JOC The Journal of Organic Chemistry

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Straightforward Access to Enantioenriched 2-Allylpiperidine: Application to the Synthesis of Alkaloids

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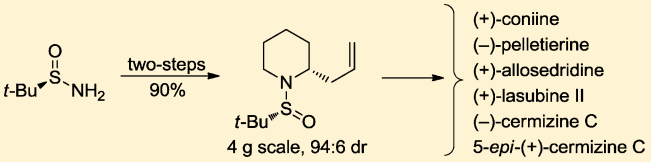
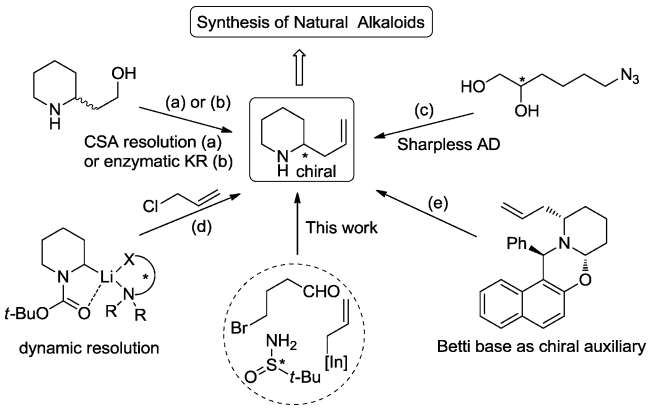
Supporting Information

ABSTRACT: An efficient stereocontrolled preparation of ($2R,R_S$)-2-allyl-(*N*-*tert*-butylsulfinyl)piperidine and its enantiomer is detailed. The sequence requires only two synthetic operations with one-column chromatography and is readily scaled up. The versatility of these chiral building blocks was exemplified by the total or formal synthesis of some natural and unnatural alkaloids.



2-Substituted piperidines are widespread subunits in natural alkaloids[1] and pharmaceuticals.[2] Among them, chiral 2-allylpiperidines constitute prominent examples that have been extensively used as building blocks for the synthesis of biologically active natural products.[3−5] Notably, the natural alkaloids structurally related to 2-allylpiperidine have different biosynthetic origins, and the stereocenter adjacent to the nitrogen atom can show different configurations (*R*/*S*).[6] The exceptional versatility of these small molecules is obviously related to the wide range of synthetical manipulations that can be done in the allyl moiety, as well as in the amino group. Consequently, their synthesis has garnered much attention using diverse approaches (Scheme 1). The most common

Scheme 1. Prior Syntheses of Enantioenriched 2-Allylpiperidine



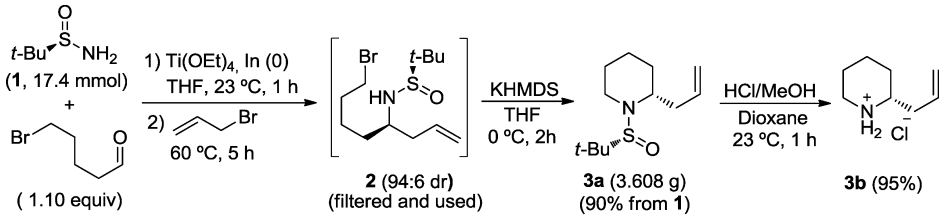
asymmetric strategies to access these molecules are (a) resolution of racemic piperidine-2-ethanol with enantiopure camphorsulfonic acid;[7] (b) enzymatic resolution of racemic piperidine-2-ethanol;[8] (c) Sharpless asymmetric dihydroxylation (AD) of 5-hexenyl azide;[3] and (d) dynamic resolution of enantioenriched *N*-Boc-2-lithio-piperidine, followed by transmetalation and reaction with allyl chloride.[9,10] These methods, though elegant and efficient, suffer from some drawbacks including limitations in the maximal yield attainable in classical or kinetic resolutions, long reaction sequences, and the use of expensive or dangerous starting materials that are restricted from use on a large scale. Another practical approach that has recently afforded enantioenriched 2 allylpiperidine in gram-scale is the use of Betti base as chiral auxiliary (e).[11] Despite important progresses, new general, efficient, and scalable methods to access both enantiomers of 2-allylpiperidine are still highly desirable to expand the synthetic utility of these versatile building blocks.

