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Stereoselective transformation of pyrazinones into substituted analogues of *cis*-5-amino-6-oxo-2-piperidinemethanol and *cis*-5-amino-2-piperidinemethanol

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Abstract—Various analogues of *cis*-5-amino-6-oxo-2-piperidinemethanol and *cis*-5-amino-2-piperidinemethanol have been prepared via Diels–Alder reaction of substituted pyrazinones with ethene followed by acid methanolysis of the bridged lactam adducts. Further reduction of the resulting methyl 2-piperidinecarboxylate ester compounds led to the corresponding 2-piperidinemethanol products that were converted into potential SP antagonists.

1. Introduction

Substance P, an undecapeptide isolated from animal tissue by von Euler and Gaddum in the early thirties,[1] displays a broad range of biological effects. During the past few decades, several peptide and non-peptide antagonists of Substance P have been developed. Researchers at Merck have claimed Substance P antagonistic activity for the β-hydroxypiperidine derivative **1** (Fig. 1).[2] In a previous communication we reported on the synthesis of 2,(2,)5,5-tri- and tetrasubstituted piperidines **2** containing the same bioactive moiety as **1** plus an additional OH and alkyl/aryl substituents in position 5.[3] In an ongoing effort to expand the substitution pattern of model **1**, we envisaged the synthesis of compounds of type **3** and **4** having an amide and aryl/alkyl (or H) substituents at position 5.

Here we present a short, versatile and stereoselective route towards these substituted piperidin(on)es, according to the retrosynthetic analysis shown in Figure 1. The two key steps in our approach involve (i) Diels–Alder addition of ethene on a 5-chloro-2(1*H*)-pyrazinone azadiene system followed by hydrolysis to form the bridged bislactam product and (ii) selective acid-catalysed methanolysis of the secondary amide group to produce the corresponding methyl 2-piperidinecarboxylate esters.[4] Further reduction and O-alkylation steps provide access to the target compounds. A *cis*-relationship between the acetamide and benzyl ether moieties is imposed by the cycoaddition step with ethene.

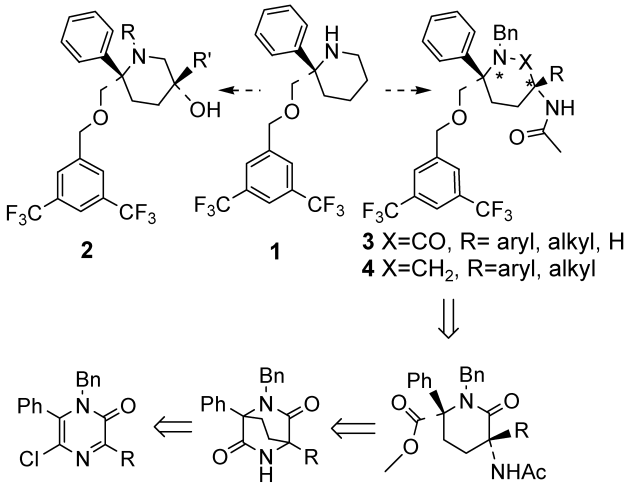

Figure 1. Proposed target compounds and retrosynthetic analysis.

2. Results and discussion

2.1. Functionalisation of pyrazinones

1-Benzyl-3,5-dichloro-6-phenyl-2(1*H*)-pyrazinone **5a** served as a starting material for both piperidinones **3** and piperidines **4** (Scheme 1). It can be prepared on a multigram scale (67%) by reaction of 2-(benzylamino)-phenylacetonitrile **6** with oxalyl chloride and triethylammonium chloride in chlorobenzene.[5] The 3-functionalised

Keywords: substituted piperidines; substituted piperidinones; Diels–Alder reaction; Substance P antagonists.

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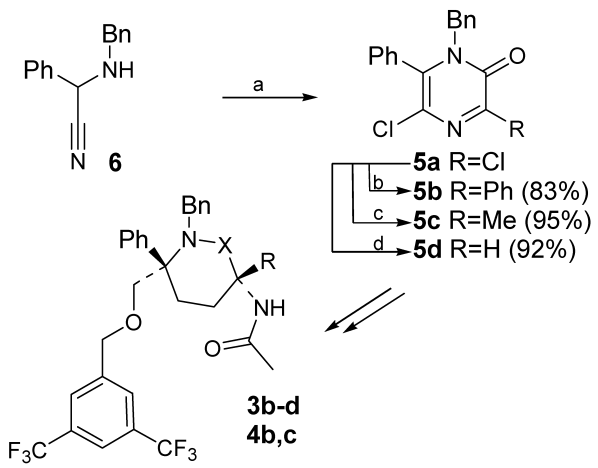


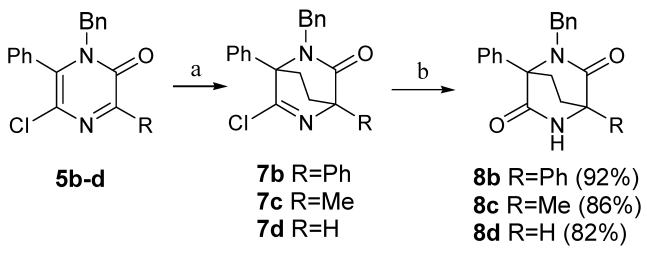
Scheme 1. *Reagents and conditions*: (a) oxalyl chloride, $Et_3NH^+Cl^-$ (b) Ph_4Sn, $Pd(PPh_3)_4$, toluene reflux (c) Me_4Sn, $Pd(PPh_3)_4$, toluene reflux (d) HCOONa, $Pd(PPh_3)_4$, DMF, 110°C.

compounds **5b**,**c** and 5-H-compound **5d** were prepared using Pd^0-catalysed Stille and hydrogen transfer reactions.[6]

2.2. Diels–Alder reaction with ethene

Pyrazinones **5b–d** were converted into the corresponding ethylene bridged intermediates **7b–d** by heating at 135°C in toluene under ethene pressure (35 atm) (Scheme 2). After opening the steel bomb, compounds **7c** and **7d** underwent hydrolysis by air moisture to form bislactams **8c** and **8d**. Hydrolysis of the 1,4-diphenyl substituted adduct **7b** was found to be slow, probably due to steric factors, and efficient conversion into bislactam product **8b** required overnight reaction in EtOAc containing a drop of aqueous HCl solution. Compounds **8b–d** were purified by column chromatography and crystallisation.

The ^1H NMR spectra of compounds **8b–d** exhibit a complex coupling pattern in the region 2–4 ppm, due to two pairs of diastereotopic protons on the ethylene bridge. In the spectrum of compound **8d**, this pattern is complicated further by additional coupling with the bridgehead proton. For compound **8c** complete assignment of the ethylene bridge protons and carbon atoms was based on ^1H coupled ^{13}C NMR, XHCORR and NOESY spectra. In the C–H coupled NMR-spectrum, the triplet pattern of C8 is broadened due to ^3J couplings with the methyl protons. Protons H7–H7′ and H8–H8′ are differentiated by a NOE observed between the *ortho* protons of the benzyl group and both H7 and H8 (Fig. 2).



Scheme 2. *Reagents and conditions*: (a) ethene 35 atm, toluene, 135°C, steel bomb, (b) air moisture or EtOAc containing a drop of HCl.

