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Enantiopure 2-piperidylacetaldehyde as a useful building block in the diversity-oriented synthesis of polycyclic piperidine derivatives

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ABSTRACT

Novel, simple, and convenient strategies for diversely functionalized piperidine derivatives have been developed by using different metal catalyzed reactions starting from enantiopure (*R*)- and (*S*)-2-piperidylacetaldehyde.

1. Introduction

2-Piperidylacetaldehyde **1** has been proven to be a successful synthon in the convenient syntheses of several 2-piperidyl alkaloids, some of which are described in Figure 1.[1]

The syntheses were based upon exploitation of the electrophilic character of the aldehyde group and took advantage of the presence of the installed stereogenic center at the 2-position of the piperidine ring.

The attractiveness of the piperidine-based skeletons[2] and the interest towards transition metal catalyzed reactions prompted us to search new synthetic strategies to obtain fused- and spiro-ring structures containing a piperidine unit in enantiopure form (Fig. 2). In order to achieve such a goal, we relied on the easy availability of enantiopure (*R*)- and (*S*)-2-allylpiperidines **2**, obtained by Wittig reaction on the aldehyde derivative **1**.[1b] We envisioned some suitable reactions to functionalize the piperidyl nitrogen aimed at paving the way to a range of intramolecular transition metal catalyzed reactions involving the allylic carbon–carbon double bond. Herein we report some synthetic procedures based on Pd(0)-, Pd(II)- and Ru-catalyzed reactions to access useful enantiopure six- or seven-membered rings fused on the piperidine moiety, products whose analogues already show interesting properties.[3] Moreover, as most of them present a carbon–carbon double bond susceptible to further functionalization, their intrinsic value and molecular complexity was increased by subsequent transformation into tri- or tetracyclic compounds.

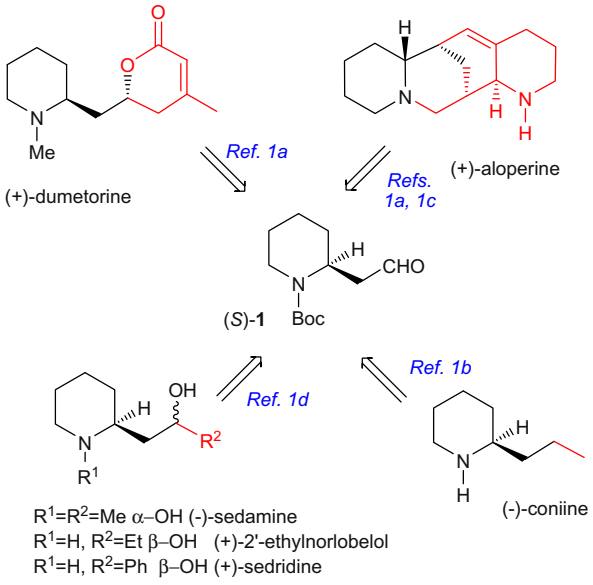

Figure 1. Previously reported synthesis of 2-piperidyl alkaloids.

2. Results and discussion

2.1. A synthetic sequence based on intramolecular Heck reactions

In the context of our studies on the Pd(0)-catalyzed reactions,[4] we first took into consideration compound **3**, suitable for intramolecular Heck reactions.

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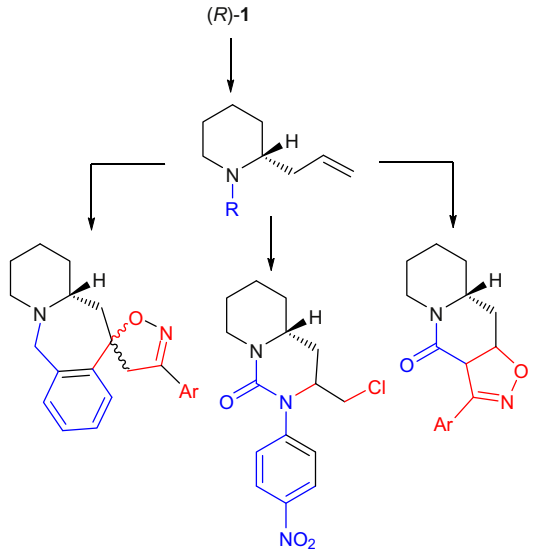


Figure 2. Diversity-oriented approach towards piperidine-containing structures.

