dd, *J* = 13.5 Hz, *J* = 3.5 Hz, 1 H, benzyl-H), 3.34 (dd, *J* = 15.5 Hz, *J* = 8.0 Hz, 1 H, C*H*−COX_c), 3.53 (dt, *J* = 8.0 Hz, *J* = 4.5 Hz, 1 H, 2′-H), 3.57 (d, *J* = 13.8 Hz, 1 H, *N*-benzyl-H), 3.73 (d, *J* = 13.8 Hz, 1 H, *N*-benzyl-H), 4.04 (t, *J* = 8.8 Hz, 1 H, 5-H), 4.10 (dd, *J* = 8.8 Hz, *J* = 2.5 Hz, 1 H, 5-H), 4.61 (mc, 1 H, 4-H), 7.15−7.30 (m, 10 H, phenyl-H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.55 (C-3′′), 15.94 (CH_3), 19.17 (C-2′′), 28.24 (C-1′′), 30.45 (C-5′), 35.45 (CH_2−COX_c), 36.20 (C-3′), 36.46 (C-4′), 37.79 (benzyl-C), 45.51 (*N*-benzyl-C), 55.43 (C-4), 58.46 (C-6′), 60.19 (C-2′), 65.87 (C-5), 126.7, 127.2, 128.0, 128.6, 128.9, 129.4, 135.4, 140.4 (phenyl-C), 153.4 (C-2), 172.9 (C-1′). − IR (film): $\tilde{\nu}$ = 2958 cm^{-1}, 2928, 2870 (CH), 1782, 1700 (C=O), 1382, 1354 (CH, CH_3), 702 (phenyl). − EI-MS; *m*/*z*: 448 (6) [M^+], 358 (3) [M^+-benzyl], 230 (100) [M^+ − CH_2COX_c]. − $C_{28}H_{36}N_2O_3$ (448.60): calcd. C 74.97, H 8.09; found C 74.95, H 8.26.

Piperidine 4c: Yield 98 mg (68%). − R_f = 0.34 (diethyl ether/pentane, 1:2). − $[\alpha]_D^{20}$ = −9.0 (*c* = 0.5, $CDCl_3$). − ^1H NMR (300 MHz, $CDCl_3$): δ = 0.61 (d, *J* = 6.0 Hz, 3 H, CH_3), 1.52−1.63 (m, 1 H, 5′-H), 1.85 (dq, *J* = 4.8 Hz, *J* = 12.0 Hz, 1 H, 5′-H), 2.31−2.40 (m, 1 H, 3′-H), 2.45 (dt, *J* = 3.0 Hz, *J* = 12.0 Hz, 1 H, 4′-H), 2.64−2.72 (m, 1 H, 6′-H), 2.80 (dd, *J* = 13.5 Hz, *J* = 9.0 Hz, 1 H, benzyl-H), 2.85 (dt, *J* = 3.0 Hz, *J* = 12.0 Hz, 1 H, 6′-H), 3.07 (dd, *J* = 15.3 Hz, *J* = 4.5 Hz, 1 H, C*H*−COX_c), 3.33 (dd, *J* = 13.5 Hz, *J* = 3.0 Hz, 1 H, benzyl-H), 3.45 (dd, *J* = 15.3 Hz, *J* = 7.5 Hz, 1 H, C*H*−COX_c), 3.66 (d, *J* = 13.5 Hz, 1 H, *N*-benzyl-H), 3.75 (dt, *J* = 7.5 Hz, *J* = 4.5 Hz, 1 H, 2′-H), 3.90 (d, *J* = 13.5 Hz, 1 H, *N*-benzyl-H), 4.12 (m, 2 H, 5-H_2), 4.65 (mc, 1 H, 4-H), 7.15−7.40 (m, 15 H, phenyl-H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.31 (CH_3), 29.70 (C-5′), 32.20 (CH_2−COX_c), 36.72 (C-3′),

37.79 (benzyl-C), 44.89 (C-4′), 45.39 (*N*-benzyl-C), 55.43 (C-4), 58.68 (C-6′), 59.94 (C-2′), 65.93 (C-5), 126.1, 126.8, 127.3, 127.5, 128.1, 128.4, 128.6, 128.9, 129.4, 135.3, 139.8, 144.9 (phenyl-C), 153.4 (C-2), 172.7 (C-1′). − IR (KBr): $\tilde{\nu}$ = 3027 cm^{-1}, 2930 (CH_2), 1779, 1702 (C=O), 1384 (CH, CH_3), 700 (phenyl). − EI-MS; *m/z*: 482 (2) [M^+], 391 (1), [M^+ − benzyl], 264 (100) [M^+ − CH_2−COX_c]. − HRMS for $C_{31}H_{34}N_2O_3$: calcd. 482.2569; found 482.2569.

Piperidine 4d: Yield 117 mg (72%). − R_f = 0.42 (diethyl ether/pentane, 1:2). − $[\alpha]_D^{20}$ = −2.0 (*c* = 0.5, $CHCl_3$). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.33 (s, 3 H, Si−CH_3), 0.38 (s, 3 H, Si−CH_3), 0.80 (d, *J* = 6.9 Hz, 3 H, CH_3), 0.98 (dt, *J* = 3.5 Hz, *J* = 13.0 Hz, 1 H, 4′-H), 1.37 (dq, *J* = 3.0 Hz, *J* = 13.0 Hz, 1 H, 5′-H), 1.54 (mc, 1 H, 3′-H), 2.13 (mc, 1 H, 5′-H), 2.58 (ddd, *J* = 13.0 Hz, *J* = 5.0, *J* = 2.8 Hz, 1 H, 6′-H), 2.63 (dt, *J* = 3.0 Hz, *J* = 13.0 Hz, 1 H, 6′-H), 2.79 (dd, *J* = 13.0 Hz, *J* = 9.5 Hz, 1 H, benzyl-H), 2.95 (dd, *J* = 15.5 Hz, *J* = 4.8 Hz, 1 H, C*H*−COX_c), 3.34 (dd, *J* = 13.0 Hz, *J* = 3.1 Hz, 1 H, benzyl-H), 3.40 (dd, *J* = 15.5 Hz, *J* = 7.5 Hz, 1 H, C*H*−COX_c), 3.52 (dt, *J* = 7.5 Hz, *J* = 4.8 Hz, 1 H, 2′-H), 3.55 (d, *J* = 13.5 Hz, 1 H, *N*-benzyl-H), 3.77 (d, *J* = 13.5 Hz, 1 H, *N*-benzyl-H), 4.09 (t, *J* = 8.0 Hz, 1 H, 5-H), 4.14 (dd, *J* = 8.0 Hz, *J* = 2.8 Hz, 1 H, 5-H), 4.64 (mc, 1 H, 4-H), 7.20−7.40 and 7.54−7.58 (m, 15 H, phenyl-H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = −3.43 (Si−CH_3), −3.35 (Si−CH_3), 19.31 (CH_3), 24.27 (C-4′), 25.26 (C-5′), 29.18 (*C*H_2−COX_c), 33.97 (C-3′), 37.80 (benzyl-C), 45.79 (*N*-benzyl-C), 55.42 (C-4), 58.68 (C-6′), 60.27 (C-2′), 65.88 (C-5), 126.7, 127.3, 127.7, 128.0, 128.6, 128.7, 128.9, 129.4, 133.7, 135.4, 139.3, 139.8 (phenyl-C), 153.4 (C-2), 172.9 (C-1′). − IR (film): $\tilde{\nu}$ = 2958 cm^{-1}, 2928 (CH), 1782, 1700 (C=O), 1382, 1354 (CH, CH_3), 736, 702 (phenyl). − EI-MS; *m/z*: 540 (2) [M^+], 322 (100) [M^+ − CH_2COX_c], 228 (9) [M^+ − oxazolidinone − $SiMe_2Ph$]. − $C_{33}H_{40}N_2O_3Si$ (540.77): calcd. C 73.31, H 7.46; found C 73.55, H 7.63.

