Stereodivergent Diversity-Oriented Synthesis: Exploiting the Versatility of 2-Piperidine Ethanol

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Abstract: A sequence of seven reactions (stereocontrolled allylation, Mitsunobu reaction, ring closing metathesis and amino/amido intramolecular nucleophilic addition) efficiently convert the inexpensive starting 2-piperidine ethanol in a small library of enatiomerically pure nitrogen containing compounds characterized by three new scaffolds that present a relevant diversity. The simple approach results challenging to continue the exploration of the chemical space.

Introduction

Nowadays, small molecules are an efficient tool in medicinal chemistry, as entities to probe biological pathways and as potential drug candidates. Among the methods useful for the generation of small molecules, diversity-oriented synthesis (DOS) is a really appealing one. Significant achievements were recently obtained in this field, and DOS confirmed its importance as a tool for the discovery of novel, biologically interesting small molecules.[1-3] In contrast to other approaches, such as the targeted-oriented synthesis (TOS) or combinatorial chemistry, DOS aims to obtain a wide distribution of compounds in the chemical space, investigating in this way its unexplored or poorly populated portions, that can be promising sources for drug discovery.[4, 5]

In the field of DOS, different efforts were made in our laboratory in the last years, exploiting the 2-piperidine ethanol as versatile precursor. This reagent, which is really cheap in its racemic form, contains two handles – the piperidine nitrogen and the hydroxyl group – which can be easily further functionalized, increasing in this way the structural complexity. This prompted us to exploit the 2-piperidine ethanol in a diversity-oriented approach aimed at the obtainment of a small library of piperidine-containing derivatives. Considering our interest in natural products, we took advantage of this approach to synthesize some alkaloids (aloperine,[6] different sedum alkaloids,[7] dumetorine, epidihydropinidine, coniine,[8] boehmeriasin A[9]) but also some synthetic derivatives, such as polyheterocyclic derivatives[10] and hybrid compounds (Figure 1).[11,12]

Results and Discussion

Encouraged by the demonstrated versatility of the 2-piperidine ethanol, we devised to further expand the library of piperidine-based derivatives according to the synthetic plan depicted in Scheme 1.

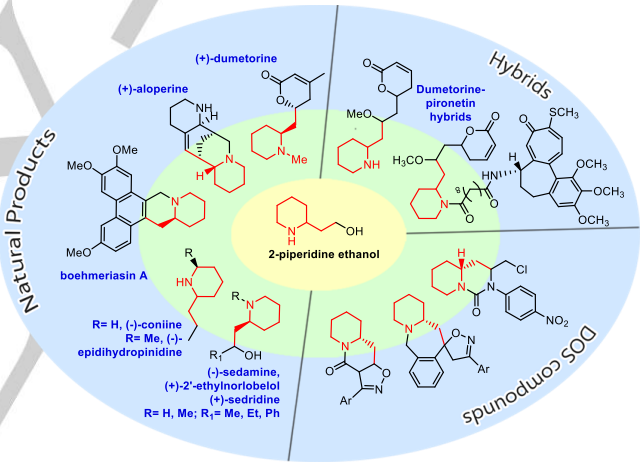
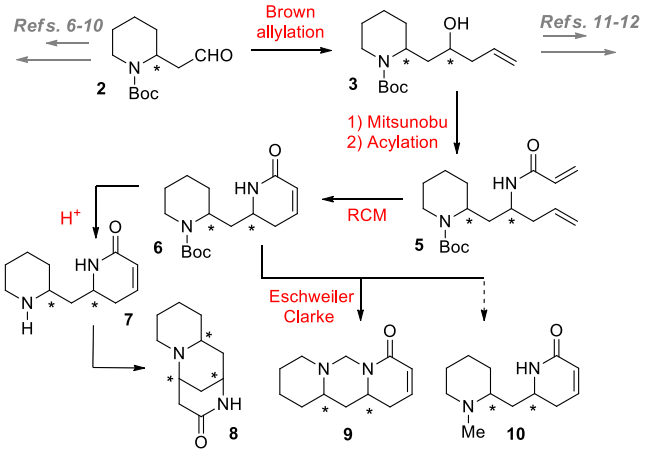


Figure 1. Structures of the previously synthesized compounds

The exploitation of the reactivity of the aminoaldehyde **2** and the reaction sequence based on stereocontrolled allylation, Mitsunobu reaction, ring closing metathesis (RCM) and intramolecular amine/amide addition, sounded challenging for a further investigation of the unexplored chemical space.



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Scheme 1. Forward-synthetic approach.

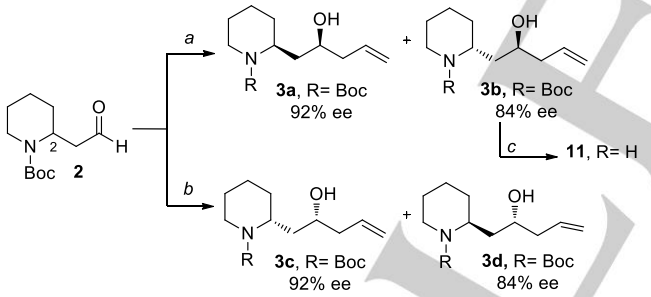
The homoallylic alcohol **3**, resulting from the stereocontrolled allylation of **2**, would be converted into the corresponding amine. Acylation, followed by a ring closing metathesis, should lead to a 6-membered unsaturated lactam **6**. This scaffold appears to be a versatile starting point to achieve further structural diversifications. The cleavage of the Boc protecting group should lead to the free amine **7**, which could eventually undergo an intramolecular aza-Michael addition, to generate the tricyclic compound **8**. Under Eschweiler-Clarke conditions, the obtained iminium salt could be reduced by hydrogen transfer, leading to compound **10**, or attacked by the lactam nitrogen, affording the octahydrodipyrido pyrimidone **9**.

Thus, starting from **2**, the synthesis of four new polyheterocyclic scaffolds should be possible.

