Asymmetric Synthesis of Pyrido[1,2-*c*]pyrimidinones

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Dedicated to Professor Gerhard Maas with best wishes on the occasion of his 60th birthday

"Asymmetric Electrophilic α-Amidoalkylation" reactions with a chiral alkylaminocarbonyl unit as chiral auxiliary are used for the stereoselective synthesis of 2-substituted piperidine derivatives. Intramolecular condensation of the nitrogen of the aminocarbonyl group with the keto function present in the newly introduced side chain of the amidoalkylation products results in the formation of hexahydropyrido[1,2-*c*]pyrimidinones. After reduction and removal of the *N*-alkyl moiety of the chiral auxiliary the target compounds, enantiopure octahydro-1*H*-pyrido[1,2-*c*]pyrimidin-1-ones, are obtained.

Key words: α-Amidoalkylation, Asymmetric Synthesis, Heterocycles, *N*-Acyliminium Ion, Pyridopyrimidinone

Introduction

The piperidine ring is a common structure in many natural products [1] and is found in numerous biologically active compounds [2]. Accordingly, the synthesis of isolated as well as fused piperidine derivatives has represented a field of intense research efforts for many decades with increasing attention being paid to methods providing access to enantiopure compounds [3].

Previously, we reported on a cationic type of asymmetric synthesis involving chiral *N*-acyliminium ions provided with an *N*-acyl group as chiral auxiliary [4]. This methodology, which we termed "Asymmetric Electrophilic α-Amidoalkylation" (AEαA), has been successfully employed in the stereoselective synthesis of α-substituted piperidines [5], pyrrolidines [6], 1,2,3,4-tetrahydroisoquinolines [7], and 1,2,3,4-tetrahydro-β-carbolines [8]. Further efforts aimed at extending this concept to iminium ions **1** (Scheme 1) in which a chiral *N*-alkylaminocarbonyl substituent instead of a chiral *N*-acyl group serves as a chiral auxiliary. The successful implementation of this plan was expected to give access to the alkylation products **2** (Scheme 1) which in turn should be suitable starting materials for the preparation of stereoisomeric pyrido[1,2-*c*]pyrimidinones **3** and **4** in enantiopure form (Scheme 1). As pyrido[1,2-*c*]pyrimidinones **3** and **4** are structurally related to the tetraponerines T3, T4, T7 and T8 (Fig. 1), toxic alkaloids found in the New Guinean ant Tetraponera sp., the realization of

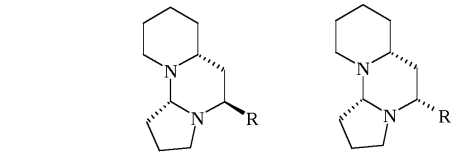
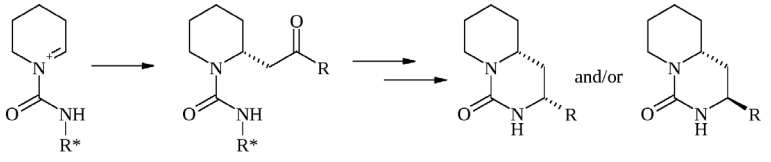
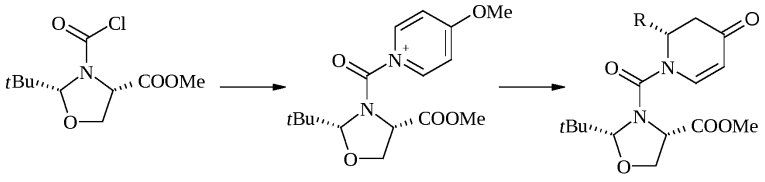


Fig. 1. Tetraponerines T3, T4, T7 and T8.



Scheme 1.



5 **6** **7**

Scheme 2.

the aforementioned synthetic concept seemed highly rewarding [9].

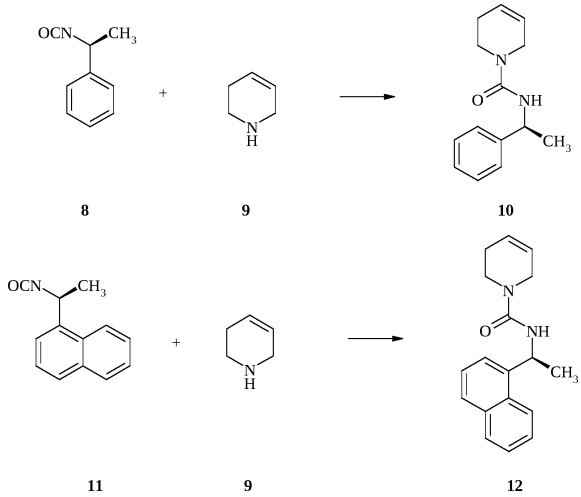
Interestingly, amidoalkylation reactions of this type with the asymmetric induction arising from acyclic stereocontrol utilizing an alkylaminocarbonyl group are still unprecedented for piperidine so far. The only related study has been published by Streith *et al.* [10]. They successfully used the oxazolidine **5** to generate the chiral pyridinium ion **6**, which when treated with RMgBr yielded the dihydropyridone **7** (Scheme 2).

Results and Discussion

We selected the piperidine derivatives **13** and **16** as amidoalkylation reagents for this study (Scheme 4). The enamide moiety present in **13** and **16** was intended to serve as a precursor for the generation of acyliminium ions, for which purpose it had often been used in previous studies [11]. The (*S*)-1-pheny-1-ethylaminocarbonyl and the (*S*)-1-naphthyl-1-ethylaminocarbonyl moieties in **13** and **16** had been chosen as chiral auxiliaries as the commercial availability of the isocyanates (*S*)-1-(1-isocyanatoethyl)benzene (**8**) and (*S*)-1-(1-isocyanatoethyl)naphthalene (**11**) (Scheme 3) was expected to facilitate the synthesis of the required piperidine derivatives.

The synthesis of the enamides **13** and **16** was performed as outlined in Scheme 3. Upon treatment of 1,2,3,6-tetrahydripyridine **9** with either (*S*)-1-(1-isocyanatoethyl)benzene (**8**) or (*S*)-1-(1-isocyanatoethyl)naphthalene (**11**) the tetrahydropyridine derivatives **10** and **12** were obtained, in 91 % and 94 % yield, respectively.

Subsequent isomerization of the allyl amides **10** and **12** employing Pd on γ-Al_2O_3 as catalyst in the presence of triethylamine led to the corresponding enamides **13** and **16** in 82 % and 68 % yield, respectively (Scheme 4). For analogous isomerization reactions reported previously [11a] Pd on carbon had been used as a catalyst. In the case of **10** and **12**, however, distinctly higher yields were reached when Pd



8 **9** **10**

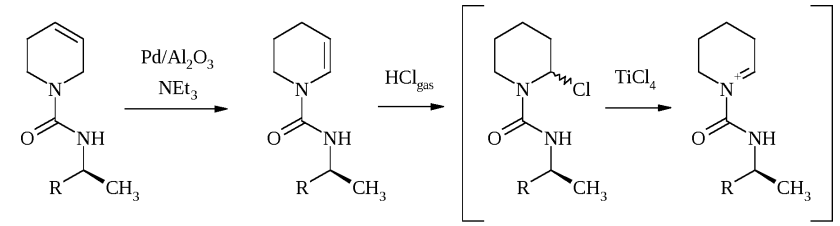
11 **9** **12**

Scheme 3.

on γ-Al_2O_3 instead of Pd on carbon was employed as catalyst.