Piperidine 4e: Yield 105 mg (81%). − R_f = 0.29 (diethyl ether/pentane, 1:2). − $[\alpha]^{20}_D$ = −4.0 (*c* = 1, $CHCl_3$). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.92 (d, *J* = 6.3 Hz, 3 H, CH_3), 0.95 (t, *J* = 3.8 Hz, 3 H, CH_2−C*H*$_3$), 1.30−1.55 (m, 5 H, 5′-H_2, C*H*$_2$−CH_3), 1.65−1.75 (m, 1 H, 3′-H), 2.55 (ddd, *J* = 12.5 Hz, *J* = 3.0 Hz, *J* = 1.9 Hz, 1 H, 6′-H), 2.71−2.80 (m, 3 H, benzyl-H, 6′-H, C*H*COX_c), 3.32 (dd, *J* = 13.6 Hz, *J* = 3.4 Hz, 1 H, benzyl-H), 3.51 (d, *J* = 14.0 Hz, 1 H, *N*-benzyl-H), 3.52 (dd, *J* = 15.3 Hz, *J* = 9.3 Hz, 1 H, C*H*COX_c), 3.75 (dt, *J* = 9.3 Hz, *J* = 4.3 Hz, 1 H, 2′-H), 3.83 (d, *J* = 14.0 Hz, 1 H, *N*-benzyl-H), 4.05−4.13 (m, 2 H, 5-H_2), 4.65 (mc, 1 H, 4-H), 7.15−7.30 (m, 10 H, phenyl-H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 11.73 (CH_2−*C*H_3), 20.16 (CH_3), 22.20 (*C*H_2−CH_3), 29.96 (C-5′), 31.14 (C-3′), 32.22 (*C*H_2−COX_c), 37.78 (benzyl-C), 44.76 (*N*-benzyl-C), 45.14 (C-4′), 55.47 (C-4), 57.01 (C-2′), 58.64 (C-6′), 65.84 (C-5), 126.7, 127.2, 128.0, 128.6, 128.9, 129.4, 135.4, 140.1 (phenyl-C), 153.3 (C-2), 172.9 (C-1′). − IR (film): $\tilde{\nu}$ = 2924 cm^{-1}(CH, CH_3), 1780, 1698 (C=O), 1454, 1381, 1207, 700. − EI-MS; *m/z*: 434 (6) [M^+], 216 (58) [M^+ − CH_2COX_c], 91 (100) benzyl]. − HRMS for $C_{27}H_{34}N_2O_3$: calcd. 434.2569, found 434.2569. − $C_{27}H_{34}N_2O_3$ (434.25): calcd. C 74.62, H 7.89; found C 74.70, H 7.91.

Piperidine 4f: Yield 107 mg (85%). − R_f = 0.47 (diethyl ether/pentane, 1:2). − $[\alpha]_D^{20}$ = +11.0 (*c* = 0.8, $CHCl_3$). − ^{1}H NMR(500 MHz, $CDCl_3$): δ = 0.88 (d, *J* = 6.8 Hz, 3 H, CH_3), 1.12 (d, *J* = 7.0 Hz, 3 H, CH_3), 1.25−1.30 (m, 1 H, 5′-H), 1.43 (dq, *J* = 5.0, 12.0 Hz, 1 H, 5′-H), 1.65 (m, 1 H, 3′-H), 1.90−1.96 (m, 1 H, 4′-H), 2.41 (dt, *J* = 3.3 Hz, *J* = 12.0 Hz, 1 H, 6′-H), 2.51 (ddd, *J* = 12.0 Hz, *J* = 5.0 Hz, *J* = 2.5 Hz, 1 H, 6′-H), 2.72 (dd, *J* = 13.5 Hz, 9.5 Hz 1 H, benzyl-H), 3.19 (dd, *J* = 15.5, 8.8 Hz, 1 H, C*H*COX_c), 3.29 (dd, *J* = 13.5 Hz, *J* = 3.5 Hz, 1 H, benzyl-H), 3.35 (dd, *J* = 15.5 Hz, *J* = 4.0 Hz, 1 H, C*H*COX_c), 3.39 (ddd, *J* = 8.8 Hz, *J* = 4.0 Hz, *J* = 1.8 Hz, 1 H, 2′-H), 3.50 (d, *J* = 14.0 Hz, 1 H, *N*-benzyl-H_a), 3.75 (d, *J* = 14.0 Hz, 1 H, *N*-benzyl-H), 4.11−4.19 (m, 2 H, 5-H_2), 4.67 (ddt, *J* = 9.5 Hz, *J* = 8.0 Hz, *J* = 3.5 Hz, 1 H, 4-H), 7.22−7.35 (m, 5 H, phenyl-H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.23 (CH_3), 19.34 (CH_3), 27.71 (C-3′), 28.56 (C-5′), 30.57 (*C*H_2−COX_c), 37.32 (C-4′), 37.87 (benzyl-C), 45.94 (*N*-benzyl-C), 55.20 (C-4), 59.01 (C-6′), 61.66 (C-2′), 66.02 (C-3), 126.6, 127.3, 127.4, 128.3, 128.9, 129.3, 135.2, 140.2 (phenyl-C), 153.4 (C-2), 173.0 (C-1′). − IR (film): $\tilde{\nu}$ = 2958 cm^{-1}, 2922 (CH), 1782, 1694 (C=O), 1382, 1370, 1352, (CH, CH_3), 702 (phenyl). − EI-MS; *m/z*:420 (3) [M^+], 202 (100) [M^+ − CH_2COX_c]. − $C_{26}H_{32}N_2O_3$ (420.24): calcd. C 74.26, H 7.67; found C 74.54, H 7.56.