Removal of the terbutoxycarbonyl group from (*R*)-**2** with TFA and treatment of a toluene solution of the deprotected piperidine with the commercially available 2-iodobenzyl bromide in the presence of K_2CO_3 gave the (*R*)-2-allyl-1-(2-iodobenzyl)-piperidine **3** (Scheme 1). The Heck reaction was performed either in the presence of $Pd(PPh_3)_4$ as catalyst and TEA as base in acetonitrile, or under ligand-free conditions[5] in the presence of $Pd(OAc)_2$ as catalyst, Na_2CO_3 and Bu_4NCl in DMF. Both procedures were effective in promoting the formation of the pyrido[1,2-*b*][2]benzazepine derivative (*R*)-**4**, even if the best result was obtained working with the former procedure (76% vs 38% yield). The presence of the exomethylenic carbon–carbon double bond on compound (*R*)-**4** furnished the means to reach more complex spiro-annulated structures by 1,3-dipolar cycloadditions, exploiting our expertise in this field.[6] The dipolarophilic behaviour of the exocyclic carbon–carbon double bond was proven toward the 3,5-dichloro-2,4,6-trimethylbenzonitriloxide **5**, chosen as 1,3-dipole due to its excellent stability.[7] The reaction between (*R*)-**4** and **5** was performed in toluene at reflux by using equimolar amounts of the reactants. The nitrile oxide intramolecular cycloaddition took place regioselectively according to the results reported in the literature[8] and gave a mixture of two diastereoisomeric products in an approximately 2:1 ratio, which were isolated by column chromatography in 42% and 29% yield, respectively. The 11–5′ junction of the pyrido[1,2-*b*][2]benzazepine-isoxazole system was inferred by the ^1H and ^{13}C NMR data, in particular by the geminal coupling constants greater than 17 Hz, which is compatible only with the methylenic group at a 4-position of the isoxazole ring.[9] The distinction between the diastereoisomeric spiro-compounds **6** and **7** was established by an X-ray diffraction analysis on **6** (Fig. 3).

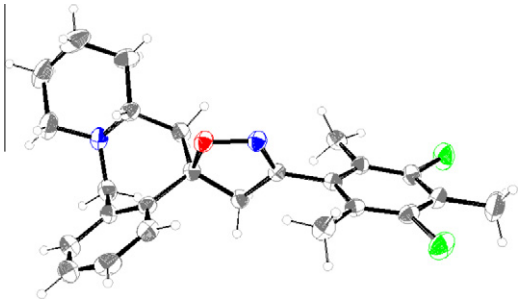
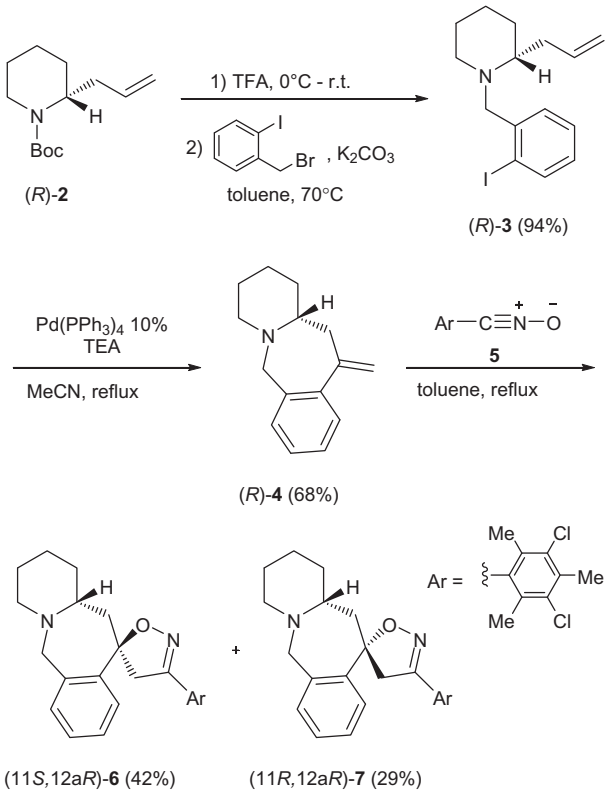


Figure 3. ORTEP plot of the molecular structure of compound **6** at 30% probability level.

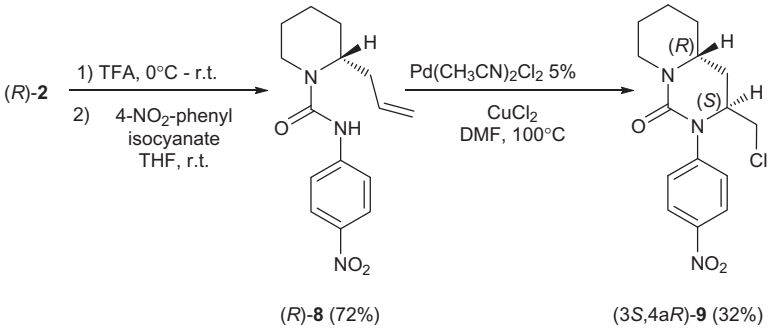


Scheme 1. Growing molecular complexity by an intramolecular Heck reaction/intermolecular 1,3-dipolar cycloaddition sequence.

The synthetic sequence described in Scheme 1 was also carried out on the enantiomeric 2-allylpiperidine (*S*)-**2**, affording (11*R*,12a*S*)-**6** and (11*S*,12a*S*)-**7** in yields similar to those obtained from (*R*)-**2**. HPLC analysis with ODH chiral column, performed on both enantiomers of compounds **6** and **7**, proved a 90% enantiomeric excess for the ones deriving from (*R*)-**1** and 95% for those deriving from (*S*)-**1**[10,1d] to strengthen the configurational stability of the early stereogenic center.