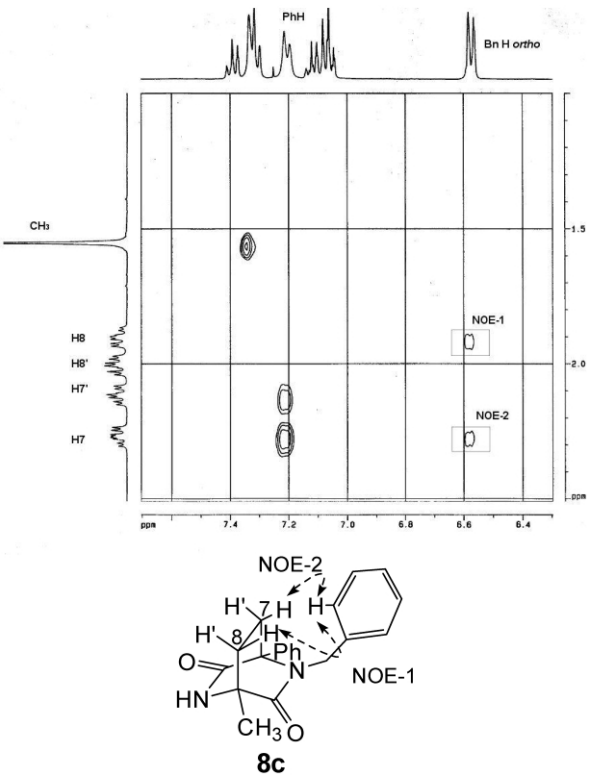
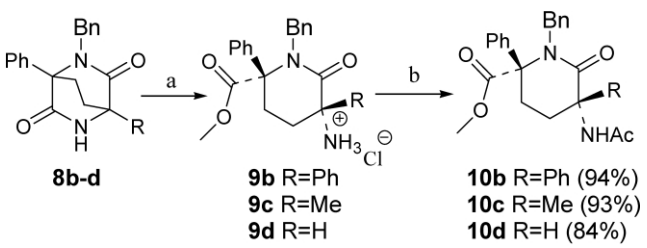


Figure 2. NOE effects used in the assignment of protons H7 and H8.

2.3. Methanolysis of the adducts

Bislactam products **8b–d** were cleaved selectively by acid-catalysed methanolysis to produce only the primary amino esters **9b–d** (Scheme 3). In view of the near-symmetric character of the 2,5-diphenyl bislactam structure **8b** (except for the presence of the CONBn vs. CONH amide group), the selectivity for cleavage of the secondary amide clearly must be ascribed to the higher steric requirements for attack of methanol on the protonated tertiary amide group. The conversion of **8** into **9b–d** was effected by heating at 50°C with HCl in methanol until all starting material had disappeared. However, to prevent back conversion of amino esters **9** into starting bislactams as was observed upon workup by alkaline extraction, the free amines were subjected to in situ acetylation. Thus, following evaporation of the HCl–methanol reagent, an excess of acetic anhydride was added to the cooled (0°C) oily residue followed by addition of Et_3N. Ammonium salts were removed by filtration, the filtrate was evaporated, and the residue purified by column chromatography to afford the N–Ac products **10b–d** in good yields.



Scheme 3. *Reagents and conditions*: (a) MeOH–HCl, (b) Ac_2O, Et_3N.

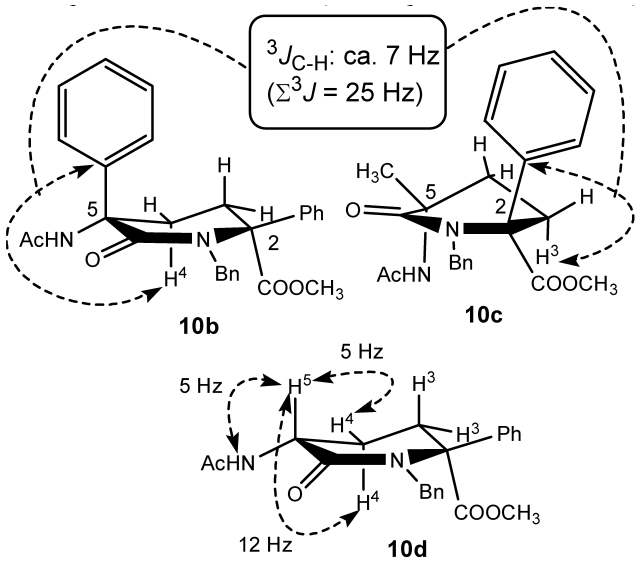
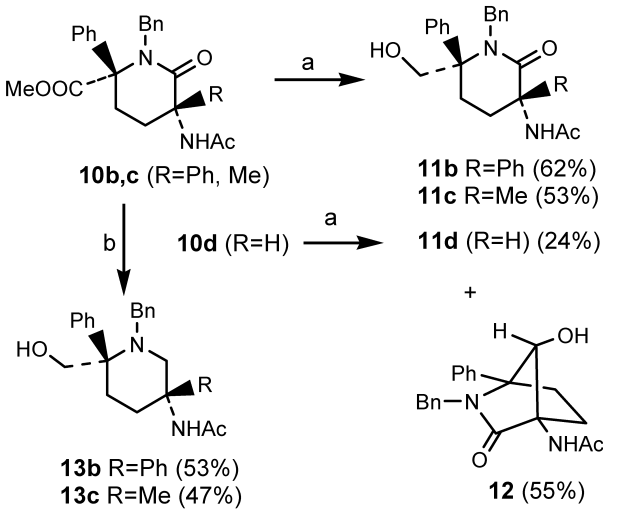


Figure 3. NMR conformational analysis of compounds **10b–d**.



Scheme 4. *Reagents and conditions*: (a) 1.1 equiv. $LiBH_4$, 0.1 equiv. $LiEt_3BH$, THF, reflux, (b) 1.5 equiv. $LiBH_4$, 0.15 equiv. $LiEt_3BH$, THF, reflux.

The NMR spectra of **10b–d** in each case reveal a preferred half-chair conformation (Fig. 3). For 5-H compound **10d** this half-chair corresponds to an equatorial orientation of two large groups, i.e. 2-Ph and 5-NHAc, and an axial disposition of H5. In the ^{1}H NMR spectrum of **10d**, the axial position of H5 is demonstrated by a dxt signal at 4.52 ppm with one large (≈12 Hz) and two smaller (≈5 Hz) ^3J coupling constants. For compounds **10b–c** lacking a proton at the 5-position, conformational assignments are based on the sum of the $^3J(C_{Ph\text{-}ipso}, H)$ couplings measured in the ^{1}H coupled ^{13}C NMR spectra. These data reveal a similar half-chair form for 2,5-diphenyl compound **10b** as for **10d** while the 2-Ph, 5-Me compound **10c** exists as the opposite half-chair conformer. For **10b** an equatorial disposition of 2-Ph is apparent from the small value found for $\sum^3J$ (15 Hz) of the 2-Ph-*ipso* carbon atom, and an axial one for the 5-Ph group from the large value measured for $\sum^3J_{5\text{-Ph-}ipso}$ (25 Hz). For **10c** the $\sum^3J$ of the Ph-*ipso* carbon atom is about 25 Hz: this value is consistent with a pseudo-axial position of the phenyl group characterised by a large ^3J *trans* (ca. 7 Hz) with H3ax. The methyl group of **10c** is in a pseudo-equatorial position ($\sum^3J(C_{Me}, H)$≈9.5 Hz). Clearly, in these lactam half-chair structures a planar axial 5-phenyl group is better tolerated than an axial 5-methyl group, possibly due to alleviation of 1,3-diaxial repulsions.