Piperidine 4g: Yield 109 mg (81%). − R_f = 0.41 (diethyl ether/pentane, 1:2). − $[\alpha]_D^{20}$ = +11.0 (*c* = 0.4, $CHCl_3$). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.0 Hz, 3 H, 3′′-H_3), 1.11 (d, *J* = 7.5 Hz, 3 H, CH_3), 1.15−1.35 (m, 5 H, 5′-H, 1′′-H_2, 2′′-H_2), 1.40 (dq, *J* = 5.0, 12.0 Hz, 1 H, 5′-H), 1.69−1.78 (m, 2 H, 3′-H, 4′-H), 2.40 (dt, *J* = 3.2 Hz, *J* = 12.0 Hz, 1 H, 6′-H), 2.53 (ddd, *J* = 12.0 Hz, *J* = 5.0 Hz, *J* = 2.5 Hz, 1 H, 6′-H), 2.73 (dd, *J* = 13.4 Hz, *J* = 9.4 Hz, 1 H, benzyl-H), 3.20 (dd, *J* = 15.6 Hz, *J* = 8.8 Hz, 1 H, C*H*−COX_c), 3.29 (dd, *J* = 13.4 Hz, *J* = 3.4 Hz, 1 H, benzyl-H), 3.35 (dd, *J* = 15.6 Hz, *J* = 4.0 Hz, 1 H, C*H*−COX_c), 3.40 (ddd, *J* = 8.8 Hz, *J* = 4.0 Hz, *J* = 1.6 Hz, 1 H, 2′-H), 3.48 (d, *J* = 14.0 Hz, 1 H, *N*-benzyl-H), 3.77 (d, *J* = 14.0 Hz, 1 H, *N*-benzyl-H), 4.13−4.25 (m, 2 H, 5-H_2), 4.60 (mc, 1 H, 4-H), 7.20−7.38 (m, 10 H, phenyl-H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.31 (CH_3), 14.37 (C-3′′), 19.98 (C-2′′), 27.00 (C-1′′), 30.33 (C-5′), 32.53 (C-3′), 35.37 (C-4′), 35.97 (*C*H_2−COX_c), 37.89 (benzyl-C), 46.03 (*N*-benzyl-C), 55.24 (C-4), 59.10 (C-6′), 61.92 (C-2′), 66.02 (C-5), 126.7, 127.3, 128.1, 128.3, 128.9, 129.4, 135.3, 140.2 (phenyl-C), 153.4 (C-2), 173.1 (C-1′). − IR (film): $\tilde{\nu}$ = 2924 cm^{-1} (CH), 1781, 1695 (C=O), 1350 (CH, CH_3), 701 (phenyl). − EI-MS; *m/z*: 448 (1) [M^+], 230 (100) [M^+ − CH_2COX_c]. − $C_{28}H_{36}N_2O_3$ (448.60): calcd. C 74.97, H 8.09; found C 74.72, H 8.17.

Piperidine 5: Yield 159 mg (76%). − $R_{f'}$ = 0.32 (diethyl ether/pentane, 1:2). − $[\alpha]_D^{20}$ = +13.8 (*c* = 0.5, MeOH). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85 (d, *J* = 6.6 Hz, 3 H, CH_3), 0.90 (d, *J* = 6.0 Hz, 3 H, CH_3), 1.22−1.45 (m, 3 H, 4′-H, 5′-H_2), 1.65−1.76 (m, 1 H, 3′-H), 2.57 (dt, *J* = 2.0 Hz, *J* = 12.0 Hz, 1 H, 6′-H), 2.75 (dd, *J* = 12.9 Hz, *J* = 9.6 Hz, 1 H, benzyl-H), 2.76 (mc, 1 H, 6′-H), 2.96 (dd, *J* = 15.0 Hz, *J* = 4.5 Hz, 1 H, C*H*−COX_c), 3.30 (dd, *J* = 12.9 Hz, *J* = 3.3 Hz, 1 H, benzyl-H), 3.30 (dd, *J* = 15.0 Hz, *J* = 6.3 Hz, 1 H, C*H*COX_c), 3.51 (d, *J* = 13.5 Hz, 1 H, *N*-benzyl-H), 3.52 (mc, 1 H, 2′-H), 3.72 (d, *J* = 13.5 Hz, 1 H, *N*-benzyl-H), 3.75 (s, 3 H, O−CH_3), 4.07−4.14 (m, 2 H, 5-H_2), 4.61 (mc, 1 H, 4-H), 6.78 (d, *J* = 9.0 Hz, 2 H, phenyl-H), 7.15−7.36 (m, 7 H, phenyl-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.88 (CH_3), 19.80 (CH_3), 30.16 (C-5′), 31.98 (C-3′), 32.04 (*C*H_2−COX_c), 37.84 (benzyl-C), 38.01 (C-4′), 45.36 (*N*-benzyl-C), 55.19 (O−CH_3), 55.46 (C-4), 57.85 (C-6′), 59.87 (C-2′), 65.89 (C-5), 113.4, 127.3, 128.9, 129.5, 129.8, 132.2, 135.4, 158.5 (phenyl-C), 153.4 (C-2), 173.0 (C-1′). − IR (film): $\tilde{\nu}$ = 2928 cm^{-1} (CH), 1780, 1702 (C=O), 1452, 1207. − EI-MS; *m/z*: 450 (< 1) [M^+], 319 (1) [M^+ − C_6H_4OMe], 232 (57)[M^+ − CH_2COX_c], 121 (100) [CH_2−C_6H_4OMe]. − HRMS for $C_{27}H_{34}N_2O_4$: calcd. 450.2518; found 450.2518.

Piperidine 6: Yield 151 mg (73%). − R_f = 0.29 (diethyl ether/pentane, 1:2). − $[\alpha]_D^{20}$ = +7.6 (*c* = 0.5, $CHCl_3$). − ^{1}H NMR

(300 MHz, $CDCl_3$): δ = 0.87 (d, *J* = 6.8 Hz, 3 H, CH_3), 0.91 (d, *J* = 6.8 Hz, 3 H, CH_3), 1.30−1.49 (m, 3 H, 4′-H, 5′-H_2), 1.71−1.77 (m, 1 H, 3′-H), 2.58 (dt, *J* = 1.8 Hz, *J* = 12.0 Hz, 1 H, 6′-H), 2.75 (dd, *J* = 13.0 Hz, *J* = 9.6 Hz, 1 H, benzyl-H), 2.83 (dt, *J* = 1.8 Hz, *J* = 12.0 Hz, 1 H, 6′-H), 2.98 (dd, *J* = 15.0 Hz, *J* = 4.5 Hz, 1 H, C*H*−COX_c), 3.30 (dd, *J* = 13.0 Hz, *J* = 3.8 Hz, 1 H, benzyl-H), 3.30 (dd, *J* = 15.0 Hz, *J* = 8.4 Hz, 1 H, C*H*−COX_c), 3.55 (dt, *J* = 8.4 Hz, *J* = 4.5 Hz, 1 H, 2′-H), 3.70 (d, *J* = 15.0 Hz, 1 H, *N*-benzyl-H), 3.85 (d, *J* = 15.0 Hz, 1 H, *N*-benzyl-H), 4.07−4.13 (m, 2 H, 5-H_2), 4.60 (mc, 1 H, 4-H), 7.10−7.50 (m, 9 H, phenyl-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.89 (CH_3), 19.81 (CH_3), 30.67 (C-5′), 31.85 (C-3′), 32.10 (*C*H_2−COX_c), 37.83 (benzyl-C), 38.30 (C-4′), 45.59 (*N*-benzyl-C), 55.34 (O−CH_3), 55.47 (C-4), 55.50 (C-6′), 60.35 (C-2′), 65.95 (C-5), 126.5, 127.3, 127.8, 128.9, 129.4, 129.5, 130.3, 134.0, 135.5, 137.6 (phenyl-C), 153.4 (C-2), 172.9 (C-1′). − IR (film): $\tilde{\nu}$ = 2956 cm^{-1} (CH), 1786, 1700 (C=O), 1202. − EI-MS; *m*/*z*: 454 (2) [M^+], 236 (100) [M^+ − CH_2COX_c], 202 (35) [M^+ − CH_2COX_c − Cl + 1]]. − HRMS for $C_{26}H_{31}N_2O_3Cl$: calcd. 454.2023; found 454.2023.