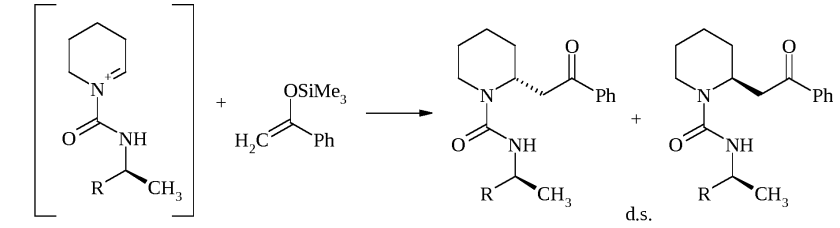
For the amidoalkylation reactions, enamides **13** and **16** were activated following a common procedure developed for related compounds. Thus CH_2Cl_2 was saturated with a large excess of HCl gas, and the enamides **13** and **16** were added to this solution. Then, after vacuum had been applied to remove unbound HCl, $TiCl_4$ was added to transform the presumed intermediates, the α-chloroamides **14** and **17**, into the corresponding *N*-acyliminium ions **15** and **18** (Scheme 4).

When silylenolether **19** selected as trapping reagent was added to the reaction mixture that had been generated as described above, the expected addition products, **20/21** and **22/23**, were indeed formed, but the yields for the addition products **20/21** (34 %) and **22/23** (50 %) were far from being satisfying, and also the stereoselectivity was low (**20/21** = 60/40; **22/23** = 78/22). For both the poor yield and low selectivity HCl gas was blamed that despite evacuation might have remained in the reaction solution. Therefore, in further experiments in contrast to the original procedure instead of a large excess a definite amount of HCl gas (4.5 equivalents) was introduced into the reaction mix-



R = Ph **10** **13** **14** **15**
R = Naph **12** **16** **17** **18**

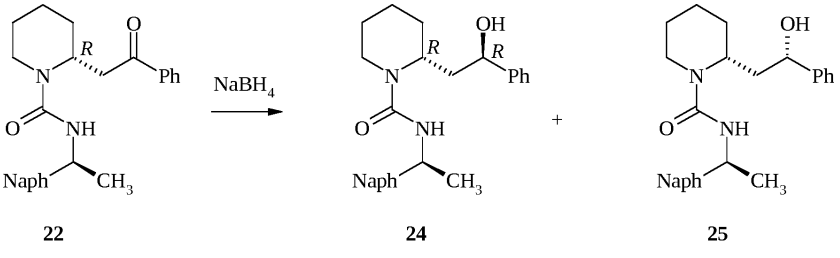
Scheme 4.



R = Ph **15** **19** **20** 71/29 **21**
R = Naph **18** **22** 84/16 **23**

d.s.

Scheme 5.



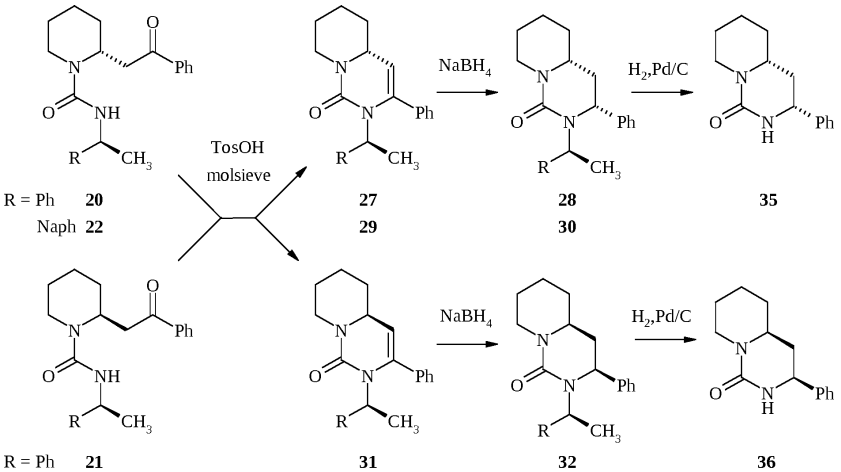
22 **24** **25**

26

Scheme 6.

ture by means of a gas-tight syringe. Keeping everything else the same, the yields for the addition products **20/21** and **22/23** then rose to 75 % and 58 %, and the diastereoselectivity to 71/29 (**20/21**) and 84/16 (**22/23**), respectively (Scheme 5). Obviously, excessive HCl gas (or its complex with $TiCl_4$) that had remained in the reaction mixture had partly decomposed the silylenolether **19** in the first reaction thus leading to a lower yield. The formation of a complex between $TiCl_4$ and HCl could also explain why, when excessive HCl is absent, a higher diastereoselectivity is reached. Free $TiCl_4$ (or $TiCl_5^-$ after abstraction of Cl^- from the substrate) will have a higher capability to coordinate to the chiral auxiliary which might positively influence the extent of its asymmetric induction.

In order to assign the stereochemistry at the newly created stereocenter in 2-position of the piperidine ring, the major diastereomer **22** was transformed into the known aminoalcohol **26** [12]. Reduction of **22** with $NaBH_4$ yielded the alcohols **24** and **25** (diastereoselectivity 66/34). Finally, treatment of the stereoisomer **24** with LiOH led to the known amino alcohol **26** [12] (Scheme 6). Comparison of the optical rotation and the ^{1}H NMR data of **26** with those of an authentic sample [11a] allowed the assignment of the relative and the absolute configuration of this compound. In this way,



Scheme 7.

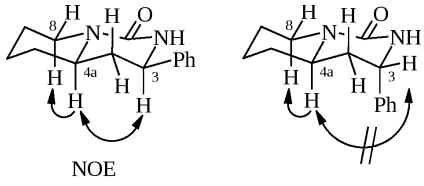
compound **26** turned out to be of (*R*,*R*)-configuration which, of course, must apply to the corresponding stereocenters in the amidoalcohol **24** as well. Finally, according to these results the main product of the trapping reaction of the *N*-acyliminium ion **18** with the silylenolether **19**, **22** must have (*R*)-configuration at the newly created stereocenter at 2-position of the piperidine ring (Scheme 6) as well.

The ^{1}H NMR spectra of the major isomer **20** and the minor isomer **21** from the trapping reaction of the *N*-acyliminium ion **15** with **19** were very similar to the major and minor isomer **22** and **23**, respectively, that had resulted from the corresponding reaction with the *N*-acyliminium ion **18**. Only the ^{1}H NMR signals arising from the aryl groups, the phenyl and the naphthyl moiety, present in the chiral auxiliaries of **20/21** and **22/23**, differed, of course, significantly. Accordingly, the newly created stereocenter of the major isomer **20** and the minor isomer **21** was assigned (*R*)- and (*S*)-stereochemistry, respectively, based on the similarities with the major and minor isomers **22** and **23**.

In the next step, the amidoalkylation products **20/21** and **22/23** were transformed to the bicyclic enamides **27/31** and **29/33**. As starting materials, the mixtures of the diastereomeric amidoalkylation products were employed since the diastereomers of the cyclized products turned out to be easier to separate than those of the precursors. The cyclization was effected by heating the starting materials in the presence of molecular sieve and catalytic amounts of *p*-toluenesulfonic acid for 8 h to reflux. The pure diastereomers of the thus formed cyclic enamides **27/31** and **29/33** were obtained after column chromatography in yields of 21 % (**27**), 25 % (**31**), 37 % (**29**), and 13 % (**33**), respectively (Scheme 7). As the compounds turned out to be unstable at r. t., which was likely to be a result of the enamide moiety present, they were quickly transformed to the saturated compounds which, indeed, appeared to be stable.