2.2. Synthetic sequence based on intramolecular Pd(II)-catalyzed chloroamination

The Pd(II)-catalyzed functionalization of unactivated C–H bonds is a challenging field in organic chemistry,[11] where we recently reported our interest.[12] Recent literature seems particularly attracted by the reactions achieving a double functionalization of double bonds, more specifically towards diamination or heteroamination processes.[13] In this light, the appropriate functionalization of piperidine nitrogen could exploit the reactivity of the ethylenic double bond of compound **2** toward Pd(II)-catalysis (Scheme 2). Removal of the terbutoxycarbonyl group by TFA and subsequent reaction with 4-nitro-phenylisocyanate afforded compound (*R*)-**8**, which bears a nucleophile nitrogen atom. This compound easily reacts with the carbon–carbon double bond using $Pd(CH_3CN)_2Cl_2$ as a catalyst and $CuCl_2$ as an oxidant; the high amount of $CuCl_2$ warrants the significant presence of chloride anions in the reaction medium, thus letting them intercept the σ-alkyl-palladium intermediate before a competitive β-hydride elimination process could occur.[14] Consequently, bicyclic pyrido[1,2-*c*]pyrimidinone (3*S*, 4a*R*)-**9** is formed (ee 90%). This chlorinated product, whose



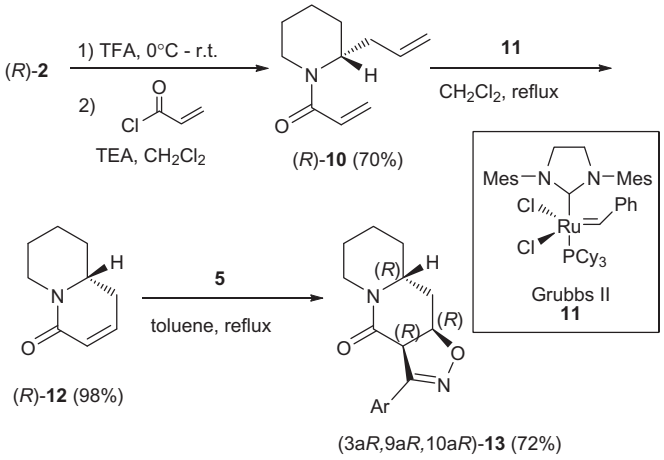
Scheme 2. Growing the molecular complexity by an intramolecular oxidative Pd(II)-catalyzed chloroamination reaction.

stereochemistry has been assigned by a NOESY experiment, arises from a domino chloroamination process.

Also in this case, the reaction performed on the (*S*)-**2** enantiomer led to (3*R*,4a*S*)-**9** in 95% enantiomeric excess by HPLC analysis.[10,1d]

2.3. Synthetic sequence based on the RCM reaction

The application of ring closing metathesis to build large- and medium-ring heterocycles has greatly increased in recent years, due to the high efficiency this process usually warrants.[15] Starting once more for substrate (*R*)-**2**, we thought to built a six-membered fused-ring on the piperidine by a RCM process performed on a substrate obtained by functionalization of the nitrogen with an acryloyl group (Scheme 3). The reaction of the deprotected allyl piperidine with acryloyl chloride furnished the appropriate substrate (*R*)-**10**, containing two ethylenic double bonds, which lie juxtaposed for the construction of a six-membered fused-ring. The presence of an amide group should allow an easy outcome of RCM.[16] In fact, amide (*R*)-**10**, treated with a Grubbs catalyst of 2nd generation **11** in DCM at reflux, furnished hexahydroquinolizinone (*R*)-**12** in quantitative yield.[17] The reaction proceeds through an initial coordination of the Ru-species to the allylic carbon–carbon double bond; the olefin metathesis of electron-poor double bonds was less favoured compared to neutral olefins because of the relative instability of electron-deficient metal carbene bonds.[18]



Scheme 3. Growing molecular complexity by a RCM/intermolecular 1,3-dipolar cycloaddition sequence.

Next, we decided to increase the molecular complexity of our product by employing the endocyclic double bond as a dipolarophile in a 1,3-dipolar cycloaddition with nitriloxide **5**. As in the case of the 1,1-disubstituted ethylenic compound (*R*)-**4**, the outcome of the cycloaddition on the 1,2-disubstituted ethylenic double bond was totally regioselective, allowing the formation of a 4,5-dihydroisoxazole product in 72% yield. Spectroscopic data was in agreement with the structure (3a*R*,9a*R*,10a*R*)-**13**, with the carbonyl group at the 4-position of the newly formed isoxazoline. HPLC analysis with an ODH chiral column proved a 90% enantiomeric excess.[10]

From a stereochemical point of view, the cycloaddition process exclusively allowed a *cis*-disposition of the two new stereocentres, the relative configuration of which, with respect to the pre-existing one, was proven to be *trans* by X-ray diffraction analysis (Fig. 4). Finally, we performed the RCM/nitriloxide cycloaddition sequence on the (*S*)-**2** enantiomer, achieving the final product (3a*S*,9a-*S*,10a*S*)-**13** with a 95% enantiomeric excess.[10]

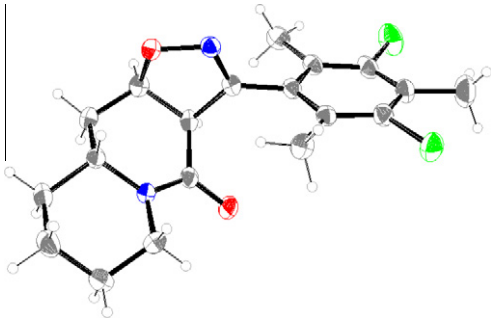


Figure 4. ORTEP plot of the molecular structure of compound **13** at 30% probability level.