General Procedure for the Synthesis of the *N*-Alkyl Piperidines 7−10: A mixture of the 7-oxo-2-enimide **2a** (100 mg, 0.30 mmol) and the amine (0.30 mmol) was stirred in 4 mL of ethyl acetate containing a small amount of $MgSO_4$ at 0°C for 1 h. $MgSO_4$ was removed by filtration and the filtrate was directly hydrogenated with H_2 (1 atm) in the presence of Pd/C (32 mg, 10%) for 45 min. The reaction mixture was filtered and the solvent removed in vacuo. The residue was purified by silica gel column chromatography (diethyl ether/pentane, 1:2) to afford the piperidines **7−11** as colorless oils.

Piperidine 7: Yield 75 mg (65%). − R_f = 0.32 (diethyl ether/pentane, 1:1). − $[\alpha]_D^{20}$ = +14.7 (*c* = 1, $CHCl_3$). − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.83 (d, *J* = 6.8 Hz, 3 H, CH_3), 0.87 (d, *J* = 5.8 Hz, 3 H, CH_3), 0.87 (t, *J* = 6.0 Hz, 3 H, CH_3 (*n*-butyl)), 1.22−1.65 (m, 8 H, butyl-H_4, 3′-H, 4′-H, 5′-H_2), 2.36−2.49 (m, 2 H, butyl-H_2), 2.55−2.66 (m, 2 H, 6′-H_2), 2.75 (dd, *J* = 13.5 Hz, *J* = 9.5 Hz, 1 H, benzyl-H), 2.83 (dd, *J* = 16.0 Hz, *J* = 5.0 Hz, 1 H, C*H*−COX_c), 3.25 (dd, *J* = 13.5 Hz, *J* = 3.5 Hz, 1 H, benzyl-H), 3.28 (dd, *J* = 16.0 Hz, *J* = 8.0 Hz, 1 H, C*H*−COX_c), 3.55 (mc, 1 H, 2′-H), 4.12−4.21 (m, 2 H, 5-H), 4.65 (ddt, *J* = 9.5 Hz, *J* = 8.0 Hz, *J* = 3.5 Hz, 1 H, 4-H), 7.18−7.35 (m, 5 H, phenyl-H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.07 (butyl−CH_3), 15.93 (CH_3), 19.69 (CH_3), 20.62 (butyl−CH_2), 28.83 (butyl−CH_2), 30.40 (C-5′), 31.81 (C-3′), 32.77 (*C*H_2−COX_c), 37.73 (benzyl-C), 38.85 (C-4′), 46.52 (butyl-CH_2), 54.07 (C-6′), 55.43 (C-4), 59.50 (C-2′), 65.90 (C-5), 127.3, 128.9, 129.4, 135.3 (phenyl-C), 153.4 (C-2), 173.2 (C-1′). − IR (film): $\tilde{\nu}$ = 2923 cm^{-1} (CH), 1778, 1703 (C=O), 1385 (CH, CH_3), 745, 702 (phenyl). − EI-MS; *m*/*z*: 386 (3) [M^+], 343 (19) [M^+ − propyl], 168 (100) [M^+ − CH_2COX_c]. − $C_{23}H_{34}N_2O_3$ (386.53): calcd. C 71.47, H 8.87; found C 71.50, H 8.83.

Piperidine 8: Yield 72 mg (62%). − R_f = 0.32 (diethyl ether/pentane, 1:1). − $[\alpha]_D^{20}$ = +13.6 (*c* = 1, $CHCl_3$). − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.81 (d, *J* = 7.5 Hz, 3 H, CH_3), 0.82 (d, *J* = 7.5 Hz, 3 H, CH_3), 0.84 (d, *J* = 6.0 Hz, 3 H, CH_3), 0.87 (d, *J* = 5.8 Hz, 3 H, CH_3), 1.22−1.40 (m, 3 H, 3′-H, 4′-H, 5′-H), 1.55−1.70 (m, 2 H, C*H*(CH_3)$_2$, 5′-H), 2.20 (dd, *J* = 12.5, 7.0 Hz, 1 H, N−CH), 2.26 (dd, *J* = 12.5 Hz, *J* = 7.0 Hz, 1 H, N−CH), 2.48−2.60 (m, 2 H, 6′-H), 2.76 (dd, *J* = 13.5 Hz, *J* = 9.5 Hz, 1 H, benzyl-H), 2.77 (dt, *J* = 2.5 Hz, *J* = 2.5 Hz, 1 H, 6′-H), 2.93 (dd, *J* = 15.5 Hz, *J* = 4.5 Hz, 1 H, C*H*−COX_c), 3.24 (dd, *J* = 15.5 Hz, *J* = 7.8 Hz, 1 H, C*H*−COX_c), 3.30 (dd, *J* = 13.5 Hz, *J* = 3.0 Hz, 1 H, benzyl-H), 3.40 (dt, *J* = 7.8 Hz, *J* = 4.5 Hz, 1 H, 2′-H), 4.15 (mc, 2 H, 5-H), 4.65 (ddt, *J* = 9.5 Hz, *J* = 8.0 Hz, *J* = 3.5 Hz, 1 H, 4-H), 7.18−7.35 (m, 5 H, phenyl-H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.95 (CH_3), 19.87 (CH_3), 20.69 (CH_3), 20.73 (CH_3), 26.81 (*C*H-(CH_3)$_2$), 30.28 (C-5′), 31.93 (C-3′), 32.05 (*C*H_2−COX_c), 37.76 (benzyl-C), 37.92 (C-4′), 46.42 (*iso*-butyl-CH_2), 55.52 (C-4), 60.64 (C-2′), 62.66 (C-6′), 65.93 (C-5), 127.3, 128.9, 129.5, 135.4 (phenyl-C), 153.5 (C-2), 173.2 (C-1′). − IR (film): $\tilde{\nu}$ = 2953 cm^{-1} (CH), 1782, 1699 (C=O), 1383 (CH, CH_3), 742, 702 (phenyl). − EI-MS; *m*/*z*: 386 (3) [M^+], 343 (100) [M^+ − propyl], 168 (44) [M^+ − CH_2COX_c]. − $C_{23}H_{34}N_2O_3$ (386.53): calcd. C 71.47, H 8.87; found C 71.22, H 8.84.