2.4. Reduction of the aminopiperidinecarboxylates

In a next step piperidinecarboxylate esters **10** must be converted into primary alcohols **11**. For **10b** and **10c** selective reduction of the ester group was accomplished by reaction with $LiBH_4$ and a catalytic amount of lithium triethylborohydride;[7] this procedure furnished alcohols **11b,c** in 62 and 53% yield (Scheme 4). By contrast, from the analogous reaction of **10d** the corresponding alcohol **11d** was isolated only as a minor constituent (24%) besides the major product (55%), to which the bridged secondary alcohol structure **12** was assigned. The ^{1}H NMR spectrum of **12** reveals two coupled protons absorbing at 4.64 and 5.76 ppm. The latter signal was attributed to an OH group bound to CH since it was shifted to higher field when increasing the recording temperature. This assignment was confirmed by selective decoupling of the CH proton at 4.64 ppm, which converted the OH doublet into a singlet; concurrently the broad txd signals observed at 1.47 and 1.55 ppm were converted into sharp signals. The broadening of signals in the coupled spectrum is attributed to unresolved ^4J couplings of H7 with semi-axial protons $H5^a$ and $H6^a$ (see W-patterns in Fig. 4).

A plausible mechanism accounting for the formation of **12** is presented in Scheme 5: after partial reduction of the ester to form an aldehyde and abstraction of the acidic CONH amide proton, equilibration may occur between the N- and

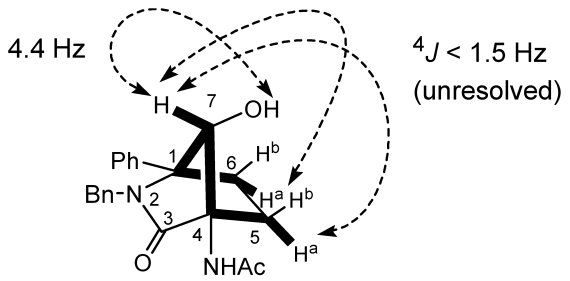
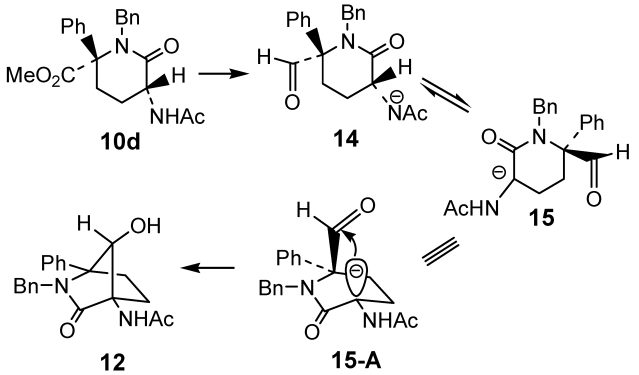
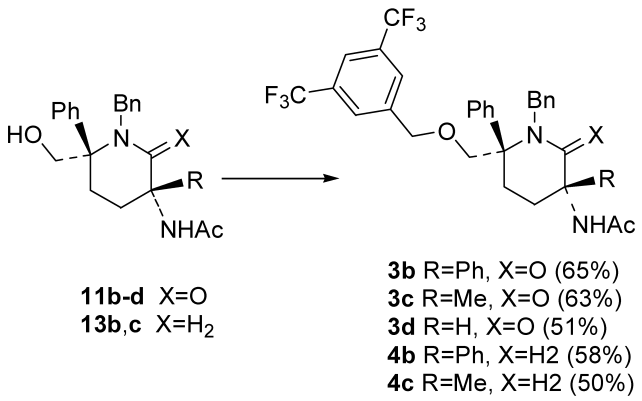


Figure 4. Coupling constants observed for structure **12**.



Scheme 5. Mechanism proposed for the formation of compound **12**.



Scheme 6. *Reagents and conditions*: (a) 1.1 equiv. NaH, DMF, bis-3,5-(trifluoromethyl)benzylbromide, 0°C→rt.

C-based anions **14** and **15**. Cyclisation probably proceeds via internal attack of the C-anion on aldehyde conformer **15**–**A** to give product **12**.

When compounds **10b**,**c** were treated with 1.5 instead of 1.1 equiv. of $LiBH_4$, further reduction of the lactam carbonyl group also occurred, affording piperidines **13b**,**c** in ca. 50% yield besides some remaining piperidinones **11b**,**c** and other unidentified byproducts (Scheme 4). Addition of more reducing agent did not improve the yield of piperidines **13** but led to a complex reaction mixture that was not analysed further.

2.5. Conversion of alcohols into target products

To convert **11b**–**d** and **13b**,**c** into functionalised analogues of compound **1**, the alcohol group must be transformed into a bis(trifluoromethyl)benzyl ether. This was accomplished in 50–65% yield by reacting **3b**–**d** and **4b**,**c** with NaH and bis(trifluoromethyl)benzyl bromide in DMF (Scheme 6).

The target compounds were characterised by prominent molecular ions (MH^+) in the CI-mass spectra, which also revealed fragment ions due to loss of HF or elimination of the side chain. In the ^1H NMR spectra, the methylene protons of the two benzyl groups show up as AB-patterns.

3. Conclusion

Substituted analogues of *cis*-5-amino-6-oxo-2-piperidinemethanol and *cis*-5-amino-2-piperidinemethanol are prepared via intermolecular Diels–Alder reaction of functionalised 2(1*H*)-pyrazinones with ethene followed by hydrolysis of the imidoyl chloride adducts. Subsequent acid-catalysed methanolysis of the resulting bridged bislactam products followed by selective reduction and alkylation steps provides target products **3b**–**d** and **4b**,**c** as potential SP antagonists.

4. Experimental

4.1. Analytical instruments

Melting points were taken using a Reichert-Jung Thermovar apparatus and an Electrothermal IA 9000 digital melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer 1600 Fourier transform spectrometer. Mass spectra were run using a Hewlett Packard MS-Engine 5989A apparatus for EI and CI spectra, and a Kratos MS50TC instrument for exact mass measurements performed in the EI mode at a resolution of 10,000. For the NMR spectra (δ, ppm) a Bruker AMX 400 and a Bruker Avance 300 spectrometer were used. Coupling constants are rounded to the nearest 0.5 Hz. Analytical and preparative thin layer chromatography was carried out using Merck silica gel 60 PF-224; for column chromatography 70–230 mesh silica gel 60 (E.M. Merck) was used as the stationary phase. HPLC separations were performed using a HIBAR column [Merck, cat. 151435].

4.2. Synthesis

For the synthesis of compound **5a** we refer to Ref. 5.

4.3. General procedure for the Stille reaction

To a solution of 13.4 g (0.04 mol) of pyrazinone **5a** in 120 mL of toluene is added 0.048 mol of tetraphenyltin or tetramethyltin and 0.4 mmol of $Pd(PPh_3)_4$. The solution is stirred under a nitrogen atmosphere for 0.5–5 days at 120°C (temperature oil bath) until all starting material has disappeared (TLC monitoring). After evaporation of the solvent, 60 mL of ethyl acetate and an excess of KF is added to the residue. The suspension is stirred at room temperature for 4 h. Following removal of the precipitates by filtration, the solution is evaporated. The crude product is purified by column chromatography (silica gel, EtOAc–CH_2Cl_2 95–5) and subsequently crystallised from EtOH.