Considering that the main scaffold **6** is characterized by the presence of two stereocenters, we envisaged a stereodivergent protocol, aimed at the obtainment of all the possible stereoisomers. We planned to introduce stereo-divergency taking advantage of a highly stereoselective allylation on the racemic aldehyde **2**.[13,14]

In detail, aldehyde **2**, obtained from the 2-piperidine ethanol as reported previously,[10] underwent a Brown's asymmetric allylboration, to access all the four stereoisomers of the homoallylic alcohol **3**. To this extent, **2** was treated with both (+)- and (-)- B-allyl di-isopinocampheylboranes, generated reacting the proper di-isopinocampheylboron chloride (DIP-Cl) enantiomer with allylmagnesium bromide. The diastereomeric alcohols **3a** and **3b** were obtained reacting the aldehyde with (-)- B-allyl di-isopinocampheylborane, and were separated through column chromatography (*d.r.* ≈ 1 : 1).

Using (+)-B-allyl di-isopinocampheylborane in the same conditions, **3c** and **3d** were accessed as well (*d.r.* ≈ 1 : 1), (Scheme 2).

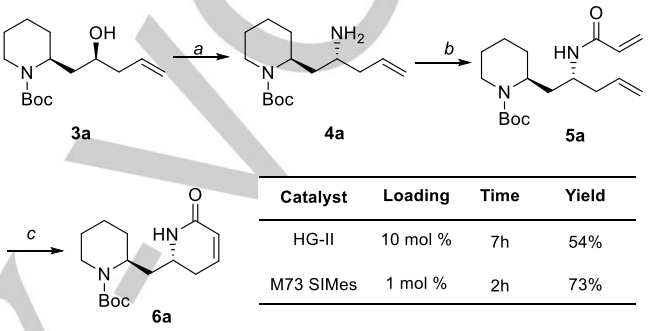


Scheme 2. *Reagent and conditions. a*) (-)-allylBIpc$_2$ (from (-)-DIP-Cl and allylmagnesium bromide), THF, -78°C to r.t., 4 h, 90% overall yield; *b*) (+)-allylBIpc$_2$ (from (+)-DIP-Cl and allylmagnesium bromide), THF, -78°C to r.t., 4 h, 88% overall yield; *c*) TFA, CH_2Cl_2, 0°C to r.t., 18h, yield: 90%.

The relative *syn/anti* configuration was assigned on the basis of X-rays analysis, performed on one of the anti- isomer, after the cleavage of the Boc protecting group, leading to **11** (Scheme 2). The relative (*S*, *R*) configuration was secured by single-crystal X-ray diffraction. Full details are reported in the Supplementary Materials (see also Figure S1). The absolute configuration is determined by the configuration of the used DIP-Cl. To confirm the absolute configuration, a stereoselective allylation with (+)-DIP-Cl was performed on small scale on the enantiopure aldehyde **2**-(R),[15,16] confirming the obtainment of **3c**.

The enantiopurity of our alcohols was determined through chiral HPLC on reverse phase. *Syn*-isomers (**3a** and **3c**), were obtained with a 92% ee while the *anti*-alcohols (**3b** and **3d**), were accessed with 84% ee. For *syn*-compounds, the result was also confirmed through ^{1}H-NMR, registering the spectra in the presence of (R)-(−)-1-(9-anthryl)-2,2,2-trifluoroethanol[17] as chiral solvating agent. (Figure S3, Supp.Info.).

With compounds **3a-d** in our hands, a Mitsunobu reaction in the presence of diphenylphosphoryl azide (DPPA) was performed,[18] followed by a Staudinger reduction of the obtained azide.[19] In this way, the interconversion of compounds **3a-d** into the corresponding amines (**4a-d**) was achieved with inversion of configuration. The amines were treated with acryloyl chloride (**5a-d**), affording the amides, which were converted into lactams (**6a-d**) through a ring-closing metathesis (RCM). Scheme 3 reports the three steps procedure for the conversion of **3a** into **6a**.

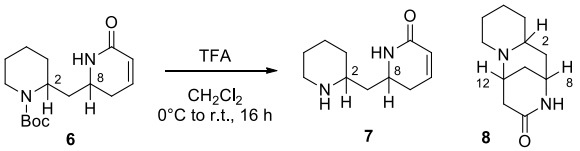


Catalyst	Loading	Time	Yield
HG-II	10 mol %	7h	54%
M73 SIMes	1 mol %	2h	73%

Scheme 3. *Reagent and conditions*: *a)* i. PPh_3, DIAD, DPPA, THF, 0°C to r.t., 4h; ii. PPh_3, THF/H_2O 10:1, 5h, 40°C, yield: 62% over two steps; *b)* TEA, acryloyl chloride, CH_2Cl_2, 0°C to r.t., 2h, yield: 63%; *c)* Ru-catalyst, CH_2Cl_2, 50°C, 1.5-7 h, yield: 73%. (Reported on compounds **a** as example)

To this extent, two different catalysts were used: a 2nd generation Hoveyda-Grubbs (HG-II) (yields 54-60%) and a Umicore M73 SIMes (yields 73-80%).[20] The latter resulted to be our catalyst of choice, because it proved to be more efficient for the obtainment of products **6a-d,** as reported in Scheme 3. Chiral HPLC analysis of these fundamental building blocks confirmed the maintenance of the previously observed enantiomeric excesses.

Compounds **6a-d** were treated with TFA, to remove the Boc protecting group. We realized that while *syn*-compounds gave the expected deprotected amines **7b** and **7d**, the *anti*-substrates underwent directly the intramolecular aza-Michael addition on the *α,β*-unsaturated lactam, leading to the formation of the tricyclic compounds **8a** and **8c** (Scheme 4).The configuration of the newly formed stereocenter at position 12 is defined by the configuration of the present stereocenters (Scheme 4).



	Starting material			Product				
		H-2	*H-8*		*H-2*	*H-8*	*H-12*	Yield
Syn	**6b**(2*R*, 8*R*)	β	β	**7b**(2*R*,8*R*)	β	β	-	66%
	6d(2*S*,8*S*)	α	α	**7d**(2*S*,8*S*)	α	α	-	70%
Anti	**6a**(2*S*, 8*R*)	α	β	**8a**(2*S*,8*S*,12*R*)	α	α	α	>95%
	6c(2*R*, 8*S*)	β	α	**8c**(2*R*,8*R*,12*S*)	β	β	β	>95%

Scheme 4. Outcome of compounds **6** Boc removal.