Piperidine 9: Yield 82 mg (63%). − R_f = 0.30 (diethyl ether/pentane, 1:1). − $[\alpha]_D^{20}$ = +19.7 (*c* = 1, $CHCl_3$). − ^1H NMR (200 MHz, $CDCl_3$): δ = 0.83 (d, *J* = 6.8 Hz, 3 H, CH_3), 0.85 (d, *J* = 5.8 Hz, 3 H, CH_3), 1.14−1.72 (m, 4 H, 3′-H, 4′-H, 5′-H_2), 2.55−2.85 (m, 7 H, *N*-ethyl-H_4, benzyl-H, 6′-H_2), 2.85 (dd, *J* = 16.0 Hz, *J* = 4.5 Hz, 1 H, C*H*−COX_c), 3.20 (dd, *J* = 13.5 Hz, *J* = 3.5 Hz, 1 H, benzyl-H), 3.28 (dd, *J* = 16.0, 7.0 Hz, 1 H, C*H*−COX_c), 3.65 (dt, *J* = 7.0, 4.5 Hz, 1 H, 2′-H), 4.10 (mc, 2 H, 5-H), 4.65 (mc, 1 H, 4-H), 7.08−7.35 (m, 5 H, phenyl-H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.96 (CH_3), 19.66 (CH_3), 28.94 (C-5′), 31.77 (C-3′), 32.83 (*C*H_2−COX_c), 34.90 (C-2′′), 37.63 (benzyl-C), 38.94 (C-4′), 46.69 (C-1′′), 55.38 (C-4), 56.62 (C-6′), 59.59 (C-2′), 65.94 (C-5), 125.9, 127.2, 128.2, 128.7, 128.8, 129.4, 135.3, 140.5 (phenyl-C), 153.5 (C-2), 173.1 (C-1′). − IR (film): $\tilde{\nu}$ = 2925 cm^{-1} (CH), 1780, 1698 (C=O), 1384 (CH, CH_3), 744, 700 (phenyl). − EI-MS; *m*/*z*: 434 (1) [M^+], 343 (100) [M^+ − benzyl], 259 (40). − $C_{27}H_{34}N_2O_3$ (434.25): calcd. C 74.62, H 7.89; found C 74.68, H 8.04.

Piperidine 10: Yield 72 mg (60%). − R_f = 0.21 (diethyl ether/pentane, 1:1). − $[\alpha]_D^{20}$ = +15.2 (*c* = 1, $CHCl_3$). − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.84 (d, *J* = 7.0 Hz, 3 H, CH_3), 0.88 (d, *J* = 5.5 Hz, 3 H, CH_3), 1.30−1.38 (m, 2 H, 3′-H, 4′-H), 1.43−1.49 (m, 1 H, 5′-H), 1.60−1.67 (m, 1 H, 5′-H), 1.71−1.79 (m, 2 H, 2′′-H_2), 2.52−2.61 (m, 2 H, 1′′-H_2), 2.61−2.72 (m, 2 H, 6′-H_2), 2.77 (dd, *J* = 13.5 Hz, *J* = 9.5 Hz, 1 H, benzyl-H), 2.85 (dd, *J* = 16.0 Hz, *J* = 3.8 Hz, 1 H, C*H*−COX_c), 3.26 (s, 3 H, O−CH_3), 3.26−3.35 (m, 2 H, benzyl-H, C*H*−COX_c), 3.32−3.45 (m, 2 H, 3′′-H_2), 3.55 (mc, 1 H, 2′-H), 4.17 (mc, 2 H, 5-H_2), 4.67 (ddt, *J* = 9.5 hz, *J* = 8.0 Hz, *J* = 3.5 Hz, 1 H, 4-H), 7.22−7.35 (m, 5 H, phenyl-H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.96 (CH_3), 19.72 (CH_3), 28.41 (C-2′′), 29.12 (C-5′), 31.83 (C-3′), 32.64 (*C*H_2−COX_c), 37.74 (benzyl-C), 38.62 (C-4′), 46.52 (C-1′′), 51.22 (C-6′), 55.46 (C-4), 58.50 (O−CH_3), 59.67 (C-2′), 65.94 (C-5), 71.12 (C-3′′), 127.3, 128.9, 129.5, 135.4 (phenyl-C), 153.5 (C-2), 173.2 (C-1′). − IR (film): $\tilde{\nu}$ = 2924 cm^{-1} (CH), 1780, 1699 (C=O), 1385 (CH, CH_3), 734, 703 (phenyl). − EI-MS; *m*/*z*: 402 (2) [M^+], 343 (8) [M^+ − methoxy − propyl], 184 (100) [M^+ − CH_2COX_c]. − HRMS for $C_{23}H_{34}N_2O_3$: calcd. 402.2518; found 402.2518.

Piperidine 11a: The piperidine **4e** (100 mg, 0.23 mmol) was dissolved in 3 mL of ethanol and hydrogenated with H_2 (3 atm) in the presence of Pd/C (30 mg, 10%) for 24 h at ambient temperature. After filtration, the crude product was purified by column chromatography on silica gel (diethyl ether/methanol, 4:1) to yield 45 mg (91%) of the debenzylated piperidine **11a**. − R_f = 0.15 (diethyl ether/methanol, 4:1). − $[\alpha]_D^{20}$ = −63.0 (*c* = 1, $CHCl_3$). − ^1H NMR (200 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.5 Hz, 3 H, CH_3), 0.97 (d, *J* = 6.4 Hz, 3 H, CH_3), 1.00−1.12 (m, 1 H), 1.21−1.30 (m, 2 H), 1.28 (t, *J* = 7.5 Hz, 3 H, OCH_2−CH_3), 1.50−1.64 (m, 3 H, 4-H, 5-H_2), 2.23 (dd, *J* = 15.0, 3.2 Hz, 1 H, C*H*−CO_2Et), 2.55 (br. s, 1 H, NH), 2.65 (dd, *J* = 15.0, 10.5 Hz, 1 H, C*H*−CO_2Et), 2.80−2.91 (m, 2 H, 6-H_2), 3.47 (dt, *J* = 10.5, 3.2 Hz, 1 H, 2-H),

4.15 (q, J = 7.5 Hz, 2 H, O−CH_2−CH_3). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 11.67 (CH_2−CH_3), 14.14 (O−CH_2−CH_3), 19.68 (CH_3), 21.30 (CH_2−CH_3), 30.18 (C-4), 32.36, 33.05 (CH_2CO_2Et, C-5)), 40.00 (C-6), 46.86 (C-3), 50.73 (C-2), 60.31 (O−CH_2−CH_3), 173.1 (C=O). − IR (film): $\tilde{\nu}$ = 3340 cm^{-1} (N−H), 2962, 2929, 2874 (CH, CH_3), 1732 (C=O), 1179, 1034. − EI-MS: *m/z* = 213 (5) [M$^+$], 126 (100) [M$^+$ − CH_2CO_2Et]. − HRMS for $C_{12}H_{23}NO_2$: calcd. 213.1728; found 213.1728.