4.3.1. 1-Benzyl-5-chloro-3,6-diphenyl-2(1*H*)-pyrazinone (5b). Yield: 83%; white crystals, mp: 184°C (EtOH); IR (KBr, cm^{-1}): 1545 (CN), 1650 (CO); ^1H NMR (400 MHz, $CDCl_3$, ppm): 7.48–6.89 (m, 15H, PhH), 5.15 (s, 2H, $PhCH_2$); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 155.0 (C2), 150.9 (C3), 137.4 (C6), 135.5–127.3 (PhC), 126.7 (C5), 50.2 (CH_2Ph); EIMS [*m*/*z* (%)]: 372 (M^+, 16), 91 ($PhCH_2^+$, 100); HRMS: calcd for $C_{23}H_{17}ClN_2O$: 372.1029, found 372.1029.

Spectral data for compound **5c** can be found in Ref. 8.

4.3.2. 1-Benzyl-5-chloro-6-phenyl-2(1*H*)-pyrazinone (5d). To a solution of 660 mg (2 mmol) of pyrazinone **5a** in 20 mL of DMF is added 204 mg (3 mmol) of sodium formate and 115 mg of $Pd(PPh_3)_4$. The solution is stirred at 110°C under nitrogen atmosphere for 4 h. Following evaporation of the solvent, the residue is treated with 50 mL of water and extracted with 3×50 mL of CH_2Cl_2. The extract is evaporated and the residue purified by column chromatography using a solvent gradient (silica gel, CH_2Cl_2→CH_2Cl_2–EtOAc (80–20)).

Yield: 92%; white crystals, mp: 105°C (EtOH); IR (KBr, cm^{-1}): 1552 (CN), 1654 (CO); ^1H NMR (400 MHz, $CDCl_3$, ppm): 8.12 (s, 1H, H3), 7.48–6.80 (m, 10H, PhH), 5.00 (s, 2H, $PhCH_2$); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 155.8 (C2), 147.0 (C3), 138.6 (C6), 135.2–127.3 (PhC), 127.2

(C5), 49.5 (CH_2Ph); EIMS [*m/z* (%)]: 296 (M^+, 61), 261 (M^+-Cl, 10), 91 ($PhCH_2^+$, 100); HRMS: calcd for $C_{17}H_{13}ClN_2O$: 296.0716, found 296.0717.

4.4. General procedure for the synthesis of cycloadducts 8b–d

Pyrazinone **5b–d** (1 mmol) is dissolved in 30 mL of toluene and the solution is transferred to a steel bomb. The mixture is heated at 135°C under ethene pressure (35 atm) for 5–10 days. After cooling and removal of ethene, the solvent is evaporated under reduced pressure. The intermediate adducts of **5c** and **5d** spontaneously hydrolyse at the air to produce bislactams **8c** and **8d**, which are purified by column chromatography (silica gel, CH_2Cl_2–EtOAc (95–5)). The bicyclic imidoyl chloride **7b** is treated with 50 mL of moisturised EtOAc containing a drop of HCl solution for one night. Following addition of 10 mL of water, the solution is neutralised with K_2CO_3. The organic phase is separated, dried over $MgSO_4$, and evaporated under reduced pressure. The crude product is further purified by column chromatography (silica gel, CH_2Cl_2).

4.4.1. (1*S,4*S**)-2-Benzyl-1,4-diphenyl-2,5-diazabicyclo-[2.2.2]octane-3,6-dione (8b).** Yield: 92%; white crystals, mp: 218°C (EtOH); IR (KBr, cm^{-1}): 1696 (CO), 1710 (CO); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 7.56–6.60 (m, 14H, PhH and NH), 6.65 (d, 2H, BnH*ortho*), 4.92 (d, 1H, *J*=15 Hz, $PhCH_2$), 3.97 (d, 1H, *J*=15 Hz, $PhCH_2$), 2.32 (ddd, 1H, *J*=14.0, 10.0, 5.0 Hz, H7), 2.22 (ddd, 1H, *J*=14.0, 10.0, 5.0 Hz, H7′), 2.14 (ddd, 1H, *J*=14.5, 10.0, 5.0 Hz, H8′), 1.98 (ddd, 1H, *J*=14.5, 10.0, 5.0 Hz, H8); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 172.3 (CO), 171.3 (CO), 137.5–127.3 (PhC), 68.0 (C1), 63.3 (C4), 46.4 (CH_2Ph), 29.3 (CH_2), 29.8 (CH_2); EIMS [*m/z* (%)]: 382 (M^+, 33), 249 ($M^+-CONCH_2Ph$, 97), 221 ($M^+-CONCH_2Ph-CO$, 100), 91 ($PhCH_2^+$, 93); HRMS: calcd for $C_{25}H_{22}N_2O_2$: 382.1682, found 382.1686.

4.4.2. (1*S,4*R**)-2-Benzyl-4-methyl-1-phenyl-2,5-diazabicyclo[2.2.2]octane-3,6-dione (8c).** Yield: 86%; white crystals, mp: 212°C (CH_2Cl_2/hexane); IR (KBr, cm^{-1}): 1706 (CO), 1715 (CO); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 7.20–7.48 (m, 9H, PhH and NH), 6.57 (d, 2H, BnH*ortho*), 4.82 (d, 1H, *J*=16 Hz, $PhCH_2$), 3.93 (d, 1H, *J*=16 Hz, $PhCH_2$), 2.27 (ddd, 1H, *J*=12.5, 10.5, 4.5 Hz, H7), 2.11 (ddd, 1H, *J*=12.5, 10.5, 4.0 Hz, H7′), 2.00 (ddd, 1H, *J*=13.0, 10.5, 4.5 Hz, H8′), 1.90 (ddd, 1H, *J*=13.0, 10.5, 4.0 Hz, H8), 1.55 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 173.0 (CO), 171.5 (CO), 137.6–127.2 (PhC), 68.1 (C1), 57.2 (C4), 46.0 (CH_2Ph), 32.9 (CH_2), 29.2 (CH_2, 18.7 (CH_3); EIMS [*m/z* (%)]: 320 (M^+, 54), 158 ($M^+-CONCH_2Ph-CO$, 100), 91 ($PhCH_2^+$, 92); HRMS: calcd for $C_{20}H_{20}N_2O_2$: 320.1525, found 320.1527.

4.4.3. (1*S,4*R**)-2-Benzyl-1-phenyl-2,5-diazabicyclo-[2.2.2]octane-3,6-dione (8d).** Yield: 82%; white crystals, mp: 157°C (CH_2Cl_2/hexane); IR (KBr, cm^{-1}): 1698 (CO); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 7.48–6.57 (m, 11H, PhH and NH), 4.84 (d, 1H, *J*=16 Hz, $PhCH_2$), 3.92 (d, 1H, *J*=16.0 Hz, $PhCH_2$), 2.28 (ddd, 1H, *J*=14.0, 10.0, 5.0 Hz, H7), 2.18 (ddd, 1H, *J*=14.0, 10.0, 5.0 Hz, H7′), 2.10–1.95 (m, 2H, H8 and H8′), 1.61 (s, 1H, H4); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 171.8 (CO), 171.6 (CO), 137.4–127.2 (PhC), 68.1 (C1), 54.4 (C4), 45.6 (CH_2Ph), 28.2 (CH_2), 25.8 (CH_2); EIMS [*m/z* (%)]: 306 (M^+, 22), 91 ($PhCH_2^+$, 100); HRMS: calcd for $C_{19}H_{18}N_2O_2$: 306.1368, found 306.1369.