The ready availability of both enantiomers of *tert*-butanesulfinamide in large-scale processes,[12] the easy deprotection of the amine under acidic conditions, and practical procedures for recycling the chiral auxiliary[13] have contributed to its widespread use in many practical asymmetric synthesis of amines.[14] Recently, an efficient asymmetric synthesis of 2-substituted pyrrolidines by addition of Grignard reagents to γ-chloro-*N*-*tert*-butanesulfinyl aldimines followed by base-mediated cyclization was reported.[15] We reasoned that the indium-mediated α-aminoallylation of 5-bromopentanal with (R_S)- or (S_S)-*tert*-butanesulfinamide could be implemented in a similar approach to enantioenriched 2-allylpiperidine derivatives (Scheme 1).[16]

As outlined in Scheme 2, indium-mediated one-pot α-aminoallylation of 5-bromo-pentanal[17] with (R_S)-*tert*-butanesulfinamide (**1**) and allylbromide took place smoothly. It is worthy to point out that using this one-pot protocol, we did not observe any reaction product of *tert*-butanesulfinamide or allyl indium reagent at C-5 of 5-bromopentanal, or elimination products, and the desired compound **2** was obtained with high chemo- and diasteroselectivity (94:6 dr by ^{1}H NMR). After filtration of crude **2** through Celite, its cyclization was

Received: October 27, 2011
Published: November 27, 2011

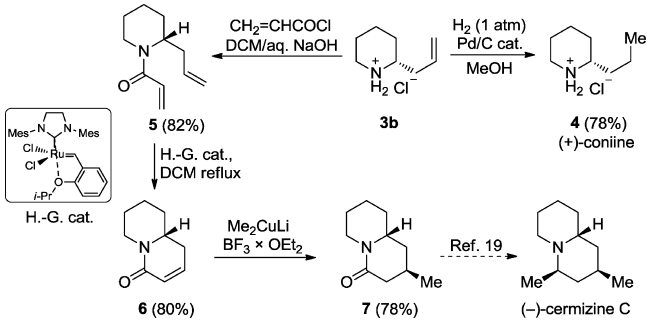
Scheme 2. Preparation of (*R*)-2-Allylpiperidine (3b) from (R_S)-*tert*-Butanesulfinamide (1)



attempted with different bases and conditions (like Et_3N/MeCN 80 °C or KOH/THF-H_2O 80 °C), obtaining the best results with KHMDS in THF at 0 °C (at 23 °C, other byproducts were observed). Notably, only two synthetic operations were needed to efficiently prepare pure compound **3a** (90% yield from **1**) in 4 g scale within a few hours. Moreover, *ent*-**3a** was prepared from *ent*-**1** using the same pathway with similar efficiency. Importantly, the sulfinyl group was readily cleaved under mild acidic conditions to provide enantioenriched (*R*)-2-allylpiperidine hydrochloride **3b** in excellent yield.

As depicted in Scheme 3, hydrogenation of **3b** afforded (*S*)-(+)-coniine hydrochloride (**4**), the major alkaloid extracted

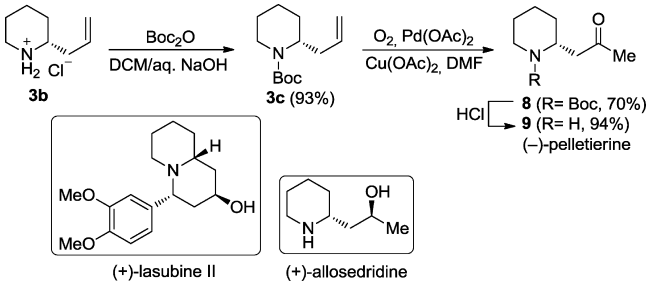
Scheme 3. Synthesis of (+)-Coniine and Formal Synthesis of (−)-Cermizine C from 3b