Piperidine 11b: 40 μL (0.12 mmol) of MeMgCl (3 M in diethyl ether) were added to 1 mL of methanol at 0°C and stirred for 5 min. In a second flask the piperidine **4f** (48 mg, 0.11 mmol) was dissolved in 1 mL of CH_2Cl_2 and 1 mL of methanol and treated with the Mg alkoxide solution at 0°C for 2−3 min. After aqueous workup with saturated NH_4Cl solution and removal of the solvents, the crude product was purified by column chromatography on silica gel (diethyl ether/pentane, 1:1) to yield 25 mg (84%) of the piperidine methyl ester **11b**. − $[\alpha]_D^{20}$ = −27.0 (c = 0.5, $CHCl_3$). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (d, J = 7.0 Hz, 3 H, CH_3), 1.07 (d, J = 7.0 Hz, 3 H, CH_3), 1.20−1.32 (m, 1 H, 5-H), 1.40 (dq, J = 2.5 Hz, J = 12.0 Hz, 1 H, 5-H), 1.60 (mc, 1 H, 3-H), 1.80−1.95 (m, 1 H, 4-H), 2.32 (dt, J = 3.0 Hz, J = 12.0 Hz, 1 H, 6-H), 2.45 (ddd, J = 12.0 Hz, J = 3.0 Hz, J = 2.5 Hz, 1 H, 6-H), 2.56 (dd, J = 15.0 Hz, J = 9.0 Hz, 1 H, CH−CO_2Me), 2.64 (dd, J = 15.0 Hz, J = 4.5 Hz, 1 H, CH−CO_2Me), 3.18 (mc,1 H, 2-H), 3.45 (d, J = 16.5 Hz, 1 H, *N*-benzyl-H), 3.62 (d, J = 16.5 Hz, 1 H, *N*-benzyl-H), 3.65 (s, 3 H, OMe), 7.16−7.30 (m, 5 H, phenyl-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.19, 19.18 (2 × CH_3), 27.68 (C-3), 28.65 (C-5), 29.81 (CH_2CO_2Me), 37.29 (C-4), 45.91 (*N*-benzyl-C), 51.59 (OMe), 59.04 (C-6), 62.11 (C-2), 126.7, 128.1, 128.4, 140.0 (phenyl-C), 174.1 (CO). − IR (film): $\tilde{\nu}$ = 2955 cm^{-1}, 2874 (CH, CH_3), 1737 (C=O), 1452, 1366 (CH, CH_3), 1179 (C−O). − EI-MS; *m/z*: 275 (3) [M$^+$], 202 (100) [M$^+$ − CH_2CO_2Me]. − $C_{17}H_{25}NO_2$ (275.39): calcd. C 74.14, H 9.15; found C 74.00, H 9.29.

General Procedure for the Synthesis of the Cyanopiperidines 13 and 17: A solution of 1.00 mmol of the aldehyde **2** or **16** and cyclohexylamine or benzylamine (0.10 mL, 1.00 mmol), respectively, in 5 mL of toluene containing a small amount of $MgSO_4$ was stirred at room temperature for 1 h. The reaction mixture was filtered and concentrated in vacuo. The crude imines were dissolved in CH_2Cl_2, treated with freshly distilled TMSCN (0.14 mL, 1.10 mmol) and stirred at room temperature for 2 h. The solvent was removed in vacuo and the residue was purified by short flash-chromatography (diethyl ether/pentane, 2:1). Cyclization of the amino nitriles was accomplished with Triton B (0.42 mL, 1.00 mmol, 40% in methanol) in 5 mL of methanol for 12 h at room temp. Aqueous workup and chromatographic purification (silica gel, diethyl ether/pentane, 2:1) gave usually two stereoisomers of the cyano piperidines **13/17** with respect to the C-6 configuration which could not be stored for long periods of time and were consequently prepared just prior to use.

Cyanopiperidine 13a: Yield 293 mg (67%) of a 3:1 mixture of C-2 stereoisomers which were not separable by flash chromatography. − R_f = 0.32 (diethyl ether/pentane, 1:1). − Selected spectroscopic data for the major isomer: − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.37, 18.86 (2 × CH_3), 25.03, 25.10, 25.86, 28.09, 30.18, 31.00, 31.04, 37.92 (benzyl-C), 38.06 (C-3′), 41.58 (C-4′), 44.59 (*N*-cyclohexyl-C), 55.08, 55.35, 58.74 (C-4, C-2′, C-6′), 66.01 (C-5), 121.2 (CN), 127.3, 128.9, 129.3, 135.3 (phenyl-C), 153.2 (C-2), 172.9 (C-1′). − IR (film): $\tilde{\nu}$ = 2930 cm^{-1}, 2856 (CH), 1782, 1698 (C=O), 1386 (CH, CH_3), 704 (phenyl). − EI-MS; *m/z*: 438 (21) [M$^+$ +1], 411 (100) [M$^+$ − CN].

Cyanopiperidine 13b: Yield 284 mg (65%) of a 4:1 mixture of C-2 stereoisomers which were not separable by flash chromatography. − R_f = 0.32 (diethyl ether/pentane, 1:1).). − Selected spectroscopic data for the major isomer: − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.27 (CH_3), 18.94 (CH_3), 26.00, 26.13, 26.65, 27.77, 31.82, 32.25, 32.40, 36.77, 37.58, 37.93 (benzyl-C), 46.91, 55.32, 56.01, 57.68 (C-4, C-2′, C-6′), 66.19 (C-5), 120.9 (CN), 127.4, 129.0, 129.5, 135.1 (phenyl-C), 153.3 (C-2), 171.0 (C-1′). − IR (film): $\tilde{\nu}$ = 2932 cm^{-1}, 2856 (CH), 1782, 1698 (C=O), 1388 (CH, CH_3), 1110 (CH−O). − EI-MS; *m/z*: 438 (100) [M$^+$ + 1].

Cyanopiperidine 17a: Yield 243 mg (81%) of a 2:1 mixture of C-6 stereoisomers. The major C-2-α stereoisomer could be separated by flash chromatography for characterization purposes. − R_f = 0.52 (diethyl ether/pentane, 1:1). − $[\alpha]_D^{20}$ = +12.3 (c = 0.5, $CHCl_3$). − ^{1}H NMR (500 MHz, C_6D_6): δ = 0.58 (d, J = 7.0 Hz, 3 H, CH_3), 0.76 (d, J = 7.0 Hz, 3 H, CH_3), 0.89 (dt, J = 4.7 Hz, J = 13.4 Hz, 1 H, 3-H), 1.13 (dt, J = 13.4 Hz, J = 3.9 Hz, 1 H, 3-H), 1.19 (mc, 1 H, 5-H), 1.37 (mc, 1 H, 4-H), 2.38 (dd, J = 16.5 Hz, J = 4.0 Hz, 1 H, CH−CO_2Me), 2.44 (dd, J = 16.5 Hz, J = 9.8 Hz, 1 H, CH−CO_2Me), 2.65 (dt, J = 4.0 Hz, J = 9.8 Hz, 1 H, 6-H), 3.30 (d, J = 14.0 Hz, 1 H, *N*-benzyl-H), 3.30 (s, 3 H, OMe), 3.45 (dd, J = 4.7 Hz, J = 3.9 Hz, 1 H, 2-H), 7.10−7.38 (m, 5 H, phenyl-H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.11 (CH_3), 19.86 (CH_3). 33.29 (C-4), 35.52 (CH_2−CO_2Me), 36.97 (C-3), 41.38 (C-5), 51.02 (C-2), 51.76 (OMe), 55.60 (benzyl-C), 61.30 (C-6), 117.2 (CN), 127.7, 128.7, 128.9, 137.4 (phenyl-C), 172.2 (C=O). − IR (film): $\tilde{\nu}$ = 2930 cm^{-1}, 2856 (CH), 1784 (C=O), 1386, 1352 (CH, CH_3), 1114 (CH_2−O). − EI-MS; *m/z*: 301 (100) [M$^+$ + 1]. − $C_{18}H_{24}N_2O_2$ (300.39): calcd. C 71.90, H 8.05; found C 71.64, H 8.42.