Interestingly, the reductions that had been accomplished by means of $NaBH_4$ in acetic acid must have proceeded with high asymmetric induction, as in each case only a single diastereomer could be isolated, their yields amounting to 72 % (**28**), 43 % (**32**), 72 % (**30**), and 67 % (**34**), respectively. The last step of our synthetic sequence to pyrido[1,2-*c*]pyrimidinones required the removal of the chiral auxiliary from the nitrogen atom in 2-position of the ring system. This last step was only performed for compounds **28** and **32** which upon hydrogenation over Pd/C provided the desired target compounds **35** and **36** in 76 % and 68 % yield, respectively (Scheme 7).

The stereochemistry of the new stereocenter in the reduction products **28**, **30**, **32**, and **34** was assigned by means of ^{1}H coupling constants observed in the ^{1}H NMR spectra for the protons in positions 3, 4 and 4a in the bicyclic ring system. In addition, this assignment was further verified by NO experiments performed for the enantiopure target compound **35**. These experiments revealed positive NO effects between the protons in positions 3, 4a and 8 as indicated in Fig. 2. Of course, such effect would not be found in the (*R,S*)-configurated isomer **37** as the distance between the protons in 3- and 4a-position is too large (Fig. 2). Taking into account the stereochemistry of the 4a-position identified by correlation with the aminoalcohol **26**,



35 **37** (not found)

Fig. 2. NOE experiments.

compound **35** must be of (*R,R*)- and its enantiomer **36** self-evidently of (*S,S*)-configuration.

Conclusion

In the work presented, we demonstrated that "Asymmetric Electrophilic α-Amidoalkylation" reactions can also be performed with piperidine derivatives provided with a carboxamide unit as a chiral auxiliary. The C-2 substituted piperidine derivatives obtained by utilizing this new type of asymmetric amidoalkylation reactions turned out to be well suited for the preparation of enantiopure pyrido[1,2-*c*]pyrimidones, compounds with a core structure analogous to that of the natural products tetraponerines.

Experimental Section

All reactions were performed using dried glassware under N_2 atmosphere. All solvents were freshly dried using standard [13] procedures. Melting points were determined on a Büchi melting point 510 apparatus and are uncorrected. ^{1}H spectra were recorded in $CDCl_3$ or CD_2Cl_2 at 400 MHz. Infrared spectra were obtained on a Perkin-Elmer Paragon 1000 FTIR spectrometer. Microanalytical data for carbon, hydrogen and nitrogen were determined on a Heraeus Rapid Analyzer. Commercially obtained reagents were used without further purification. Flash chromatography was carried out using silica gel 60 (0.032 – 0.063 mm). HPLC: Merck Hitachi Series 6000, column: LiChrospher 250-4/250-25 Si 60 (5 μm).

General procedure for the reduction of the cyclic enamides (GP1)

The corresponding enamide was dissolved in glacial acetic acid, and $NaBH_4$ was added at 0 °C. After 10 min the reaction mixture was allowed to warm to r. t. and stirred over night (16 h). The resulting solution was laced with H_2O and HCl (0.1 M) and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The resulting crude product was purified by CC on silica gel (EtOAc / *n*-heptane 1 : 1).

*N-[(1S)-1-Phenylethyl]-3,6-dihydropyridine-1(2H)-carboxamide (**10**)*

(*S*)-1-(1-Isocyanatoethyl)benzene (**8**) (4.91 g, 33.3 mmol) dissolved in THF (18 mL) was cooled to 0 °C, and 1,2,3,6-tetrahydropyridine (**9**) (5.54 g, 66.7 mmol) was added with stirring. After 10 min the mixture was warmed to r. t. and stirred for 13 h. The solvent was removed from the resulting mixture, and the remaining residue was dissolved in EtOAc and washed with aqueous $NaHSO_4$ solution (3×) and H_2O (3×). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified by CC on silica gel (EtOAc / *n*-heptane 1 : 1). Colorless crystals, 7.44 g (91 %). – M. p. 96 – 98 °C. – $[\alpha]_D^{20}$ = −2.7° (*c* = 0.075, $CHCl_3$). – IR (KBr): ν = 3029, 2969, 2971, 2834, 1615, 1534, 1446, 1409, 1340, 1254, 762, 702, 653, 567, 532 cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.50 (d, *J* = 6.7 Hz, 3 H, HCC*H*$_3$), 2.13 – 2.19 (m, 2 H, NCH$_2$C*H*$_2$), 3.47 – 3.52 (m, 2 H, NC*H*$_2$CH$_2$), 3.80 – 3.83 (m, 2 H, NC*H*$_2$CH), 4.59 (d, *J* = 6.7 Hz, 1 H, N*H*), 5.06 (quin, *J* = 6.7 Hz, 1 H, *H*CCH$_3$), 5.62 – 5.59 (m, 1 H, HC=CH), 5.84 – 5.92 (m, 1 H, HC=CH), 7.22 – 7.29 (m, 1 H, H$_{ar}$), 7.29 – 7.37 (m, 4 H, H$_{ar}$). – MS (EI): *m/z* = 230 [M]$^+$, 125, 105. – $C_{14}H_{18}N_2O$ (230.31): calcd. C 73.01, H 7.88, N 12.16; found C 73.01, H 8.00, N 12.02.

*N-[(1S)-Naphthylethyl]-3,6-dihydropyridine-1(2H)-carboxamide (**12**)*

Preparation according to **10** from (*S*)-1-(1-isocyanatoethyl)naphthalene (**11**) (0.473 mg, 2.39 mmol) in THF (20 mL) and **9** (0.397 mg, 4.80 mmol). Colorless crystals, 630 mg (94 %). – M. p. 153 – 155 °C. – $[\alpha]_{578}$ = 35.0° (*c* = 0.915, $CHCl_3$). – IR (KBr): ν = 3320, 3050, 2981, 2917, 2833, 1610, 1534, 1407, 1252, 1214, 774, 665 cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.67 (d, *J* = 6.8 Hz, 3 H, HCC*H*$_3$), 2.14 – 2.17 (m, 2 H, NCH$_2$C*H*$_2$), 3.47 – 3.50 (m, 2 H, NC*H*$_2$), 3.70 – 3.85 (m, 2 H, NC*H*$_2$), 4.63 (d, *J* = 7.3 Hz, 1 H, N*H*), 5.59 (m, 1 H, HC=CH), 5.82 – 5.89 (m, 2 H, *H*CCH$_3$, HC=CH), 7.43 – 7.56 (m, 4 H, H$_{ar}$), 7.77 – 7.79 (m, 1 H, H$_{ar}$), 7.84 – 7.85 (m, 1 H, H$_{ar}$), 817 – 8.19 (m, 1 H, H$_{ar}$). – MS (EI): *m/z* = 280 [M]$^+$, 155, 127, 115. – $C_{18}H_{20}N_2O$ (280.36): calcd. C 77.11, H 7.19, N 9.99; found C 77.18, H 7.20, N 9.91.