4.5. General procedure for methanolysis of 8b–d and subsequent acetylation to form *N*–Ac compounds 10b–d

A solution of 1 mmol of adduct **8b–d** in 15 mL of MeOH is cooled to 0°C. This solution is saturated with dry HCl gas for 5 min. Alternatively, after cooling of the methanol solution, 1 mL of $SOCl_2$ is slowly added (CAUTION vigorous reaction). After reaction at 50°C overnight, the solution is evaporated under reduced pressure and the residue is dissolved in 8 mL of acetic anhydride. The mixture is cooled in an ice bath and Et_3N is added. Formation of triethyl ammonium salts is observed. Following removal of the ammonium salts by filtration, the solution is evaporated and the residue is purified by column chromatography (silicagel, EtOAc).

4.5.1. Methyl (2*S,5*S**)-5-(acetylamino)-1-benzyl-6-oxo-2,5-diphenyl-2-piperidinecarboxylate (10b).** Yield: 94%; white crystals, mp: 157°C (CH_2Cl_2/hexane); IR (KBr, cm^{-1}): 1640 (CO), 1735 (CO); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 7.50–6.82 (m, 14H, PhH and NH), 6.69 (d, 2H, BnH*ortho*), 5.20 (d, 1H, *J*=14.0 Hz, $PhCH_2$), 3.95 (s, 3H, OCH_3), 3.89 (d, 1H, *J*=14.0 Hz, $PhCH_2$), 3.05 (dt (ddd), 1H, *J*=14, 1.4 Hz, H3eq), 2.76 (td (ddd), 1H, *J*=14.0, 1.4 Hz, H3ax), 2.53 (dt (ddd), 1H, *J*=14.0, 1.4 Hz, H4eq), 2.29 (td (ddd), 1H, *J*=14.0, 1.4 Hz, H4ax), 1.97 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 172.6 (CO), 172.3 (CO), 169.8 (CO), 141.7 and 138.8 and 141.7 (PhC-*ipso*), 126.6–128.8 (PhC), 74.6 (C2), 63.0 (C5), 53.0 (OCH_3), 51.4 (CH_2Ph), 33.1 and 30.0 (C3 and C4), 24.2 (CH_3); EIMS [*m/z* (%)]: 456 (M^+, 4), 397 (M^+-NH_2-$COCH_3$, 30), 351 (M^+-NCH_2Ph, 85), 91 ($PhCH_2^+$, 100); HRMS: calcd for $C_{28}H_{28}N_2O_4$: 456.2049, found 456.2044.

4.5.2. Methyl (2*S,5*R**)-5-(acetylamino)-1-benzyl-5-methyl-6-oxo-2-phenyl-2-piperidinecarboxylate (10c).** Yield: 93%; white crystals, mp: 109°C (CH_2Cl_2/hexane); IR (KBr, cm^{-1}): 1663 (CO), 1736 (CO); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 7.15–6.71 (m, 9H, PhH and NH), 6.51 (d, 2H, BnH*ortho*), 5.20 (d, 1H, *J*=15.8 Hz, $PhCH_2$), 3.91 (s, 3H, OCH_3), 3.74 (d, 1H, *J*=15.8 Hz, $PhCH_2$), 2.65–2.56 (m, 2H, H3eq and H4eq), 2.47 (td (ddd), 1H, *J*=15.0, 4.0 Hz, H3ax), 2.26 (td (ddd), 1H, *J*=15.0, 4.0 Hz, H4ax), 1.99 (s, 3H, $NCOCH_3$), 1.76 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 175.0 (CO), 172.5 (CO), 169.8 (CO), 138.6 and 138.3 (PhC-*ipso*), 126.2–128.5 (PhC), 74.6 (C2), 56.6 (C5), 53.0 (OCH_3), 50.6 (CH_2Ph), 33.4 and 30.8 (C3 and C4), 25.5 (CH_3) and 24.1 ($COCH_3$); EIMS [*m/z* (%)]: 394 (M^+, 10), 335 (M^+-NH_2-$COCH_3$, 44), 289 (M^+-NCH_2Ph, 100); HRMS: calcd for $C_{23}H_{26}N_2O_4$: 394.1893, found 394.1891.

4.5.3. Methyl (2*S,5*R**)-5-(acetylamino)-1-benzyl-6-oxo-2-phenyl-2-piperidinecarboxylate (10d).** Yield: 84%; white powder, mp: 177°C (CH_2Cl_2/hexane); IR (KBr, cm^{-1}): 1645 (CO), 1656 (CO); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 7.26–6.73 (m, 9H, PhH and NH), 6.51 (d, 2H, BnH*ortho*), 5.10 (d, 1H, *J*=15.4 Hz, $PhCH_2$), 4.52 (dt

(ddd), 1H, J=12, 5 Hz, H5), 3.83 (s, 3H, OCH_3), 3.79 (d, 1H, J=15.4 Hz, $PhCH_2$), 2.62–2.74 (m, 2H, CH_2CH_2), 2.60 (td (ddd), 1H, J=15.4, 5.1 Hz, H3ax), 2.04 (s, 3H, $NCOCH_3$), 1.58–1.66 (m, 1H, CH_2CH_2); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 172.2 (CO), 171.4 (CO), 170.6 (CO), 138.2 and 138.0 (PhC-*ipso*), 128.5–126.4 (PhC), 74.6 (C2), 53.0 (OCH_3), 52.0 (C5), 50.5 (CH_2Ph), 35.2 (CH_2), 26.3 (CH_2), 23.3 (CH_3); EIMS [*m/z* (%)]: 380 (M^+, 1), 321 ($M^+-NH_2COCH_3$, 9), 275 (M^+-NCH_2Ph, 31), 91 ($PhCH_2^+$, 100); HRMS: calcd for $C_{22}H_{24}N_2O_4$: 380.1736, found 380.1730.

4.6. General procedure for reduction of compounds 10b–d

To a solution of 1 mmol of **10b–d** in 15 mL of THF is added a solution of 1.1 mmol of $LiBH_4$ and 0.1 mmol of $LiEt_3BH$ in 5 mL of THF with a syringe under an inert atmosphere. The mixture is refluxed overnight. Upon cooling (0°C), 5 mL of MeOH is added and the mixture is filtered over Celite. The filtrate is evaporated under reduced pressure and the residue is purified by column chromatography (silica gel, CH_2Cl_2–MeOH 95–5) to afford compounds **11b–d** and **12**.

For the synthesis of compounds **13b–d** this procedure is modified by using 1.5 mmol of $LiBH_4$ and 0.15 mmol of $LiEt_3BH$.

4.6.1. (3*S,6*S**)-*N*-[1-Benzyl-6-(hydroxymethyl)-2-oxo-3,6-diphenyl-3-piperidinyl]acetamide (11b).** Yield: 62%; white crystals, mp: 96°C (Et_2O); IR (KBr, cm^{-1}): 1629 (CO), 3316 (OH and NHCO); ^1H NMR (400 MHz, $CDCl_3$, ppm): 7.19–7.56 (m, 14H, PhH and NH), 6.48 (d, 2H, BnH*ortho*), 4.95 (d, 1H, J=15.4 Hz, $PhCH_2$), 4.19 (d, 1H, J=11.7 Hz, CH_2OH), 4.10 (d, 1H, J=11.7 Hz, CH_2OH), 3.89 (d, 1H, J=15.4 Hz, $PhCH_2$), 3.42 (td (ddd), 1H, J=13.9, 3.3 Hz, H4ax), 2.92 (br s, 1H, OH), 2.48 (dt (ddd), 1H, J=13.9, 3.3 Hz, H4eq), 2.20 (dt (ddd), 1H, J=14.6, 3.3 Hz, H5eq), 2.02 (s, 3H, $COCH_3$), 1.87 (td, 1H, J=14.6, 3.3 Hz, H5ax); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 172.1 (CO), 170.6 (CO), 141.4 and 138.6 (PhC-*ipso*), 126.8–128.9 (PhC), 68.2 (CH_2OH), 65.5 (C6), 63.7 (C3), 49.0 (CH_2Ph), 32.0 and 29.5 (C4 and C5), 23.9 (CH_3); CIMS [*m/z* (%)]: 429 (MH^+, 100), 397 (MH^+-CH_3OH, 14), 370 ($MH^+-NHCOCH_3$, 14); HRMS: calcd for $C_{27}H_{28}N_2O_3$: 428.2099, $-CH_2OH$: 397.1916, found 397.1920.