The different outcome of compounds **6** deprotection can be explained taking into consideration the 3D structures and energies of the transition states leading to the tricyclic compounds **8** (Figure 2). We hypothesize a late transition state (TS), similar in energy to the final products, according to Hammond's postulate. The reactant and TS structure have been optimized with semi-empirical calculations using the PM6 model.[21] The Intrinsic Reaction Coordinate pathway connecting reactants to the TS has been also calculated for both the diastereomers. *Syn*-compounds showed a higher activation energy with respect to the *anti*-ones. In particular, the activation energy associated to the *anti*-compounds is 9.28 Kcal/mol, while the activation energy of the *syn*-compounds is 11.54 Kcal/mol. The calculated activation energy difference of 2.26 Kcal/mol is in qualitative agreement with experimental results. This could explain why *syn*-products **6b** and **6d** can be effectively deprotected, leading to **7b** and **7d**, while *anti*-products tend to cyclize, producing **8a** and **8c**.

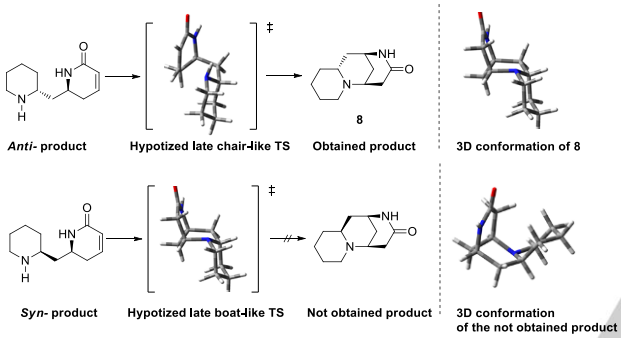
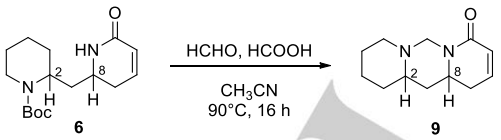


Figure 2. Hypothetic transition states leading to the formation of the Michael adducts.

Finally, an Eschweiler-Clarke reaction[22-24] was performed on all the stereoisomers of the fundamental scaffold **6**, affording in all of the cases the octahydrodipyrido pyrimidinones **9** (Scheme 5) and not the corresponding methyl amines **10** (Scheme 1).



	Starting material			Product			
		H-2	*H-8*		*H-2*	*H-8*	Yield
Syn	**6b**(2*R*, 8*R*)	β	β	**9b**(2*R*, 8*R*)	α	β	80%
	6d(2*S*,8*S*)	α	α	**9d**(2*S*, 8*S*)	β	α	77%
Anti	**6a**(2*S*, 8*R*)	α	β	**9a**(2*S*, 8*R*)	β	β	68%
	6c(2*R*, 8*S*)	β	α	**9c**(2*R*, 8*S*)	α	α	65%

Scheme 5. Outcome of Eschweiler-Clarke reaction.

The formation of scaffold **9** was explained by the intramolecular nucleophilic attack of the lactam nitrogen on the imminium salt, which resulted to be favored over the hydride transfer by the formate anion.
To obtain scaffold **10**, a reduction of the imminium salt with a stronger reducing agent, such as $NMe_3 \cdot BH_3$ complex, was attempted. Unfortunately, this reaction resulted in a complex mixture of products, impossible to purify.
In summary, 16 compounds, presenting three new scaffolds, were obtained through this DOS approach. It is noteworthy that compounds **8** presents the isomeric scaffold of some lupin alkaloids, such as cytisine, sparteine and anagyramide,[25-28] while products **9** are characterized by a simplified structure of several Lycopodium alkaloids, like lycocernuine and cernuine.[29,30]]

Conclusions

The described results confirm 2-piperidine ethanol as a valuable and versatile building block for the obtainment of diversified library of new polycyclic nitrogen containing compounds. The availability of a versatile synthon makes diversity-oriented synthesis a fruitful tool for the exploration of the chemical space.[31] Seven reaction steps based on stereocontrolled allylation, Mitsunobu reaction, ring closing metathesis and amino/amido intramolecular nucleophilic additions generated three new scaffolds with a relevant diversity. Computational studies support the different experimental outcomes of two diastereomeric compounds in the intramolecular aza-nucleophilic addition.

Experimental Section

Chemistry

General: Unless otherwise stated, reagents and solvents were purchased from Sigma Aldrich, Fluorochem or TCI and used without further purification. All reactions were carried out in oven-dried glassware and dry solvents, under nitrogen atmosphere and were monitored by thin layer chromatography (TLC) on silica gel (Merck precoated 60F254 plates), with detection by UV light (254 nm) or by solutions of potassium permanganate stain or ninhydrin. Flash chromatography was performed using silica gel (240-400 mesh, Merck) as stationary phase.
^{1}H-NMR spectra were recorded on a Bruker Avance Spectrometer and are reported relative to residual $CDCl_3$ or CD_3OD. ^{13}C-NMR spectra were recorded on the same instruments (100 MHz) and are reported relative to residual $CDCl_3$ or CD_3OD. All 1D and 2D NMR spectra were collected using the standard pulse sequences available with Bruker Topspin 1.3. Chemical shifts (δ) for proton and carbon resonances are quoted in parts per million (ppm) relative to tetramethylsilane (TMS), used as an internal standard. Data for ^{1}H-NMR are reported as follows: chemical shift (δ/ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, m = multiplet, bs = broad singlet. Data for ^{13}C-NMR are reported in terms of chemical shift (δ/ppm).
Mass spectra were registered exploiting the electrospray ionization (ESI) technique, on a Q-Tof micro mass spectrometer. Specific rotation values were measured on a P-1030 Jasco polarimeter, using 1 mL cells, with path length of 10 cm. Measures were collected at 20-25°C, using sodium D line wavelength λ=589 nm. HPLC analysis were performed using a 15 cm X 4.6 mm Chiralcel® AD-RH RP column at 35°C. Detection occurred at two different wavelengths (254 nm and 204 nm).