from poison hemlock and responsible for its toxicity, which confirms the absolute configuration of the stereogenic center introduced in the α-aminoallylation step. Treatment of compound (*R*)-**3b** with acryloyl chloride under basic conditions, followed by ring-closing metathesis with Hoveyda−Grubbs catalyst, allowed the efficient preparation of unsaturated lactam (*R*)-**6** (Scheme 3), the enantiomer of a key intermediate in the synthesis of lycopodium alkaloids.[18] The stereoselective conjugate addition of Me_2CuLi to the convex face of compound (*R*)-**6** was performed with good selectivity to afford lactam **7**, following a protocol described by Snider in the first total synthesis of senepodine-G and cermizine-C.[19] This method represents a formal synthesis of the enantiomers of the above-mentioned quinolizidine alkaloids.[20,21]

Pelletierine has been recognized to play an important role in the biosynthesis of a number of alkaloids, and consequently this molecule is potentially a key intermediate in the biomimetic synthesis of natural alkaloids.[22] However, the application of pelletierine in synthesis is limited, probably because its asymmetric preparation in the required amounts to be used as building block is not straightforward. Wacker oxidation of *N*-sulfinyl-protected compound **3a** under different reaction conditions gave always a complex mixture of products. Better results were obtained when the *N*-Boc-protected compound (*R*)-**3c** was submitted to Wacker oxidation conditions, which after conventional acidic deprotection, afforded unnatural (*R*)-(−)-pelletierine (**9**) in good overall yield (Scheme 4).

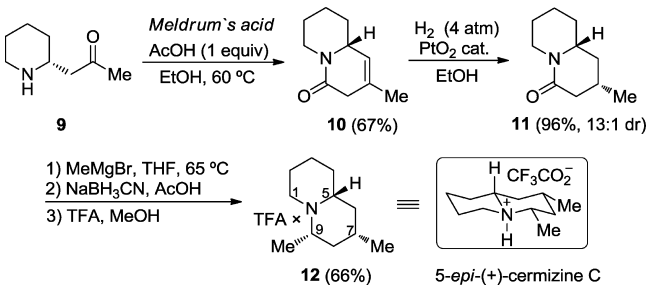
Scheme 4. Synthesis of (−)-Pelletierine and Formal Synthesis of (+)-Lasubine II and (+)-Allosedridine



Importantly, stereoselective reduction of (*R*)-*N*-Boc-pelletierine (**8**) has been recently reported to obtain natural (+)-allosedridine,[23] as well as a two-step transformation of (*S*)-(+)-pelletierine into (−)-lasubine II.[11]

As previously reported for racemic 5-*epi*-cermizine C,[19] the Knoevenagel condensation of the ammonium acetate salt of (*R*)-pelletierine (**9**) with Meldrum's acid took place with concomitant lactam formation, followed by decarboxylation and kinetic protonation to provide the unconjugated lactam (*R*)-**10** in good yield (Scheme 5). Hydrogenation of (*R*)-**10** at 4 atm of

Scheme 5. Synthesis of 5-*epi*-(+)-Cermizine C



H_2 occurred mainly on the convex face, affording the desired lactam **11** in excellent yield and good selectivity (13:1 dr). Addition of MeMgBr to compound **11** was followed by in situ stereoselective reduction of the iminium-intermediate to afford 5-*epi*-cermizine C in good overall yield, which was further transformed to its trifluoroacetate salt (**12**). It is worth pointing out that protonation of 5-*epi*-cermizine C should render a stereogenic nitrogen via equilibration through the most stable *trans*-quinolizidine conformation of the free amine.[24] Importantly, since 2-allyl piperidines **3a** and *ent*-**3a** are available using the present methodology, formally all four diasteroisomers of

dx.doi.org/10.1021/jo202211u | J. Org. Chem. 2012, 77, 780−784

senepodine G and the corresponding cermizine C diastereoisomers could be prepared following the pathways described in Schemes 3 and 5.

In conclusion, we have developed a highly efficient two-step process for the synthesis of enantioenriched 2-allylpiperidine **3a** in 4 g scale. Because of its operational ease, we believe this method provides a useful complement to existing methods for the preparation of both enantiomers of **3a**. The usefulness of **3a** as a building block was illustrated by the total synthesis of alkaloids such as (+)-coniine, (−)-pelletierine, and 5-*epi*-(+)-cermizine C as well as in the formal synthesis of (−)-cermizine C, (+)-allosedridine, and (+)-lasubine II. Extension of this work is currently underway in our laboratory.

