# Synthesis of 2,6-Disubstituted Piperidine-Bearing α-Amino Acid Side-Chains

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A straightforward synthesis of 2,6-disubstituted piperidines bearing α-amino acid side-chains was developed. Synthesis was based on a Horner–Wadsworth–Emmons condensation of a β-ketophosphonate derived from an α-amino acid residue with a β-homologated aldehyde of an *N*-protected amino acid residue. The generated α-β unsaturated ketones were then reduced, deprotected, and cyclized in a hydrogenation/hydrogenolysis one-pot procedure to yield piperidine moieties. Introduction of a new conformational restriction in the obtained molecules allowed total assignment of the stereocenters by NMR experiments. This assignment allowed us to propose a mechanistic pathway during the cyclization process, explaining the loss of exocyclic carbon-center configuration.


## Introduction

Peptides are usually reported as being poor drug candidates. They do not cross biological barriers well and are subject to enzymatic degradation. For these reasons, great efforts have been made in peptide-based drug design towards the development of a wide range of non-peptidic structural modifications (pseudopeptides, peptidomimetics, conformational-mimetics).[1] On the other hand, small cyclic organic molecules, to which essential pharmacophoric groups can be appended in a suitable way, are frequently used as nonpeptidic scaffolds to stabilize or to probe a putative bioactive conformation.[2] Functionalized heterocyclic compounds such as piperazine,[3] piperidine,[4] or ketopiperazine[5] are very good tools to achieve this challenge and are often found in natural and synthetic bioactive ligands, making them interesting synthetic targets.

We have demonstrated that, in the case of a peptide amide, the amide moiety was not always essential for binding of hormones to their receptors.[6,7] In this case, molecule **B** (Figure 1) could be used as starting material for rigidified molecules. Cyclization through a dimethylene or trimethylene bridge between the carbonyl group of residue *i* and the α-carbon of residue *i*+1 of the C-terminal dipeptide would respectively lead to pyrrolidine (molecule **D**) or piperidine (molecule **C**) moieties which could be interesting tools to probe side-chain orientations in the active conformation.

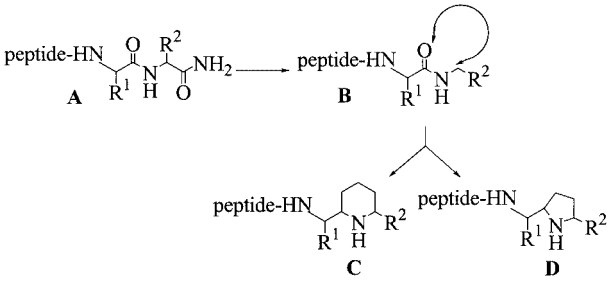
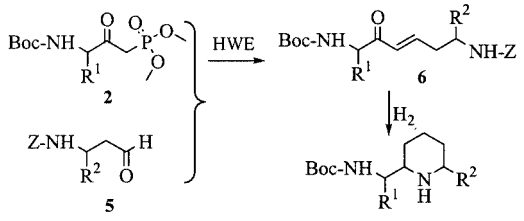



Figure 1. C-terminus-constrained pseudo-peptides

Our current interest in such chemical templates, onto which relevant groups can be appended, led us to describe the preparation of various 2,6-disubstituted piperidine-based scaffolds bearing α-amino acid side-chains.[8] This cyclic platform was designed by introduction of a trimethylene bridge generated through a Horner−Wadsworth−Emmons condensation of an amino acid β-ketophosphonate derivative with an aldehyde of an *N*-protected β-amino acid residue (Scheme 1). This synthetic pathway allowed the introduction of a wide variety of side chains. Furthermore, these heterocycles present two amino functional groups for additional structural diversification and can be useful as plat-




Scheme 1. Synthetic pathway for 2,6-substituted piperidine synthesis

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forms for the design of biologically active peptidomimetics or non-peptide small molecule ligands (Figure 2).

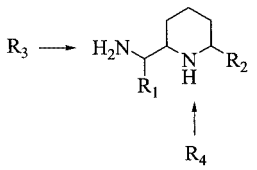
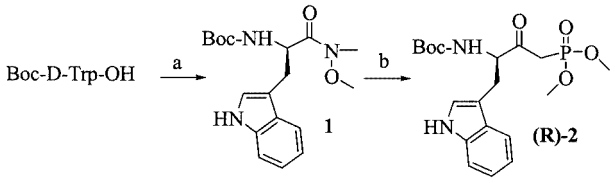


Figure 2. 2,6-Substituted piperidine template

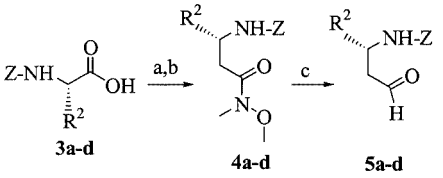
## Results and Discussion

The chosen synthetic pathway for 2,6-disubstituted piperidine derivatives involved two key steps: a Horner−Wadsworth−Emmons (HWE) reaction between two amino acid derivatives **2** and **5** followed by an intramolecular reductive amination (Scheme 1). As an example, a D-Trp α-amino acid residue was selected as the single precursor of **2** but this procedure could be extended to other amino acid residues. β-Ketophosphonate **(*R*)-2** was synthesized in two steps from commercial Boc-D-Trp-OH. Boc-D-Trp-OH was first converted into the Weinreb amide **1** by using BOP[9] as coupling reagent. It was then reacted with a sixfold excess of lithium dimethyl methylphosphonate anion at −78 °C to give enantiopure β-ketophosphonate **(*R*)-2** in good yield (Scheme 2).



(a) HCl,HN(Me)OMe, DIEA, BOP, DCM, 98%;
(b) $LiCH_2PO(OMe)_2$, THF, -78°C, 75%

Scheme 2. Synthesis of β-ketophosphonates



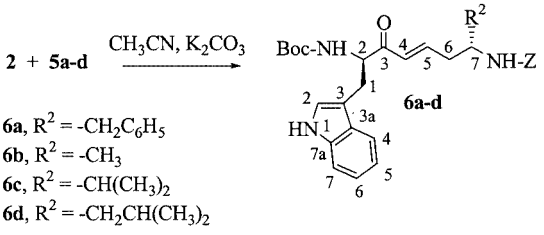
Z = benzyloxycarbonyl
**a**, $R^2 = -CH_2C_6H_5$
**b**, $R^2 = -CH_3$
**c**, $R^2 = -CH(CH_3)_2$
**d**, $R^2 = -CH_2CH(CH_3)_2$

(a) IBCF, NMM, THF, 0°C then $CH_2N_2$ in $Et_2O$;
(b) HN(Me)OMe, $C_6H_5CO_2$,Ag cat, $NEt_3$, THF, 0°C
(c) $LiAlH_4$, 0°C, THF

Scheme 3. Preparation of the aldehyde moiety

Aldehydes **5a−d** (Scheme 3) were prepared in three steps from commercial Z-α-amino acids. These latter were first converted into their corresponding α-diazo ketones via the mixed anhydride method (isobutyl chloroformate, IBCF, in the presence of one equivalent of base, then diazomethane excess). The latter upon treatment with free *N*,*O*-dimethylhydroxylamine, excess of $Et_3N$ and a catalytic amount of silver benzoate in THF yielded Weinreb amides (Z-*N*-protected-β-amino dimethylhydroxamates) **4a−d**.[10]

Z-*N*-protected-β-amino dimethylhydroxamates **4a−d** were treated with $LiAlH_4$ (1.1 equivalent)[11] in THF at 0 °C to yield aldehydes **5a−d** which were treated without purification with **2** (0.9 equivalent) in an HWE reaction (Scheme 4). Olefination proceeded slowly using anhydrous potassium carbonate in $CH_3CN$ at room temperature without decomposition of the aldehyde moiety and gave the expected unsaturated ketones **6a−d** with up to 70% yield after chromatography. The reaction was accelerated using cesium carbonate in $CH_3CN$ and went to completion in less than four hours with similar yields. Olefins **6a−d** were of *E*-configuration as indicated by the large (15.5−15.9 Hz) vicinal coupling constant for the vinyl protons.