General procedure for the synthesis of (S)-tert-butyl 2-((S)-2-hydroxypent-4-enyl)piperidine-1-carboxylate (3a), (R)-tert-butyl 2-((S)-2-hydroxypent-4-enyl)piperidine-1-carboxylate (3b), (R)-tert-butyl 2-((R)-2-hydroxypent-4-enyl)piperidine-1-carboxylate (3c), (S)-tert-butyl 2-((R)-2-hydroxypent-4-enyl)piperidine-1-carboxylate, (3d).[11]

Allylmagnesium bromide (1 M solution in Et_2O, 2.86 mL, 2.86 mmol) was added dropwise to a solution of (–)-DIP-Cl (1.06 g, 3.30mmol) in anhydrous THF (13.5 mL), previously cooled at –78 °C. The reaction mixture was warmed to 0 °C and stirred at this temperature for 1 h. The solution was allowed to stand until magnesium chloride precipitated. The supernatant solution was carefully transferred to another flask and cooled at -78°C.Then, a solution of aldehyde **2** (0.500 g, 2.20 mmol) in anhydrous THF (6.5 mL) was added dropwise. The resulting solution was stirred at -78°C for 1 h and then 16 h at room temperature. The reaction was quenched with NaH_2PO_4 buffer solution at pH 7 (13.5 mL), MeOH (13.5 mL) and 30 % H_2O_2 (6.7 mL). After stirring for 30 min, the mixture was washed with saturated aqueous $NaHCO_3$ and extracted with Et_2O. The combined organic phases were dried over Na_2SO_4 and filtered. The solvent was evaporated under vacuum, and the residue was purified by column chromatography on silica gel (hexane/EtOAc, 8:2) to give **3a** and **3b** as yellow oils (90% overall yield). In order to obtain the other couple of diastereomers (**3c** and **3d**), the reaction was performed in the same way, using the (+)-DIP-Cl.

(S)-tert-butyl 2-((S)-2-hydroxypent-4-enyl)piperidine-1-carboxylate (3a). Yield: 44%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.81–5.91 (m, 1H), 5.08 (d, J = 17.4 Hz, 1H), 5.05 (d, J =9.7 Hz, 1H), 4.47 (bs, 1H), 3.95 (bs, 1H), 3.39 (bs, 1H), 2.66 (dt, J = 12.7, 2.0 Hz, 1H), 2.27–2.33 (m, 1H), 2.16–2.23 (m, 1H), 2.01 (dt, J = 12.5, 1.8 Hz, 1H), 1.73–1.76 (m, 1H), 1.42 (s, 9H), 1.35–1.59 (m, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.1, 135.5, 116.6, 80.2, 67.1, 46.2, 41.1, 39.3, 36.9, 29.2, 28.6, 25.3, 19.4 ppm. $[\alpha]_D^{20}$ = –33 (*c* = 1, $CHCl_3$). ESIMS *m/z* $[M + H]^+$ calcd. for $C_{15}H_{28}NO_3$: 270.2069, found: 270.2072. HPLC analysis: Chiralcel AD-RH RP column, 1 mL/min, $CH_3CN:H_2O$ = 35:65, 96 bar, λ: 204 nm, t_R: 21.342 min, ee%: 92%.

(R)-tert-butyl 2-((R)-2-hydroxypent-4-enyl)piperidine-1-carboxylate (3c). Yield: 42% $[\alpha]_D^{20}$ = +35 (*c* = 0.8, $CHCl_3$). ESIMS *m/z* $[M + H]^+$ calcd. for $C_{15}H_{28}NO_3$: 270.2069, found: 270.2073. HPLC analysis: Chiralcel AD-RH RP column, 1 mL/min, $CH_3CN:H_2O$ = 35:65, 96 bar, λ: 204 nm, t_R: 11.05 min, ee%: 92%.

(R)-tert-butyl 2-((R)-2-hydroxypent-4-enyl)piperidine-1-carboxylate (3b). Yield: 46%. ^{1}H NMR (400 MHz, $CDCl_3$): *δ*= 5.85–5.75 (m, 1H), 5.10 (d, *J* = 17.3 Hz, 1H), 5.08 (d, *J* = 9.8 Hz, 1H), 4.32 (br. s, 1H), 3.88–3.93 (m, 1H), 3.88–3.93 (m, 1H), 3.65 (tt, *J* = 7.5, 2.4 Hz,1H), 2.79 (dt, *J* = 12.8, 0.2 Hz,1 H), 2.27–2.32 (m, 1H), 2.14–2.21 (m, 1H), 1.77–1.82 (m, 1H), 1.42 (s,9 H), 1.35–1.59 (m, 6H) ppm. ^{13}C NMR (100 MHz,$CDCl_3$): *δ*= 155.29, 135.06, 117.4, 79.6, 71.3, 48.0, 41.8, 38.8, 37.0, 28.9, 28.4, 25.5, 18.9 ppm. $[\alpha]_D^{20}$ = +15 (*c* = 0.9, $CHCl_3$). ESIMS *m/z* $[M+ H]^+$ calcd. for $C_{15}H_{28}NO_3$: 270.2069, found: 270.2071. HPLC analysis: Chiralcel AD-RH RP column, 1 mL/min, $CH_3CN:H_2O$ = 35:65, 96 bar, λ: 204 nm, t_R: 8.12 min, ee%: 84%.

(S)-tert-butyl 2-((R)-2-hydroxypent-4-enyl)piperidine-1-carboxylate, (3d). Yield: 46%. $[\alpha]_D^{20}$ = –14 (*c* = 13.3, $CHCl_3$). ESIMS *m/z* $[M +H]^+$ calcd. for $C_{15}H_{28}NO_3$: 270.2069, found: 270.2068. HPLC analysis: Chiralcel AD-RH RP column, 1 mL/min, $CH_3CN:H_2O$ = 35:65, 96 bar, λ: 204 nm, t_R: 9.24 min, ee%: 84%.

General procedure for the synthesis of (S)-tert-butyl 2-((R)-2-aminopent-4-enyl)piperidine-1-carboxylate (4a), (R)-tert-butyl 2-((R)-2-aminopent-4-enyl)piperidine-1-carboxylate (4b), (R)-tert-butyl 2-((S)-2-aminopent-4-enyl)piperidine-1-carboxylate (4c), (S)-tert-butyl 2-((S)-2-aminopent-4-enyl)piperidine-1-carboxylate (4d).