EXPERIMENTAL SECTION

General Remarks. (R_S)-*tert*-Butanesulfinamide and its enantiomer were a gift of Medalchemy (>99% ee by chiral HPLC on a Chiracel AS column, 90:10 *n*-hexane/*i*-PrOH, 1.2 mL/min, λ = 222 nm). TLC was performed on silica gel 60 F_{254} using aluminum plates and visualized with phosphomolybdic acid (PMA) stain. Flash chromatography was carried out on handpacked columns of silica gel 60 (230−400 mesh). Melting points are uncorrected. Optical rotations were measured using a polarimeter with a thermally jacketted 5 cm cell at approximately 20 °C, and concentrations (c) are given in g/100 mL. Infrared analyses were performed with a spectrophotometer equipped with an ATR component; wavenumbers are given in cm^{-1}. Mass spectra (EI) were obtained at 70 eV, and fragment ions in m/z with relative intensities (%) are in parentheses. HRMS analyses were also carried out in the electron impact mode (EI) at 70 eV. ^{1}H NMR spectra were recorded at 300 or 400 MHz for ^{1}H NMR and 75 or 100 MHz for ^{13}C NMR, using $CDCl_3$ as the solvent and TMS as internal standard (0.00 ppm). The data is reported as s = singlet, d = doublet, t = triplet, m = multiplet or unresolved, br s = broad signal, coupling constant(s) in Hz, integration. ^{13}C NMR spectra were recorded with ^{1}H-decoupling at 100 MHz and referenced to $CDCl_3$ at 77.16 ppm. DEPT-135 experiments were performed to assign CH, CH_2, and CH_3.

(4*R*,*R*$_S$)-*N*-(*tert*-Butylsulfinyl)-8-bromooct-1-en-4-amine (2). To a dry flask was added (R_S)-*N*-*tert*-butanesulfinamide (**1**, 2.109 g, 17.40 mmol) followed by indium powder (2.485 g, 21.80 mmol), and the mixture was evacuated and put under Ar. Then, a solution of 5-bromopentanal (3.141 g, 19.15 mmol) in dry THF (34.9 mL) and $Ti(OEt)_4$ (7.8 mL, 34.80 mmol) were added successively, and the reaction mixture was stirred under Ar for 1 h at 23 °C. At this time, allyl bromide (2.3 mL, 26.10 mmol) was added to the mixture, and it was heated to 60 °C for 5 h. The mixture was allowed to reach room temperature and was carefully added over a stirring mixture of 4:1 EtOAc/brine (200 mL). The resulting white suspension was filtered through a short pad of Celite and washed with EtOAc, and the organics were concentrated in vacuo. The resulting suspension was diluted in 4:1 EtOAc/hexane (200 mL) and filtered again through Celite. Organics were concentrated to afford the expected compound **2** (5.050 g, 94%, 94:6 dr according ^{1}H NMR) as a yellow oil, pure enough to be used in the next step. To provide the spectroscopy data, a sample of compound **2** was purified by column chromatography (7:3 hexane/EtOAc): R_f 0.15 (7:3 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85−5.71 (m, 1H), 5.16 (dd, J = 14.0, 1.5 Hz, 2H), 3.41 (t, J = 6.6 Hz, 2H), 3.32 (dt, J = 11.3, 5.8 Hz, 1H), 3.23 (d, J = 6.1 Hz, 1H), 2.42 (dt, J = 13.0, 5.9 Hz, 1H), 2.33 (dt, J = 13.8, 6.8 Hz, 1H), 1.92−1.80 (m, 2H), 1.62−1.46 (m, 4H), 1.21 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.1 (CH), 119.3 (CH_2), 56.0 (C), 54.7 (CH), 40.5 (CH_2), 34.1 (CH_2), 33.8 (CH_2), 32.6 (CH_2), 24.1 (CH_2), 22.8 (CH_3); LRMS (EI) m/z (%) 237 ($M^+ - C_4H_8$, 19), 235 ($M^+ - C_4H_8$, 20), 213 (67), 211 (67), 156 (100).