*N-[(1S)-1-Phenylethyl]-3,4-dihydropyridine-1(2H)-carboxamide (**13**)*

In a pressure tube under N_2, a mixture of **10** (997 mg, 4.33 mmol) in THF (4 mL), NEt_3 (1 mL) and Pd on γ-Al_2O_3 (85 mg; 5 %) was heated to 105 °C for 4 h. After cooling to r. t., filtration and evaporation of the solvent the resulting residue was purified by CC on silica gel (EtOAc / *n*-heptane / CH_2Cl_2 1 : 2 : 2). Colorless crystals, 813 mg (82 %). – M. p.

121 – 125 °C. – $[\alpha]_D^{20}$ = 43.4° (*c* = 2.015, $CHCl_3$). – IR (KBr): ν = 2972, 1625, 1535, 13,76, 1270, 986, 758, 698 cm^{-1}. – ^1H NMR (400 MHz, $CDCl_3$): δ = 1.51 (d, *J* = 6.9 Hz, 3 H, HCCH_3), 1.81 – 1.88 (m, 2 H, NCH_2CH_2), 2.01 – 2.08 (m, 2 H, $NCH_2CH_2CH_2$), 3,46 – 3.57 (m, 2 H, NCH_2), 4.72 (d, *J* = 6.8 Hz, 1 H, N*H*), 4.88 (td, *J* = 4.0/8.2 Hz, 1 H, NCH=C*H*), 5.05 (quin, *J* = 6.9 Hz, 1 H, *H*CCH_3), 6.70 (d, *J* = 8.2 Hz, 1 H, N*H*C=CH), 7.25 – 7.27 (m, 1 H, H_{ar}), 7.32 – 7.37 (m, 4 H, H_{ar}). – MS (EI): *m/z* = 230 $[M]^+$, 105. – $C_{14}H_{18}N_2O$ (230.31): calcd. C 73.01, H 7.88, N 12.16; found C 72.85, H 8.06, N 12.15.

*N-[(1S)-1-Naphthylethyl]-3,4-dihydropyridine-1(2H)-carboxamide (**16**)*

Preparation according to **13** from **12** (720 mg, 2.57 mmol) in THF (4 mL), NEt_3 (1 mL) and Pd on γ-Al_2O_3 (85 mg; 5 %). Purification by CC on silica gel (EtOAc / *n*-heptane 1 : 1). Colorless crystals, 485 mg (68 %). – M. p. 148 – 151 °C. – $[\alpha]_D^{20}$ = +109.3° (*c* = 0.45, $HCCl_3$). – IR (KBr): ν = 3049, 2932 2872, 1634, 1538, 1454, 1373, 1353, 1268, 1254, 1188, 1070, 988, 800, 778, 736, 717 cm^{-1}. – ^1H NMR (400 MHz, $CDCl_3$): δ = 1.69 (d, *J* = 6.9 Hz, 3 H, HCCH_3), 1.82 (quin, *J* = 6.0 Hz, 2 H, NCH_2CH_2), 2.00 – 2.06 (m, 2 H, NCH=CHCH_2), 3.49 (t, *J* = 5.6 Hz, 2 H, NCH_2), 4.76 (d, *J* = 7.2 Hz, 1 H, N*H*), 4.84 (td, *J* = 4.0/8.0 Hz, 1 H, NCH=C*H*), 5.86 (quin, *J* = 7.0 Hz, 1 H, *H*CCH_3), 6.69 (d, *J* = 8.0 Hz, 1 H, NC*H*), 7.43 – 7.58 (m, 4 H, H_{ar}), 7.78 – 7.82 (m, 1 H, H_{ar}), 7.85 – 7.89 (m, 1 H, H_{ar}), 8.14 – 8.18 (m, 1 H, H_{ar}). – MS (EI): *m/z* = 280 $[M]^+$, 155, 125, 105. – $C_{18}H_{20}N_2O$ (280.36): calcd. C 77.11, H 7.19, N 9.99; found C 77.19, H 7.33, N 9.78.

*(2R)-2-(2-Oxo-2-phenylethyl)-N-[(1S)-1-phenylethyl]piperidine-1-carboxamide (**20**) and (2S)-2-(2-oxo-2-phenylethyl)-N-[(1S)-1-phenylethyl]piperidine-1-carboxamide (**21**)*

HCl gas (175 mL, 7.81 mmol) was dissolved in CH_2Cl_2 (8 mL) at −87 °C using a gas-tight syringe. A solution of **13** (400 mg, 1.73 mmol) in CH_2Cl_2 (4.5 mL) was slowly added over a period of 30 min. The excess of HCl was removed at 10^{-2} mbar and −60 °C (2 h). After cooling to −87 °C, $TiCl_4$ (386 mg, 1.91 mmol) was added, and the resulting yellow solution was stirred for 50 min. Afterwards trimethyl(1-phenylvinyloxy)silane (**19**) (501 mg, 2.61 mmol) in CH_2Cl_2 (2 mL) was added over a period of 15 min. The resulting mixture was stirred for 16 h at −87 °C and quenched with H_2O (10 mL). After neutralization with $NaHCO_3$ solution the aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by CC on silica gel (EtOAc / *n*-heptane 4 : 6) yielded 450 mg (74 %) of the mixture of diastereomers **20** and **21**, which were separated by prep. HPLC (EtOAc / *n*-heptane 4 : 6; 15 mL/min). Analytical HPLC (EtOAc / *n*-heptane 4 : 6; 1.0 mL/min): d. s. **20/21** = 28.7/71.3.

20: Colorless crystals, 168 mg (43 %). – M. p. 84 – 85 °C. – $[\alpha]_D^{20}$ = 51.2° (*c* = 0.44, $CHCl_3$). – IR (KBr): ν = 3409, 3026, 2933, 2863, 1674, 1622, 1506, 1448, 1372, 1264, 1016, 752, 703 cm^{-1}. – ^1H NMR (400 MHz, $CDCl_3$): δ = 1.44 – 1.80 (m, 6 H, CH_2), 1.48 (d, *J* = 7.0 Hz, 3 H, HCCH_3), 2.71 (dt, *J* = 3.0/13.3 Hz, 1 H, NCH_2ax.), 3.00 (dd, *J* = 4.6/17.2 Hz, 1 H, CH_2CO), 3.65 (dd, *J* = 8.0/17.2 Hz, 1 H, CH_2CO), 4.20 (d_{br}, *J* = 13.7 Hz, 1 H, NCH_2eq.), 4.49 – 4.76 (m, 1 H, NC*H*), 4.97 (quin, *J* = 7.0 Hz, 1 H, *H*CCH_3), 6.07 (d, *J* = 7 Hz, 1 H, N*H*), 7.22 – 7.28 (m, 1 H, H_{ar}), 7.33 – 7.38 (m, 2 H, H_{ar}), 7.40 – 7.44 (m, 2 H, H_{ar}), 7.47 – 7.53 (m, 2 H, H_{ar}), 7.59 – 7.64 (m, 1 H, H_{ar}), 7.99 – 8.03 (m, 2 H, H_{ar}). – MS (EI): *m/z* = 350 $[M]^+$, 231, 202. – $C_{22}H_{26}N_2O_2$ (350.46): calcd. C 75.40, H 7.48, N 7.99; found C 75.44, H 7.46, N 7.97.