PPh_3 (0.277 g, 1.06 mmol) was added to a solution of **3** (0.237 g, 0.88 mmol) in anhydrous THF (7.5 mL) at room temperature. The reaction mixture was cooled at 0°C and diisopropylazodicarboxylate (DIAD) (209 µL, 1.06 mmol) was carefully added dropwise. After 10 minutes, diphenylphosphorylazide (DPPA) (228 µL, 1.06 mmol) was slowly added as well. The reaction mixture was warmed to room temperature and stirred for 4 h. The solvent was evaporated under vacuum and the residue was purified by column chromatography on silica gel (Hexane/EtOAc, 95:5), to give the azide as a light yellow oil, which was immediately used in the next step. The azide (0.194 g, 0.66 mmol), was dissolved in THF (11.5 mL) and treated with PPh_3 (0.346 g, 1.32 mmol) and water (1.2 mL). The reaction mixture was warmed to 40°C and stirred at that temperature for 5 h. The reaction mixture was cooled to room temperature and water (5 mL) was added carefully. The layers were separated and the aqueous one was extracted with Et_2O. The collected organic phases were washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 9:1) to give **4** as a light yellow oil.

(S)-tert-butyl 2-((R)-2-aminopent-4-enyl)piperidine-1-carboxylate (4a). Yield: 62% over two steps. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87 – 5.73 (m, 1H), 5.20 – 5.10 (m, 2H), 4.37 (m, 1H), 3.96-3.94 (m, 1H), 3.30 (bs, 2H), 2.86-2.80 (m, 2H), 2.48 – 2.37 (dt, J = 13.5, 5.3 Hz, 1H), 2.15 (dt, J = 13.3, 6.4 Hz, 1H), 1.97 – 1.86 (m, 1H), 1.67 – 1.49 (m, 6H), 1.45 (s, 9H), 1.41-1.35 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.97, 134.67, 118.38, 79.50, 48.76, 47.80, 40.86, 38.99, 36.20, 29.02, 28.49 (3 CH_3), 25.56, 19.07 ppm. $[\alpha]_D^{20}$ = -30 (*c* = 1.02, $CHCl_3$). ESIMS m/z $[M + Na]^+$ calcd. for $C_{15}H_{28}N_2O_2Na$: 291.2048, found: 291.2051.

(R)-tert-butyl 2-((S)-2-aminopent-4-enyl)piperidine-1-carboxylate (4c). Yield: 65% over two steps, $[\alpha]_D^{20}$ = +33 (*c* = 0.98, $CHCl_3$). ESIMS m/z $[M + Na]^+$ calcd. for $C_{15}H_{28}N_2O_2Na$: 291.2048, found: 291.2049.

(R)-tert-butyl 2-((R)-2-aminopent-4-enyl)piperidine-1-carboxylate (4b). Yield: 67% over two steps, ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (ddt, J = 17.3, 10.1, 7.1 Hz, 1H), 5.15 (m, 2H), 4.43 (m, 1H), 4.09 (bs, 2H), 3.96 (m, 1H), 2.81 – 2.62 (m, 2H), 2.58 – 2.39 (m, 1H), 2.38-2.23 (m, 1H), 2.17 – 1.98 (m, 1H), 1.72 (m, 1H), 1.63 – 1.50 (m, 4H), 1.47 (s, 9H), 1.43 – 1.32 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.16, 118.90, 80.78, 48.43, 46.96, 40.66, 39.70, 35.73, 30.01, 29.11 ($3CH_3$), 26.15, 19.73 ppm (detected signals). $[\alpha]_D^{20}$ = +14 (*c* = 0.72, $CHCl_3$). ESIMS m/z $[M + Na]^+$ calcd. for $C_{15}H_{28}N_2O_2Na$: 291.2048, found: 291.2052.

(S)-tert-butyl 2-((S)-2-aminopent-4-enyl)piperidine-1-carboxylate (4d). Yield: 64% over two steps, $[\alpha]_D^{20}$ = -11 (*c* = 0.85, $CHCl_3$). ESIMS m/z $[M + Na]^+$ calcd. for $C_{15}H_{28}N_2O_2Na$: 291.2048, found: 291.2050.

General procedure for the synthesis of (S)-tert-butyl 2-((R)-2-acrylamidopent-4-enyl)piperidine-1-carboxylate (5a), (R)-tert-butyl 2-((R)-2-acrylamidopent-4-enyl)piperidine-1-carboxylate (5b), (R)-tert-butyl 2-((S)-2-acrylamidopent-4-enyl)piperidine-1-carboxylate (5c), (S)-tert-butyl 2-((S)-2-acrylamidopent-4-enyl)piperidine-1-carboxylate (5d).

TEA (0.311 mL, 2.24mmol) was added to a solution of **4** (0.272 g, 1.02 mmol) in anhydrous CH_2Cl_2 (3.2 mL) cooled at 0°C. After 10 minutes, acryloyl chloride (0.124 mL, 1.52 mmol) was slowly added dropwise. The reaction mixture was stirred for 2 h at room temperature, then NH_4Cl was added and the reaction mixture was extracted with CH_2Cl_2. The collected organic phases were

washed twice with brine, dried over Na_2SO_4, filtered and concentrated under vacuum. The crude was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 9:1) to give **5** as a light yellow oil.

(S)-tert-butyl 2-((R)-2-acrylamidopent-4-enyl)piperidine-1-carboxylate (5a). Yield: 63%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.30 (dd, J = 17.0, 1.2 Hz, 1H), 6.13 (dd, J = 17.0, 10.3 Hz, 1H), 5.86 – 5.69 (m, 1H), 5.64 (dd, J = 10.3, 1.2 Hz, 1H), 5.20 – 4.96 (m, 2H), 4.28 (m, 1H), 4.07 (m, 1H), 3.96 (m, 1H), 2.85 (t, 1H), 2.38 – 2.16 (m, 2H), 1.83 – 1.64 (m, 2H), 1.63 – 1.63 (m, 5H), 1.47 (s, 9H), 1.38-1.32 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.96, 155.84, 135.23, 131.93, 126.65, 118.40, 80.26, 47.80, 47.13, 40.32, 39.55, 34.21, 29.18 ($3CH_3$), 28.81, 26.09, 19.63 ppm. $[\alpha]_D^{20}$ = -26 (*c* = 0.88, $CHCl_3$). ESIMS m/z $[M + Na]^+$ calcd. for $C_{18}H_{30}N_2O_3Na$: 345.2154, found: 345.2153.

(R)-tert-butyl 2-((S)-2-acrylamidopent-4-enyl)piperidine-1-carboxylate (5c). Yield: 61%, $[\alpha]_D^{20}$ = +28 (*c* = 0.91, $CHCl_3$), ESIMS m/z $[M + Na]^+$calcd. for $C_{18}H_{30}N_2O_3Na$: 345.2154, found: 345.2156.