Cyanopiperidine 17b: Yield 225 mg (75%) of a 4:1 mixture of C-2 stereoisomers which were not separable by flash chromatography. − R_f = 0.52 (diethyl ether/pentane, 1:1). − Selected spectroscopic data for the major isomer: − ^{13}C NMR (200 MHz, $CDCl_3$): δ = 12.57 (CH_3), 18.83 (CH_3), 24.36 (C-4), 30.26 (CH_2−CO_2Me), 31.13 (C-3), 36.33 (C-5), 46.83, 51.74 (OMe), 57.21 (*N*-benzyl), 62.41 (C-2), 120.4 (CN), 127.6, 128.2, 128.6, 137.3 (phenyl-C), 173.2 (C=O). − IR (film): $\tilde{\nu}$ = 2958 cm^{-1}, 2932 (CH), 1738 (C=O), 1452, 1438, 1374 (CH, CH_3), 1118 (CH_2−O). − EI-MS; *m/z*: 301 (100) [M$^+$ + 1]. − $C_{18}H_{24}N_2O_2$ (300.39): calcd. C 71.90, H 8.05; found C 71.61, H 8.31.

General Procedure for the Organozinc Addition to the Cyanopiperidines 13/17: Zn dust (98 mg, 1.50 mmol) was activated by the addition of three drops of dibromoethane and stirring in 3 mL of DMF at 60°C for 10 min. After the reaction flask had been cooled to 0°C, allyl or propargyl bromide (0.75 mmol) was added and the mixture was stirred for 4 h. In a second flask the appropriate cyanopiperidine **13/17** (0.50 mmol) was dissolved in 5 mL of THF and treated with silver trifluoromethanesulfonate (298 mg, 1.15 mmol) at 0°C for 10 min under strictly anhydrous conditions. The mixture was transferred to the organozinc bromide suspension at 0°C and stirred for an additional 10 min. Aqueous workup and purification by column chromatography gave the addition products as pale yellow oils.

Piperidine 14a: Yield 183 mg (81%) of a 1:1 mixture of C-6′ stereoisomers. − R_f = 0.35 (diethyl ether/pentane, 1:1). − Selected spectroscopic data for both isomers: − ^{13}C NMR (200 MHz, $CDCl_3$): δ = 16.29, 20.03 (CH_3), 20.06, 20.55 (CH_3), 25.96, 26.09, 26.21, 26.44, 26.57, 26.85, 27.09, 31.25, 32.43, 32.35, 32.86, 34.28, 36.74, 36.86, 36.91, 37.91 and 38.02 (benzyl-C), 39.77, 41.44, 44.00, 44.40, 47.02, 52.19, 55.26 und 55.47 (C-2′), 56.04 and 56.13 (C-4), 57.61, 61.81 and 62.41 (C-6′), 65.88 and 65.95 (C-5), 115.5 and 115.6 (C-3′′), 127.2, 128.9, 129.3, 129.4, 135.4, 135.5 (phenyl-C), 136.9 and

138.0 (C-2′′), 153.4 (C-2), 172.3 and 173.1 (CO). − IR (film): $\tilde{\nu}$ = 2928 cm^{-1}, 2852 (CH), 1784, 1702 (C=O), 1384 (CH, CH_3), 704 (aromatic). − CI-MS; *m/z*: 453 (100) [M^+ + 1]. − $C_{28}H_{40}N_2O_3$ (452.63): calcd. C 74.30, H 8.91; found C 74.09, H 8.86.

Piperidine 14b: Yield 179 mg (79%). − R_f = 0.36 (diethyl ether/pentane, 1:1). − Diastereoselectivity at C-6′: 10:1 (by ^1H and ^{13}C NMR). − $[\alpha]_D^{20}$ = +45.2 (*c* = 0.43, $CHCl_3$). − Spectroscopic data for the major stereoisomer: ^1H NMR (500 MHz, $CDCl_3$): δ = 0.85 (d, *J* = 5.8 Hz, 3 H, CH_3), 0.97 (d, *J* = 5.8 Hz, 3 H, CH_3), 1.15−1.50 and 1.70−1.90 (m, 13 H, cyclohexyl-H, 4′-H, 5′-H_2), 2.00−2.12 (m, 1 H, 3′-H), 2.15 (mc, 1 H, 1′′-H), 2.27 (mc, 1 H, 1′′-H), 2.54−2.65 (m, 1 H, cyclohexyl-H), 2.75 (dd, *J* = 13.0 Hz, *J* = 9.0 Hz, 1 H, benzyl-H), 2.98 (dd, *J* = 16.0 Hz, *J* = 2.2 Hz, 1 H, C*H*−COX_c), 3.05 (m, 1 H, 6′-H), 3.30 (dd, *J* = 13.0 Hz, *J* = 3.0 Hz, 1 H, benzyl-H), 3.34 (dd, *J* = 16.0 Hz, *J* = 10.0 Hz, 1 H, C*H*−COX_c), 3.50 (dt, *J* = 10.0 Hz, *J* = 2.2 Hz, 1 H, 2′-H), 4.14−4.29 (m, 2 H, 5-H_2), 4.68 (mc, 1 H, 4-H), 4.92−5.06 (m, 2 H, 3′′-H_2), 5.75 (ddt, *J* = 17.0 Hz, *J* = 10.5 Hz, *J* = 6.5 Hz, 1 H, 2′′-H), 7.20−7.40 (m, 5 H, phenyl-H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 12.91 (CH_3), 19.75 (CH_3), 22.88 (C-3′), 25.21, 25.38, 26.18 (cyclohexyl-C), 29.78 (C-5′), 31.97 (C-1′′), 32.20 (*C*H_2−COX_c), 36.63 (C-4′), 37.09 (cyclohexyl-C), 37.94 (benzyl-C), 38.26 (cyclohexyl-C), 53.25 (cyclohexyl-C), 55.26 (C-4), 56.31, 58.26 (C-2′, C-6′), 65.99 (C-5), 115.7 (C-3′′), 127.3, 128.9, 129.4, 135.3 (Phenyl-C), 137.9 (C-2′′), 153.4 (C-2), 1731 (C-1′). − IR (film): $\tilde{\nu}$ = 2928 cm^{-1}, 2854 (CH), 1784, 1700 (C=O), 1384, 1352 (CH, CH_3), 1116 (O−CH_2). − CI-MS; *m/z*: 453 (100) [M^+ + 1]. − $C_{28}H_{40}N_2O_3$ (452.63): calcd. C 74.30, H 8.91; found C 74.19, H 8.76. − For the assignment of product configuration and conformation the piperidine **14b** was converted into the methyl ester **15** in 72% yield with MgClOMe.[10] − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.86 (d, *J* = 6.3 Hz, 3 H, CH_3), 0.94 (d, *J* = 6.5 Hz, 3 H, CH_3), 1.10−1.22 (m, 7 H, cyclohexyl-H, 5-H), 1.35 (dt, *J* = 13.0, 5.9 Hz, 1 H, 5-H), 1.47 (mc, 1 H, 3-H), 1.53 (mc, 1 H, cyclohexyl-H), 1.68−1.85 (m, 3 H, 5-H, cyclohexyl-H), 1.91−1.99 (m, 1 H, 4-H), 2.05 (mc, 1 H, 1′-H), 2.19 (mc, 1 H, 1′-H), 2.45 (dd, *J* = 14.5 Hz, *J* = 10.0 Hz, 1 H, C*H*−CO_2Me), 2.52 (dd, *J* = 14.5 Hz, *J* = 3.8 Hz, 1 H, C*H*−CO_2Me), 2.54 (mc, 1 H, cyclohexyl-H), 3.01 (dddd, *J* = 10.3 Hz, *J* = 5.9 Hz, *J* = 2.8 Hz, *J* = 2.0 Hz, 1 H, 6-H), 3.32 (ddd, *J* = 10.0 Hz, *J* = 3.8 Hz, *J* = 1.6 Hz, 1 H, 2-H) 3.64 (s, 3 H, OMe), 4.92−4.99 (m, 2 H, 3′-H_2), 5.68 (ddt, *J* = 17.0 Hz, *J* = 10.5 Hz, *J* = 6.5 Hz, 1 H, 2′-H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 12.92 (CH_3), 16.68 (CH_3), 22.71 (C-3), 25.14, 25.31, 26.14 (3 × cyclohexyl-C), 29.58 (*C*H_2−CO_2Me), 31.75 (C-1′), 32.13 (cyclohexyl-C), 35.87 (C-5), 36.22 (C-4), 37.38 (cyclohexyl-C), 51.39 (OMe), 53.04 (C-6), 57.36 (C-2), 58.22 (cyclohexyl-C), 115.8 (C-3′), 137.9 (C-2′), 173.9 (CO).