21: Colorless crystals, 69 mg (18 %). – M. p. 85 – 87 °C. – $[\alpha]_D^{20}$ = −8.1 (*c* = 0.51, $CHCl_3$). – IR (KBr): ν = 3340, 3062, 2929, 2858, 1681, 1633, 1520, 1448, 1373, 1266, 1018, 755, 698 cm^{-1}. – ^1H NMR (400 MHz, $CDCl_3$): δ = 1.36 – 1.76 (m, 6 H, CH_2), 1.44 (d, *J* = 6.8 Hz, 3 H, HCCH_3), 2.62 (dt, *J* = 3.1/13.1 Hz, 1 H, NCH_2ax.), 2.95 (dd, *J* = 5.2/16.8 Hz, 1 H, CH_2CO), 3.46 (dd, *J* = 7.3/16.8 Hz, 1 H, CH_2CO), 4.04 (d_{br}, *J* = 13.1 Hz, 1 H, NCH_2eq.), 4.64 – 4.71 (m, 1 H, NC*H*), 4.86 (quin, *J* = 6.8 Hz, 1 H, *H*CCH_3), 5.86 (d, *J* = 6.8 Hz, 1 H, N*H*), 7.08 – 7.13 (m, 1 H, H_{ar}), 7.16 – 7.21 (m, 2 H, H_{ar}), 7.23 – 7.27 (m, 2 H, H_{ar}), 7.38 – 7.44 (m, 2 H, H_{ar}), 7.50 – 7.55 (m, 1 H, H_{ar}), 7.88 – 7.92 (m, 2 H, H_{ar}). – MS (EI): *m/z* = 350 $[M]^+$, 231, 202. – $C_{22}H_{26}N_2O_2$ (350.46): calcd. C 75.40, H 7.48, N 7.99; found C 75.36, H 7.40, N 7.99.

*(2R)-N-[(1S)-1-Naphthylethyl]-2-(2-oxo-2-phenylethyl)-piperidine-1-carboxamide (**22**) and (2S)-N-[(1S)-1-naphthylethyl]-2-(2-oxo-2-phenylethyl)piperidine-1-carboxamide (**23**)*

Preparation according to **20/21** from **16** (430 mg, 1.53 mmol) in CH_2Cl_2 (4.5 mL), HCl gas (175 mL, 7.81 mmol) in CH_2Cl_2 (8 mL), $TiCl_4$ (387 mg, 2.04 mmol) and **19** (556 mg, 2.89 mmol). Purification by CC on silica gel (EtOAc / *n*-heptane 1 : 1) yielded 395 mg (58 %) of the mixture of diastereomers **22** and **23**, which were separated by prep. HPLC (EtOAc / *n*-heptane 4 : 6; 15 mL/min). Analytical HPLC (EtOAc / *n*-heptane 4 : 6; 1.0 mL/min): d. s. **22/23** = 15.7/84.3.

22: Colorless crystals. – M. p. 163 °C. – $[\alpha]_{578}$ = 120.8° (*c* = 0.625, $CHCl_3$). – IR (KBr): ν = 3350, 2940, 1680, 1630, 1510 cm^{-1}. – ^1H NMR (400 MHz, $CDCl_3$): δ = 1.40 – 1.75 (m, 6 H, CH_2), 1.64 (d, *J* = 6.9 Hz, 3 H, HCCH_3), 2.72 (dt, *J* = 2.7/13.6 Hz, 1 H, NCH_2), 2.97 (dd, *J* = 4.4/17.2 Hz, 1 H, CH_2CO), 3.66 (dd, *J* = 8.1/17.2 Hz, 1 H, CH_2CO), 4.18 (d_{br}, *J* = 13.6 Hz, 1 H, NCH_2), 4.66 – 4.75 (m, 1 H, NC*H*), 5.81

(quin, J = 6.9 Hz, 1 H, $HCCH_3$), 6.09 (d, J = 6.9 Hz, 1 H, N*H*), 7.47 – 8.02 (m, 11 H, H_{ar}), 8.21 – 8.23 (m, 1 H, H_{ar}). – MS (EI): *m/z* = 400 $[M]^+$, 202, 155, 105. – $C_{26}H_{28}N_2O_2$ (400.52): calcd. C 77.97, H 7.05, N 6.99; found C 78.08, H 7.18, N 6.84.

23: Colorless crystals. – M. p. 43 °C. – $[\alpha]_{578}$ = 52.6° (*c* = 0.38, $CHCl_3$). – IR (KBr): ν = 3350, 2930, 2850, 1730, 1680, 1530 cm^{-1}. – ^1H NMR (400 MHz, $CDCl_3$): δ = 1.40 – 1.80 (m, 6 H, CH_2), 1.67 (d, J = 6.8 Hz, 3 H, $HCCH_3$), 2.73 (dt, J = 2.7/14.3 Hz, 1 H, NCH_2), 3.02 (dd, J = 5.7/16.7 Hz, 1 H, CH_2CO), 3.45 (dd, J = 7.1/16.7 Hz, 1 H, CH_2CO), 4.10 (d_{br}, J = 14.3 Hz, 1 H, NCH_2), 4.66 – 4.75 (m, 1 H, NC*H*), 5.78 (quin, J = 7.0 Hz, 1 H, $HCCH_3$), 5.88 (d, J = 7.0 Hz, 1 H, N*H*), 7.37 – 7.82 (m, 11 H, H_{ar}), 8.12 – 8.15 (m, 1 H, H_{ar}). – MS (EI): *m/z* = 400 $[M]^+$, 202, 155, 105. – $C_{26}H_{28}N_2O_2$ (400.52): calcd. C 77.97, H 7.05, N 6.99; found C 78.15, H 7.21, N 6.79.

*(2R)-2-[(2R)-2-Hydroxy-2-phenylethyl]-N-[(1S)-1-naphthylethyl]piperidine-1-carboxamide (**24**) and (2R)-2-[(2S)-2-hydroxy-2-phenylethyl]-N-[(1S)-1-naphthylethyl]piperidine-1-carboxamide (**25**)*

$NaBH_4$ (56.8 mg, 1.5 mmol) was added to a solution of **23** (120.2 mg, 0.3 mmol) in EtOH (25 mL) at 0 °C and the mixture stirred for 15 h at r. t. and subsequently laced with HCl (2 M) and H_2O and extracted with Et_2O (3×). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The resulting residue was purified by CC on silica gel (EtOAc / *n*-heptane 6 : 4). Separation with prep. HPLC (EtOAc / *n*-heptane 4 : 1; 13 mL/min) yielded **24** and **25**. Analytical HPLC (EtOAc / *n*-heptane 3 : 7; 2.0 mL/min; 35 °C): d. s. **24/25 =** 66/34.

24: Colorless crystals, 63.3 mg (51.6 %). – M. p. 96 °C. – $[\alpha]_{578}$ = 142.2° (*c* = 0.225, $CHCl_3$). – IR (KBr): ν = 3320, 2930, 2860, 1620, 1540 cm^{-1}. – ^1H NMR (400 MHz, $CDCl_3$): δ = 1.25 – 1.66 (m, 6 H), 1.66 (d, J = 6.9 Hz, 3 H, CH_3), 1.90 (ddd, J = 4.2/10.1/14.3 Hz, 1 H, CH_2CHOH), 2.00 (ddd, J = 3.4/7.7/14.3 Hz, 1 H, CH_2CHOH), 2.66 (dt, J = 2.8/12.9 Hz, 1 H, NCH_2ax.), 3.17 (s_{br}, 1 H, C*H*OH), 3.83 (d, J = 12.9 Hz, 1 H, NH_2eq.), 4.20 – 4.23 (m, 1 H, NCH), 4.68 (d, J = 7.7 Hz, 1 H, C*H*OH), 5.43 (d, J = 6.9 Hz, 1 H, NH), 5.87 (quint, J = 6.9 Hz, 1 H, $CHCH_3$), 7.24 – 7.37 (m, 4 H, H_{ar}), 7.75 – 7.77 (m, 1 H, H_{ar}), 7.84 – 7.86 (m, 1 H, H_{ar}), 8.19 – 8.21 (m, 1 H, H_{ar}). – MS (EI): *m/z* = 402 $[M]^+$. – $C_{22}H_{26}N_2O$ (402.54): calcd. C 77.58, H 7.51, N 6.96; found C 77.63, H 7.64, N 6.81.