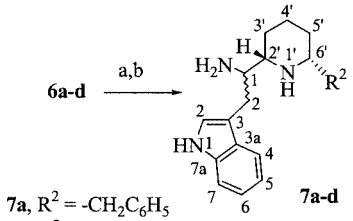


**6a**, $R^2 = -CH_2C_6H_5$
**6b**, $R^2 = -CH_3$
**6c**, $R^2 = -CH(CH_3)_2$
**6d**, $R^2 = -CH_2CH(CH_3)_2$

Scheme 4. Horner−Wadsworth−Emmons condensation

Compounds **6a−d** were hydrogenated overnight at room temperature and 150 psi pressure, using Pd-C as catalyst. In these conditions, removal of the Z protecting group, saturation of the double bond, and reductive amination took place in a one-pot reaction (Scheme 5) and proceeded very cleanly (no side-product could be detected during the formation of the piperidine ring). Boc removal in acidic conditions yielded **7a−d**. This synthetic pathway, HWE condensation followed by cyclization and reductive amination, was described for generation of pipecolic acid derivatives.[12] Starting from enantiomerically pure compound **6**, we expected to obtain a single diastereomer with a cis configuration on the piperidine ring as already described[13] for other piperidine derivatives. Examination of LC-MS of the obtained piperidine compounds revealed the presence of two diastereomers in a ratio of about 60:40 which could be separated after removal of the Boc protecting group by acidolysis (Table 1). Their separations were performed by reversed-phase preparative HPLC and all compounds were characterized and studied by mass spectrometry and $^1H$ and $^{13}C$ NMR spectroscopy, with the exception of **7b**, for which only one pure diastereomer was obtained.




**7a**, $R^2 = -CH_2C_6H_5$
**7b**, $R^2 = -CH_3$
**7c**, $R^2 = -CH(CH_3)_2$
**7d**, $R^2 = -CH_2CH(CH_3)_2$

(a) $H_2$ Pd-C, EtOH, 0.1% AcOH, 150 psi, RT, 12 h;
(b) HCl, AcOEt/MeOH then preparative RP HPLC

Scheme 5. Piperidine ring formation

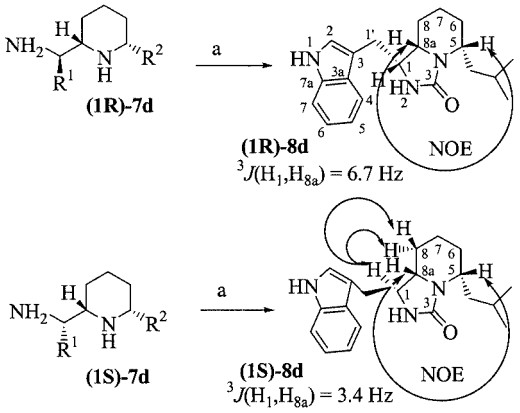
Table 1. Results for the preparation of compounds **6** and **7**

| Entry | 3 | Yield **6** (%) | Yield **7** (%) | HPLC $t_R$ (min)[a] of (1S)-**7**/(1*R*)-**7** | (%) (1*S*)-**7**/(1*R*)-**7** |
|---|---|---|---|---|---|
| a | L-Phe | 63 | 66 | 8.92:9.13 | 40:60[a] |
| b | L -Ala | 68 | 59 | 6.88:6.80 | 34:66[b] |
| c | L -Val | 65 | 71 | 7.45:7.33 | 39:61[c] |
| d | L -Leu | 51 | 71 | 12.10:12.43 | 42:58[a] |
| d′[d] | L -Leu | 37 | 69 | 12.10:12.43 | 57:43[a] |

[a] Determined by RP-HPLC, linear gradient 100% A to 50:50% (A/B) in 15 min, A: 0.1% TFA in water/B: 0.1% TFA in $CH_3CN$. [b] Determined by RP-HPLC, isocratic run 85:15% (A/B). [c] Determined by RP-HPLC, isocratic run 84:16% (A/B). [d] Starting from (*S*)-2.

## Configuration Assignment

Compounds **7a**−**d** contained three asymmetric carbons. Two of them came from the starting amino acid residues and the third one was formed during the cyclization step. The enantiomeric purity of ketophosphonate **(*R*)-2** was confirmed by optical rotation measurements which were in agreement with the literature.[14] Furthermore, its enantiomeric purity was also ascertained by chiral column HPLC analysis of both *R* and *S* synthetic ketophosphonates **2**, which showed an *ee* ≥ 98%. In this reaction care must be taken to keep a low temperature during addition of Weinreb amide **1** to lithium dimethyl methylphosphonate to prevent epimerization. The best conditions for this reaction were the use of *n*-butyllithium (*n*BuLi) as base and THF as solvent. For compounds **5a**−**d**, the Arndt−Eistert homologation is known to proceed with retention of configuration and the generated aldehyde could not racemize by enolization as the aldehyde function was in the β-position of the asymmetric carbon. Furthermore these aldehydes were prepared just before use. Starting from pure **(*R*)-2** and **5a**−**d** compounds, the olefins **6a**−**d** were obtained enantiomerically pure. Hydrogenolysis/hydrogenation and reductive amination steps were then performed. Two diastereomers were obtained and separated as described earlier. NOE effects observed between $H^{2'}$ and $H^{6'}$ (see Scheme 5 for numbering) in the two diastereomers clearly demonstrated that these two protons are in a *cis* disposition towards the piperidine ring. As $C^{6'}$ epimerization has never been observed during such a ring-closure procedure,[12,13,15,16] we assumed that configuration of the starting amino acid derivative **5** was conserved. This allowed us to ascertain the configuration of asymmetric carbons $C^{2'}$ and $C^{6'}$. Unfortunately, it was not possible to determine the configuration of the third asymmetric carbon $C^1$ by NOE experimental analysis. To ascertain its absolute configuration, both diastereomers of **7d** were separately converted into their respective hexahydroimidazo[1,5-*a*]pyridin-3-one derivatives (1*R*)- and (1*S*)-**8d**. Attempts to form cyclic urea with triphosgene as described[2] yielded the expected compound in poor yield and with several side-products. This conversion was then performed using *p*-nitrophenylchloroformate in dilute solution. The *p*-nitrophenylcarbamate formation was followed by TLC. After its completion, a catalytic amount of DMAP was added to start cyclization. It was achieved overnight and led to cleaner compounds.



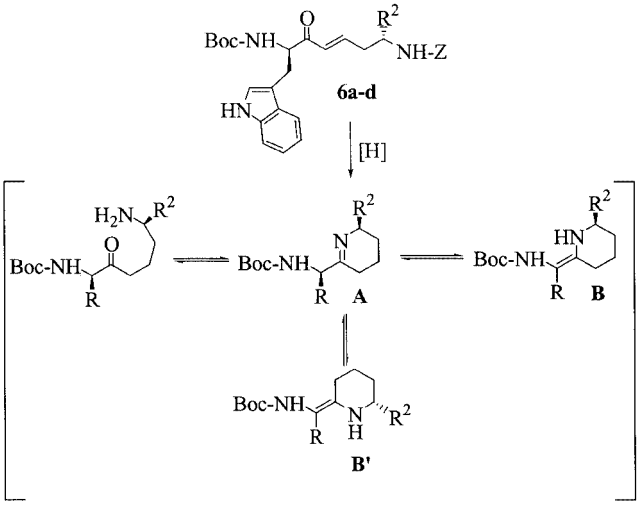

(a) *p*-nitrophenylchloroformate, NMM, DCM, DMAP

Scheme 6. Configuration assignment

The observed NOE effects and the coupling constants in the $^1H$ NMR spectra of compounds **8d** allowed the unequivocal assignment of the absolute configuration at $C^1$ in each epimer (Scheme 6). Indeed, in the major compound, a NOE effect could be observed between $H^{8a}$ and $H^5$ and the $^3J(H^{8a}\text{-}H^1)$ coupling constant was 6.7 Hz indicating a *cis* disposition between $H^1$, $H^5$, and $H^{8a}$ and a configuration (1*R*,8-*aS*,5*R*) for this isomer. In the minor compound, a NOE effect between $H^{8a}$ and $H^5$ and the $^3J(H^{8a}\text{-}H^1)$ coupling constant of 3.4 Hz indicated a trans disposition between $H^1$ and $H^{8a}$ and a configuration (1*S*,8-*aS*,5*R*) for this isomer. Furthermore, in this minor isomer, two extra NOE effects were observed between $H^1$ and the two $H^8$ protons confirming the *trans* disposition between $H^1$ and $H^{8a}$. These results clearly demonstrated that the hydrogenation proceeded via a syn addition which is always imposed by the $R^2$ group orientation. These results confirmed the epimerization at $C^1$ which could be explained by the equilibrium between the A imine and B or B′ enamines (Scheme 7). Such an enamine−imine equilibrium has already been de-

scribed for cyclic structures.[16] All these data allowed attribution of the (1*R*,2′*S*,6′*R*) configuration to the major diastereoisomer of **7d** and the (1*S*,2′*S*,6′*R*) configuration to the minor diastereoisomer of **7d**. By analogy, as in all compounds **7a**−**d** the $C^1$ carbon is bearing the same substituent and the $R^2$ groups are of the same nature, the same configurations were assigned to the major and minor compounds **7a**−**d**. All ratios (1*R*)/(1*S*)-**7a**−**d** were found to be around 60:40% indicating: (i) the minor influence of the $R^2$ group in epimerization at $C^1$; (ii) that the formation of the enamine form must be slow compared to hydrogenation of the imine form, excluding a 50:50% ratio.