3. Conclusion

In conclusion, the easy conversion of aldehyde **1** into the conformationally stable 2-allylpiperidine synthon **2** made a diversity-oriented approach possible by exploiting the reactivity of the vinyl moiety towards metal catalyzed intramolecular reactions. The compounds obtained present a visibly increased molecular complexity which confirms the value of 2-pyperidinylacetaldeyde as a synthon for the generation of diversified collections of products in both enantiomeric series.

4. Experimental section

4.1. General

Enantiomerically enriched (*R*)-**2** and (*S*)-**2** were prepared as previously described.[1b] Melting points were determined on a Büchi

B-540 heating apparatus and are uncorrected. Optical rotations were measured on a Jasco P-1010 polarimeter. ^{1}H NMR and ^{13}C NMR spectra were obtained on an AVANCE Bruker 400 spectrometer. Chemical shifts are given in ppm downfield from $SiMe_4$; ^{13}C NMR spectra are ^{1}H-decoupled and the determination of the multiplicities was achieved by the APT pulse sequence. IR spectra were recorded on a Jasco FT/IR 5300 spectrophotometer. Mass spectra were determined on a WG-70EQ instrument. Elemental analyses were executed on CHN Analyzer. Column chromatography was performed on a Merck silica gel 60, (mesh size 63–200 μm). Chiral HPLC was performed using Chiralpak® AD column (0.46_25 cm, Daicel industries) with Merck Hitachi L 7100 chromatograph coupled with DAD Hp 1050.

4.2. Preparation of (*R*)-2-allyl-1-(2-iodobenzyl)-piperidine (*R*)-3

A solution of compound (*R*)-**2** (355 mg, 1.58 mmol) in trifluoroacetic acid (1.8 mL, 23.65 mmol) was stirred under a nitrogen atmosphere for 3 h at room temperature. After evaporation of the solvent, the residue was dissolved in anhydrous toluene (4 mL) and the resulting solution was dropped in a suspension of K_2CO_3 (6.45 g, 46.7 mmol) and 2-iodobenzylbromide (468 mg, 1.58 mmol) in anhydrous toluene (12 mL) at 40 °C. Then the reaction mixture was heated to 70 °C overnight. Ice-cold water (22 mL) was added to the reaction mixture and then extracted by Et_2O (2 × 17 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum. The crude was purified by silica gel column chromatography (hexane/AcOEt 98:2) to afford (*R*)-**3** in 94% yield. Pale yellow oil. $[\alpha]_D^{23} = +31.1$ (*c* 1.09, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.32–1.61 (m, 4H), 1.63–1.78 (m, 2H), 2.17–2.28 (m, 1H), 2.30–2.45 (m, 2H), 2.50–2.62 (m, 1H), 2.68–2.76 (m, 1H), 3.39, 3.91 (AB system, *J* = 14.8 Hz, 2H), 5.03 (d, *J* = 9.6 Hz, 1H), 5.05 (d, *J* = 17.6 Hz, 1H), 5.84 (ddt, *J* = 9.6, 17.6, 7.1 Hz, 1H), 6.94 (dd, *J* = 7.3, 7.8 Hz, 1H), 7.33 (dd, *J* = 7.3, 7.5 Hz, 1H), 7.54 (d, *J* = 7.5 Hz, 1H), 7.81 (d, *J* = 7.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 23.3 (t), 26.1 (t), 30.6 (t), 35.9 (t), 51.7 (t), 60.8 (d), 62.9 (t), 100.6 (s), 116.8 (t), 128.5 (d), 128.8 (d), 130.5 (d), 136.7 (d), 139.6 (d), 142.6 (s). MS: *m*/*z* 341 (M^+). Anal. Calcd for $C_{15}H_{20}IN$: C, 52.80; H, 5.91; N, 4.10. Found: C, 52.95; H, 5.83; N, 4.28.

4.2.1. (*S*)-2-Allyl-1-(2-iodobenzyl)-piperidine (*S*)-3

Obtained in 92% yield from (*S*)-**2** according to the procedure described for its enantiomer. $[\alpha]_D^{23} = -32.0$ (*c* 1.12, $CHCl_3$). Anal. Calcd for $C_{15}H_{20}IN$: C, 52.80; H, 5.91; N, 4.10. Found: C, 52.78; H, 5.97; N, 4.03.