25: Colorless crystals, 27.8 mg (23 %). – M. p. 165 °C. – $[\alpha]_{578}$ = 186.7° (*c* = 0.15, $CHCl_3$). – IR (KBr): ν = 3270, 2930, 2860, 1610, 1540 cm^{-1}. – ^1H NMR (400 MHz, $CDCl_3$): δ = 1.39 – 1.82 (m, 7 H), 1.69 (d, J=6.6 Hz, 3 H, CH_3), 2.19 (ddd, J = 2.2/12.1/14.3 Hz, 1 H), 2.80 (t, J = 12.5 Hz, 1 H, NCH_2ax.), 3.52 – 3.72 (m_{br}, 1 H, NCH_2eq.), 4.51 (d, J = 11.0 Hz, 1 H, C*H*-OH), 4.68 (m, 1 H, NCH), 5.13 (s_{br}, 1 H, NH), 5.92 (quint, J = 6.6 Hz, 1 H, C*H*-CH_3), 7.25 – 7.37 (m, 5 H, H_{ar}), 7.43 – 7.55 (m, 4 H, H_{ar}), 7.78 – 7.80 (m, 1 H, H_{ar}), 7.83 – 7.87 (m, 1 H, H_{ar}), 8.15 – 8.17 (m, 1 H, H_{ar}). – MS (EI): *m/z* = 402 $[M]^+$. – $C_{22}H_{26}N_2O$ (402.54): calcd. C 77.58, H 7.51, N 6.96; found C 77.56, H 7.59, N 6.88.

*(1R)-1-Phenyl-2-[(2R)-piperidin-2-yl]ethanol (**26**) [12]*

To a solution of **24** (80.5 mg, 0.2 mmol) in dioxane (10 mL) was added $LiOH{\cdot}H_2O$ (209 mg, 5.00 mmol) in H_2O (1 mL) and the mixture stirred for 72 h at 150 °C in a pressure tube. After evaporation of the solvent the residue was laced with HCl solution and washed with Et_2O. The remaining aqueous solution was brought to pH = 9 with KOH and extracted with Et_2O. The combined organic layers were dried ($MgSO_4$), concentrated *in vacuo* and recrystallized from *n*-hexane. Colorless crystals, 25.2 mg (61 %). – $[\alpha]_{546}$ = 40.0° (*c* = 0.175, $CHCl_3$). – $[\alpha]_{578}$ = 34.3° (*c* = 0.15, $CHCl_3$). – ^1H NMR (400 MHz, $CDCl_3$): δ = 1.09 – 1.19 (m, 1 H), 1.28 – 1.39 (m, 1 H), 1.48 – 1.73 (m, 5 H), 1.81 – 1.87 (m, 1 H), 2.67 (ddd, J = 2.9/12.1/13.6 Hz, 1 H, NCH_2ax.), 2.92 (tt, J = 2.5/10.7 Hz, 1 H, NCH), 3.09 (d, J = 13.6 Hz, 1 H, NCH_2eq.), 4.95 (dd, J = 2.6/10.6 Hz, 1 H, C*H*-OH), 7.21 – 7.38 (m, 5 H, H_{ar}).

*(4aR)-3-Phenyl-2-[(1S)-1-phenylethyl]-2,4a,5,6,7,8-hexahydro-1H-pyrido[1,2-c]pyrimidin-1-one (**27**) and (4aS)-3-phenyl-2-[(1S)-1-phenylethyl]-2,4a,5,6,7,8-hexahydro-1H-pyrido[1,2-c]pyrimidin-1-one (**31**)*

A mixture of **20** and **21** (450 mg, 1.28 mmol) in toluene (10 mL) together with some crystals of *p*-toluenesulfonic acid and molecular sieve (600 mg) was heated to reflux for 8 h. After filtration the solution was washed with aqueous $NaHCO_3$ solution (1×) and H_2O (3×) and dried over $MgSO_4$. Evaporation of the solvent gave a crude product which was purified by CC on silica gel (EtOAc / *n*-heptane 2 : 8). The diastereomers **27** and **31** were obtained by prep. HPLC (EtOAc / *n*-heptane 1 : 9; 14.4 mL/min).

27: Colorless oil (decomposition at r. t.), 89 mg (21 %). – IR (film): ν = 3060, 2934, 2857, 1706, 1660, 1446, 1265, 1250, 1074, 1028, 756, 699 cm^{-1}. – 1H NMR (400 MHz, $CDCl_3$): δ = 1.16 – 1.94 (m, 6 H, CH_2), 1.73 (d, J = 7.1 Hz, 3 H, $HCCH_3$), 2.43 (dt, J = 2.5/13.2 Hz, 1 H, NCH_2ax.), 4.82 – 4.85 (m, 1 H, NC*H*), 4.35 (d, J = 13.2 Hz, 1 H, NCH_2eq.), 4.64 (q, J = 7.1 Hz, 1 H, $HCCH_3$), 4.69 (d, J = 4.6 Hz, 1 H, NC=C*H*), 7.14 – 7.32 (m, 10 H, H_{ar}). – MS (EI): *m/z* = 332 $[M]^+$, 227, 105. – $C_{22}H_{24}N_2O$ (332.45): calcd. C 79.48, H 7.28, N 8.43; found C 79.37, H 7.38, N 7.84.

31: Colorless oil (decomposition at r. t.), 107 mg (25 %). – IR (film): ν = 3060, 2937, 2857, 1710, 1660, 1446, 1268, 1250, 1074, 1028, 735, 699 cm^{-1}. – ^1H NMR (400 MHz, $CDCl_3$): δ = 1.21 – 1.92 (m, 6 H, CH_2), 1.72 (d, J = 6.8 Hz,

3 H, HCCH_3), 2.45 (dt, J = 3.1/12.7 Hz, 1 H, NCH_2ax.), 3.94 (td, J = 2.8/10.9 Hz, 1 H, NCH), 4.37 (d_{br}, J = 13.0 Hz, 1 H, NCH_2eq.), 4.67 (d, J = 3.1 Hz, 1 H, NC=CH), 4.74 (q, J = 7.1 Hz, 1 H, HCCH$_3$), 7.14 – 7.36 (m, 10 H, H_{ar}). – MS (EI): m/z = 332 $[M]^+$, 227, 105. – $C_{22}H_{24}N_2O$ (332.45): calcd. C 79.48, H 7.28, N 8.43; found C 79.88, H 7.58, N 7.73.

*(4aR)-2-[(1S)-1-Naphthylethyl]-3-phenyl-2,4a,5,6,7,8-hexahydro-1H-pyrido[1,2-c]pyrimidin-1-one (**29**) and (4aS)-2-[(1S)-1-naphthylethyl]-3-phenyl-2,4a,5,6,7,8-hexahydro-1H-pyrido[1,2-c]pyrimidin-1-one (**33**)*

Preparation according to **27**/**31** from a mixture of **22** and **23** (361 mg, 0.90 mmol) in toluene (15 mL). Purification by CC on silica gel (EtOAc / *n*-heptane 2 : 8) and separation by prep. HPLC (EtOAc / *n*-heptane 4 : 6; 13.5 mL/min) yielded the diastereomers **29** and **33**.