Scheme 7. Proposed stereochemical course of the hydrogenation/cyclization step

Olefin **6d**′ (2*S*,4*E*,7*S*) [diastereoisomer of **6d** (2*R*,4*E*,7*S*)] was synthesized from β-ketophosphonate **(*S*)-2** and β-aminoaldehyde **5d** and submitted to the hydrogenation/cyclization step. After removal of the Boc protecting group, two diastereoisomers **(1*R*)-/(1*S*)-7d**′ were obtained. They showed identical physico-chemical data to **(1*R*)-** and **(1*S*)-7d** and the (1*R*)/(1*S*) ratio was the opposite to the component obtained previously starting from D-Trp residue. This result validated the proposed equilibrium imine/enamine during the hydrogenation/cyclization step leading to epimerization at $C^1$ and the fact that formation of the enamine form is slower than hydrogenation of the imine form.

## Conclusion

We have developed a methodology for synthesizing piperidines incorporating two amino acid side-chains. The cyclization step was performed by reductive amination of δ-amino-ketones **6** concurrently with deprotection of the amine moiety and reduction of the double bond. During ring closure, epimerization occurred at the $C^1$ center. We proposed an equilibrium between imine and enamine forms that led to the partial loss of $C^1$ stereo-integrity. NMR analysis of bicyclic constrained derivatives **8d** allowed attribution of the absolute configuration of both diastereomers. These piperidine derivatives bearing α-amino acid side-chains should find general interest in the conformational analysis of bioactive peptido-mimetics and should be useful templates.

On the other hand, Michael 1,4-additions to the α-β unsaturated δ-amino ketones could also provide additional diversity on the heterocyclic derivatives. This present methodology is actually used in our laboratory for pyrrolidine derivative synthesis starting from N-protected α-aminoaldehydes instead of N-protected β-aminoaldehydes (Figure 1, compound **D**).

## Experimental Section

**General Remarks:** All reagents were of commercial quality. Solvents were dried and purified by standard methods. Analytical TLC was performed on aluminum sheets coated with a 0.2-mm layer of silica gel 60 $F_{254}$. Silica gel 60 (40−63 μm) was used for flash chromatography. $^1H$, $^{13}C$, and $^{31}P$ NMR spectra were recorded in [$D_6$]DMSO at 400, 100, and 100 MHz respectively at 300 K. $H_3PO_4$ was used as external reference for $^{31}P$ NMR spectra. Chemical shifts were reported as δ values (ppm) indirectly referenced to the solvent signal. $^1H$ NMR assignments were made by means of homonuclear H-H correlations (COSY) when needed and $^{13}C$ NMR assignments made by means of heteronuclear H-C correlations (HMQC and HMBC when needed). Mass spectra were recorded on a Platform II (Micromass, Manchester, UK) quadrupole mass spectrometer operating at an ionization potential of 30 eV by positive ES fitted with an electrospray interface and coupled with an Alliance Waters LC. HR-Mass spectra were recorded on a JEOL SX 102 spectrometer (FAB positive mode) using NBA (3-nitrobenzylic acid) or GT (glycerol-thioglycerol) as the matrix. RP-HPLC analysis were performed on a $RPC_{18}$ SymmetryShield™ (4.6 × 50 mm, 3.5 μm) from Waters with a flow rate of 1 mL/min and using a tunable UV detector set at 214 nm. Solutions of 0.1% TFA in $H_2O$ (solvent A) and of 0.1% TFA in $CH_3CN$ (solvent B) were used as mobile phases. Preparative RP-HPLC was performed on $C_{18}$ Delta-Pak™ (40 × 100 mm, 15 μm, 100 Å) from Waters with a flow rate of 50 mL/min and using a tunable UV detector set at 214 nm. Solvents A and B were used as mobile phases. Optical rotations were measured at 589 nm on a Perkin−Elmer 341 polarimeter. Chiral HPLC analyses were performed on a Chiralcel OJ column at 30 °C with a flow rate of 1 mL/min, detection at 214 nm and using a 80:20 (v/v) solution of hexane/2-propanol as mobile phase.

**(3*R*)-3-(*tert*-Butyloxycarbonylamino)-1-(dimethoxyphosphoryl)-4-(3-indolyl)butan-2-one [(*R*)-2]:** $MePO(OMe)_2$ (5.57 g, 44.9 mmol) was dissolved in THF (30 mL), cooled to −78 °C, and then treated with *n*BuLi (1.6 M in hexane, 25.7 mL, 41.1 mmol), maintaining the temperature below −70 °C. The reaction mixture was stirred for 10 min before adding dropwise a precooled solution of Boc-D-Trp-$N(CH_3)O(CH_3)$ (2.6 g) dissolved in THF (10 mL). The reaction mixture was stirred at −70 °C for 30 min before the reaction was quenched with saturated $NH_4Cl$. The resulting mixture was extracted with EtOAc and the organic layer washed with brine, dried with sodium sulfate, and concentrated in vacuo. The residue was purified by flash chromatography (elution EtOAc) to yield the title compound as a colorless oil (2.31 g, 75%). $R_f$ = 0.30 (EtOAc); $t_R$ 17.450 min (chiral HPLC). $[\alpha]_D^{20}$ = +26.3 (*c* = 1.2, MeOH). $^1H$ NMR: δ = 1.31 (s, 9 H), 2.90 (dd, *J* = 14.7, *J* = 9.3 Hz, 1 H), 3.20 (dd, *J* = 14.8, *J* = 4.6 Hz, 1 H), 3.40 (d, *J* = 21.3 Hz, 2 H), 3.63 (d, *J* = 11.2 Hz, 6 H), 4.30 (m, 1 H), 6.95 (t, *J* = 7.2 Hz, 1 H),

7.05 (t, $J$ = 7.2 Hz, 1 H), 7.11 (br. s, 1 H), 7.16 (d, $J$ = 8.0 Hz, 1 H), 7.30 (d, $J$ = 7.9 Hz, 1 H), 7.55 (d, $J$ = 7.6 Hz, 1 H), 10.82 (br. s, 1 H). $^{13}$C NMR: δ = 25.9 (s), 28.96 (s,), 37.3 (d, $J_{C,P}$ = 129.5 Hz), 53.4 (d, $J_{C,P}$ = 5.9 Hz), 53.4 (d, $J_{C,P}$ = 6.3 Hz), 61.8 (d, $J_{C,P}$ = 3.5 Hz), 80.0 (s), 110.7 (s), 112.2 (s), 2 × 119.2 (s), 121.8 (s), 124.6 (s), 128.1 (s), 137.0 (s), 156.2 (s), 202.4 (d, $J_{C,P}$ = 6.3 Hz) ppm. $^{31}$P NMR: δ = 24.5 ppm. MS (ES): $m/z$ = 311.0 [M + H − 100]$^+$, 355.1 [M + H − 56]$^+$, 411.1 [M + H]$^+$, 433.1 [M + Na]$^+$, 821.2 [2 M + H]$^+$, 843.1 [2 M + Na]$^+$.

**(3*S*)-3-(*tert*-Butyloxycarbonylamino)-1-(dimethoxyphosphoryl)-4-(3-indolyl)butan-2-one [(*S*)-2]:** $t_R$ 22.250 min (chiral HPLC). $[\alpha]_D^{20}$ = −24.6 ($c$ = 0.9, MeOH).

**General Procedure for the Synthesis of Aminoalkyl-α,β-unsaturated Ketones 6a−d:** $AlLiH_4$ (1.54 mmol) was added to a stirred solution of **4a**−**d** (1.46 mmol) in anhydrous THF (10 mL) placed in an ice bath. After 10 min, excess hydride was quenched by addition of a 1 M $KHSO_4$ aqueous solution and the expected aldehydes **5a**−**d** were extracted with EtOAc. The organic layers were washed with 1 M $KHSO_4$ and brine, dried with $Na_2SO_4$, and concentrated under reduced pressure. **5a**−**d** were used in the next step without further purification. **5a**−**d** and β-ketophosphonate **2** (1.19 mmol) were dissolved in acetonitrile (5 mL) then $K_2CO_3$ (1.82 mmol) was added to the reaction mixture which was stirred at room temperature for 16 h. The reaction mixture was diluted with EtOAc and quenched by addition of a 1 M $KHSO_4$ solution. The organic layers were washed with 1 M $KHSO_4$ solution, brine, dried with sodium sulfate, and concentrated in vacuo. The residue was purified by flash chromatography on a silica-gel column to yield title compounds **6a**−**d** as colorless oils. Structures of compounds **6a**−**d** were checked by NMR and mass spectroscopy; yields are reported in Table 1.