4.3. Preparation of (*R*)-11-methylene-1,2,3,4,6,11,12,12a-octahydropyrido[1,2-*b*][2]benzazepine (*R*)-4

At first, $Pd(PPh_3)_4$ 99% (108.71 mg, 0.09 mmol) and triethylamine (389 μL, 2.79 mmol) were added to a solution of (*R*)-**3** (317.8 mg, 0.93 mmol) in anhydrous acetonitrile (10 mL). The reaction mixture was refluxed for 2 h, and then the solvent was evaporated under reduced pressure. Water (10 mL) was added to the residue and then extracted by CH_2Cl_2 (2 × 10 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under vacuum. The crude was purified by silica gel column chromatography (hexane/AcOEt 5:1) to afford (*R*)-**4** in 68% yield. Dark yellow oil. $[\alpha]_D^{23} = -41.8$ (*c* 0.25, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.32–1.40 (m, 1H), 1.54–1.77 (m, 5H), 2.35–2.47 (m, 2H), 2.48–2.62 (m, 2H), 2.88–2.96 (m, 1H), 3.74, 3.80 (AB system, *J* = 14.9 Hz, 2H), 5.09 (s, 1H), 5.25 (s, 1H), 7.10 (d, *J* = 8.4 Hz, 1H), 7.16–7.26 (m, 2H), 7.34 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR 24.0 (t), 26.3 (t), 30.1 (t), 32.8 (t), 42.0 (t), 55.8 (t), 62.2 (t), 64.5 (d), 114.2 (t), 127.7 (d), 127.8 (d), 129.4 (d), 136.3 (s), 142.7 (s), 148.3 (s). MS: *m*/*z* 213 (M^+). Anal. Calcd for $C_{15}H_{19}N$: C, 84.46; H, 8.96; N, 6.57. Found: C, 84.31; H, 9.05; N, 6.43.

4.3.1. (*S*)-11-Methylene-1,2,3,4,6,11,12,12a-octahydro pyrido[1,2-*b*][2]benzazepine (*S*)-4

Obtained in 71% yield from (*S*)-**3** according to the procedure described for its enantiomer. $[\alpha]_D^{23} = +44.5$ (*c* 0.31, $CHCl_3$). Anal. Calcd for $C_{15}H_{19}N$: C, 84.46; H, 9.05; N, 6.57. Found: C, 84.52; H, 8.88; N, 6.70.

4.4. Cycloaddition reaction of 4 with 3,5-dichloro-2,4,6-trimethylbenzonitriloxide 5

Compound **5** (65.8 mg, 0.289 mmol) was added to a solution of (*R*)-**4** (61.0 mg, 0.29 mmol) in dry toluene (1.5 mL). The reaction mixture was refluxed for 12 h, then the solvent was evaporated under reduced pressure. The crude was purified by silica gel column chromatography (AcOEt/MeOH 98:2) to afford **6** and **7**.

4.4.1. (11*S*,12a*R*)-3′-(3,5-Dichloro-2,4,6-trimethylphenyl)-spiro{pyrido[1,2-*b*][2]benzazepine-11,5′-isoxazole} (11*S*,12a*R*)-6

Yield: 42%. White solid. Mp 185–186 °C (diisopropyl ether). $[\alpha]_D^{23} = +33.3$ (*c* 0.27, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.15–1.25 (m, 2H), 1.38–1.52 (m, 1H), 1.58–1.74 (m, 3H), 2.13–2.35 (m, 2H), 2.19 (s, 3H), 2.24 (s, 3H), 2.38–2.49 (m, 2H), 2.53 (s, 3H), 2.80–2.89 (m, 1H), 3.29, 3.39 (AB system, *J* = 17.5 Hz, 2H), 3.62, 4.29 (AB system, *J* = 14.8 Hz, 2H), 7.14 (d, *J* = 7.4 Hz, 1H), 7.25–7.43 (m, 2H), 7.63 (d, *J* = 7.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 18.5 (q), 19.4 (q), 24.7 (t), 26.6 (t), 33.5 (t), 48.0 (t), 54.4 (t), 55.2 (t), 59.1 (d), 59.4 (t), 90.8 (s), 125.9, (d), 128.5 (d), 129.2 (s), 130.3 (s), 130.9 (d), 133.7, (s), 133.9 (s), 135.9 (s), 142.8 (s), 156.6 (s). MS: *m*/*z* 442 (M^+). Anal. Calcd for $C_{25}H_{28}Cl_2N_2O$: C, 67.72; H, 6.36; N, 6.32. Found: C, 67.67; H, 6.21; N, 6.33.

Single crystals suitable for X-ray diffraction were obtained from $CHCl_3$. Relevant crystal data for **6**: $C_{25}H_{28}Cl_2N_2O$, FW = 443.4 g mol^{-1}, yellow prism. λ(Mo-Kα) = 0.71073 Å, *T* = 298 K; monoclinic $P2_1/n$, *a* = 5.353(2), *b* = 25.465(9), *c* = 16.758(6) Å, *V* = 2275(1) Å^3, *Z* = 4, *F*(000) = 936, ρ_{calc} = 1.294 g cm^{-3}, μ(Mo-Kα) = 0.305 mm^{-1}. With 268 parameters, the *R*, *wR* figures of merit reached final values of 0.046, 0.106 for the 1605 observed reflections [$I > 2\sigma(I)$], and of 0.072, 0.121 for the 2255 unique reflections. Goodness of fit, highest peak and deepest hole reached final values of 1.046, 0.12 e Å^{-3} and −0.13 e Å^{-3}. The crystallographic data (excluding structure factors) for **6** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications number 802924. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

4.4.1.1. (11*R*,12a*S*)-3′-(3,5-Dichloro-2,4,6-trimethylphenyl)-spiro-{pyrido[1,2-*b*][2]benzazepine-11,5′-isoxazole} (11*R*,12a*S*)-6.