Piperidine 18a: Yield 115 mg (73%) of a 1:1 mixture of C-6′ stereoisomers. − R_f = 0.46 (diethyl ether/pentane, 2:1). − Selected spectroscopic data for both isomers: − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.70, 21.95, 22.63, 26.03, 31.61, 35.95, 33.30, 35.16, 36.91, 36.95, 40.23, 51.14, 51.49, 51.51, 51.76, 54.32, 55.99, 56.08, 56.50, 115.4, 116.0 (C-3′), 126.5, 128.5, 126.8, 128.1, 128.2, 128.2, 137.3, 137.5 (phenyl-C), 140.3, 140.9 (C-2′), 172.8 und 173.4 (CO). − IR (film): $\tilde{\nu}$ = 2948 cm^{-1}, 2922 (CH), 1740 (C=O), 1450 (CH, CH_3), 1168 (CH_2−O). − CI-MS; *m/z*: 316 (100) [M^+ + 1]. − $C_{20}H_{29}NO_2$ (315.45): calcd. C 76.15; H 9.27; found C 76.50, H 8.87.

Piperidine 18b: Yield 123 mg (78%). − R_f = 0.58 (diethyl ether/pentane, 1:1). − Diastereoselectivity at C-6: 10:1 (by ^1H and ^{13}C NMR). − $[\alpha]_D^{20}$ = +9.4 (*c* = 0.5, $CHCl_3$). − Spectroscopic data for the major isomer: ^1H NMR (500 MHz, $CDCl_3$): δ = 0.88 (d, *J* = 6.3 Hz, 3 H, CH_3), 0.99 (d, *J* = 6.8 Hz, 3 H, CH_3), 1.32 (dt, *J* = 12.5 Hz, *J* = 3.0 Hz, 1 H, 5-H), 1.48 (dt, *J* = 5.0 Hz, *J* = 12.5 Hz, 1 H, 5-H), 1.54−1.62 (m, 1 H, 3-H), 1.89−2.07 (m, 2 H, 1′-H, 4-H), 2.38 (mc, 1 H, 1′-H), 2.40 (dd, *J* = 15.0 Hz, *J* = 10.0 Hz, 1 H, C*H*−CO_2Me), 2.63 (dd, *J* = 15.0 Hz, *J* = 2.8 Hz, 1 H, C*H*−CO_2Me), 2.77 (mc, 1 H, 6-H), 3.12 (dt, *J* = 10.0 Hz, *J* = 2.8 Hz, 1 H, 2-H) 3.64 (s, 3 H, OMe), 3.72 (d, *J* = 14.5 Hz, 1 H, benzyl-H), 3.80 (d, *J* = 14.5 Hz, 1 H, benzyl-H), 4.95−5.08 (m, 2 H, 3′-H_2), 5.57 (ddt, *J* = 17.0 Hz, *J* = 10.5 Hz, *J* = 6.5 Hz, 1 H, 2′-H), 7.25−7.32 (m, 5 H, phenyl-H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.20 (CH_3), 18.84 (CH_3), 23.33 (C-3), 29.76 (*C*H_2−CO_2Me), 34.68 (C-1′), 35.87 (C-5), 36.67 (C-4), 51.51 (OMe), 55.92 (C-6), 55.98 (*N*-benzyl), 61.17 (C-2), 116.1 (C-3′), 126.7, 128.1, 128.3, 140.3 (phenyl-C), 137.5 (C-2′), 173.6 (CO). − IR (film): $\tilde{\nu}$ = 2956 cm^{-1}, 2928 (CH), 1738 (C=O), 1450, 1440 (CH, CH_3). − CI-MS; *m/z*: 316 (100) [M^+ + 1]. − $C_{20}H_{29}NO_2$ (315.45): calcd. C 76.15; H 9.27; found C 75.92; H 9.44.

Piperidine 18c: Yield 129 mg (82%). − R_f = 0.58 (diethyl ether/pentane, 1:1). − Diastereoselectivity at C-6: 10:1 (by ^1H and ^{13}C NMR). − $[\alpha]_D^{20}$ = +5.0 (*c* = 0.3, $CHCl_3$). − Spectroscopic data for the major isomer: − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.92 (d, *J* = 7.0 Hz, 3 H, CH_3), 0.98 (d, *J* = 7.0 Hz, 3 H, CH_3), 1.47−1.65 (m, 3 H, 3-H, 5-H_2), 1.92 (t, *J* = 2.5 Hz, 1 H, 3′-H), 1.95 (mc, 1 H, 4-H), 2.11 (ddd, *J* = 16.3 Hz, *J* = 10.3 Hz, *J* = 2.5 Hz, 1 H, 1′-H), 2.34 (dd, *J* = 15.0 Hz, *J* = 10.0 Hz, 1 H, C*H*−CO_2Me), 2.47 (dt, *J* = 16.3 Hz, *J* = 2.5 Hz, 1 H, 1′-H), 2.57 (dd, *J* = 15.0 Hz, *J* = 3.0 Hz, 1 H, C*H*−CO_2Me), 3.05−3.13 (m, 2 H, 2-H, 6-H), 3.63 (s, 3 H, OMe), 3.73 (d, *J* = 15.0 Hz, 1 H, benzyl-H), 3.81 (d, *J* = 15.0 Hz, 1 H, benzyl-H), 7.25−7.32 (m, 5 H, phenyl-H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.10 (CH_3), 18.70 (CH_3), 20.09 (C-1′), 23.23 (C-3), 30.24 (*C*H_2−CO_2Me), 35.90 (C-5), 36.62 (C-4), 51.56 (OMe), 56.22 (C-6), 56.30 (*N*-benzyl), 60.66 (C-2), 69.14 (C-2′), 83.45 (C-3′), 126.9, 128.2, 128.2, 139.8 (phenyl-C), 173.2 (CO). − IR (film): $\tilde{\nu}$ = 2956 cm^{-1}, 2930 (CH), 1736 (C=O), 1452, 1436, 1374 (CH, CH_3), 1118 (CH_2−O−). − CI-MS; *m/z*: 314 (100) [M^+ + 1]. − $C_{20}H_{27}NO_2$ (314.44): calcd. C 76.64, H 8.68; found C 76.92; H 8.86.

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