**(2*R*,4*E*,7*R*)-2-(*tert*-Butyloxycarbonylamino)-7-(benzyloxycarbonylamino)-1-(3-indolyl)-8-phenyloct-4-en-3-one (6a):** $R_f$ = 0.42 (EtOAc/hexane, 3:7). $[\alpha]_D^{21}$ = −23.1 ($c$ = 0.91, MeOH). $^1$H NMR: δ = 1.31 (s, 9 H, Boc), 2.39 (m, 2 H, 6-H), 2.71 (m, 2 H, 8-H), 2.88 (dd, $J$ = 14.8, $J$ = 9.2 Hz, 1 H, 1-H), 3.10 (dd, $J$ = 14.8, $J$ = 4.6 Hz, 1 H, 1-H), 3.84 (m, 1 H, 7-H), 4.46 (m, 1 H, 2-H), 4.91 [d, $J$ = 12.2 Hz, 1 H, -$CH_2$-(Z)], 4.98 [d, $J$ = 12.2 Hz, 1 H, -$CH_2$-(Z)], 6.41 (d, $J$ = 15.7 Hz, 1 H, 4-H), 6.88 (m, 1 H, 5-H), 6.96 (t, $J$ = 7.8 Hz, 1 H, 5-H indole), 7.03 (d, $J$ = 9.0 Hz, 1 H, NH urethane Boc), 7.05 (t, $J$ = 7.8 Hz, 1 H, 6-H indole), 7.11 (s, 1 H, 2-H indole), 7.15−7.30 (m, 10 H ar), 7.32 (d, $J$ = 7.8 Hz, 1 H, 7-H indole), 7.37 (d, $J$ = 8.5 Hz, 1 H, NH urethane Z), 7.53 (d, $J$ = 7.8 Hz, 1 H, 4-H indole), 10.80 (s, 1 H, NH indole) ppm. $^{13}$C NMR: δ = 25.8 (C1), 28.1 ($CH_3$, Boc), 37.2 (C6), 39.9 (C8), 51.5 (C7), 58.8 (C2), 64.9 ($CH_2$,Z), 78.1 (C, Boc), 109.9 (C3 indole), 111.3 (C7 indole), 118.2 (C4 and C5 indole), 120.8 (C6 indole), 123.6 (C2 indole), 126.0 (C ar), 127.2 (C3a indole), 127.3 (2 C ar), 127.5 (C ar), 128.1 (2 C ar), 128.2 (2 C ar), 128.4 (C4), 129.1 (2 C ar), 136.0 (C7a indole), 137.1 (C ar), 138.6 (C ar), 144.1 (C5), 155.2 and 155.5 [-NH-*C*(O)-O- (Z and Boc)], 197.8 (C3) ppm. MS (ES): $m/z$ = 582.4 [M + H]$^+$; 526.2 [M + H − 56]$^+$, 482.3 [M + H − 100]$^+$.

**(2*R*,4*E*,7*S*)-2-(*tert*-Butyloxycarbonylamino)-7-(benzyloxycarbonylamino)-1-(3-indolyl)oct-4-en-3-one (6b):** $R_f$ = 0.11 (EtOAc/hexane, 3:7). $[\alpha]_D^{21}$ = −23.3 ($c$ = 1.0, MeOH). $^1$H NMR: δ = 1.05 (d, $J$ = 6.4 Hz, 3 H, 8-H), 1.33 (s, 9 H, Boc), 2.33 (m, 2 H, 6-H), 2.89 (dd, $J$ = 14.8, $J$ = 9.2 Hz, 1 H, 1-H), 3.10 (dd, $J$ = 14.8, $J$ = 4.7 Hz, 1 H, 1-H), 3.66 (m, 1 H, 7-H), 4.45 (m, 1 H, 2-H), 5.00 [m, 2 H, -$CH_2$-(Z)], 6.39 (d, $J$ = 15.7 Hz, 1 H, 4-H), 6.82 (m, 1 H, 5-H), 6.97 (t, $J$ = 7.8 Hz, 1 H, 5-H indole), 7.04 (m, 1 H, NH urethane Boc), 7.07 (t, $J$ = 7.8 Hz, 1 H, 6-H indole); 7.11 (s, 1 H, 2-H indole), 7.26−7.37 (m, 5H ar), 7.29 (m, 1 H, NH urethane Z), 7.33 (m, 1 H, 7-H indole), 7.53 (d, $J$ = 7.8 Hz, 1 H, 4-H indole), 10.80 (s, 1 H, NH indole) ppm. $^{13}$C NMR: δ = 20.4 (C8), 25.8 (C1), 28.1 ($CH_3$, Boc), 38.9 (C6), 45.8 (C7), 58.6 (C2), 65.1 ($CH_2$,Z), 78.1 (C, Boc), 109.9 (C3 indole), 111.3 (C7 indole), 118.2 (C4 and C5 indole), 120.8 (C6 indole), 123.6 (C2 indole), 127.1 (C3a indole), 127.5 (C ar), 127.6 (2C ar, Z), 128.2 (2C ar, Z), 128.4 (C4), 136.0 (C7a indole), 137.1 (C ar), 144.2 (C5), 155.2 and 155.4 [-NH-*C*(O)-O-, Z and Boc], 197.9 (C3) ppm. MS (ES): $m/z$ = 528.3 [M + Na]$^+$, 506.1 [M + H]$^+$, 450.3 [M + H − 56]$^+$, 406.1 [M + H − 100]$^+$.

**(2*R*,4*E*,7*R*)-2-(*tert*-Butyloxycarbonylamino)-7-(benzyloxycarbonylamino)-1-(3-indolyl)-8-methylnon-4-en-3-one (6c):** $R_f$ = 0.34 (EtOAc/hexane, 3:7). $[\alpha]_D^{21}$ = −22.2 ($c$ = 0.80, MeOH). $^1$H NMR: δ = 0.84 (d, $J$ = 6.4 Hz, 3 H, 9-H), 0.86 (d, $J$ = 6.4 Hz, 3 H, 9-H), 1.33 (s, 9 H, Boc), 1.67 (m, 1 H, 8-H), 2.28 (m, 1 H, 6-H), 2.39 (dd, $J$ = 14.0, $J$ = 6.7 Hz, 1 H, 6-H), 2.87 (dd, $J$ = 14.6, $J$ = 9.2 Hz, 1 H, 1-H), 3.10 (dd, $J$ = 14.6, $J$ = 4.6 Hz, 1 H, 1-H), 3.45 (m, 1 H, 7-H), 4.45 (m, 1 H, 2-H), 4.96 [d, $J$ = 12.5 Hz, 1 H, -$CH_2$-(Z)], 5.02 [d, $J$ = 12.5 Hz, 1 H, -$CH_2$-(Z)], 6.43 (d, $J$ = 15.7 Hz, 1 H, 4-H), 6.85 (m, 1 H, 5-H), 6.98 (t, $J$ = 7.8 Hz, 1 H, 5-H indole), 7.00 (m, 1 H, NH urethane Boc), 7.06 (t, $J$ = 7.8 Hz, 1 H, 6-H indole), 7.11 (s, 1 H, 2-H indole), 7.23 (d, $J$ = 9.3 Hz, 1 H, NH urethane Z), 7.33 (d, $J$ = 7.8 Hz, 1 H, 7-H indole), 7.26−7.37 (m, 5H ar), 7.54 (d, $J$ = 7.8 Hz, 1 H, 4-H indole), 10.80 (s, 1 H, NH indole) ppm. $^{13}$C NMR: δ = 18.0 (C9), 19.0 (C9), 25.8 (C1), 28.1 ($CH_3$, Boc), 31.6 (C8), 34.5 (C6), 55.2 (C7), 58.8 (C2), 65.0 ($CH_2$,Z), 78.1 (C, Boc), 109.9 (C3 indole), 111.3 (C7 indole), 118.2 (C4 and C5 indole), 120.8 (C6 indole), 123.6 (C2 indole), 127.2 (C3a indole), 127.4 (2 C ar, Z), 127.6 [1 C ar (Z)], 128.1 (C4), 128.2 (2 C ar, Z), 136.0 (C7a indole), 137.2 (C ar), 144.9 (C5), 155.2 and 156.0 [-NH-*C*(O)-O- (Z and Boc)], 197.8 (C3) ppm. MS (ES): $m/z$ = 556.3 [M + Na]$^+$, 534.2 [M + H]$^+$, 478.1 [M + H − 56]$^+$, 434.0 [M + H − 100]$^+$.