(R)-tert-butyl 2-((R)-2-acrylamidopent-4-enyl)piperidine-1-carboxylate (5b). Yield: 66%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.24 (dd, J = 17.0, 1.6 Hz, 1H), 6.06 (dd, J = 17.0, 10.2 Hz, 1H), 5.85 – 5.70 (ddt, J = 17.2, 10.2, 7.1 Hz, 1H), 5.58 (dd, J = 10.2, 1.5 Hz, 1H), 5.15 – 5.01 (m, 2H), 4.35 (m, 1H), 4.01 – 3.85 (m, 2H), 2.73 (td, J = 13.2, 2.2 Hz, 1H), 2.42 (m, 1H), 2.36 (m, 1H), 1.87 (ddd, J = 14.0, 8.0, 5.5 Hz, 1H),1.71 (dt, J = 14.0, 5.8 Hz, 1H), 1.67 – 1.50 (m, 5H), 1.45 (s, 9H), 1.43 – 1.32 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.02, 155.07, 134.71, 131.40, 125.80, 117.70, 79.67, 47.32 (2 CH), 39.27, 37.83, 33.45, 29.62, 28.49 ($3CH_3$), 25.51, 19.06 ppm. $[\alpha]_D^{20}$ = -23 (*c* = 1.17, $CHCl_3$). ESIMS m/z $[M + Na]^+$ calcd. for $C_{18}H_{30}N_2O_3Na$: 345.2154, found: 345.2155.

(S)-tert-butyl 2-((S)-2-acrylamidopent-4-enyl)piperidine-1-carboxylate (5d). Yield: 64%, $[\alpha]_D^{20}$ = +20 (*c* = 0.97, $CHCl_3$). ESIMS m/z $[M + Na]^+$ calcd. for $C_{18}H_{30}N_2O_3$ Na: 345.2154, found: 345.2157.

General procedure for the synthesis of (S)-tert-butyl 2-(((R)-6-oxo-1,2,3,6-tetrahydropyridin-2-yl)methyl)piperidine-1-carboxylate (6a), (R)-tert-butyl 2-(((R)-6-oxo-1,2,3,6-tetrahydropyridin-2-yl)methyl)piperidine-1-carboxylate (6b), (R)-tert-butyl 2-(((S)-6-oxo-1,2,3,6-tetrahydropyridin-2-yl)methyl)piperidine-1-carboxylate (6c), (S)-tert-butyl 2-(((S)-6-oxo-1,2,3,6-tetrahydropyridin-2-yl)methyl)piperidine-1-carboxylate (6d).

A solution of Umicore M73 SIMes catalyst (4.2 mg, 0.0057 mmol) in anhydrous CH_2Cl_2 (8 mL) was added dropwise to a solution of **5** (0.183 g, 0.57mmol) in anhydrous CH_2Cl_2 (24 mL). The reaction mixture was stirred for 2 h at 50°C, then the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 95:5) to give **6** as a white amorphous solid.

(S)-tert-butyl 2-(((R)-6-oxo-1,2,3,6-tetrahydropyridin-2-yl)methyl)piperidine-1-carboxylate (6a). Yield: 73%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.66 – 6.52 (m, 1H), 5.91 (d, J = 9.9 Hz, 1H), 4.33 (m, 1H), 3.98 (m, 1H), 3.59 – 3.47 (m, 1H), 2.76 (t, J = 12.9 Hz,1H), 2.56 (dt, J = 17.6, 5.0 Hz, 1H), 2.27 – 2.08 (m, 1H), 2.08 – 1.93 (m, 2H), 1.76 – 1.51 (m, 5H), 1.47 (s, 9H), 1.44-1.36 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.08, 155.61, 141.10, 125.31, 80.61, 49.79, 47.99, 39.81, 36.85, 30.57, 29.91, 29.11 ($3CH_3$), 26.06, 19.68 ppm. $[\alpha]_D^{20}$ = +13 (*c* = 0.91, $CHCl_3$), ESIMS m/z $[M + Na]^+$ calcd. for $C_{16}H_{26}N_2O_3Na$: 317.1841, found: 317.1845.

HPLC analysis: Chiralcel AD-RH RP column, 1 mL/min, CH_3CN:H_2O = 35:65, 96 bar, λ: 254 nm, t_R: 7.70 min, ee%: 92%.

(R)-tert-butyl 2-(((S)-6-oxo-1,2,3,6-tetrahydropyridin-2-yl)methyl)piperidine-1-carboxylate (6c). Yield:77%, $[\alpha]_D^{20}$ = -13 (*c* = 1.2, $CHCl_3$). ESIMS m/z $[M + Na]^+$ calcd. for $C_{16}H_{26}N_2O_3Na$: 317.1841, found: 317.1842. HPLC analysis: Chiralcel AD-RH RP column, 1 mL/min, CH_3CN:H_2O = 35:65, 96 bar, λ: 254 nm, t_R: 10.17 min, ee%: 92%.

(R)-tert-butyl 2-(((R)-6-oxo-1,2,3,6-tetrahydropyridin-2-yl)methyl)piperidine-1-carboxylate (6b). Yield: 80%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.62 – 6.44 (m, 1H), 5.89 (dd, J = 9.9, 1.4 Hz, 1H), 4.41 (m, 1H), 3.99 (m, 1H), 3.36 (m, 1H), 2.65 (t, J = 12.5 Hz, 1H), 2.59 - 2.48 (m, 1H), 2.14 (dt, J = 17.8, 4.7 Hz, 1H), 1.90 (m, 1H), 1.81 – 1.66 (m, 1H), 1.59 (m, 4H), 1.54 – 1.39 (m, 11H).^{13}C NMR (101 MHz, $CDCl_3$) δ 165.69, 139.68, 124.66, 47.34 (2CH), 38.70, 35.74, 30.04, 29.45, 28.56 ($3CH_3$), 25.61, 19.28 ppm (detected signals). $[\alpha]_D^{20}$ = -66 (*c* = 0.85, $CHCl_3$), ESIMS m/z $[M + Na]^+$ calcd. for $C_{16}H_{26}N_2O_3Na$: 317.1841, found: 317.1840, HPLC analysis: Chiralcel AD-RH RP column, 1 mL/min, CH_3CN:H_2O = 35:65, 96 bar, λ: 254 nm, t_R: 8.71 min, ee%: 83%.