29: Colorless oil (decomposition at r. t.), 127 mg (37 %). – IR (KBr): ν = 3056, 2918, 2850, 1634, 1446, 1403, 1265, 1250, 738, 704 cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.10 – 1.85 (m, 6 H, CH_2), 1.78 (d, J = 7.4 Hz, 3 H, HCCH_3), 2.46 (dt, J = 3.6/12.8 Hz, 1 H, NCH_2ax.), 3.70 (td, J = 3.7/10.5 Hz, 1 H, NCH), 4.39 (d, J = 3.9 Hz, 1 H, NC=CH), 4.45 (d_{br}, J = 12.8 Hz, 1 H, NCH_2eq), 5.92 (q, J = 7.4 Hz, 1 H, HCCH$_3$), 6.64 – 6.80 (m, 2 H, H_{ar}), 6.86 – 6.92 (m, 1 H, H_{ar}), 6.93 – 7.03 (m, 3 H, H_{ar}), 7.05 – 7.12 (m, 1 H, H_{ar}), 7.34 – 7.45 (m, 2 H, H_{ar}), 7.53 – 7.58 (m, 1 H, H_{ar}), 7.72 – 7.76 (m, 1 H, H_{ar}), 7.89 – 7.94 (m, 1 H, H_{ar}). – MS (EI): m/z = 382 $[M]^+$, 227, 155. – $C_{26}H_{26}N_2O$ (382.51): calcd. C 81.64, H 6.85, N 7.32; found C 81.93, H 6.85, N 7.03.

33: Colorless oil (decomposition at r. t.), 45 mg (13 %). – IR (KBr): ν = 3052, 2935, 2854, 1658, 1644, 1446, 1403, 1263, 1250, 779, 761, 735, 703 cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.04 (dt, J = 3.7/11.8 Hz, 1 H, CH_2), 1.23-1.78 (m, 5 H, CH_2), 1.89 (d, J = 6.9 Hz, 3 H, HCCH_3), 2.64 (dt, J = 3.0/12.8 Hz, 1 H, NCH_2ax.), 3.74 (td, J = 3.2/11.8 Hz, 1 H, NCH), 4.46 (d_{br}, J = 13.1 Hz, 1 H, NCH_2eq), 4.50 (d, J = 3.5 Hz, 1 H, NC=CH), 5.92 (q, J = 6.9 Hz, 1 H, HCCH$_3$), 6.71 – 6.87 (m, 2 H, H_{ar}), 6.97 – 7.02 (m, 1 H, H_{ar}), 7.03 – 7.11 (m, 3 H, H_{ar}), 7.14 – 7.21 (m, 1 H, H_{ar}), 7.43 – 7.53 (m, 2 H, H_{ar}), 7.61 – 7.67 (m, 1 H, H_{ar}), 7.80 – 7.85 (m, 1 H, H_{ar}), 7.91 – 7.97 (m, 1 H, H_{ar}). – MS (EI): m/z = 382 $[M]^+$, 227, 155. – $C_{26}H_{26}N_2O$ (382.51): calcd. C 81.64, H 6.85, N 7.32; found C 81.99, H 6.94, N 6.89.

*(3R,4aR)-3-Phenyl-2-[(1S)-1-phenylethyl]octahydro-1H-pyrido[1,2-c]pyrimidin-1-one (**28**)*

According to GP1 from **27** (50 mg, 0.15 mmol) in AcOH (4.5 mL) and $NaBH_4$ (136 mg, 3.60 mmol). Colorless crystals, 36 mg (72 %). – M. p. 76 – 81 °C. – $[\alpha]_D^{20}$ = 76.7 (c = 0.08, $CHCl_3$). – IR (KBr): ν = 2932, 2852, 1627, 1470, 1445, 1362, 1321, 1275, 1229, 1095, 1029, 747, 700 cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.50 (dq, J = 3.8/12.6 Hz, 1 H, CH_2), 0.88 (d, J = 13.1 Hz, 1 H, CH_2), 1.08 – 1.23 (m, 2 H, CH_2), 1.27 (d, J = 7.2 Hz, 3 H, HCCH_3), 1.45 – 1.58 (m, 2 H, CH_2), 1.73 (ddd, J = 1.7/3.2/13.5 Hz, 1 H, NCH(Ph)CH_2), 1.98 (ddd, J = 5.4/8.3/13.4 Hz, 1 H, NCH(Ph)CH_2), 2.53 (dt, J = 2.4/13.0 Hz, 1 H, NCH_2ax.), 3.10 (ddt, J = 2.1/8.2/12.2, 1 H, NCH), 4.24 (dd, J = 3.3/5.4 Hz, 1 H, NCH(Ph)), 4.51 (td, J = 2.2/13.2 Hz, 1 H, NCH_2eq.), 5.93 (q, J = 7.2 Hz, 1 H, HCCH$_3$), 7.13 – 7.31 (m, 10 H, H_{ar}). – MS (EI): m/z = 334 $[M]^+$, 229, 215, 132, 105. – $C_{22}H_{26}N_2O$ (334.46): calcd. C 79.01, H 7.84, N 8.38; found C 79.01, H 7.91, N 8.31.

*(3S,4aS)-3-Phenyl-2-[(1S)-1-phenylethyl]octahydro-1H-pyrido[1,2-c]pyrimidin-1-one (**32**)*

According to GP1 from **31** (56 mg, 0.17 mmol) in AcOH (5 mL) and $NaBH_4$ (127 mg, 3.37 mmol). Colorless crystals, 168 mg (43 %). – M. p. 77 – 73. – $[\alpha]_D^{20}$ = −111.9° (c = 0.45, $CHCl_3$). – IR (KBr): ν = 3030, 2934, 2853, 1633, 1470, 1445, 1365, 1329, 1278, 1095, 1029, 736, 699 cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 – 1.00 (m, 1 H, CH_2), 1.29 – 1.51 (m, 3 H, CH_2), 1.72 – 1.80 (m, 2 H, CH_2), 1.78 (d, J = 7.2 Hz, 3 H, HCCH_3), 2.12 (ddd, J = 5.8/6.7/13.6 Hz, 1 H, NCH(Ph)CH_2), 2.43 (ddd, J = 5.1/6.0/13.6 Hz, 1 H, NCH(Ph)CH_2), 2.66 (t, J = 12.9 Hz, 1 H, NCH_2ax.), 3.23 (dtd, J = 2.6/5.7/11.9 Hz, 1 H, NCH), 4.62 (d_{br}, J = 12.9 Hz, 1 H, NCH_2eq.), 4.73 (dd, J = 5.2/6.7 Hz, 1 H, NCH(Ph)), 5.41 (q, J = 7.2 Hz, 1 H, HCCH$_3$), 7.19 – 7.31 (m, 8 H, H_{ar}), 7.37 – 7.52 (m, 2 H, H_{ar}). – MS (EI): m/z = 334 $[M]^+$, 229, 215, 132, 105. – $C_{22}H_{26}N_2O$ (334.46): calcd. C 79.01, H 7.84, N 8.38; found C 79.08, H 7.84, N 8.32.