Obtained in 39% yield from (*S*)-**4** according to the procedure described for its enantiomer. $[\alpha]_D^{23} = -34.9$ (*c* 0.28, $CHCl_3$). Anal. Calcd for $C_{25}H_{28}Cl_2N_2O$: C, 67.72; H, 6.36; N, 6.32. Found: C, 67.75; H, 6.45; N, 6.18.

4.4.2. (11*R*,12a*R*)-3′-(3,5-Dichloro-2,4,6-trimethylphenyl)-spiro{pyrido[1,2-*b*][2]benzazepine-11,5′-isoxazole} (11*R*,12a*R*)-7

Yield: 29%. Brown oil. $[\alpha]_D^{23} = -37.3$ (*c* 0.11, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.23–1.72 (m, 7H), 1.74–1.83 (m, 1H), 2.02–2.09 (m, 1H), 2.15 (s, 6H), 2.42–2.51 (m, 1H), 2.52 (s, 3H), 2.78–2.87 (m, 1H), 3.02, 3.61 (AB system, *J* = 17.1 Hz, 2H), 3.63, 3.76

(AB system, J = 14.5 Hz, 2H), 7.20 (d, J = 7.7 Hz, 1H), 7.22–7.36 (m, 2H), 7.73 (d, J = 7.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 18.4 (q), 19.4 (q), 22.9 (t), 26.1 (t), 30.1 (t), 34.1 (t), 43.8 (t), 49.4 (t), 62.1 (d), 63.8 (t), 90.3 (s), 125.2 (d), 128.3 (d), 129.3 (s), 131.9 (d), 133.6 (s), 133.9 (s), 135.9 (s), 144.3 (s), 157.1 (s). MS: m/z 442 (M^+). Anal. Calcd for $C_{25}H_{28}Cl_2N_2O$: C, 67.72; H, 6.36; N, 6.32. Found: C, 67.88; H, 6.34; N, 6.41.

4.4.2.1. (11*S*,12a*S*)-3′-(3,5-Dichloro-2,4,6-trimethylphenyl)-spiro-{pyrido[1,2-*b*][2]benzazepine-11,5′-isoxazole} (11*S*,12a*S*)-7. Obtained in 30% yield from (*S*)-**4** according to the procedure described for the enantiomer. $[\alpha]_D^{23}$ = +38.8 (c 0.13, $CHCl_3$). Anal. Calcd for $C_{25}H_{28}Cl_2N_2O$: C, 67.72; H, 6.36; N, 6.32. Found: C, 67.61; H, 6.42; N, 6.43.

4.5. Preparation of (*R*)-2-allyl-*N*-(4-nitrophenyl)piperidine-1-carboxamide (*R*)-8

A solution of compound (*R*)-**2** (355 mg, 2.58 mmol) in trifluoroacetic acid (1.8 mL, 23.65 mmol) was stirred for 3 h at room temperature under a nitrogen atmosphere. The trifluoroacetic acid was then evaporated. The residue was dissolved in anhydrous THF (4 mL) and 4-nitrophenyl isocyanate (423 mg, 2.58 mmol) was added. Then the reaction mixture was stirred at room temperature overnight. The solvent was evaporated, after which brine (15 mL) was added to the residue and then the mixture was extracted by CH_2Cl_2 (2 × 15 mL). The organic phase was dried over Na_2SO_4 filtered and concentrated under vacuum. The crude was purified by silica gel column chromatography (hexane/AcOEt 7:3) to afford (*R*)-**8** in 72% yield. Yellow oil, $[\alpha]_D^{23}$ = +58.6 (c 0.55, $CHCl_3$). IR (nujol): ν = 3450, 1675 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62–1.69 (m, 6H), 2.27–2.33 (m, 1H), 2.49–2.55 (m, 1H), 3.96 (d, J = 16 Hz, 1H), 4.31 (br s, 1H), 5.10 (dd, J = 18.8, 28 Hz, 2H), 5.77 (q, 1H), 7.12 (br s, 1H), 7.51 (d, J = 9.2 Hz, 2H), 8.11 (d, J = 2.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.6 (t), 25.5 (t), 28.1 (t), 34.4 (t), 39.6 (t), 51.5 (d), 117.8 (t), 118.4 (d), 124.9 (d), 134.9 (d), 142.1 (s), 146.1 (s), 154.1 (s). MS: m/z 289 (M^+). Anal. Calcd for $C_{15}H_{19}N_3O_3$: C, 62.27; H, 6.62; N, 14.52. Found: C, 62.31; H, 6.53; N, 14.35.