(S)-tert-butyl 2-(((S)-6-oxo-1,2,3,6-tetrahydropyridin-2-yl)methyl)piperidine-1-carboxylate (6d). Yield: 78%, $[\alpha]_D^{20}$ = +60 (*c*= 0.94, $CHCl_3$). ESIMS m/z $[M + Na]^+$ calcd. for $C_{16}H_{26}N_2O_3$ Na: 317.1841, found: 317.1843. HPLC analysis: Chiralcel AD-RH RP column, 1 mL/min, CH_3CN:H_2O = 35:65, 96 bar, λ: 254 nm, t_R: 11.15 min, ee%: 82%.

General procedure for the synthesis of (R)-2-(((R)-6-oxo-1,2,3,6-tetrahydropyridin-2-yl)methyl)piperidinium 2,2,2-trifluoroacetate (7b) and (S)-2-(((S)-6-oxo-1,2,3,6-tetrahydropyridin-2-yl)methyl)piperidinium 2,2,2-trifluoroacetate (7d).

TFA (65 µL, 0.85 mmol) was added to a solution of **6** (0.031 g, 0.11mmol) in anhydrous CH_2Cl_2 (17 mL), cooled at 0°C. The reaction mixture was stirred at room temperature for 18 h, then the solvent was removed under vacuum, affording **7** as CF_3COOH salt (white amorphous solid).

(R)-6-((R)-piperidin-2-ylmethyl)-5,6-dihydropyridin-2(1H)-one (7b). CF_3COOH salt. Yield: 66%,^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 – 8.56 (m, 2H), 7.86 (bs, 1H), 6.67 (m, 1H), 5.90 (d, J = 9.3 Hz, 1H), 3.89 (m, 1H), 3.50 – 3.36 (m, 1H), 3.36 – 3.21 (m, 1H), 2.91 (m, 1H), 2.65 – 2.47 (m, 1H), 2.30 – 2.17 (m, 1H), 2.05 – 1.79 (m, 5H), 1.79 – 1.67 (m, 1H), 1.67 – 1.58 (m, 1H), 1.54 (m, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ 168.69, 167.18, 161.33 (q), 142.50, 123.13, 53.36, 46.06, 45,03, 38.53, 29.51, 28.87, 22.30, 22.09.$[\alpha]_D^{20}$-25 (*c*=0.62, MeOH), ESIMS m/z calcd. for $[C_{11}H_{19}N_2O]^+$: 195.1497, found: 195.1501.

(S)-6-((S)-piperidin-2-ylmethyl)-5,6-dihydropyridin-2(1H)-one (7d). CF_3COOH salt. Yield: 70%,$[\alpha]_D^{20}$ +20 (*c*=0.70, MeOH), ESIMS m/z calcd. for $[C_{11}H_{19}N_2O]^+$: 195.1497, found: 195.1499.

General procedure for the synthesis of (2S,6R,11aS)-decahydro-4H-2,6-methanopyrido[1,2-a][1,5]diazocin-4-one (8a) and (2R,6S,11aR)-decahydro-4H-2,6-methanopyrido[1,2-a][1,5]diazocin-4-one (8c).

TFA (120 µL, 1.25 mmol) was added to a solution of **6** (0.023 g, 0.08 mmol) in anhydrous CH_2Cl_2 (13 mL), cooled at 0°C. The reaction mixture was stirred at room temperature for 18 h, then the solvent was removed under vacuum. The residue was purified

by column chromatography on silica gel (CH_2Cl_2/MeOH, 95:5 to 85:15), to give the **8** as CF_3COOH salt (white amorphous solid).

(2S,6R,11aS)-decahydro-4H-2,6-methanopyrido[1,2-a][1,5]diazocin-4-one (8a). CF_3COOH salt. Yield: qt%. ^{1}H NMR (400 MHz, CD_3OD) δ 3.65 (bs, 1H), 3.33 – 3.19 (m, 1H), 2.71 (m, 3H), 2.54 (m, 1H), 2.36 (dd, *J* = 19.1, 5.8 Hz, 1H), 2.18 – 1.90 (m, 2H), 1.87 – 1.50 (m, 5H), 1.48 – 1.30 (m, 3H).^{13}C NMR (100 MHz, CD_3OD) δ 174.41, 163.05 (q), 55.00, 53.30, 53.02, 46.56, 39.88, 33.16, 31.51, 30.29, 26.21, 24.98 (detected signals). $[\alpha]_D^{20}$ =+30 (*c*= 1.18, MeOH), ESIMS m/z calcd. for $[C_{11}H_{19}N_2O]^+$: 195.1497, found: 195.1498.

(2R,6S,11aR)-decahydro-4H-2,6-methanopyrido[1,2-a][1,5]diazocin-4-one (8c). CF_3COOH salt. Yield: qt%. $[\alpha]_D^{20}$ =-29 (*c*= 1.20, MeOH), ESIMS m/z calcd. for $[C_{11}H_{19}N_2O]^+$: 195.1497, found: 195.1499.

General procedure for the synthesis of *(11aS,12aR)-6,8,9,10,11,11a,12,12a-octahydrodipyrido[1,2-c:1',2'-f]pyrimidin-4(1H)-one (9a), (11aR,12aR)-6,8,9,10,11,11a,12,12a-octahydrodipyrido[1,2-c:1',2'-f]pyrimidin-4(1H)-one (9b), (11aR,12aS)-6,8,9,10,11,11a,12,12a-octahydrodipyrido[1,2-c:1',2'-f]pyrimidin-4(1H)-one (9c), (11aS,12aS)-6,8,9,10,11,11a,12,12a-octahydrodipyrido[1,2-c:1',2'-f]pyrimidin-4(1H)-one (9d).*

A 37% aqueous solution of formaldehyde (20μL, 0.28 mmol) and formic acid (11 μL, 0.28 mmol) were added to a solution of **6** (0.050 g, 0.16 mmol) in CH_3CN (0.9 mL). The reaction mixture was stirred for 2 h at 90°C, then other 20μL of formaldehyde solution and 11 μL of formic acid were added. The reaction mixture was stirred at 90°C for 12 h. The solvent was removed under vacuum and the residue was dissolved in CH_2Cl_2 and washed with a saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 and the combined organic phases were dried over Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 98:2 to 95:5), to give **9** as a yellow amorphous solid.