(2*R*,*R*$_S$)-2-Allyl-(*N*-*tert*-butylsulfinyl)piperidine (3a). A titrated solution of KHMDS in THF (33 mL, 0.79 M, 26.10 mmol) was added via syringe to a cold solution (0 °C) of crude **2** (5.050 g, 16.30 mmol) in dry THF (36.5 mL). The reaction mixture was stirred for 2 h at 0 °C under Ar and then quenched with saturated NH_4Cl solution. The aqueous phase was extracted with EtOAc (3 times), and the combined extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (75:25 hexane/EtOAc) to provide the product as a pale-yellow oil (3.608 g, 15.76 mmol, 90% from **1**): $[\alpha]_D^{20}$ +20.7 (c 1.0, $CHCl_3$); R_f 0.30 (7:3 hexane/EtOAc); IR ν 3075, 2939, 1639, 1074, 986, 906 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.84−5.70 (m, 1H), 5.15−5.04 (m, 2H), 3.46−3.28 (m, 1H), 3.20−3.11 (m, 1H), 2.99−2.90 (m, 1H), 2.59−2.43 (m, 2H), 1.72−1.49 (m, 6H), 1.17 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.5 (CH), 117.4 (CH_2), 58.3 (C), 56.4 (CH), 40.8 (CH_2), 34.4 (CH_2), 28.1 (CH_2), 25.8 (CH_2), 23.2 (CH_3), 19.5 (CH_2); LRMS (EI) m/z (%) 229 (M^+, 0.1), 173 (28), 132 (100), 83 (11), 57 (17), 55 (20); HRMS (EI) calcd for $C_{12}H_{23}NOS$ 229.1500, found 229.1507.

(2*S*,*S*$_S$)-2-Allyl-(*N*-*tert*-butylsulfinyl)piperidine (*ent*-3a). It was prepared from (S_S)-*N*-*tert*-butanesulfinamide (*ent*-**1**, 0.52 mmol), following the same procedure described above for compound **3a** (90 mg, 0.40 mmol, 77% from *ent*-**1**). Physical and spectroscopic data were found to be same than for (2*R*,*R*$_S$)-**3a**, except for the optical rotation: $[\alpha]_D^{20}$ −22.0 (c 1.1, $CHCl_3$).

(*R*)-2-Allylpiperidine Hydrochloride (3b). A solution of HCl in dioxane (6.8 mL, 4 M) was added dropwise to a solution of **3a** (1.557 g, 6.80 mmol) in dry MeOH (40 mL) at 0 °C under Ar. The reaction mixture was allowed to reach 23 °C while being stirred for 2 h. The solvent was removed in vacuo, and the resulting solid was triturated with Et_2O (2 × 5 mL). The Et_2O was removed, and the solid was dried under reduced pressure to give a white crystalline solid (1.040 g, 95%): mp 159−161 °C (*i*-PrOH/EtOAc) [lit.[3] 175−178 °C]; $[\alpha]_D^{20}$ +2.4 (c 0.8, EtOH) [lit.[3] $[\alpha]_D^{25}$ +2.1 (c 1.3, EtOH)]. ^{1}H NMR, ^{13}C NMR, and IR data were in agreement with previously reported values.[3]

(*S*)-Coniine Hydrochloride (4). To a solution of **3b** (154 mg, 0.95 mmol) in dry MeOH (20 mL) was added 10% Pd/C (50 mg). A balloon of H_2 gas was fitted to the equipment, and the reaction mixture was stirred under H_2 for 20 h at 23 °C. The reaction mixture was filtered through a short pad of Celite and washed successively with Et_2O and a 4 M solution of HCl in dioxane. The residue was concentrated in vacuo, and the solid obtained was triturated with Et_2O (2 × 1 mL) and recrystallized from 3:1 EtOAc/EtOH (2 mL) to afford a white solid (120 mg, 78%): mp 226−230 °C [lit.[3] 216−218 °C]; $[\alpha]_D^{20}$ +7.2 (c 1.0, EtOH) [lit.[3] $[\alpha]_D^{25}$ +5.2 (c 0.35, EtOH)]. ^{1}H NMR,^{13}C NMR, and IR data were in agreement with previously reported values.[25]