4.6.2. (3*R,6*S**)-*N*-[1-Benzyl-6-(hydroxymethyl)-3-methyl-2-oxo-6-phenyl-3-piperidinyl]acetamide (11c).** Yield: 53%; white crystals, mp: 91°C (Et_2O); IR (KBr, cm^{-1}): 1628 (CO), 3312 (OH and NHCO); ^1H NMR (400 MHz, $CDCl_3$, ppm): 7.29–7.10 (m, 9H, PhH and NH), 6.65 (d, 2H, BnH*ortho*), 4.73 (d, 1H, J=15.4 Hz, $PhCH_2$), 4.16 (d, 1H, J=11.8 Hz, CH_2OH), 4.08 (d, 1H, J=11.8 Hz, CH_2OH), 4.00 (d, 1H, J=15.4 Hz, $PhCH_2$), 3.47 (br s, 1H, OH), 2.87 (td (ddd), 1H, J=13.5, 3.4 Hz, H4ax), 2.42 (dt (ddd), 1H, J=14.1, 3.6 Hz, H5eq), 2.10 (td (ddd), 1H, J=14.1, 3.6 Hz, H5ax), 1.98 (s, 3H, CH_3), 1.84 (dt (ddd), 1H, J=13.5, 3.4 Hz, H4eq), 1.65 (s, 3H, $5CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$, ppm):175.2 (CO), 170.0 (CO), 143.1 and 139.2 (PhC-*ipso*), 127.0–129.1 (PhC), 68.7 (CH_2OH), 66.2 (C6), 53.9 (C3), 49.3 (CH_2Ph), 33.1 and 30.4 (C4 and C5), 24.1 (CH_3); CIMS [*m/z* (%)]: 367 (MH^+, 100), 349 (MH^+-H_2O, 7), 335 (MH^+-CH_3OH, 7); HRMS: calcd for $C_{22}H_{26}N_2O_3$: 366.1943, $-CH_2OH$: 335.1760, found 335.1755.

4.6.3. (3*R,6*S**)-*N*-[1-Benzyl-6-(hydroxymethyl)-2-oxo-6-phenyl-3-piperidinyl]acetamide (11d).** Yield: 24%; colorless oil; ^1H NMR (400 MHz, $CDCl_3$, ppm): 7.31–7.18 (m, 9H, PhH and NH), 6.70 (d, 2H, BnH*ortho*), 5.02 (d, 1H, J=15.4 Hz, $PhCH_2$), 4.40 (dt (ddd), 1H, J=11.0, 5.6 Hz, H3), 4.02 (d, 1H, J=15.4 Hz, $PhCH_2$), 3.99 (d, 1H, J=12.1 Hz, CH_2OH), 3.90 (d, 1H, J=12.1 Hz, CH_2OH), 2.42–2.28 (m, 2H, CH_2), 2.24–2.10 (m, 1H, CH_2), 2.09–1.92 (m, 4H, CH_2 and CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 172.8 (CO), 170.4 (CO), 143.1 and 139.2 (PhC-*ipso*), 127.0–129.1 (PhC), 67.9 (CH_2OH), 67.0 (C6), 51.1 (C3), 48.2 (CH_2Ph), 34.3 and 25.1 (C4 and C5), 23.3 (CH_3); EIMS [*m/z* (%)]: 353 (M^+, 100); HRMS: calcd for $C_{21}H_{24}N_2O_3$: 353.1865, $-CH_2OH$: 321.1603, found 321.1603.

4.6.4. *N*-[(1*R,4*S**,7*S* *)-(2-Benzyl-7-hydroxy-3-oxo-1-phenyl-2-azabicyclo[2.2.1]hept-4-yl)]acetamide (12).** Yield: 55%; white crystals, mp: 204°C (CH_2Cl_2/hexane); IR (KBr, cm^{-1}): 1694 (CO), 3302 (NHCO and OH); ^1H NMR (400 MHz, DMSO-d6, ppm): 8.16 (broad s, 1H, NH), 7.32–7.34 (m, 3H, PhH), 7.21–7.23 (m, 2H, PhH), 7.15–7.17 (m, 3H, PhH), 6.75–6.80 (m, 2H, PhH), 5.76 (d, 1H, J=4.4 Hz, OH), 4.64 (d, 1H, J=4.4 Hz, H7), 4.19 (d, 1H, J=15.1 Hz, $PhCH_2$), 3.84 (d, 1H, J=15.1 Hz, $PhCH_2$), 2.20 (td (ddd), 1H, J=10.8, 3.7 Hz), $H6^b$), 2.10 (td (ddd), 1H, J=10.8, 2.5 Hz, $H5^b$), 1.91 (s, 3H, $COCH_3$), 1.55 (broad td (ddd), 1H, J=9.5, 2.5 Hz, $H6^a$), 1.47 (broad td (ddd), 1H, J=9.5, 3.7 Hz, $H5^a$); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 172.4 (CO), 169.5 (CO), 138.1 and 134.5 (PhC-*ipso*), 126.8–128.9 (PhC), 77.8 (CHOH), 71.7 (C4), 67.0 (C1), 42.8 (CH_2Ph), 27.4 and 27.0 (C5 and C6), 22.7 (CH_3); EIMS [*m/z* (%)]: 350 (M^+, 42), 291 ($M^+-CH_3CONH_2$, 15), 259 (M^+-PhCH_2, 27); HRMS: calcd for $C_{21}H_{22}N_2O_3$: 350.1630, found 350.1627.

4.6.5. (3*S-6*S**)-*N*-[1-Benzyl-6-(hydroxymethyl)-3,6-diphenyl-3-piperidinyl]acetamide (13b).** Yield: 53%; white powder, mp: 86°C (CH_2Cl_2/hexane); IR (KBr, cm^{-1}): 1659 (NHCO), 3374, 3317 (OH and NHCO); ^1H NMR (400 MHz, $CDCl_3$, ppm): 7.14–7.45 (m, 15H, PhH), 5.91 (broad s, 1H, NH), 4.56 (d, 1H, J=14.3 Hz, $PhCH_2$), 4.06 (t (dd), 1H, J=11.7 Hz, CH_2OH), 3.94 (t (dd), 1H, J=11.7 Hz, CH_2OH), 3.74 (d, 1H, J=14.3 Hz, $PhCH_2$), 2.96 (d, 1H, J=12.4 Hz, H2), 2.74 (broad d, 2H, OH and H2), 1.90–2.24 (m, 4H, CH_2CH_2), 1.89 (s, 3H, $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 169.0 (CO), 143.3 and 141.7 and 141.2 (PhC-*ipso*), 125.4–128.9 (PhC), 68.4 (CH_2OH), 65.5 (C6), 57.7 (C3), 56.8 and 55.1 (NCH_2, C2), 30.2 and 29.3 (C4 and C5), 23.9 (CH_3); CIMS [*m/z* (%)]: 415 (MH^+, 100), 397 (MH^+-H_2O, 8), 383 (MH^+-CH_3OH, 17); HRMS: calcd for $C_{27}H_{30}N_2O_2$: 414.2307, $-CH_2OH$: 383.2123, found: 383.2123.