4.5.1. (*S*)-2-Allyl-*N*-(4-nitrophenyl)piperidine-1-carboxamide (*S*)-8

Obtained in 75% yield from (*S*)-**2** according to the procedure described for its enantiomer. $[\alpha]_D^{23}$ = −62.0 (c 0.49, $CHCl_3$). Anal. Calcd for $C_{15}H_{19}N_3O_3$: C, 62.27; H, 6.62; N, 14.52. Found: C, 62.19; H, 6.72; N, 14.63.

4.6. Preparation of (3*S*,4a*R*)-3-(chloromethyl)-2-(4-nitrophenyl)octahydro-1*H*-pyrido[1,2-*c*]pyrimidin-1-one (3*S*,4a*R*)-9

A mixture of (*R*)-**8** (289 mg, 1 mmol), $Pd(CH_3CN)_2Cl_2$ 99% (10 mg, 0.05 mmol) and $CuCl_2$ 98% (132 mg, 1 mmol) in dry DMF (10 mL) was stirred at 100 °C for 3 h. Brine (15 mL) was added to the residue and then extracted by CH_2Cl_2 (3 × 15 mL). The organic phase was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude was purified by silica gel column chromatography (hexane/AcOEt 1:1) to afford **9** in 32% yield. Red oil. $[\alpha]_D^{25}$ = −7.6 (c 0.37, $CHCl_3$). IR (nujol): ν = 1680 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52–1.79 (m, 7H), 2.53 (m, 1H), 2.64 (t, J = 10.3 Hz, 1H), 3.44 (m, 1H), 3.59 (t, J = 10.3 Hz, 1H), 3.7 (dd, J = 4.2, 4.3 Hz, 1H), 4.09 (m, 1H), 4.61 (d, J = 14.6 Hz, 1H), 7.44 (d, J = 15.2 Hz, 2H), 8.20 (d, J = 15.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 23.7 (t), 25.1 (t), 31.1 (t), 33.6 (t), 42.6 (t), 43.7 (t), 50.8 (d), 57.3 (d), 124.4 (d), 125.4 (d), 144.4 (s), 148.7 (s), 152.8 (s) MS: m/z 323 (M^+). Anal. Calcd for $C_{15}H_{18}ClN_3O_3$: C, 55.64; H, 5.60; N, 12.98. Found: C, 55.45; H, 5.72; N, 12.81.

4.6.1. (3*R*,4a*S*)-3-(Chloromethyl)-2-(4-nitrophenyl)octahydro-1*H*-pyrido[1,2-*c*]pyrimidin-1-one (3*R*,4a*S*)-9

Obtained in 30% yield from (*S*)-**8** according to the procedure described for its enantiomer. $[\alpha]_D^{25}$ = +8.0 (c 0.39, $CHCl_3$). Anal. Calcd for $C_{15}H_{18}ClN_3O_3$: C, 55.64; H, 5.60; N, 12.98. Found: C, 55.71; H, 5.48; N, 13.08.

4.7. Preparation of (*R*)-2-allyl-1-propenoylpiperidine (*R*)-10

A solution of compound (*R*)-**2** (312.9 mg, 1.39 mmol) in trifluoroacetic acid (1.6 mL, 20.83 mmol) was stirred under a nitrogen atmosphere for 3 h at room temperature. After evaporation of the solvent, the residue was dissolved in anhydrous CH_2Cl_2 (3 mL), and triethylamine (581 μL, 4.17 mmol) and acryloyl chloride (150.1 mg, 1.68 mmol) were added. The reaction mixture was stirred overnight at room temperature. Water (3 mL) was added and the mixture was extracted with CH_2Cl_2 (2 × 5 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under vacuum. The crude was purified by silica gel column chromatography (hexane/AcOEt 4:1) to afford (*R*)-**10** in 70% yield. Colorless oil. $[\alpha]_D^{23}$ = +66.5 (c 0.63, $CHCl_3$). IR (nujol): ν = 1677 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.38–1.52 (m, 1H), 1.60–1.74 (m, 5H), 2.27–2.40 (m, 1H), 2.44–2.53 (m, 1H), 2.93 (br s, 1H), 4.20 (br s, 1H), 4.52 (br s, 1H), 5.03–5.14 (m, 2H), 5.61 (d, J = 10.7 Hz, 1H), 5.69–5.80 (m, 1H), 6.19 (d, J = 16.9 Hz, 1H), 6.56 (dd, J = 10.7, 16.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.3 (t), 26.0 (t), 29.9 (t), 35.0 (t), 39.6 (t), 50.8 (d), 117.5 (t), 126.7 (t), 129.2 (d), 135.0 (d), 166.4 (s). MS: m/z 179 (M^+). Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.62; H, 9.48; N, 7.76.

4.7.1. (*S*)-2-Allyl-1-propenoylpiperidine (*S*)-10

Obtained in 75% yield from (*S*)-**2** according to the procedure described for its enantiomer. $[\alpha]_D^{23}$ = −70.3 (c 0.59, $CHCl_3$). Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.82; H, 9.67; N, 7.90.