(*R*)-*tert*-Butyl 2-Allylpiperidine-1-carboxylate (3c). To a solution of **3b** (614 mg, 3.80 mmol) in CH_2Cl_2 (40 mL) at 0 °C was added aqueous NaOH solution (40 mL, 2 M) followed by Boc_2O (997 mg, 4.56 mmol). The reaction mixture was left stirring for 16 h while the temperature reached 23 °C. The mixture was extracted with CH_2Cl_2 (3 times), washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The product was obtained as a colorless oil (905 mg contaminated with 12 mol % of Boc_2O according to GC, resulted in 93% estimated yield) and was used in the next step. A sample of compound **3c** was purified by column chromatography (98:2 hexane/EtOAc) for characterization: $[\alpha]_D^{20}$ +46.5 (c 1.0, $CHCl_3$) {lit.[9] for er 78:22 $[\alpha]_D^{23}$ +39.7 (c 1.2, $CHCl_3$)}; R_f 0.60 (9:1 hexane/EtOAc). ^{1}H NMR, ^{13}C NMR, IR, and MS data were in agreement with previously reported values.[9] CSP-GC [20% β-cyclodextrin-permethylated capillary column 30 m × 0.25 mm i.d., hydrogen carrier at 12 psi; temperature at 80 °C over 60 min, then a ramp of 10 °C/min.] analysis showed 93:7 er (see chromatograms in the Supporting Information).

(*S*)-*N*-*tert*-Butyl 2-Allylpiperidine-1-carboxylate (*ent*-3c). It was prepared from *ent*-**3b** (0.30 mmol), following the same procedure described above for compound **3c**. Physical and spectroscopic data were found to be same as for (*R*)-**3c**, except for the optical rotation: $[\alpha]_D^{20}$ −41.7 (c 1.0, $CHCl_3$) {lit.[3] $[\alpha]_D^{25}$ −39.96 (c 1.23, $CHCl_3$)}. CSP-GC analysis was performed as indicated for **3c**, showing 93:7 er (see the Supporting Information).

(*R*)-*N*-Acryloyl-2-allylpiperidine (5). A mixture of **3b** (230 mg, 1.42 mmol) in a 10% solution of NaOH (1.4 mL) was cooled to 0 °C,

dx.doi.org/10.1021/jo202211u | J. Org. Chem. 2012, 77, 780−784

and a solution of acryloyl chloride (290 μL, 3.56 mmol) in CH_2Cl_2 (3.6 mL) was then added dropwise. The solution was allowed to reach room temperature and was stirred for 20 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography (7:3 hexane/EtOAc) to provide the product as a pale-yellow oil (208 mg, 82%): $[\alpha]_D^{20}$ +62.4 (*c* 0.7, $CHCl_3$) {lit.[11] for *ent*-**5** $[\alpha]_D^{20}$ −70.6 (*c* 0.42, $CHCl_3$)}; R_f 0.15 (6:4 hexane/EtOAc). ^{1}H NMR, ^{13}C NMR, IR, and MS data were in agreement with previously reported values for *ent*-**5**.[11]

(*R*)-1,6,7,8,9,9a-Hexahydro-(4*H*)-quinolizin-4-one (6). To a solution of **5** (222 mg, 1.24 mmol) in dry CH_2Cl_2 (10 mL) was added the Hoveyda−Grubbs catalyst (23 mg, 0.04 mmol) at room temperature. The reaction mixture was put under Ar and heated to 40 °C with stirring. After 30 min, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by column chromatography (6:4 hexane/EtOAc) to provide the product as a pale-yellow oil (150 mg, 80%): $[\alpha]_D^{20}$ −39.0 (*c* 0.64, $CHCl_3$), {lit.[11] for *ent*-**6** $[\alpha]_D^{20}$ +45.7 (*c* 0.42, $CHCl_3$)}; R_f 0.17 (6:4 hexane/EtOAc). ^{1}H NMR, ^{13}C NMR, IR, and MS data were in agreement with previously reported values for *ent*-**6**.[11]