(11aS,12aR)-6,8,9,10,11,11a,12,12a-octahydrodipyrido[1,2-c:1',2'-f]pyrimidin-4(1H)-one (9a). Yield: 68%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.50 (ddd, J = 10.0, 5.3, 3.0 Hz, 1H), 5.89 (dd, J = 10.0, 1.6 Hz, 1H), 5.18 (d, J = 11.0 Hz, 1H), 3.65 – 3.44 (m, 1H), 3.03 (d, J = 11.0 Hz, 1H), 2.94 (d, J = 10.6 Hz, 1H), 2.50 (dt, J = 18.0, 5.8 Hz, 1H), 2.26 (ddt, J = 16.4, 10.5, 2.7 Hz, 1H), 2.18 – 1.98 (m, 2H), 1.81 – 1.51 (m, 6H), 1.42-1.29 (m, 2H).^{13}C NMR (100 MHz, $CDCl_3$) δ 164.56, 138.70, 124.33, 65.23, 60.49, 53.17, 51.64, 39.14, 31.69, 29,65, 24.87, 23.55.$[\alpha]_D^{20}$ =+46 (*c*= 0.60, $CHCl_3$), ESIMS m/z $[M + Na]^+$calcd. for $C_{12}H_{18}N_2ONa$: 229.1317, found: 229.1319.

(11aR,12aS)-6,8,9,10,11,11a,12,12a-octahydrodipyrido[1,2-c:1',2'-f]pyrimidin-4(1H)-one (9c). Yield: 65% $[\alpha]_D^{20}$ =-47 (*c*= 0.55, $CHCl_3$), ESIMS m/z $[M + Na]^+$ calcd. for $C_{12}H_{18}N_2ONa$: 229.1317, found: 229.1318.

(11aR,12aR)-6,8,9,10,11,11a,12,12a-octahydrodipyrido[1,2-c:1',2'-f]pyrimidin-4(1H)-one (9b). Yield: 80%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.54 – 6.43 (m, 1H), 5.90 (dd, J = 9.8, 2.5 Hz, 1H), 4.63 (d, J = 10.5 Hz, 1H), 3.92 (m, 1H), 3.84 (d, J = 10.5 Hz, 1H), 2.90 (d, J = 11.6 Hz, 1H), 2.42 (m, 1H), 2.37 – 2.25 (m, 2H), 2.18 – 2.04 (m, 1H), 1.92 (ddd, J = 13.6, 11.7, 8.7 Hz, 1H), 1.78 (d, J = 12.9 Hz, 1H), 1.63 – 1.53 (m, 3H), 1.52 – 1.46 (m, 2H), 1.37-1.29 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.50, 138.62, 125.84, 62.63, 58.43, 54.22, 48.10, 37.11, 32.18, 31.26, 25.21($2CH_2$). $[\alpha]_D^{20}$ =+16 (*c*= 0.62, $CHCl_3$), ESIMS m/z $[M + Na]^+$ calcd. for $C_{12}H_{18}N_2ONa$: 229.1317, found: 229.1320.

(11aS,12aS)-6,8,9,10,11,11a,12,12a-octahydrodipyrido[1,2-c:1',2'-f]pyrimidin-4(1H)-one (9d). Yield: 77%, $[\alpha]_D^{20}$= -13 (*c*= 0.70, $CHCl_3$), ESIMS m/z $[M + Na]^+$ calcd. for $C_{12}H_{18}N_2ONa$: 229.1317, found: 229.1321.

1-piperidin-2-yl)pent-4-en-2-ol (11).

TFA (2.2 mL. 28.0 mmol) was added to a solution of **3-anti** (0.500 g, 1.84 mmol, racemic) in CH_2Cl_2 (20 mL), cooled at 0°C. The reaction mixture was stirred at room temperature for 18 h, then the solvent was removed under vacuum. The product (light yellow wax) didn't require further purification.

CF_3COOH salt. Yield: 90%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (bs, 1H), 7.83 (bs, 1H), 5.87 – 5.57 (m, 1H), 5.27 – 5.00 (m, 2H), 4.11 – 3.83 (m, 1H), 3.46 (m, 1H), 3.23 (m, 1H), 3.03 – 2.80 (m, 1H), 2.25 (m, 2H), 2.13 – 1.62 (m, 7H), 1.62 – 1.43 (m, 1H). ^{13}CNMR (100 MHz, $CDCl_3$) δ 161.34, 133.07, 119.19, 71.44, 58.56, 45.05, 42.62, 38.44, 29.68, 22.20 ($2CH_2$) (detected signals). ESIMS m/z calcd. for $[C_{10}H_{20}NO]^+$: 170.1545, found: 170.1544.

Computational Studies

Compounds *syn*- and *anti*-structures (see Figure 2) were optimized at the semiempirical level with the PM6 method.**Errore. Il segnalibro non è definito.** Transition states were built assuming a late transition state, similar in energy to the final products, according to Hammond's postulate. TS and minima were identified throughfrequency calculation.

Intrinsic reaction coordinate pathway connecting the reactants to the transition state was also computed at the semiempirical PM6 level. All calculations were performed with the Gaussian 2016 package Gaussian 16, Revision B.01.[32]

Keywords: piperidine derivatives • diversity-oriented synthesis • 2-Piperidine Ethanol • stereodivergent synthesis • piperidine alkaloids.

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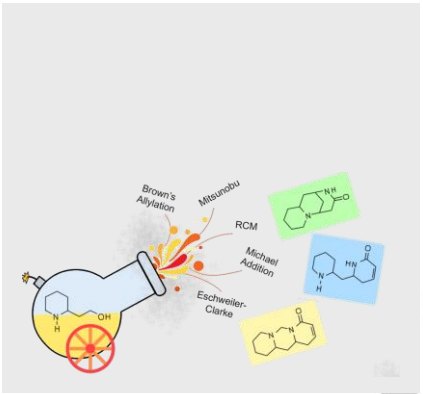
FULL PAPER

Efficient conversion of 2-piperidine ethanol in a small library of enatiomerically pure nitrogen containing compounds by a stereodivergent approch. The new scaffolds results challenging to for the exploration of the chemical space.



Exploration of the Chemical Space

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Stereodivergent Diversity-Oriented Synthesis: Exploiting the Versatility of 2-Piperidine Ethanol