4.8. Preparation of (*R*)-1,6,7,8,9,9a-hexahydroquinolizin-4-one (*R*)-12

A mixture of (*R*)-**10** (67 mg, 0.376 mmol) and Grubbs II **11** (16 mg, 0.019 mmol) in anhydrous CH_2Cl_2 (7 mL) was refluxed for 2 h. The solvent was evaporated under reduced pressure. The crude was purified by silica gel column chromatography (hexane/AcOEt 3:1) to afford (*R*)-**12** in 98% yield. Pale yellow oil. $[\alpha]_D^{23}$ = −52.1 (c 0.50, $CHCl_3$). IR (nujol): ν = 1679 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.37–1.49 (m, 3H), 1.65–1.78 (m, 2H), 1.80–1.86 (m, 1H), 2.12–2.23 (m, 1H), 2.44–2.55 (m, 2H), 3.30–3.46 (m, 1H), 4.48 (d, J = 12.0 Hz, 1H), 5.85 (d, J = 9.8 Hz, 1H), 6.41–6.48 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.3 (t), 25.2 (t), 31.4 (t), 33.7 (t), 43.3 (t), 55.1 (d), 124.9 (d), 138.5 (d), 165.8 (s). MS: m/z 151 (M^+). Anal. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.60; H, 8.48; N, 9.19.

4.8.1. (*S*)-1,6,7,8,9,9a-Hexahydroquinolizin-4-one (*S*)-12

Obtained in 95% yield from (*S*)-**10** according to the procedure described for its enantiomer. $[\alpha]_D^{23}$ = +49.0 (c 0.52, $CHCl_3$). Anal. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.34; H, 8.75; N, 9.35.

4.9. Preparation of (3a*R*,9a*R*,10a*R*)-3-(3,5-dichloro-2,4,6-trimethylphenyl)-3a,6,7,8,9,9a,10,10a-octahydroisoxazolo[5,4-*b*]quinolizin-4-one (3a*R*,9a*R*,10a*R*)-13

A mixture of (*R*)-**12** (56.8 mg, 0.38 mmol) and **5** (86.5 mg, 0.38 mmol) in anhydrous toluene (2.0 mL) was refluxed for 18 h, then the solvent was evaporated under reduced pressure. The

crude was purified by silica gel column chromatography (hexane/AcOEt 6:4) to afford (3a*R*,9a*R*,10a*R*)-**13** in 72% yield. White solid. Mp 173–174 °C (diisopropyl ether). $[\alpha]_D^{23} = -83.0$ (*c* 0.91, $CHCl_3$). IR (nujol): $\nu = 1682\ cm^{-1}$. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.26–1.37 (m, 1H), 1.41–1.50 (m, 2H), 1.74–1.81 (m, 1H), 1.83–2.00 (m, 3H), 2.14 (s, 3H), 2.33 (s, 3H), 2.34–2.37 (m, 1H), 2.38–2.42 (m, 1H), 2.52 (s, 3H), 3.60–3.68 (m, 1H), 4.16 (d, $J = 10.2$ Hz, 1H), 4.43–4.50 (m, 1H), 5.06–5.13 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 18.9 (q), 19.4 (q), 23.3 (t), 25.0 (t), 33.2 (t), 33.3 (t), 42.8 (t), 50.5 (d), 57.6 (d), 77.4 (d), 128.4 (s), 133.1, (s), 134.4 (s), 136.1 (s), 157.4 (s), 163.1 (s). MS: *m*/*z* 380 (M^+). Anal. Calcd for $C_{19}H_{22}Cl_2N_2O_2$: C, 59.85; H, 5.82; N, 7.35. Found: C, 59.99; H, 5.76; N, 7.26.

Single crystals suitable for X-ray diffraction were obtained from $CHCl_3$. Relevant crystal data for **13**: $C_{19}H_{22}Cl_2N_2O_2$, FW = 381.3 g mol^{-1}, yellow prism. λ(Mo-Kα) = 0.71073 Å, $T = 298$ K; orthorhombic *Pbca*, $a = 10.068(6)$, $b = 13.927(7)$, $c = 26.076(7)$ Å, $V = 3656(3)$ Å^3, $Z = 8$, $F(000) = 1600$, $\rho_{calc} = 1.385$ g cm^{-3}, μ(Mo-Kα) = 0.370 mm^{-1}. With 226 parameters, the *R*, *wR* figures of merit reached final values of 0.057, 0.119 for the 1917 observed reflections [$I > 2\sigma(I)$], and of 0.115, 0.143 for the 3303 unique reflections. Goodness of fit, highest peak and deepest hole reached final values of 1.026, 0.21 e Å^{-3} and −0.21 e Å^{-3}. The crystallographic data (excluding structure factors) for **13** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications number 802923. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

4.9.1. (3a*S*,9a*S*,10a*S*)-3-(3,5-Dichloro-2,4,6-trimethylphenyl)-3a,6,7,8,9,9a,10,10a-octahydroisoxazolo[5,4-*b*]quinolizin-4-one (3a*S*,9a*S*,10a*S*)-13

Obtained in 68% yield from (*S*)-**12** according to the procedure described for the enantiomer. $[\alpha]_D^{23} = +87.2$ (*c* 0.89, $CHCl_3$). Anal. Calcd for $C_{19}H_{22}Cl_2N_2O_2$: C, 59.85; H, 5.82; N, 7.35. Found: C, 59.71; H, 5.93; N, 7.41

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