**(2*R*,4*E*,7*S*)-2-(*tert*-Butyloxycarbonylamino)-7-(benzyloxycarbonylamino)-1-(3-indolyl)-9-methyldec-4-en-3-one (6d):** $R_f$ = 0.43 (EtOAc/hexane, 3:7). $[\alpha]_D^{21}$ = −32.2 ($c$ = 1.0, MeOH). $^1$H NMR: δ = 0.86 (d, $J$ = 6.4 Hz, 6 H, 10-H), 1.17 (m, 1 H, 8-H), 1.33 (s, 9 H, Boc), 1.37 (m, 1 H, 8-H), 1.61 (m, 1 H, 9-H), 2.33 (m, 2 H, 6-H), 2.88 (dd, $J$ = 14.8, $J$ = 9.0 Hz, 1 H, 1-H), 3.11 (dd, $J$ = 14.8, $J$ = 4.7 Hz, 1 H, 1-H), 3.69 (m, 1 H, 7-H), 4.45 (m, 1 H, 2-H), 4.99 [m, 2 H, -$CH_2$-(Z)], 6.41 (d, 1 H, 15.6 Hz, 4-H), 6.85 (m, 1 H, 5-H), 6.98 (t, 1 H, 7.8 Hz, 5-H indole), 7.02 (d, $J$ = 8 Hz, 1 H, NH urethane Boc), 7.06 (t, $J$ = 7.8 Hz, 1 H, 6-H indole), 7.12 (s, 1 H, 2-H indole), 7.22 (d, $J$ = 8.8 Hz, 1 H, NH urethane Z), 7.34 (d, $J$ = 7.8 Hz, 1 H, 7-H indole), 7.26−7.37 (m, 5 H ar), 7.53 (d, 1 H, 7.8 Hz, 4-H indole), 10.80 (s, 1 H, NH indole) ppm. $^{13}$C NMR: δ = 21.7 (C10), 23.0 (C10), 24.2 (C9), 25.8 (C1), 28.1 ($CH_3$, Boc), 38.3 (C6), 43.3 (C8), 48.0 (C7), 58.7 (C2), 65.0 ($CH_2$,Z), 78.1 (C, Boc), 109.9 (C3 indole), 111.3 (C7 indole), 118.2 (C4 and C5 indole), 120.8 (C6 indole), 123.6 (C2 indole), 127.2 (C3a indole), 127.5 (2C ar, Z), 127.6 (C ar, Z), 128.2 (C4), 128.2 (2 C ar), 136.0 (C7a indole), 137.2 (C ar), 144.4 (C5), 155.2 and 155.7 [−NH-*C*(O)-O-(Z and Boc)], 197.8 (C3) ppm. MS (ES): $m/z$ = 548.3 [M + H]$^+$, 492.3 [M + H − 56]$^+$, 448.1 [M + H − 100]$^+$.

**(2*S*,4*E*,7*S*)-2-(*tert*-Butyloxycarbonylamino)-7-(benzyloxycarbonylamino)-1-(3-indolyl)-9-methyldec-4-en-3-one (6d′):** $R_f$ = 0.40 (EtOAc/hexane, 3:7). $[\alpha]_D^{21}$ = −3.9 ($c$ = 1.00,MeOH). $^1$H NMR: δ = 0.86 (d, $J$ = 6.4 Hz, 6 H, 10-H), 1.17 (m, 1 H, 8-H), 1.33 (s, 9 H, Boc), 1.37 (m, 1 H, 8-H), 1.61 (m, 1 H, 9-H), 2.33 (m, 2 H, 6-H), 2.87 (dd, $J$ = 14.8, $J$ = 9.0 Hz, 1 H, 1-H), 3.09 (dd, $J$ = 14.8, $J$ = 4.7 Hz, 1 H, 1-H), 3.69 (m, 1 H, 7-H), 4.45 (m, 1 H, 2-H), 4.99 [m, 2 H, -$CH_2$-(Z)], 6.38 (d, 1 H, 15.6 Hz, 4-H), 6.85 (m, 1 H,

5-H), 6.98 (t, 1 H, 7.8 Hz, 5-H indole), 7.02 (d, $J$ = 8 Hz, 1 H, NH urethane Boc), 7.06 (t, $J$ = 7.8 Hz, 1 H, 6-H indole), 7.12 (s, 1 H, 2-H indole), 7.22 (d, $J$ = 8.8 Hz, 1 H, NH urethane Z), 7.34 (d, $J$ = 7.8 Hz, 1 H, 7-H indole), 7.26−7.37 (m, 5H ar), 7.53 (d, 1 H, 7.8 Hz, 4-H indole), 10.80 (s, 1 H, NH indole) ppm. $^{13}$C NMR: δ = 21.7 (C10), 23.0 (C10), 24.2 (C9), 25.8 (C1), 28.1 ($CH_3$, Boc), 38.3 (C6), 43.3 (C8), 48.0 (C7), 58.7 (C2), 65.0 ($CH_2$, Z), 78.1 (C, Boc), 109.9 (C3 indole), 111.3 (C7 indole), 118.2 (C4 and C5 indole), 120.8 (C6 indole), 123.6 (C2 indole), 127.2 (C3a indole), 127.5 (2 C ar, Z), 127.6 (C ar, Z), 128.2 (C4), 128.2 (2 C ar), 136.0 (C7a indole), 137.2 (C ar), 144.4 (C5), 155.2 and 155.7 [-NH-*C*(O)-O- (Z and Boc)], 197.8 (C3) ppm. MS (ES): *m*/*z* = 548.4 [M + H]$^+$, 492.2 [M + H − 56]$^+$, 448.0 [M + H − 100]$^+$.

**General Procedure for the Synthesis of 2,6-Disubstituted Piperidine 7a−d:** Compounds **6a−d** (0.40 mmol) were dissolved in a 0.1% AcOH/ethanol solution (25 mL). Solutions were placed in a Parr apparatus and a catalytic amount of 10% Pd/C was added. The Parr apparatus was purged several times and then filled with $H_2$ at 150 psi pressure. After 12 h, the reaction mixtures were filtered through celite and the filtrates evaporated under reduced pressure. Residues were treated with a 2 M HCl EtOAc/MeOH solution (10 mL) for 1 h for Boc deprotection. The reaction mixtures were evaporated and the residues were purified by RP-HPLC and then lyophilized to yield **7a−d** as their trifluoroacetate salts (white foam). The significant analytical and spectroscopic data of these compounds are summarized in Table 2; yields are reported in Table 1.

Table 2. Selected $^1$H and $^{13}$C NMR chemical shift (δ) of **7**-piperidine derivatives

| | | (1*R*)-**7a−d** | | | (1*S*)-**7a−d** | | | |
|---|---|---|---|---|---|---|---|---|
| | | $^1$H NMR (δ) | | $^{13}$C NMR (δ) | $^1$H NMR (δ) | | $^{13}$C NMR (δ) | |
| **a** | 2′-H | 3.39 | C2′ | 57.4 | 2′-H | 3.56 | C2′ | 58.4 |
| | 3′-H | 1.55/2.10 | C3′ | 21.3 | 3′-H | 1.65/2.02 | C3′ | 21.6 |
| | 4′-H | 1.42/1.85 | C4′ | 21.3 | 4′-H | 1.42/1.89 | C4′ | 21.6 |
| | 5′-H | 1.38/1.60 | C5′ | 26.8 | 5′-H | 1.49/1.65 | C5′ | 26.8 |
| | 6′-H | 3.36 | C6′ | 58.4 | 6′-H | 3.42 | C6′ | 59.3 |
| **b**[a] | 2′-H | 3.33 | C2′ | 57.1 | | | | |
| | 3′-H | 1.52/2.09 | C3′ | 21.2 | | | | |
| | 4′-H | 1.49/1.89 | C4′ | 21.7 | | | | |
| | 5′-H | 1.39/1.81 | C5′ | 29.5 | | | | |
| | 6′-H | 3.17 | C6′ | 53.8 | | | | |
| **c** | 2′-H | 3.39 | C2′ | 58.3 | 2′-H | 3.51 | C2′ | 59.5 |
| | 3′-H | 1.57/2.11 | C3′ | 21.0 | 3′-H | 1.69/2.07 | C3′ | 22.9 |
| | 4′-H | 1.50/1.95 | C4′ | 21.7 | 4′-H | 1.49/1.96 | C4′ | 22.0 |
| | 5′-H | 1.36/1.80 | C5′ | 23.1 | 5′-H | 1.45/1.86 | C5′ | 23.3 |
| | 6′-H | 2.98 | C6′ | 63.1 | 6′-H | 2.99 | C6′ | 64.1 |
| **d** | 2′-H | 3.37 | C2′ | 57.2 | 2′-H | 3.54 | C2′ | 58.4 |
| | 3′-H | 1.53/2.10 | C3′ | 21.3 | 3′-H | 1.63/2.03 | C3′ | 22.2 |
| | 4′-H | 1.55/1.90 | C4′ | 21.4 | 4′-H | 1.54/1.94 | C4′ | 21.8 |
| | 5′-H | 1.28/1.89 | C5′ | 27.6 | 5′-H | 1.40/1.94 | C5′ | 27.7 |
| | 6′-H | 3.14 | C6′ | 55.9 | 6′-H | 3.19 | C6′ | 56.9 |

[a] Only the *R* isomer was obtained pure for NMR analysis.