*(3R,4aR)-2-[(1S)-1-Naphthylethyl]-3-phenyloctahydro-1H-pyrido[1,2-c]pyrimidin-1-one (**30**)*

According to GP1 from **29** (80 mg, 0.21 mmol) in AcOH (7 mL) and $NaBH_4$ (180 mg, 4.18 mmol). Colorless crystals, 58 mg (72 %). – M. p. 137 – 139. – $[\alpha]_D^{20}$ = 5.8° (c = 0.09, $CHCl_3$). – IR (KBr): ν = 3050, 2936, 2854, 1622, 1472, 1447, 1277, 1228, 1191, 806, 783, 731, 701, 644 cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.51 – 0.63 (m, 1 H, NCHCH_2), 0.86 – 0.95 (m, 1 H, NCHCH_2), 1.13 – 1.32 (m, 2 H, CH_2), 1.47 – 1.63 (m. 2 H, CH_2), 1.69 (d, J = 7.1, Hz, 3 H, HCCH_3), 1.92 (ddd, J = 1.6/3.0/13.5 Hz, 1 H, NCH(Ph)CH_2), 2.37 (ddd, J = 5.7/8.2/13.5 Hz, 1 H, NCH(Ph)CH_2), 2.63 (dt, J = 3.0/13.2 Hz, 1 H, NCH_2ax.), 3.21 (ddt, 2.1/8.2/11.9 Hz, 1 H, NCH), 4.55 (dd, J = 3.1/5.4 Hz, 1 H, NCH(Ph)), 4.60 (, J = 13.2 Hz, 1 H, NCH_2eq.), 6.58 – 6.62 (m, 4 H, H_{ar}), 6.65 – 6.72 (m, 1 H, H_{ar}), 6.77 (q, J = 7.1, 1 H, HCCH$_3$), 7.13 – 7.19 (m, 1 H, H_{ar}), 7.35 – 7.41 (m, 2 H, H_{ar}), 7.42 – 7.47 (m, 1 H, H_{ar}), 7.55 – 7.63 (m, 2 H, H_{ar}), 8.63 – 8.68 (m, 1 H, H_{ar}). – MS (EI): m/z = 384 $[M]^+$, 229, 153, 127. – $C_{26}H_{28}N_2O$ (384.52): calcd. C 81.21, H 7.34, N 7.29; found C 81.13, H 7.33, N 7.20.

*(3S,4aS)-2-[(1S)-1-Naphthylethyl]-3-phenyloctahydro-1H-pyrido[1,2-c]pyrimidin-1-one (**34**)*

According to GP1 from **33** (25 mg, 0.07 mmol) in AcOH (3 mL) and $NaBH_4$ (49 mg, 1.31 mmol). Colorless oil, 18 mg (67 %). – $[\alpha]_D^{20}$ = 66.5° (*c* = 1.24, $CHCl_3$). – IR (KBr): ν = 3050, 2936, 2854, 1622, 1472, 1447, 1277, 1228, 1191, 806, 783, 731, 701, 644 cm^{-1}. – ^1H NMR (400 MHz, $CDCl_3$): δ = 0.43 (dq, *J* = 3.7/12.3 Hz, 1 H, CH_2), 0.71 – 0.83 (m, 1 H, CH_2), 1.01 – 1.27 (m, 2 H, CH_2), 1.40 – 1.48 (m, 3 H, CH_2), 1.45 (d, *J* = 7.0 Hz, 3 H, HCCH_3), 1.52 (d_{br}, *J* = 13.4 Hz, 1 H, CH_2), 2.58 (dt, *J* = 2.7/12.9 Hz, 1 H, NCH_2ax.), 2.88 (tt, *J* = 3.6/6.3 Hz, 1 H, NC*H*), 4.01 (t, *J* = 4.4 Hz, 1 H, NC*H*(Ph)CH_2), 4.55 (d_{br}, *J* = 12.9 Hz, 1 H, NCH_2eq), 6.51 (q, *J* = 7.0 Hz, 1 H, *H*CCH_3), 7.05 – 7.10 (m, 2 H, H_{ar}), 7.12 – 7.24 (m, 3 H, H_{ar}), 7.25 – 7.29 (m, 1 H, H_{ar}), 7.32 – 7.37 (m, 1 H, H_{ar}), 7.40 – 7.52 (m, 2 H, H_{ar}), 7.72 – 7.77 (m, 1 H, H_{ar}), 7.78 – 7.83 (m, 1 H, H_{ar}), 8.01 – 8.06 (m, 1 H, H_{ar}). – MS (EI): *m/z* = 384 $[M]^+$, 229, 153, 127. – $C_{26}H_{28}N_2O$ (384.52): calcd. C 81.21, H 7.34, N 7.29; found C 81.23, H 7.26, N 7.25.

*(3R,4aR)-3-Phenyloctahydro-1H-pyrido[1,2-c]pyrimidin-1-one (**35**)*

A mixture of **28** (0.32 mg, 0.10 mmol) and Pd/C (10 mg; 10 %) in MeOH (25 mL) was stirred at r. t. under hydrogen for 14 h. After filtration and removal of the solvent *in vacuo* the residue was purified by CC on silica gel (EtOAc / *n*-heptane 3 : 7). Colorless crystals, 15 mg (68 %). – M. p. 176 – 178 °C. – $[\alpha]_D^{20}$ = −64.3° (*c* = 0.3, $CHCl_3$). – IR (KBr): ν = 3192, 2920, 2852, 1644, 1472, 1453, 1362, 1333, 1289, 1264, 1131, 1100, 757, 698 cm^{-1}. – ^1H NMR (400 MHz, $CDCl_3$): δ = 1.15 – 1.29 (m, 1 H, CH_2), 1.29 – 1.51 (m, 2 H, CH_2), 1.69 – 1.87 (m, 4 H, CH_2), 2.13 (dtd, *J* = 2.2/3.5/13.3 Hz, 1 H, NCH(Ph)CH_2), 2.58 (dt, *J* = 3.3/13.1 Hz, 1 H, NCH_2ax.), 3.30 (ddt, *J* = 3.0/3.9/11.2 Hz, 1 H,. NC*H*), 4.47 (dd, *J* = 3.0/11.5 Hz, 1 H, NC*H*(Ph)), 4.50 – 4.58 (m, 1 H, NCH_2eq.), 4.70 (s, 1 H, N*H*), 7.28 – 7.40 (m, 5 H, H_{ar}). – MS (CI): *m/z* = 231 $[M+1]^+$. – $C_{22}H_{26}N_2O$ (230.31): calcd. C 73.01, H 7.88, N 12.16; found C 73.15, H 7.93, N 12.28.

*(3S,4aS)-3-Phenyloctahydro-1H-pyrido[1,2-c]pyrimidin-1-one (**36**)*

A mixture of **32** (0.38 mg, 0.11 mmol) and Pd/C (10 mg; 10 %) in MeOH (20 mL) was stirred at r. t. under hydrogen for 14 h. After filtration and removal of the solvent *in vacuo* the residue was purified by CC on silica gel (EtOAc / *n*-heptane 3 : 7). The spectroscopic data were identical with those of **35**. Colorless crystals, 19 mg (76 %). – M. p. 176 – 178 °C. – $[\alpha]_D^{20}$ = 64.3 (*c* = 0.35, $CHCl_3$). – $C_{22}H_{26}N_2O$ (230.31): calcd. C 73.01, H 7.88, N 12.16; found C 73.18, H 7.97, N 11.90.

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