4.6.6. (3*R-6*S**)-*N*-[1-Benzyl-6-(hydroxymethyl)-3-methyl-6-phenyl-3-piperidinyl]acetamide (13c).** Yield: 47%; viscous oil; ^1H NMR (300 MHz, $CDCl_3$, ppm): 7.25–7.38 (m, 10H, PhH), 5.44 (br s, 1H, NH), 4.35 (d, 1H,

J=13.9 Hz, $PhCH_2$), 4.05 (d, 1H, J=11.7 Hz, CH_2OH), 3.92 (d, 1H, J=11.7 Hz, CH_2OH), 3.72 (d, 1H, J=13.9 Hz, $PhCH_2$), 2.68 (d, 1H, J=12.4 Hz, NCH_2), 2.61 (dd, 1H, J=12.4, 1.5 Hz, NCH_2), 2.38 (dddd, 1H, J=13.5, 5.5, 4.0, 1.5 Hz, H4eq), 2.1 (ddd, 1H, J=13.9, 11.5, 4.0 Hz, H5ax), 1.96 (ddd, 1H, J=13.9, 5.5, 4.4 Hz, H5eq), 1.84 (s, 3H, $COCH_3$), 1.35 (ddd, 1H, J=13.5, 11.5, 4.4 Hz, H4ax), 1.24 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 169.6 (CO), 142.3 and 141.3 (PhC-*ipso*), 128.7–127.0 (PhC), 67.2 (CH_2OH), 64.5 (C6), 56.6 and 55.0 (NCH_2, C2), 52.1 (C3), 30.7 and 29.5 (C4 and C5), 24.3 and 23.8 (2×CH_3); EIMS [m/z (%)]: 352 (M^+, 1), 321 ($M^+-HOCH_2^+$, 100), 262 ($M^+-HOCH_2^+-NH_2COCH_3$); HRMS: calcd for $C_{22}H_{28}N_2O_2$: 352.2151, $-CH_2OH$: 321.1967, found 352.2140, 321.1978.

4.7. General procedure for the etherification of compounds 11b–d and 13b,c

To a suspension of 1 mmol of NaH in 2 mL of dry DMF is added a solution of 0.5 mmol of **11b**,**c**,**d** or **13b**,**c** in 2.5 mL of DMF. This mixture is stirred at room temperature for 1 h and then cooled in an ice bath. To the cooled mixture is added 0.6 mmol of 3,5-bis(trifluoromethyl)benzyl bromide. The ice bath is removed and the mixture is stirred at room temperature for 1 h. Following addition of 2 mL of CH_2Cl_2, 2 mL of MeOH and 5 mL of water, the mixture is extracted with CH_2Cl_2 (3×50 mL). The organic layers are collected and dried over $MgSO_4$, filtered and evaporated under reduced pressure. The products are purified by column chromatography (silica gel, CH_2Cl_2 for **3b**, CH_2Cl_2–MeOH (98–2) for **3c** and **3d**, CH_2Cl_2–MeOH (95–5) for **4b** and **4c**).

4.7.1. (3S^*-6S^*)-*N*-[1-Benzyl-6-({[3,5-bis(trifluoromethyl)benzyl]oxy}methyl)-2-oxo-3,6-diphenyl-3-piperidinyl]acetamide (3b). Yield: 65%; white crystals, mp: 58°C (CH_2Cl_2/hexane); IR (KBr, cm^{-1}): 1662 (CO), 1670 (CO); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 7.79 (s, 1H, ArH4), 7.68 (s, 2H, ArH2 and ArH6), 7.07–7.59 (m, 14H, PhH and NH), 6.48 (d, 2H, BnH*ortho*), 4.85 (d, 1H, J=15.1 Hz, $PhCH_2$), 4.50 (d, 1H, J=12.6 Hz, CH_2OCH_2-Ar), 4.44 (d, 1H, J=12.6 Hz, CH_2OCH_2Ar), 4.20 (d, 1H, J=10.0 Hz, CH_2OCH_2Ar), 3.95 (d, 1H, J=15.1 Hz, $PhCH_2$), 3.93 (d, 1H, J=10.0 Hz, CH_2OCH_2Ar), 3.23 (td (ddd), 1H, J=14.2, 2.9 Hz, H4ax), 2.62 (dt (ddd), 1H, J=14.2, 2.9 Hz, H5eq), 2.26 (dt (ddd), 1H, J=14.6, 2.9 Hz, H4eq), 2.01 (s, 3H, $COCH_3$), 1.92 (td (ddd), 1H, J=14.6, 2.9 Hz, H5ax); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 172.0 (CO), 170.2 (CO), 142.4 and 141.5 and 140.5 and 138.6 (PhC-*ipso*), 131.6 (q, J=33 Hz, CF_3), 126.8–128.9 (PhC), 123.3 (q, J=273 Hz, CF_3), 72.9 and 71.6 (2×CH_2O), 67.4 (C6), 63.7 (C3), 49.0 (CH_2Ph), 31.8 and 29.0 (C4 and C5), 24.0 (CH_3); CIMS [m/z (%)]: 655 (MH^+, 100), 635 (MH^+-HF, 19), 397 ($MH^+-(CF_3)_2C_6H_3CH_2OCH_3$, 23); HRMS: calcd for $C_{36}H_{32}N_2O_3F_6$: 654.2317, found 654.2314.

4.7.2. (3R^*-6S^*)-*N*-[1-Benzyl-6-({[3,5-bis(trifluoromethyl)benzyl]oxy}methyl)-3-methyl-2-oxo-6-phenyl-3-piperidinyl]acetamide (3c). Yield: 63%; white powder, mp: 69°C (CH_2Cl_2); IR (KBr, cm^{-1}): 1667 (CO), 1673 (CO); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 7.78 (s, 1H, ArH4), 7.64 (s, 2H, ArH2 and ArH6), 7.02–7.31 (m, 9H, PhH and NH), 6.26 (d, 2H, BnH*ortho*), 4.70 (d, 1H, J=15.4 Hz, $PhCH_2$), 4.44 (d, 1H, J=12.6 Hz, CH_2OCH_2-Ar), 4.30 (d, 1H, J=12.6 Hz, CH_2OCH_2Ar), 4.13 (d, 1H, J=9.9 Hz, CH_2OCH_2Ar), 4.05 (d, 1H, J=15.4 Hz, $PhCH_2$), 3.95 (d, 1H, J=9.9 Hz, CH_2OCH_2Ar), 2.70 (td (ddd), 1H, J=13.5, 4.4 Hz, H4ax), 2.41 (dt (ddd), 1H, J=14.6, 4.4 Hz, H5eq), 2.11 (td (ddd), 1H, J=14.6, 4.4 Hz, H5ax), 2.06 (dt (ddd), 1H, J=13.5, 4.4 Hz, H4eq), 2.00 (s, 3H, $COCH_3$), 1.70 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 174.6 (CO), 169.9 (CO), 142.2 and 140.5 and 138.8 (PhC-*ipso*), 131.4 (q, J=33 Hz, CF_3), 126.9–129.1 (PhC), 124.1 (q, J=273 Hz, CF_3), 73.4 and 71.6 (2×CH_2O), 67.3 (C6), 65.5 (C3), 48.9 (CH_2Ph), 32.8 and 29.5 (C4 and C5), 25.9 (CH_3), 23.9 ($NCOCH_3$); CIMS [m/z (%)]: 593 (MH^+, 100), 573 (MH^+-HF, 31), 335 ($MH^+-(CF_3)_2C_6H_3CH_2OCH_3$, 30); HRMS: calcd for $C_{31}H_{30}N_2O_3F_6$: 592.2165, found 592.2158.