**(1*S*,2*S*,6*R*)-1-[6-Benzylpiperidin-2-yl]-2-(1*H*-indol-3-yl)-ethylamine, TFA Salt (First Eluted) [(1*S*)-7a]:** $^1$H NMR: δ = 1.42 (m, 1 H, 4′-H), 1.49 (m, 1 H, 5′-H), 1.65 (m, 2 H, 3′-H, 5′-H), 1.89 (m, 1 H, 4′-H), 2.02 (m, 1 H, 3′-H), 2.78 (dd, $J$ = 12.8, $J$ = 10.7 Hz, 1 H, -C$H_2$-Ph), 2.91 (dd, $J$ = 14.8, $J$ = 11.8 Hz, 1 H, 2-H), 3.22 (dd, $J$ = 12.8, $J$ = 2.3 Hz, 1 H, -C$H_2$-Ph), 3.36 (dd, $J$ = 14.8, $J$ = 2.0 Hz, 1 H, 2-H), 3.42 (m, 1 H, 6′-H), 3.56 (m, 1 H, 2′-H), 3.77 (m, 1 H, 1-H), 7.05 (t, 1 H,, $J$ = 7.8 Hz, 5-H indole), 7.14 (t, $J$ = 7.8 Hz, 1 H, 6-H indole), 7.28 (s, 1 H, 2-H indole), 7.28−7.40 (m, 5H ar), 7.42 (d, $J$ = 7.8 Hz, 1 H, 7-H indole), 7.70 (d, $J$ = 7.8 Hz, 1 H, 4-H indole), 8.16 (br. s, 2 H, primary amine), 8.87 (br. s, 1 H, secondary amine), 9.41 (br. s, 1 H, secondary amine), 11.07 (s, 1 H, NH indole) ppm. $^{13}$C NMR: δ = 21.6 (C3′, C4′), 23.5 (C2), 26.8 (C5′), 38.8 (-*C*$H_2$-Ph), 51.6 (C1), 58.4 (C2′), 59.3 (C6′), 107.0 (C3 indole), 111.6 (C7 indole), 118.3 (C4 indole), 118.4 (C5 indole), 121.3 (C6 indole), 124.8 (C2 indole), 126.6 (C3a indole), 126.9 (C ar), 128.6 (2C ar), 129.3 (2C ar), 136.0 (C ar), 136.5 (C7a indole) ppm. MS (ES): *m*/*z* = 334.4 [M + H]$^+$. HRMS calcd. for $C_{22}H_{27}N_3$ [MH$^+$] 334.2283, found 334.2293.

**(1*R*,2*S*,6*R*)-1-[6-Benzylpiperidin-2-yl]-2-(1*H*-indol-3-yl)ethylamine, TFA Salt [(1*R*)-7a]:** $^1$H NMR: δ = 1.38 (m, 1 H, 5′-H), 1.42 (m, 1 H, 4′-H), 1.55 (m, 1 H, 3′-H), 1.60 (m, 1 H, 5′-H), 1.85 (m, 1 H, 4′-H), 2.10 (m, 1 H, 3′-H), 2.67 (dd, $J$ = 12.7, $J$ = 10.4 Hz, 1 H, -C$H_2$-Ph), 3.07 (dd, $J$ = 12.7, $J$ = 3.5 Hz, 1 H, -C$H_2$-Ph), 3.10 (d, $J$ = 7.5 Hz, 2 H, 2-H), 3.36 (m, 1 H, 6′-H), 3.39 (m, 1 H, 2′-H), 3.83 (m, 1 H, 1-H), 7.04 (t, $J$ = 7.8 Hz, 1 H, 5-H indole), 7.13 (t, $J$ = 7.8 Hz, 1 H, 6-H indole), 7.21 (d, $J$ = 7.6 Hz, 2 H, ar), 7.27 (m, 1 H, ar), 7.32 (s, 1 H, 2-H indole), 7.33 (t, $J$ = 7.6 Hz, 2 H, ar), 7.41 (d, $J$ = 7.8 Hz, 1 H, 7-H indole), 7.63 (d, $J$ = 7.8 Hz, 1 H, 4-H indole), 8.28 (br. s, 2 H, primary amine), 8.48 (br. s, 1 H, secondary amine), 8.98 (br. s, 1 H, secondary amine), 11.08 (s, 1 H, NH indole) ppm. $^{13}$C NMR: δ = 21.3 (C3′, C4′), 25.8 (C2), 26.8 (C5′), 38.9 (-*C*$H_2$-Ph), 52.5 (C1), 57.4 (C2′), 58.4 (C6′), 107.2 (C3 indole), 111.6 (C7 indole), 118.1 (C4 indole), 118.6 (C5 indole), 121.3 (C6 indole), 124.8 (C2, indole), 126.8 (C3a indole), 126.9 (C ar), 128.5 (2C ar), 129.2 (2C ar), 135.7 (C ar), 136.4 (C7a indole) ppm. MS (ES): *m*/*z* = 334.5 [M + H]$^+$. HRMS calcd. for $C_{22}H_{27}N_3$ [MH$^+$] 334.2283, found 334.2293.

**(1*R*,2*S*,6*S*)-2-(1*H*-Indol-3-yl)-1-[6-methylpiperidin-2-yl]ethylamine, TFA Salt [(1*R*)-7b]:** $^1$H NMR: δ = 1.22 (d, $J$ = 6.4 Hz, 3 H, -C$H_3$), 1.39 (m, 1 H, 5′-H), 1.49 (m, 1 H, 4′-H), 1.52 (m, 1 H, 3′-H), 1.81 (m, 1 H, 5′-H), 1.89 (m, 1 H, 4′-H), 2.09 (m, 1 H, 3′-H), 3.09 (m, 2 H, 2-H), 3.17 (m, 1 H, 6′-H), 3.33 (m, 1 H, 2′-H), 3.77 (m, 1 H, 1-H), 7.03 (t, $J$ = 7.9 Hz, 1 H, 5-H indole), 7.12 (t, $J$ = 7.9 Hz, 1 H, 6-H, indole), 7.31 (s, 1 H, 2-H indole), 7.40 (d, $J$ = 7.9 Hz, 1 H, 7-H indole), 7.61 (d, $J$ = 7.9 Hz, 1 H, 4-H indole), 8.32 (br. s, 3 H, amine), 8.87 (br. s, 1 H, secondary amine), 11.08 (s, 1 H, NH indole) ppm. $^{13}$C NMR: δ = 18.8 (-*C*$H_3$), 21.2 (C3′), 21.7 (C4′), 25.8 (C2), 29.5 (C5′), 52.6 (C1), 53.8 (C6′), 57.1 (C2′), 107.3 (C3 indole), 111.6 (C7 indole), 118.1 (C4 indole), 118.5 (C5 indole), 121.3 (C6 indole), 124.7 (C2, indole), 126.7 (C3a indole), 136.4 (C7a indole) ppm. MS (ES): *m*/*z* = 258.3 [M + H]$^+$. HRMS calcd. for $C_{16}H_{23}N_3$ [MH$^+$] 258.1970, found 258.1951.