(2*R*,9a*R*)-2-Methyloctahydro-(4*H*)-quinolizin-4-one (7). A solution of MeLi in Et_2O (2.4 mL, 1.2 M, 2.80 mmol) was added dropwise to a suspension of CuI (273 mg, 1.44 mmol) in dry THF (9.1 mL) at 0 °C. The resulting solution was stirred for 30 min and then cooled to −78 °C. $BF_3{\cdot}OEt_2$ was added dropwise, and the resulting solution was stirred for 5 min at −78 °C. A solution of **6** (106 mg, 0.70 mmol) in dry THF (4.2 mL) was carefully added to the stirring mixture, and the resulting solution was slowly allowed to reach room temperature (30 min). Saturated NH_4Cl solution (20 mL) was then added, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (98:2 to 95:5 CH_2Cl_2/MeOH) to give the product as a yellow oil (90 mg, 78%): $[\alpha]_D^{20}$ +21.0 (*c* 0.36, $CHCl_3$) {lit.[19] for *ent*-**7** $[\alpha]_D^{23}$ −21 (*c* 1.0, $CHCl_3$)}; R_f 0.36 (9:1 CH_2Cl_2/MeOH); ^{1}H NMR, ^{13}C NMR, IR, and MS data were in agreement with previously reported values for *ent*-**7**.[19]

(*R*)-*N*-*tert*-Butoxycarbonylpelletierine (8). A mixture of **3c** (905 mg with 88% purity, 3.42 mmol), $PdCl_2$ (60 mg, 0.34 mmol), and $Cu(OAc)_2$ (126 mg, 0.68 mmol) in 7:1 DMF/H_2O (27 mL) was stirred for 24 h under O_2 (1 atm) at 50 °C. The reaction was quenched with 1 M solution of $KHSO_4$ (27 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were successively washed with saturated $NaHCO_3$ solution (15 mL) and H_2O (3 × 20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (9:1 hexane/EtOAc) to provide the product as a colorless oil (577 mg, 70%): $[\alpha]_D^{20}$ +10.5 (*c* 0.95, $CHCl_3$) {lit.[23] $[\alpha]_D^{25}$ +8.2 (*c* 2.0, $CHCl_3$)}; R_f 0.18 (9:1 hexane/EtOAc). ^{1}H NMR, ^{13}C NMR, IR, and MS data were in agreement with previously reported values.[23]

(*R*)-Pelletierine Hydrochloride (9). A solution of HCl in dioxane (2.5 mL, 4 M) was added dropwise to a solution of **8** (870 mg, 3.61 mmol) in dry CH_2Cl_2 (36 mL) at 0 °C, and the reaction mixture was stirred at 23 °C for 2 h under Ar. After removal of the solvent under vacuum, the resulting solid was triturated with Et_2O (2 × 3 mL) to afford a pale brown amorphous solid (600 mg, 94%): $[\alpha]_D^{20}$ −12.0 (*c* 0.60, EtOH) {lit.[26] $[\alpha]_D^{25}$ −18.0 (*c* 0.5, EtOH)}. ^{1}H NMR, ^{13}C NMR, IR, and MS data were in agreement with previously reported values.[26]

(*R*)-2-Methyl-3,6,8,9,9a-hexahydro-(4*H*)-quinolizin-4-one (10). Meldrum's acid (478 mg, 3.32 mmol) and acetic acid (156 μL, 2.70 mmol) were successively added to a stirring solution of (*R*)-pelletierine (**9**)[27] (380 mg, 2.65 mmol) in EtOH (2.7 mL) at room temperature. The resulting solution was heated to 60 °C and stirred for 24 h. The solution was allowed to reach room temperature, and more Meldrum's acid (388 mg, 2.69 mmol) was added. The solution was heated to 60 °C and stirred for another 24 h. The reaction mixture was allowed to reach room temperature and concentrated under reduced pressure. The residue was diluted in EtOAc (18 mL), washed with a saturated solution of Na_2CO_3, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (9:1 hexane/EtOAc) to provide the product as a yellow oil (292 mg, 67%): $[\alpha]_D^{20}$ −8.7 (*c* 0.90, $CHCl_3$); R_f 0.50 (EtOAc). ^{1}H NMR, ^{13}C NMR, IR, and MS data were in agreement with previously reported values for *rac*-**10**.[19]