4.7.3. (3R^*-6S^*)-*N*-[1-benzyl-6-({[3,5-bis(trifluoromethyl)benzyl]oxy}methyl)-2-oxo-6-phenyl-3-piperidinyl]acetamide (3d). Yield: 51%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 7.76 (s, 1H, ArH4), 7.67 (s, 2H, ArH2 and ArH6), 7.07–7.29 (m, 9H, PhH and NH), 6.59 (d, 2H, BnH*ortho*), 5.02 (d, 1H, J=15.4 Hz, $PhCH_2$), 4.47 (d, 1H, J=12.6 Hz, CH_2OCH_2Ar), 4.37 (ddd, 1H, J=10.7, 5.1 Hz, H3ax), 4.28 (d, 1H, J=12.6 Hz, CH_2OCH_2Ar), 4.12 (d, 1H, J=9.9 Hz, CH_2OCH_2Ar), 4.02 (d, 1H, J=15.4 Hz, $PhCH_2$), 3.91 (d, 1H, J=9.9 Hz, CH_2OCH_2Ar), 2.02–2.39 (m, 7H, CH_2CH_2 and CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 173.2 (CO), 170.0 (CO), 143.1 and 139.3 and 138.4 (PhC-*ipso*), 131.1 (q, J=30 Hz, CF_3), 126.6–129.1 (PhC), 123.9 (q, J=272 Hz, CF_3), 73.1 and 71.4 (2×CH_2O), 68.0 (C6), 51.4 (C3), 48.6 (CH_2Ph), 33.1 and 31.2 (C4 and C5), 23.4 (CH_3); CIMS [m/z (%)]: 579 (MH^+, 100), 559 (MH^+-HF, 27), 321 ($MH^+-(CF_3)_2C_6H_3CH_2OCH_3$, 21).

4.7.4. (3S^*-6S^*)-*N*-[1-Benzyl-6-({[3,5-bis(trifluoromethyl)benzyl]oxy}methyl)-3,6-diphenyl-3-piperidinyl]-acetamide (4b). Yield: 58%; white crystals, mp: 67°C (CH_2Cl_2/hexane); IR (KBr, cm^{-1}): 1669 (CO), 3061 (NHCO); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 7.79 (s, 1H, ArH4), 7.73 (s, 2H, ArH2 and ArH6), 7.12–7.44 (m, 15H, PhH), 5.84 (s, 1H, NH), 4.68 (d, 1H, J=12.4 Hz, CH_2-OCH_2Ar), 4.62 (d, 1H, J=12.4 Hz, CH_2OCH_2Ar), 4.27 (d, 1H, J=13.5 Hz, $PhCH_2$), 4.07 (d, 1H, J=9.9 Hz, CH_2-OCH_2Ar), 3.87 (d, 1H, J=9.9 Hz, CH_2OCH_2Ar), 3.76 (d, 1H, J=13.5 Hz, $PhCH_2$), 2.92 (d, 1H, J=12.8 Hz, H2), 2.70–2.86 (m, 2H, CH_2CH_2 and H2), 2.27–2.38 (m, 1H, CH_2CH_2), 1.86–2.10 (m, 2H, CH_2CH_2), 1.85 (s, 3H, $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 169.5 (CO), 143.7 and 143.1 and 141.5 and 141.2 (PhC-*ipso*), 132.1 (q, J=33 Hz, CF_3), 125.5–129.3 (PhC), 123.7 (q, J=272 Hz, CF_3), 72.5 and 71.8 (2×CH_2O), 65.2 (C6), 57.3 (C3), 56.5 and 55.6 (2×NCH_2), 31.0 and 27.1 (C4 and C5), 24.3 (CH_3); CIMS [m/z (%)]: 641 (MH^+, 2), 581 ($MH^+-NHCOCH_3$, 41), 383 ($MH^+-(CF_3)_2C_6H_3CH_2OCH_3$, 80), 324 ($MH^+-(CF_3)_2C_6H_3CH_2OCH_3-NHCOCH_3$, 41); HRMS: calcd for $C_{36}H_{34}N_2O_2F_6$: 640.2524, $-NH_2COCH_3$: 581.2153 found: 581.2151.

4.7.5. (3R^*-6S^*)*N*-[1-Benzyl-6-({[3,5-bis(trifluoromethyl)benzyl]oxy}methyl)-3-methyl-6-phenyl-3-piperidinyl]acetamide (4c). Yield: 50%; colorless oil; ^{1}H NMR

(300 MHz, $CDCl_3$, ppm): 7.80 (s, 1H, ArH4), 7.75 (s, 2H, ArH2 and ArH6), 7.54 (d, 2H, J=7.3 Hz, PhH), 7.40–7.24 (m, 8H, PhH), 5.41 (br s, 1H, NH), 4.69 (d, 1H, J=12.8 Hz, CH_2OCH_2Ar), 4.62 (d, 1H, J=12.8 Hz, CH_2OCH_2Ar), 4.01–4.10 (m, 2H, $PhCH_2$ and CH_2OCH_2Ar), 3.94 (d, 1H, J=10.3 Hz, CH_2OCH_2Ar), 3.76 (d, 1H, J=13.9 Hz, $PhCH_2$), 2.66 (d, 1H, J=12.4 Hz, NCH_2), 2.60 (d, 1H, J=12.4 Hz, NCH_2), 2.44 (ddd, 1H, J=13.4, 7.5, 4.0 Hz, H4eq), 2.17 (ddd, 1H, J=13.9, 9.2, 4.0 Hz, H5ax), 2.03 (ddd, 1H, J=13.9, 7.5, 4.0 Hz, H5eq), 1.80 (s, 3H, $COCH_3$), 1.39 (ddd, 1H, J=13.4, 9.2, 4.0 Hz, H4ax), 1.26 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 169.6 (CO), 143.6 and 141.3 and 140.9 (PhC-*ipso*), 131.6 (q, J=33 Hz, CF_3), 126.9–128.4 (PhC), 123.3 (q, J=272 Hz, CF_3), 73.8 and 72.0 (2×CH_2O), 63.8 (C6), 55.5 ($PhCH_2N$), 55.1 (NCH_2), 52.2 (C3), 31.6 and 29.7 (C4 and C5), 24.2 and 23.8 (2×CH_3); EIMS [m/z (%)]: 578 (M^+, 2), 519 ($M^+-NH_2COCH_3$, 64), 321 ($M^+-(CF_3)_2C_6H_3CH_2OCH_2^+$, 100), 262 ($M^+-(CF_3)_2C_6H_3CH_2OCH_2^+-NH_2COCH_3$, 69); HRMS: calcd for $C_{31}H_{32}F_6N_2O_2$: 578.2368, found 578.2367.

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