**(1*R*,2*S*,6*R*)-2-(1*H*-Indol-3-yl)-1-[6-isopropylpiperidin-2-yl]ethylamine, TFA Salt (First Eluted) [(1*R*)-7c)]:** $^1$H NMR: δ = 0.92 [d, $J$ = 6.2 Hz, 3 H, -CH(C$H_3$)$_2$], 0.94 [d, $J$ = 6.2 Hz, 3 H, -CH(C$H_3$)$_2$], 1.36 (m, 1 H, 5′-H), 1.50 (m, 1 H, 4′-H), 1.57 (m, 1 H, 3′-H), 1.80 (m, 1 H, 5′-H), 1.88 [m, 1 H, -C*H*(CH$_3$)$_2$], 1.95 (m, 1 H, 4′-H), 2.11 (m, 1 H, 3′-H), 2.98 (m, 1 H, 6′-H), 3.05 (dd, $J$ = 15.1, $J$ = 8.1 Hz, 1 H, 2-H), 3.11 (dd, $J$ = 15.1, $J$ = 7.5 Hz, 1 H, 2-H), 3.39 (m, 1 H, 2′-H), 3.90 (m, 1 H, 1-H), 7.04 (t, $J$ = 7.8 Hz, 1 H, 5-H indole), 7.12 (t, $J$ = 7.8 Hz, 1 H, 6-H, indole), 7.30 (s, 1 H, 2-H indole), 7.40 (d, $J$ = 7.8 Hz, 1 H, 7-H indole), 7.61 (d, $J$ = 7.8 Hz, 1 H, 4-H indole), 7.78 (br. s, 1 H, secondary amine), 8.28 (br. s, 2 H, primary amine), 8.45 (br. s, 1 H, secondary amine), 11.08 (s, 1 H, NH indole) ppm. $^{13}$C NMR: δ = 16.7 [-CH(*C*H$_3$)$_2$], 18.7 [-CH(*C*H$_3$)$_2$], 21.0 (C3′), 21.7 (C4′), 23.1 (C5′), 26.0 (C2), 30.3 [-*C*H(CH$_3$)$_2$], 52.3 (C1), 58.3 (C2′), 63.1 (C6′), 107.3 (C3 indole), 111.6 (C7 indole), 118.1 (C4 indole), 118.5 (C5 indole), 121.3 (C6 indole), 124.8 (C2, indole), 126.8 (C3a indole), 136.4 (C7a indole)

ppm. MS (ES): $m/z$ = 286.5 [M + H]$^+$. HRMS calcd. for $C_{18}H_{27}N_3$ [MH$^+$] 286.2283, found 286.2296.

**(1*S*,2*S*,6*R*)-2-(1*H*-Indol-3-yl)-1-[6-isopropylpiperidin-2-yl]ethylamine, TFA Salt [(1*S*)-7c]:** $^1$H NMR: δ = 0.98 [d, $J$ = 6.2 Hz, 3 H, -CH(C$H_3$)$_2$], 1.02 [d, $J$ = 6.2 Hz, 3 H, -CH(C$H_3$)$_2$], 1.45 (m, 1 H, 5′-H), 1.49 (m, 1 H, 4′-H), 1.69 (m, 1 H, 3′-H), 1.86 (m, 1 H, 5′-H), 1.96 (m, 1 H, 4′-H), 1.99 [m, 1 H, -C$H$(CH$_3$)$_2$], 2.07 (m, 1 H, 3′-H), 2.90 (dd, $J$ = 15.3, $J$ = 11.6 Hz, 1 H, 2-H), 2.99 (m, 1 H, 6′-H), 3.35 (dd, $J$ = 15.3, $J$ = 2.6 Hz, 1 H, 2-H), 3.51 (m, 1 H, 2′-H), 3.86 (m, 1 H, 1-H), 7.03 (t, $J$ = 7.8 Hz, 1 H, 5-H indole), 7.13 (t, $J$ = 7.8 Hz, 1 H, 6-H indole), 7.28 (s, 1 H, 2-H indole), 7.41 (d, $J$ = 7.8 Hz, 1 H, 7-H indole), 7.66 (d, $J$ = 7.8 Hz, 1 H, 4-H indole), 8.13 (br. s, 2 H, primary amine), 8.30 (br. s, 1 H, secondary amine), 8.43 (br. s, 1 H, secondary amine), 11.09 (s, 1 H, NH indole) ppm. $^{13}$C NMR: δ = 17.1 [-CH(*C*H$_3$)$_2$], 19.2 [-CH(*C*H$_3$)$_2$], 22.0 (C4′), 22.9 (C3′), 23.3 (C5′), 24.0 (C2), 30.3 [-*C*H(CH$_3$)$_2$], 51.7 (C1), 59.5 (C2′), 64.1 (C6′), 107.1 (C3 indole), 111.6 (C7 indole), 118.4 (C4 indole, C5 indole), 121.3 (C6 indole), 124.8 (C2, indole), 126.7 (C3a indole), 136.5 (C7a indole) ppm. MS (ES): $m/z$ = 286.0 [M + H]$^+$. HRMS calcd. for $C_{18}H_{27}N_3$ [MH$^+$] 286.2283, found 286.2296.

**(1*S*,2*S*,6*R*)-2-(1*H*-Indol-3-yl)-1-[6-isobutylpiperidin-2-yl]ethylamine, TFA Salt (First Eluted) [(1*S*)-7d]:** $^1$H NMR: δ = 0.91 [d, $J$ = 6.6 Hz, 3 H, -CH$_2$-CH(C$H_3$)$_2$], 0.94 [d, $J$ = 6.6 Hz, 3 H, -CH$_2$-CH(C$H_3$)$_2$], 1.40 (m, 1 H, 5′-H), 1.53 [m, 2 H, -C$H_2$-CH(CH$_3$)$_2$], 1.54 (m, 1 H, 4′-H), 1.63 (m, 1 H, 3′-H), 1.77 [m, 1 H, -CH$_2$-C$H$(CH$_3$)$_2$], 1.94 (m, 2 H, 4′-H, 5′-H), 2.03 (m, 1 H, 3′-H), 2.88 (dd, $J$ = 14.8, $J$ = 11.6 Hz, 1 H, 2-H), 3.19 (m, 1 H, 6′-H), 3.32 (dd, $J$ = 14.8, $J$ = 2.3 Hz, 1 H, 2-H), 3.54 (m, 1 H, 2′-H), 3.76 (m, 1 H, 1-H), 7.03 (t, $J$ = 7.8 Hz, 1 H, 5-H indole), 7.13 (t, $J$ = 7.8 Hz, 1 H, 6-H indole), 7.27 (s, 1 H, 2-H indole), 7.41 (d, $J$ = 7.8 Hz, 1 H, 7-H indole), 7.68 (d, $J$ = 7.8 Hz, 1 H, 4-H indole), 8.15 (br. s, 2 H, primary amine), 8.63 (br. s, 1 H, secondary amine), 8.97 (br. s, 1 H, secondary amine), 11.06 (s, 1 H, NH indole) ppm. $^{13}$C NMR: δ = 21.5 [-CH$_2$-CH(*C*H$_3$)$_2$], 21.8 (C4′), 22.2 (C3′), 23.2 [-CH$_2$-CH(*C*H$_3$)$_2$], 23.4 (C2), 23.5 [-CH$_2$-*C*H(CH$_3$)$_2$], 27.7 (C5′), 42.0 [-*C*H$_2$-CH(CH$_3$)$_2$], 51.5 (C1), 56.9 (C6′), 58.4 (C2′), 107.0 (C3 indole), 111.6 (C7 indole), 118.4 (C4 indole, C5 indole), 121.3 (C6 indole), 124.8 (C2, indole), 126.6 (C3a indole), 136.5 (C7a indole) ppm. MS (ES): $m/z$ = 300.4 [M + H]$^+$. HRMS calcd. for $C_{19}H_{29}N_3$ [MH$^+$] 300.2440, found 300.2445.

**(1*R*,2*S*,6*R*)-2-(1*H*-Indol-3-yl)-1-[6-isobutylpiperidin-2-yl]ethylamine, TFA salt [(1*R*)-7d]:** $^1$H NMR: δ = 0.84 [d, $J$ = 6.4 Hz, 3 H, -CH$_2$-CH(C$H_3$)$_2$], 0.89 [d, $J$ = 6.4 Hz, 3 H, -CH$_2$-CH(C$H_3$)$_2$], 1.28 (m, 1 H, 5′-H), 1.39 [m, 2 H, -C$H_2$-CH(CH$_3$)$_2$], 1.53 (m, 1 H, 3′-H), 1.55 (m, 1 H, 4′-H), 1.69 [m, 1 H, -CH$_2$-C$H$(CH$_3$)$_2$], 1.89 (m, 1 H, 5′-H), 1.90 (m, 1 H, 4′-H), 2.10 (m, 1 H, 3′-H), 3.08 (m, 2 H, 2-H), 3.14 (m, 1 H, 6′-H), 3.37 (m, 1 H, 2′-H), 3.80 (m, 1 H, 1-H), 7.03 (t, $J$ = 7.8 Hz, 1 H, 5-H indole), 7.13 (t, $J$ = 7.8 Hz, 1 H, 6-H indole), 7.31 (s, 1 H, 2-H indole), 7.40 (d, $J$ = 7.8 Hz, 1 H, 7-H indole), 7.61 (d, $J$ = 7.8 Hz, 1 H, 4-H indole), 8.22 (br. s, 3 H, amine), 8.54 (br. s, 1 H, secondary amine), 11.07 (s, 1 H, NH indole) ppm. $^{13}$C NMR: δ = 21.3 (C3′), 21.4 [C4′, -CH$_2$-CH(*C*H$_3$)$_2$], 23.1 [-CH$_2$-CH(*C*H$_3$)$_2$], 23.4 [-CH$_2$-*C*H(CH$_3$)$_2$], 25.8 (C2), 27.6 (C5′), 42.1 [-*C*H$_2$-CH(CH$_3$)$_2$], 52.4 (C1), 55.9 (C6′), 57.2 (C2′), 107.2 (C3 indole), 111.6 (C7 indole), 118.1 (C4 indole), 118.5 (C5 indole), 121.3 (C6 indole), 124.7 (C2, indole), 126.7 (C3a indole), 136.4 (C7a indole) ppm. MS (ES): $m/z$ = 300.0 [M + H]$^+$. HRMS calcd. for $C_{19}H_{29}N_3$ [MH$^+$] 300.2440, found 300.2445.