(2*S*,9a*R*)-2-Methyl-1,6,7,8,9,9a-hexahydro-(4*H*)-quinolizin-4-one (11). PtO_2 (9 mg, 0.04 mmol) was added to a solution of **10** (282 mg, 1.71 mmol) in EtOH (8.5 mL). The resulting suspension was shaken under H_2 atmosphere (4 atm) for 6 h at 23 °C. The reaction mixture was diluted in EtOAc (3 mL) and the catalyst was removed by filtration through Celite. The resulting solution was concentrated under reduced pressure to give the product as a colorless oil (274 mg, 96%, 13:1 dr by ^{1}H NMR): $[\alpha]_D^{20}$ −33.2 (*c* 1.00, $CHCl_3$); R_f 0.24 (1:1 hexane/EtOAc). ^{1}H NMR, ^{13}C NMR, IR, and MS data were in agreement with previously reported values for *rac*-**11**.[19]

(+)-5-*epi*-Cermizine C-TFA Salt (12). To a stirring solution of **11** (151 mg, 0.90 mmol) in dry THF (9 mL) was added dropwise a solution of MeMgBr in THF (3.8 mL, 0.95 M, 3.61 mmol). The mixture was heated to 60 °C for 3 h and then allowed to cool to 0 °C. $NaBH_3CN$ (340 mg, 5.40 mmol) and glacial acetic acid (450 μL, 7.86 mmol) were successively added, and the mixture was stirred for 30 min at 0 °C followed by another 30 min at 23 °C. The reaction mixture was diluted with 5% aqueous solution of Na_2CO_3 (20 mL), verifying pH 10, and extracted with EtOAc (3 × 40 mL). The combined extracts were dried over $MgSO_4$, concentrated under reduced pressure, and purified by column chromatography (90:9:1 $CHCl_3$/MeOH/NH_4OH). The obtained oil was dissolved in MeOH (2 mL) and treated with TFA (0.50 mL). The solution was concentrated under reduced pressure, and the latter process was repeated to afford 180 mg (66%) of the TFA salt as a yellow oil: $[\alpha]_D^{20}$ +5.0 (*c* 0.53, MeOH); R_f 0.32 (90:9:1 $CHCl_3$/MeOH/NH_4OH); IR ν 2962, 1666, 1781, 1451, 1142, 797 cm^{-1}; ^{1}H NMR (300 MHz, MeOD) δ 3.79 (br d, J = 12.5 Hz, 1H), 3.23−3.12 (m, 1H), 3.06 (br t, J = 11.5 Hz, 1H), 2.73 (br t, J = 12.9 Hz, 1H), 2.04−1.90 (m, 3H), 1.90−1.62 (m, 4H), 1.62−1.48 (m, 2H), 1.37 (d, J = 6.4 Hz, 3H), 1.33−1.12 (m, 2H), 0.98 (d, J = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, MeOD) δ 65.6 (CH), 62.5 (CH), 52.0 (CH_2), 41.8 (CH_2), 40.5 (CH_2), 32.3 (CH_2), 30.1 (CH), 24.9 (CH_2), 23.2 (CH_2), 21.4 (CH_3), 18.0 (CH_3).

A sample of compound **12** was dissolved in EtOAc, washed with 2 M NaOH (3 times), and dried over $MgSO_4$. After being concentrated under reduced pressure, the free amine was submitted to ^{1}H NMR, IR, and MS analysis, obtaining a data in agreement with previously reported values for free amine *rac*-**12**.[19]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra for compounds **2**−**12** and chromatograms of CSP-GC for **3c** and *ent*-**3c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENTS

We thank the Spanish Ministerio de Ciencia e Innovación (Grant No. CTQ2007-65218, Consolider Ingenio 2010-CSD-2007-00006 and CTQ2011-24165), the Generalitat Valenciana (Grant No. PROMETEO/2009/039 and FEDER) and the University of Alicante for generous and continuous financial support.

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