**Procedure for the Conversion of (1*R*)- and (1*S*)-7d into (1*R*)- and (1*S*)-8d:** NMM (42 μL) and *p*-nitrophenylchloroformate (9.5 mg, 47 μmol) were added at 0 °C to a solution of **(1*S*)-7d** (14.2 mg, 47 μmol) in $CH_2Cl_2$. (4.5 mL) After 1 h, a catalytic amount of 4-(dimethylamino)pyridine was added and the reaction mixture was stirred overnight at room temperature. A 1 M $KHSO_4$ aqueous solution (10 mL) and $CH_2Cl_2$ (10 mL) were added to the reaction mixture, the organic layer was separated and washed with a saturated solution of $NaHCO_3$ and brine, dried with $Na_2SO_4$, and concentrated. The obtained residue was directly purified by RP-HPLC and then lyophilized to yield **(1*S*)-8d** as a white foam. **(1*R*)-8d** was obtained in a similar manner starting from **(1*R*)-7d**. For selected NMR data see Table 3.

Table 3. Selected NMR spectroscopic data of compounds **8d**

| | (1*R*)-**8d** | | | | (1*S*)-**8d** | | | |
|---|---|---|---|---|---|---|---|---|
| | $^1$H NMR (δ) | | $^{13}$C NMR (δ) | | $^1$H NMR (δ) | | $^{13}$C NMR (δ) | |
| 1-H | 3.95 | C1 | 52.8 | 1-H | 3.28 | C1 | 55.7 | |
| 2-H | 6.10 | C3 | 160.7 | 2-H | 6.27 | C3 | 159.8 | |
| 5-H | 2.95 | C5 | 55.2 | 5-H | 2.88 | C5 | 54.8 | |
| 6-H/6′-H | 1.13/1.50 | C6 | 31.0 | 6-H/6′-H | 1.09/1.51 | C6 | 31.3 | |
| 7-H/7′-H | 1.35/1.80 | C7 | 23.6 | 7-H/7′-H | 1.31/1.68 | C7 | 23.6 | |
| 8-H/8′-H | 1.48 | C8 | 22.9 | 8-H/8′-H | 1.24/1.32 | C8 | 29.3 | |
| 8a-H | 3.30 | C8a | 60.3 | 8a-H | 3.07 | C8a | 61.9 | |

**(1*S*,8a*S*,5*R*)-1-(1*H*-Indol-3-ylmethyl)-5-isobutylhexahydroimidazo-[1,5-*a*]pyridin-3-one [(1*S*)-8d]:** White foam (6.8 mg, 44%); $R_f$ = 0.26 (EtOAc/hexane, 1:1). $^1$H NMR: δ = 0.83 [d, $J$ = 6.6 Hz, 3 H, -CH$_2$-CH(C$H_3$)$_2$], 0.86 [d, $J$ = 6.6 Hz, 3 H, -CH$_2$-CH(C$H_3$)$_2$], 1.09 (m, 1 H, 6-H), 1.20 [m, 1 H, -C$H_2$-CH(CH$_3$)$_2$], 1.24 (m, 1 H, 8-H), 1.31 (m, 1 H, 7-H), 1.32 (m, 1 H, 8-H), 1.51 (m, 1 H, 6-H), 1.68 (m, 1 H, 7-H), 1.70 [m, 1 H, -CH$_2$-C$H$(CH$_3$)$_2$], 2.40 [m, 1 H, -C$H_2$-CH(CH$_3$)$_2$], 2.81 (m, 2 H, 1′-H), 2.88 (m, 1 H, 5-H), 3.07 (m, 1 H, 8a-H), 3.28 (m, 1 H, 1-H), 6.27 (s, 1 H, 2-H), 6.97 (t, $J$ = 7.9 Hz, 1 H, 5-H indole), 7.06 (t, $J$ = 7.9 Hz, 1 H, 6-H indole), 7.18 (s, 1 H, 2-H indole), 7.33 (d, $J$ = 7.9 Hz, 1 H, 7-H indole), 7.50 (d, $J$ = 7.9 Hz, 1 H, 4-H indole), 10.84 (s, 1 H, NH indole) ppm. $^{13}$C NMR: δ = 22.5 [-CH$_2$-CH(*C*H$_3$)$_2$], 22.6 [-CH$_2$-CH(*C*H$_3$)$_2$], 23.6(C7), 24.5 [-CH$_2$-*C*H(CH$_3$)$_2$], 29.3 (C8), 29.6 (C1′), 31.3 (C6), 40.9 [-*C*H$_2$-CH(CH$_3$)$_2$], 54.8 (C5), 55.7 (C1), 61.9 (C8a), 110.0 (C3 indole), 111.3 (C7 indole), 118.0 (C4 indole), 118.2 (C5 indole), 120.8 (C6 indole), 123.2 (C2 indole), 127.5 (C3a indole), 136.1 (C7a indole), 159.8 (C3) ppm. MS (ES): $m/z$ = 326.1 [M + H]$^+$, 367.1 [M + H + CH$_3$CN]$^+$, 651.4 [2 M + H]$^+$. HRMS calcd. for $C_{20}H_{28}ON_3$ [MH$^+$] 326.2232, found 326.2241.

**(1*R*,5a*S*,5*R*)-1-(1*H*-Indol-3-ylmethyl)-5-isobutylhexahydroimidazo-[1,5-*a*]pyridin-3-one [(1*R*)-8d]:** White foam (8.4 mg, 51%); $R_f$ = 0.26 (EtOAc/hexane, 1:1). $^1$H NMR: δ = 0.83 [d, 3 H, -CH$_2$-CH(C$H_3$)$_2$], 0.86 [d, 3 H, -CH$_2$-CH(C$H_3$)$_2$], 1.13 (m, 1 H, 6-H), 1.24 [m, 1 H, -C$H_2$-CH(CH$_3$)$_2$], 1.35 (m, 1 H, 7-H), 1.48 (m, 2 H, 8-H), 1.50 (m, 1 H, 6-H), 1.73 [m, 1 H, -CH$_2$-C$H$(CH$_3$)$_2$], 1.80 (m, 1 H, 7-H), 2.38 [m, 1 H, -C$H_2$-CH(CH$_3$)$_2$], 2.78 (dd, $J$ = 14.8, $J$ = 6.3 Hz, 1 H, 1′-H), 2.85 (dd, $J$ = 14.8, $J$ = 8.8 Hz, 1 H, 1′-H), 2.95 (m, 1 H, 5-H), 3.30 (m, 1 H, 8a-H), 3.95 (m, 1 H, 1-H), 6.10 (s, 1 H, 2-H), 6.95 (t, $J$ = 8.1 Hz, 1 H, 5-H indole), 7.06 (t, $J$ = 8.1 Hz, 1 H, 6-H indole), 7.21 (s, 1 H, 2-H indole), 7.33 (d, $J$ = 8.1 Hz, 1 H, 7-H indole), 7.51 (d, $J$ = 8.1 Hz, 1 H, 4-H indole), 10.84 (s, 1 H, NH indole) ppm. $^{13}$C NMR: δ = 22.3 [-CH$_2$-CH(*C*H$_3$)$_2$], 22.7 [-CH$_2$-CH(*C*H$_3$)$_2$], 22.9 (C8), 23.6(C7), 24.4 [-CH$_2$-*C*H(CH$_3$)$_2$], 24.6 (C1′), 31.0 (C6), 41.4 [-*C*H$_2$-CH(CH$_3$)$_2$], 52.8 (C1), 55.2 (C5), 60.3 (C8a), 110.3 (C3 indole), 111.3 (C7 indole), 118.1 (C4 indole), 118.2 (C5 indole), 120.9 (C6 indole), 122.8 (C2, indole), 127.1 (C3a indole), 136.1 (C7a indole), 160.7 (C3) ppm. MS (ES): $m/z$ = 326.2 [M +

$H]^+$, 367.1 $[M + H + CH_3CN]^+$, 651.4 $[2 M + H]^+$. HRMS calcd. for $C_{20}H_{28}ON_3$ $[MH^+]$ 326.2232, found 326.2251.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